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Reaching transmission elimination of the soil-transmitted helminths

Measuring the multiple heterogeneities in transmission and control

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Statement of Originality

I hereby confirm that this thesis contains the work solely created, analysed, and summarised by myself, under the supervision of my PhD supervisors, Professor Sir Roy Anderson and Dr Anna Phillips. Any datasets used or research undertaken that are not my own have been appropriately referenced and cited, as per the regulations and guidance provided by Imperial College London.

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This thesis reports upon the work of the Geshiyaro project, the largest and longest study of its kind to date. The analysis of this data for both the project and this thesis would not be possible without the work of the hundreds of health extension workers (HEW) who have taken on the extra data collection requirements for this project, alongside their usual duties of caring for their community. This workforce is the backbone of health provision for Ethiopia and now the documentation of the Geshiyaro project. I thank each and every HEW that I have worked alongside as part of this project.

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Abstract

Soil-transmitted helminths (STH) currently infect just under a quarter of the world's population, primarily in tropical climates where access to safe water, sanitation, and hygiene (WaSH) infrastructure is poor, creating optimal conditions for helminth transmission. Guidance for the control of these parasites by the World Health Organisation (WHO) centres upon integrated control: the combination of anthelmintic treatment and improved access to WaSH infrastructure, with community sensitisation to both. National control programs predominantly target school-aged children (SAC), expanding treatment to high-risk groups such as preSAC and women of reproductive age (WRA) in highly endemic areas. Treatment is administered at a prevalence-dependent frequency (biennial, annual, biannual) through mass drug administration (MDA) campaigns, regardless of individual infection status. Such control is targeted with first achieving morbidity control, and subsequently reaching elimination as a public health problem (EPHP), defined by the WHO as <2% moderate and heavy intensity infections (MHII). Despite the immediate efficacy of treatment, STH re-infection is common due to untreated members of the community acting as infection reservoirs, particularly in areas with poor WaSH access.

The Geshiyaro project, located in south Ethiopia, aims to define the optimal combination of MDA and WaSH access to eliminate STH transmission in a low prevalence setting. Using a longitudinal dataset following individuals over six years, this thesis analyses changes in STH prevalence and intensity by the different interventions, using age-sex stratifications across individual, village, and district aggregation levels. This thesis will critically appraise the interventions implemented and fine-scale monitoring methods used to evaluate them, in the context of STH transmission elimination, discussing whether the improvements made to Ethiopia's Federal Ministry of Health's (FMoH) NTD control program by the Geshiyaro project justify recommendations for future national control programs.

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Abbreviations

AOR: adjusted odds ratio

BCC: behavioural change communication

CDD: community drug distributer

CES: coverage evaluation survey

CIFF: Children's Investment Fund Foundation

cMDA: community-wide mass drug administration

DOT: directly observed treatment

EPHI: Ethiopian Public Health Institute

EPHP: elimination as a public health problem

ESPEN: Expanded Special Project for Elimination of Neglected Tropical Diseases

FMoH: Ethiopian Federal Ministry of Health

GDP: gross domestic product

GUID: global unique identifier

HEW: health extension worker

ID: identification

IU: implementation unit

LF: lymphatic filariasis

LMIC: low-and-middle-income country

MDA: mass drug administration

MHII: moderate and heavy intensity infections

M&E: monitoring and evaluation

NTD: neglected tropical disease

OR: odds ratio

OWNP: One WaSH national program

OV: Onchocerca volvulus

PC: preventative chemotherapy

PCR: polymerase chain reaction

preSAC: pre-school-aged children

qPCR: quantitative polymerase chain reaction

QR: quick response

R_e: effective reproductive number

R_0: basic reproductive number

SAC: school-aged children

SCH: schistosomiasis

SERS: South Ethiopian Regional State

sMDA: school-based mass drug administration

SSNPR: Southern Nations, Nationalities and People's Region

STH: soil-transmitted helminths

TPPs: target product profiles

US: United States of America

WaSH: water, sanitation, and hygiene

WHO: World Health Organisation

WRA: women of reproductive age

Chapter 1: The global effort to control soil-transmitted helminths: the progress, lessons learnt, and remaining challenges

1. Introduction to the soil-transmitted helminths

It is estimated that 1.5 billion people, equating to just under a quarter of the world's population, are infected with at least one species of soil-transmitted helminth (STH) [1]. This umbrella term describes the parasitic helminthiases: Ascariasis (*Ascaris lumbricoides*), trichuriasis (*Trichuris trichiura*), hookworm (*Ancylosoma duodenale*, *Necator americanus*), and more recently, *Strongyloides stercoralis* [2,3]. STH are the most prevalent neglected tropical disease (NTD), a group of 21 predominantly parasitic infections characterised by their chronic or debilitating nature, which are often intrinsically linked to a downward spiral of poverty [4]. Chronic infection impedes development and hinders learning and productivity, thus continuing the poverty-disease cycle [5].

Critical to the transmission cycle, and modelling of such, is the dioecious nature of the helminths, requiring reproductively viable male and female worms in the human host intestines for sexual reproduction, followed by the subsequent release of infectious material into environment via the host's faeces. The infectious lifecycle stage of STH, eggs for *A. lumbricoides* and *T. trichiura* and larvae for hookworm, require several weeks to become viably infective after faecal expulsion [1]. Consequently, STH infections (and re-infections) are a proxy of poor water, sanitation and hygiene (WaSH) access, and thus their prevalence can broadly be mapped to that of poverty [4].

A. lumbricoides and *T. trichiura* transmit via the faecal-oral pathway whereby individuals become infected after ingesting eggs in water, fomites, hands, soil, and food [1]. Hookworms are propagated transdermally by infective stages penetrating bare skin, often feet or hands, coming into contact with soil [1]. These distinct transmission pathways impact the infection profile in a population due to age-related risk factors. *A. lumbricoides* and *T. trichiura* infections are found disproportionately higher in children, who for instance, may eat with unwashed contaminated hands. Conversely, hookworm infections are disproportionately

found higher in adults which, in an agricultural-dominated nation such as Ethiopia, are often labourers working bare-foot and thus in constant contact with contaminated soil.

1.1. Treatment of soil-transmitted helminths

Despite the high global prevalence, STH infection is easily treatable via a single anthelmintic dose of either albendazole (400mg) or mebendazole (500mg) [6]. Typically, this is delivered via mass drug administration (MDA), regardless of individual infection status, using the World Health Organisation's (WHO) prevalence-dependent algorithm (see **Figure 1.1**) to defined population groups, namely pre-school age children (preSAC) aged one to four years, school-aged children (SAC) aged five to 14 years, and women of reproductive age (WRA) (including pregnant women in the second and third trimesters and breastfeeding women) [4,6]. Neither infection nor drug treatment confers significant acquired immunity to infection, as helminths are believed to actively modulate the human immunological attack via secreted molecules [7]. Therefore re-infection post treatment occurs frequently in areas with poor access to WaSH infrastructure, stimulating the requirement for repeated rounds of MDA for effective, long-term control [8].

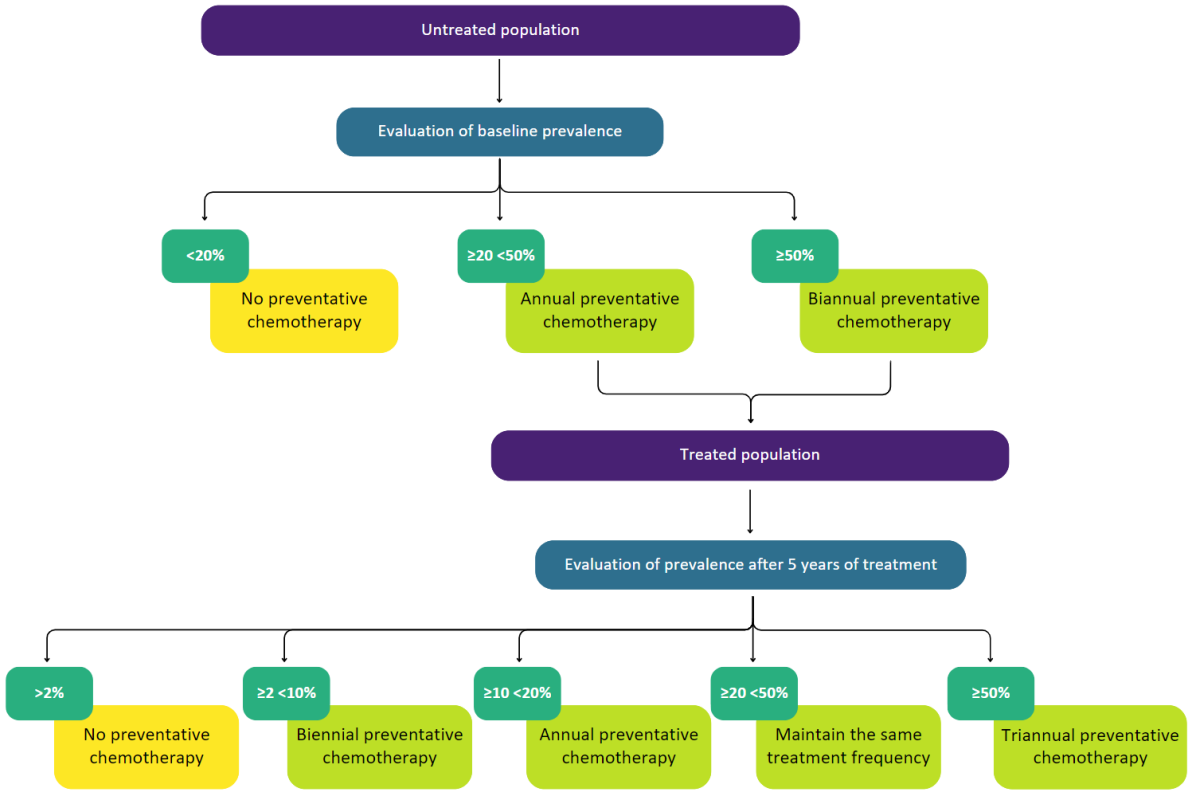


Figure 1.1: Guidelines for the control of soil-transmitted helminths (STH) in school-aged children (SAC) using preventative chemotherapy (PC) with albendazole, as recommended by the WHO. *The guidelines for programmatic treatment are dependent on the local prevalence and treatment history of the targeted population. Prevalence is evaluated in either treatment naïve populations, or populations being re-assessed having received five to six years of PC using a transmission assessment survey (TAS) as part of lymphatic filariasis (LF) control programs or integrated schistosomiasis/STH impact assessment. LF and STH control programs overlap due to the shared distribution of albendazole. The resulting frequency is based both upon the prevalence, and the treatment history of the population* [9].

Donated anthelmintics from major pharmaceutical companies underpin the global STH control strategy. Currently, pledges of albendazole from GlaxoSmithKline, and mebendazole from Johnson & Johnson are confirmed from 2012 through to 2025, totalling 200 million tablets of each anthelmintic annually [10]. The commitment of such donations beyond 2025 is currently unknown. In 2022, 898 million children (265 million pre-SAC and 633 million SAC) required MDA for STH control across 87 countries, yet 493 million children (102 million pre-SAC and 391 million SAC) were treated, about 50% of those required [11]. Similarly, of the 108 million adolescent girls, and 139 million pregnant and lactating women requiring treatment, 89 million WRA were treated through the lymphatic filariasis (LF) elimination programs [11].

The sheer scale of donations for STH control is staggering, world record breaking even, yet the supply still does not meet the demand, and many people remain untreated due to the enormity of the global burden [12]. Just 21 of the 50 countries implementing MDA for STH control reached the targeted 75% coverage. In these countries, coverage in pre-SAC and SAC reached 38.4% and 61.8%, respectively [11]. It should be noted that donations from non-governmental organisations and self-treatment are not recorded but will improve these figures. Nevertheless, such sub-optimal coverage will not suitably control the release of infectious material, and transmission will continue in endemic communities.

Transmission of STH (infection and re-infection) within and between communities is propagated via reservoirs of infection created by the untreated targeted population who missed or refused treatment, in addition to currently untargeted (adult) population groups [8,13–15]. The age-dependent distribution of infection across age classes is an important determinant of the size of these reservoirs of untreated infection [16]. Re-infection in a

community, or 'bounce-back', is rapid due to the relatively short adult worm life span (1-2 years). Therefore, recrudescence can be highly probable if sufficient reservoirs persist in the community and access to WaSH infrastructure is poor [14]. Hence, in lieu of WaSH improvements intrinsic to improved socioeconomic status, much recent research has focused on whether MDA alone will be enough to sufficiently reduce the continued cycle of re-infection, eventually leading to the interruption of transmission [8]. If so, what level of continued treatment compliance and coverage are required to achieve this goal, in what population demographic, and over what length of time [8]? If not, what complementary interventions can realistically be implemented to ensure the interruption of transmission?

1.2. The history of soil-transmitted helminth control

Deworming has been implemented as a public health response for the control of STH since the start of 20th century, with the earliest, notable, large-scale programs including treatment campaigns in southern USA lead by the Rockefeller Foundation [17,18]. The turn of the century saw an acceleration of interest, funding, and awareness, of the need for global STH control. By this juncture, many elements of transmission dynamics had been elucidated, the seminar work of which still underpins transmission modelling studies today [19–22]. 2005 marked the formation of the WHO Department of NTDs, previously coined "Great Neglected Diseases of Mankind", which cemented the importance of these diseases, including STH, on the agenda for global control [23]. Latterly, the London Declaration in 2012 triggered pledges of millions of chemotherapeutics for NTDs from large pharmaceutical companies, including albendazole and mebendazole for the control of STH from GlaxoSmithKline and Johnson & Johnson, respectively [24]. Despite decades of STH control centred on MDA, an acrimonious debate termed the 'worm wars' brought the scientific analysis of the long-term benefits of deworming into the public eye in 2015 [25–27]. This did not change control protocols, and WHO still recommends the mass treatment of SAC.

1.3. Previously implemented large-scale control programs

Seminal STH studies have analysed the proposed additional impact of cMDA, including DeWorm3 (Benin, Malawi, and India, results not published), TUMIKIA (Kenya), (S)WASH for Worms (Timor-Leste), and CoDe-STH (Vietnam), the results of which are summarised in **Table 1.1** [28–31]. As shown in **Table 1.1**, countering the theoretical work of modelling studies, the

impact of cMDA for the control of STH does not always show a positive or significant association [30,31].

Study	Baseline parasitology	Impact of cMDA	Notes
TUMIKIA (Kenya) [28]	*A. lumbricoides* 0.5% (sDMA) 0.3% (annual cMDA) 0.4% (biannual cMDA) *T. trichiura* 4.3% (sMDA) 2.9% (annual cMDA) 3.7% (biannual cMDA) Hookworm 18.6% (sMDA) 17.9% (annual cMDA) 20.6% (biannual cMDA)	*T. trichiura* AOR: 1.18 (0.80 - 1.74, non-significant) (annual cMDA) AOR: 1.16 (0.82 - 1.65, non-significant) (biannual cMDA) Hookworm AOR: 0.77 (95% CI: 0.65 - 0.91) (annual cMDA) AOR 0.65 (95% CI: 0.53 - 0.78) (biannual cMDA)	Reduction in prevalence after 12 months compared to sMDA. Either two annual rounds, or four biannual rounds of MDA delivered. Adjustments include subcounty, baseline cluster prevalence, and cluster size, urban or rural status and baseline cluster mean socioeconomic status, access to sanitation, and access to improved water. *A. lumbricoides* prevalence was too low to conduct analysis. Diagnostics by duplicate Kato Katz of community.
(S)WASH-D for Worms (Timor-Leste) [31]	Hookworm 13.7% (95% CI: 10.6 – 17.6%) (sMDA) 15.1% (95% CI: 9.4 – 23.3%) (cMDA)	Hookworm OR: 0.42 (0.07 – 2.36, non-significant)	Reduction in prevalence after 6 months following intervention including WASH infrastructure in schools (access to reliable, tapped water source, construction of pit latrines, and hygiene education) and cMDA. Diagnostics by qPCR of SAC.
CoDe-STH (Vietnam) [30]	Hookworm 16.7% (95% CI: 12.1–22.7%) (sMDA) 11.7% (95% CI: 7.8–17.3%) (cMDA)	Hookworm Relative reduction in prevalence: 30.1% (95% CI: 20.5 – 39.6%) (sMDA) 34.6% (95% CI: 19.9 – 49.4%, non-significant) (cMDA)	Reduction in prevalence after one round of sMDA or cMDA. Diagnostics by qPCR of SAC.

Table 1.1: A summary of results reported from studies investigating the impact of community-wide mass drug administration (cMDA) upon the control of soil-transmitted helminths (STH). *All studies compare the impact of cMDA to the current standard of school-based MDA (sMDA). To ensure correct interpretation of results, some grounding characteristics of each study are shown including the baseline parasitology recorded, the diagnostic used to measure this and in what population, and any other interventions assessed in parallel to cMDA.*

1.4. Current control progress and guidance

Despite the prevalence-based definition of MDA treatment frequency guidelines, control targets instead rely upon infection intensity. Due to the enormity of STH global burden, the WHO efforts initially focused upon the reduction of morbidity, defined as being proportional to infection intensity. Currently, the guidance for STH elimination of morbidity as a public health problem (EPHP) is defined as whole countries recording <2% moderate and heavy intensity infections (MHII) as diagnosed by Kato Katz in at-risk populations: preSAC and SAC [32]. This is targeted to be achieved through 75% treatment coverage of SAC in endemic areas [33–35].

After many decades of control, heterogeneity remains between the STH status classification of endemic countries. Positively, in 2022, a total of eight countries (Bhutan, Burkina Faso, French Polynesia, Malaysia, Maldives, Mali, Nepal, and Niger) reported a national prevalence of <2% after five or more years of PC, and a further three (Ghana, United Republic of Tanzania, and Indonesia) reported prevalence between 2-10% [11]. As an increasing number of countries reach these low prevalence levels, global progress is edging closer to the 98 countries targeted by WHO to reach EPHP by 2030 [9].

Beyond the achievement of EPHP, is transmission break or elimination of transmission which remains undefined by the WHO to date. The literature has proposed this to be 6% for *A. lumbricoides*, whereas for hookworm it has been proposed to be 2% or 0.5% as measured by Kato Katz, or <2% "true" prevalence as diagnosed by polymerase chain reaction (PCR), with caveats in relation to baseline prevalence, and basic reproductive number (R_0) of STH transmission [36–38]). The feasibility of reaching such a target has been critically evaluated and theorised to be possible in countries with a low intensity of transmission, supportive household environments, strong health systems, and the availability of suitable delivery platforms and in-country funds [39].

Despite the lack of clarity in transmission elimination validation, Japan, South Korea and China have claimed to have achieved this status through consistent high coverage and compliance to repeated MDA rounds delivered in parallel with infrastructural developments consequential with significant socioeconomic improvements, such as improved WaSH access and improved agricultural technology [40–42]. Interestingly, small pockets of STH

recrudescence have already been reported in distinct rural areas, for example the persistent infection of *T. trichiura* in China, which was found to be significantly associated with limited access to sanitary toilets and low levels of health education [43].

1.5. The validation of elimination as a public health problem using Geshiyaro program data

The target of EPHP is well defined. There is less clarity, however, on the validation of this measure, including the survey strategies used to verify this, and at what spatial scale [44]. In a response to this, the WHO have recently called for the development of thorough MDA impact-evaluation methods, and the scale-up of surveys to monitor progress toward and consolidate guidance on how to conduct STH surveys to validate EPHP [10].

This thesis aims to contribute to a growing evidence base of monitoring and evaluation (M&E) recommendations for STH, using data analysis of the Geshiyaro project. The project is currently the longest running, individual-based, STH research study and as such, has generated a data-rich resource that can be used for this purpose. Launched in 2018, the project aims to help define the most effective interventions for the control of STH in the "end-game" of control, that is reaching EPHP and potentially transmission break in defined regions [45].

2. Motivation and objectives

This thesis will conduct a series of epidemiological analyses on the fine-scale longitudinal data of the Geshiyaro project, with the aim to improve our understanding of the transmission dynamics and control of STH infections. The chapters will evaluate the current available literature reporting longitudinal compliance to chemotherapeutic control (Chapter 2); the use of biometric technology in a large epidemiological control program (Chapter 3); measurement of coverage and compliance to MDA rounds (Chapter 4); spatial scale of infection and treatment (Chapter 5); changes in parasite prevalence and intensity over time (Chapter 6); and epidemiological patterns of infection in relation to WaSH infrastructure access (Chapter 7). As a result of the highly annotated dataset collected by the project, this thesis reports analysis that has not been possible by any previous study of STH control, making the results of Chapter 3, Chapter 4, and Chapter 6 through to Chapter 8, novel. The analysis of the

Geshiyaro project will be compared to those reported from the few similar studies conducted on STH control programs, namely TUMIKIA implemented in Kenya, and DeWorm3 implemented across India, Malawi and Benin [16,46].

In summary, this thesis will aim to answer the following key questions:

i. How informative are unique individual identifiers such as biometrics in measuring the impact of STH control programs?

ii. What spatial scale and demographic sample is appropriate for accurate M&E of STH control program impact in low prevalence settings?

iii. What is the magnitude of difference in STH control between sMDA versus cMDA, and to what extent is that further enhanced by the construction of WaSH infrastructure and BCC?

The objectives above are underpinned by key heterogeneities of STH transmission and control. These heterogeneities can be categorised as those arising from the epidemiology of STH transmission, and those arising from control program measurement (MDA, diagnostics measurements, and WaSH impact). As such, they underly the analysis of the subsequent chapters, and therefore are discussed in full here to avoid repetition.

Pairing the understanding of these key concepts with the interpretation of the results from the Geshiyaro project will provide a robust evidence base to the interpretation of the dynamics of STH control in low prevalence areas. In turn, this can be added to the body of evidence required to answer the recent call made by the WHO for clear M&E of EPHP validation. More broadly, a better epidemiological understanding of STH transmission, such as that gained through this thesis, helps to underpin good policy formulation.

2.1. Heterogeneities of soil-transmitted helminth transmission epidemiology

2.1.1. Worm aggregation in a community

Research into the transmission dynamics of STH mainly expands on the work of Anderson, 1980 [47], which delineates the varied factors influencing transmission success. These include the threshold required for a sustained infection within a defined host population, the probability distribution of parasite numbers in the human host population, and density dependent restrictions (fecundity and or mortality) upon the growth of parasites within a

host. The understanding of these biological characteristics of STH infection has remained unchanged over the past 40 years, and many current mathematical models of transmission dynamics and control interventions modulating this relationship are based on the parameters and equations outlined by Anderson and May in studies published in the 1980s [8,13,48–54].

Central to the understanding of STH transmission, is the negative binomial distribution of worm burdens per person within infected human populations [55]. This distribution dictates a non-linear relationship between the prevalence and intensity of infection within a community, whereby most of the population harbour no or low levels of infection, and just a few people harbour the majority of infection [17,53]. The level of negative binomial aggregation is measured inversely by the aggregation parameter, *k*, where small values of *k* indicate very high levels of aggregation. Recent studies have demonstrated that this aggregation of infection is changed by control interventions. For instance, as infection intensity decreases through continued MDA, aggregation in a community increases, siloing infection in an increasingly smaller proportion of the host population [49,56,57].

Of interest to STH control, is how this parasite aggregation affects the probability of reaching the elimination of transmission whereby the basic reproductive number (R_0) of the parasite in a defined human host community is $R_0<1$. This is defined as a scenario where each female worm fails to generate enough female offspring of viable sexual maturity to sustain future generations [20,48,53]. R_0 is modified further by two extra density-dependent processes: density-dependent fecundity, and the dioecious nature of the worm [20,48].

Transmission break is a hypothesised unstable state that lies between the two stable transmission states: endemic infection and elimination of transmission [54]. Much research attention has focused on where this unstable equilibrium point lies, since the worm burden must be driven below this value to achieve transmission elimination. The distance between this unstable transmission break-point, and transmission elimination is determined by the degree of parasite aggregation, *k* [20,48,58]. Mathematical models reveal that as the aggregation of worms in the host population rises, the probability of successful worm mating increases and thus this unstable state becomes closer to zero [8,13,47,48,59].

2.1.2. Other sources of worm aggregation

Individual-level studies have shown that people can be pre-disposed to a high or low level of infection, regardless of treatment behaviour, determined by one or many unknown factors, presumed to be a combination of host genetics, human behaviour, and cultural and environmental settings [60]. The number of treatment rounds in which an individual swallowed treatment may not correlate with low prevalence and intensity, as predisposition may exceed treatment frequency. Furthermore, the previously mentioned age-dependent infection profile for each STH species will affect which age group in the population is likely to be burdened with infection. Thus, heterogeneity of infection within a host population is modulated by several transmission related factors including the parasite aggregation (*k*) within the community, pre-disposition to infection intensity, and species-specific age dependence of infection as demonstrated in **Figure 1.2**.

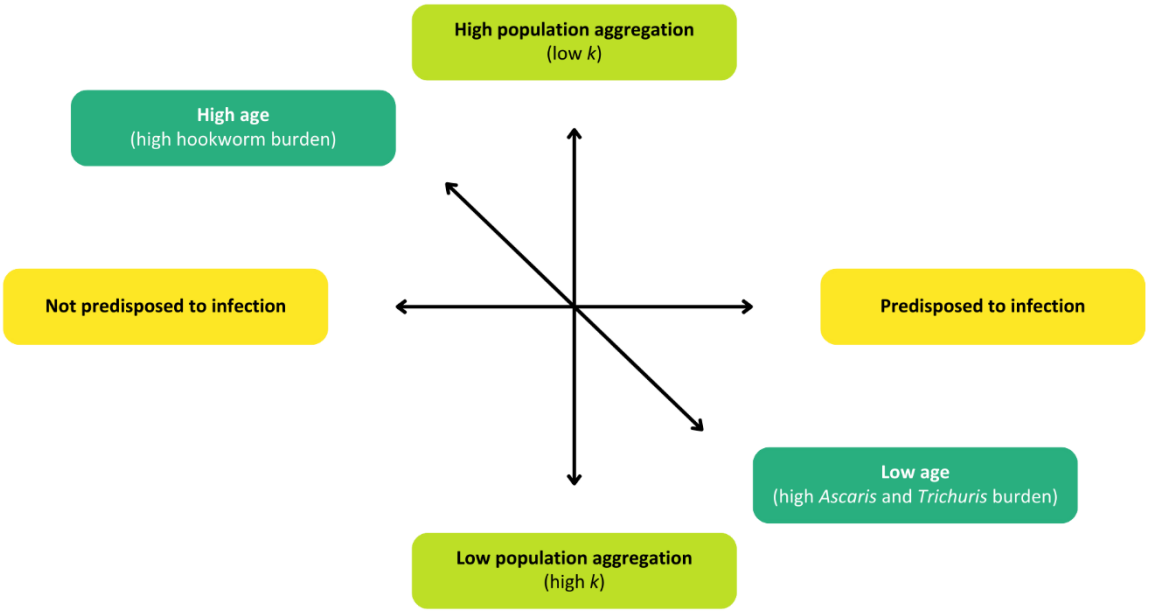


Figure 1.2: Sources of heterogeneity of soil-transmitted helminth (STH) infection. *A depiction of some of the different sources of heterogeneity that may impact the aggregation of worms within an individual, including the age-dependent distribution of STH species, predisposition to infection, and aggregation of infection as measured inversely by the parameter, k.*

2.2. Heterogeneities of soil-transmitted helminth control programs

2.2.1. Treatment

The delivery of MDA has been historically targeted at SAC as this age group is typically harbours a higher burden of infection by *A. lumbricoides* and *T. trichiura* [61]. Hookworm has a distinctly opposing age-dependent infection pattern making this blanket age-based distribution of sMDA unsuitable for its control [28]. Adult hookworm burden has been recorded as high as 80% in the population, contrasting with 30% for *A. lumbricoides* and *T. trichiura* [13]. This highlights the inequity of treatment in adults caused by sMDA strategies. To assess the impact the population not targeted for treatment has upon the sustained transmission in a treated community, numerous research studies and mathematical model-based analyses have agreed on the importance of expanding the standard sMDA approach to target all age groups through cMDA [8,13]. The recommendation of such expansion is dependent upon the defined communities R_0, and the average treatment coverage achieved over multiple rounds [37]. It should be noted too, that this blanket treatment does not necessarily equate to equitable access to treatment as marginalised individuals may be missed from treatment, who will likely be infected [62]. Adding to the heterogeneity created by blanket treatment across different age-groups, drug efficacy also varies by species, as illustrated in **Figure 1.3**. Albendazole has a markedly different cure rate between *T. trichiura* (30.7.%), and *A. lumbricoides* (95.7%) and hookworm (79.5%) [63].

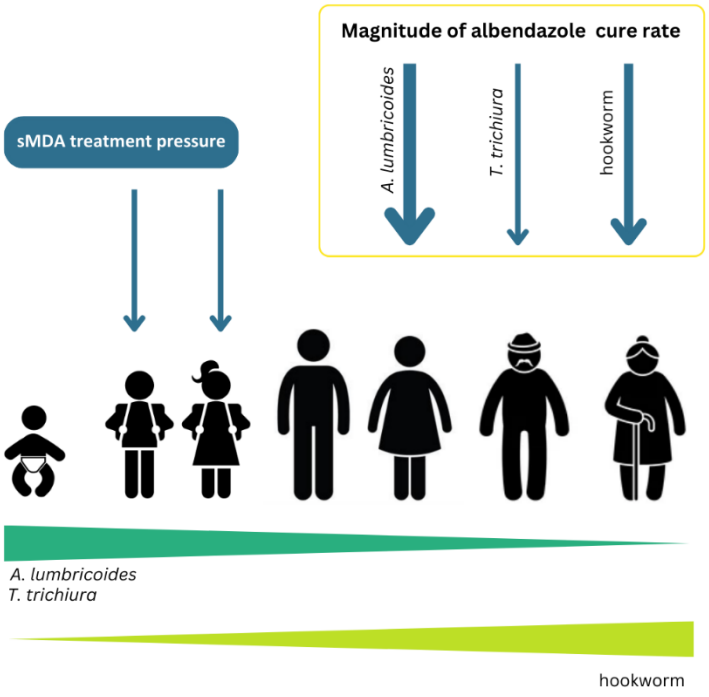


Figure 1.3: Heterogeneities in the treatment of soil-transmitted helminths (STH). *The impact of a school-based mass drug administration (sMDA) strategy is demonstrated, showing the impact of this upon the distinct age-dependent distribution of the three STH species illustrated by the green gradients. The difference in the drug efficacy of albendazole is also shown, adding to the heterogeneity of control.*

Furthermore, models building upon the original Anderson-May model of *A. lumbricoides* transmission have also analysed treatment with respect to seasonal variations [64,65]. Geographic regions with a defined bimodal variation in rainfall and temperature were associated with pronounced changes in *A. lumbricoides* transmission caused by optimal environmental conditions for the propagation of infectious stages. Consequently, optimum MDA timings can be proposed, targeted at the lowest point of transmission before a season-dependent peak. Implementing MDA at a time when infected hosts are suspected to have the lowest worm burdens was estimated to have a 74.5% (43.3-89.1%) relative improvement on the average number of days an individual is infected annually [64].

2.2.2. WaSH

Infective STH life-stages can remain viable in the environment for weeks (hookworm) and months (*A. lumbricoides* and *T. trichiura*) [66]. As such, maintaining the temporary gains in infection control resultant from MDA will be dependent upon good access to, and the consistent usage of, WaSH infrastructure as this acts to reduce the magnitude of transmission success (i.e. the value of R_0) and hence diminishes the environmental reservoir of infection. Intuitively, improved access to, and consistent use of, WaSH infrastructure will aid the reduction of STH re-infection, amongst other diarrhoeal diseases. Accurately measuring the use of such infrastructure and therefore the impact this has upon infection transmission been fraught with difficulties in M&E, and reviews of the impact of WaSH upon STH control rarely shows a positive correlation to a reduction in prevalence [67,68].

The existence of WaSH infrastructure is easy to quantify, however its existence should not be conflated with its use or indeed its effective maintenance. Usage of infrastructure measured by community questionnaires are subject to desirability and recall bias and measuring (consistent) usage is explicably linked with ethical issues [66]. Furthermore, heterogeneity in the low-risk and high-risk behaviours confuse associations between WaSH variables. For

example, a child may go to a school with a safe water supply and well maintained toilets, but when they come home their family may only be able to access unimproved water (e.g. surface water from a nearby lake) and share an unimproved toilet [69]. When asked to answer a questionnaire, which behaviour will be reported? If the child was infected with a high *A. lumbricoides* burden, would that have been falsely associated with the access to safe, well-maintained school toilets? Recent research found that although individual association between WaSH and STH prevalence was difficult to establish, there were clearer trends when household data was aggregated at a community level [66]. This highlights the importance of homogeneous access and usage by the whole community if transmission of STH is to be effectively impacted.

2.2.3. Diagnostics

Diagnostics are definitional in the planning, monitoring, and cessation of control programs, as demonstrated in **Figure 1.1**. Parasite burden (intensity of infection) is measured most accurately by worm expulsion studies, which are rarely performed due to the lengthy and unsavoury task of stool collection and examination [70,71]. As such, worm burden is inferred indirectly through egg counts using coprological techniques such as wet-mount (Kato Katz), or flotation methods (McMaster, FLOTAC) [72]. However, these egg counts are complicated by density-dependent fecundity, the heterogeneity of eggs expelled by the female worms in the sample thus eggs are not uniformly distributed in the stool, and the aggregated distribution of infection within a community, the latter of which will impact the likelihood of an infection being recorded if an inadequate sample size is chosen [53].

Microscopy sensitivity has been widely shown to decrease as the average parasite intensity of infection and prevalence reaches low levels [73,74]. This has led to the increased use of molecular methods such as qPCR, which are substantially higher in sensitivity in low prevalence settings but are restrictive in their cost and resource demands. Once constructed however, the multifaceted capacity of the molecular diagnostic equipment will greatly benefit any institute hosting the technology, broadening research capabilities due to the applicability of qPCR beyond STH diagnostics. MicroRNAs found in host blood, urine, or faeces present an alternative species-specific molecular target for qPCR diagnostics rather than helminth egg DNA [75]. Moving from proof of principle, to manufacturing a cheap point of care diagnostic, however, will remain challenging in settings with low resources for health care. Historically,

the development of diagnostics from conception through to implementation requires years to decades, and as such, as the reality of such techniques being widely and readily available in the near future is small.

Therefore, the definition of infection level-based criteria for specific diagnostic methods has been recently published by WHO, named target product profiles (TPPs) [72]. These profiles set out guidance for optimal diagnosis in lower transmission settings. This concludes Kato Katz is the only microscopy-based method suitable for the planning and M&E of a control program, and qPCR is the most suitable method for assessing the elimination of transmission [76]. Studies have shown increasing the number of Kato Katz slides employed per stool sample has a significant impact on improving diagnostic sensitivity. Increasing the routinely implemented double slide (two slides from one sample), to quadruple (two slides produced from two separate samples collected on consecutive days) have been shown to increase accuracy, particularly in low prevalence settings [36]. This is significantly cheaper to implement than qPCR, which demands markedly enhanced laboratory expertise and infrastructure [73]. Novel technology using artificial intelligence may also present alternative methods for increasing diagnostic sensitivity, such as screening of Kato Katz slides using machine learning [77]. Such precise methods could incorporate the definition between embryonated and un-embryonated *A. lumbricoides* eggs for example. Their presence suggests the absence of a sexually mature male to fertilise eggs, and therefore could be an indicator of transmission interruption.

3. The Geshiyaro project, assessing the possibility of the transmission interruption of soil-transmitted helminths in Ethiopia

3.1. Ethiopia background and setting

Ethiopia is the second most populous country in Africa, with one of highest population growth rates of the continent (2.7% per annum) according to the United Nations Department of Economic and Social Affairs [78]. Just over 39% of GDP is dependent on rainfed agriculture, and consequently 80% of the population live in rural areas [79]. The most recent figures from the World Bank published in 2015, noted just under a quarter (24%) of the population live

below the poverty line [80]. Nevertheless, large developmental changes are taking place. Ethiopia is recipient to the largest foreign direct investment in east Africa, receiving up to USD 4 billion (ranging from USD 1.9 billion to USD 4.1 billion) between 2014 and 2019 [81]. The country recorded an annual economic growth rate of 5.3% in 2023, almost double the global average (2.7%), resulting in large infrastructure projects such as improving road coverage connecting small administrative units [79,82].

Electricity is available to 35% of the population, 83% of which is in urban areas [79]. Sanitation disparity is high, as access to improved latrines was reported in 2019 to be 20%, yet access to improved drinking water source was much higher at 69% [79]. Ethiopia's national access to WaSH infrastructure still demands further development, and as such, the national strategy for STH control relies heavily upon MDA. Due to the rapidly growing population at present and improved child survival rates, the already limited national health resources requires careful allocation across many competing health care needs.

3.2. Ethiopia's soil-transmitted helminth control and elimination targets

According to the Expanded Special Project for Elimination of Neglected Tropical Diseases (ESPEN) in 2022, STH is most prevalent in Gambela, Southern Nations, Nationalities and Peoples Region (SNNPR), and Oromia found in west and central regions of Ethiopia. This geographic focalisation of infection has remained consistent since mapping began in 2014, as shown in **Figure 1.4**. The national deworming program was initiated in 2015 by the Ethiopian Federal Ministry of Health (FMoH), implementing school-based MDA (sMDA) according to the WHO treatment strategy (**Figure 1.1**), tasked with reaching 75% coverage of SAC nationally. Between 2015-2020, 100 million albendazole tablets were distributed to SAC, and in 2018 the WHO target of 75% was reached [83]. The number of districts (herein referred to as "woredas") receiving treatment has more than doubled from 249 in 2014 to 536 in 2018 [79].

Ethiopia has set the ambitious target to eliminate transmission of STH by 2025, defined by the FMoH as reaching <2% prevalence by Kato Katz across implementation units (IU) (defined in Ethiopia as a woreda), and <1% prevalence of MHII diagnosed by quantitative (qPCR) in all risk groups (preSAC, SAC, WRA) [79]. To achieve this national target, by 2023 the FMoH planned to expand sMDA to community-wide MDA (cMDA) to all endemic woredas, reaching 90% treatment coverage in high-risk groups [79]. Given the current endemicity of high prevalence

infection nationally, the target for 2025 is unlikely to be reached uniformly across the country. It is, however, likely in smaller, defined localities such as woredas or villages (herein referred to as “kebeles”) [84]. A more feasible target instead would be achievement of EPHP across endemic IUs.

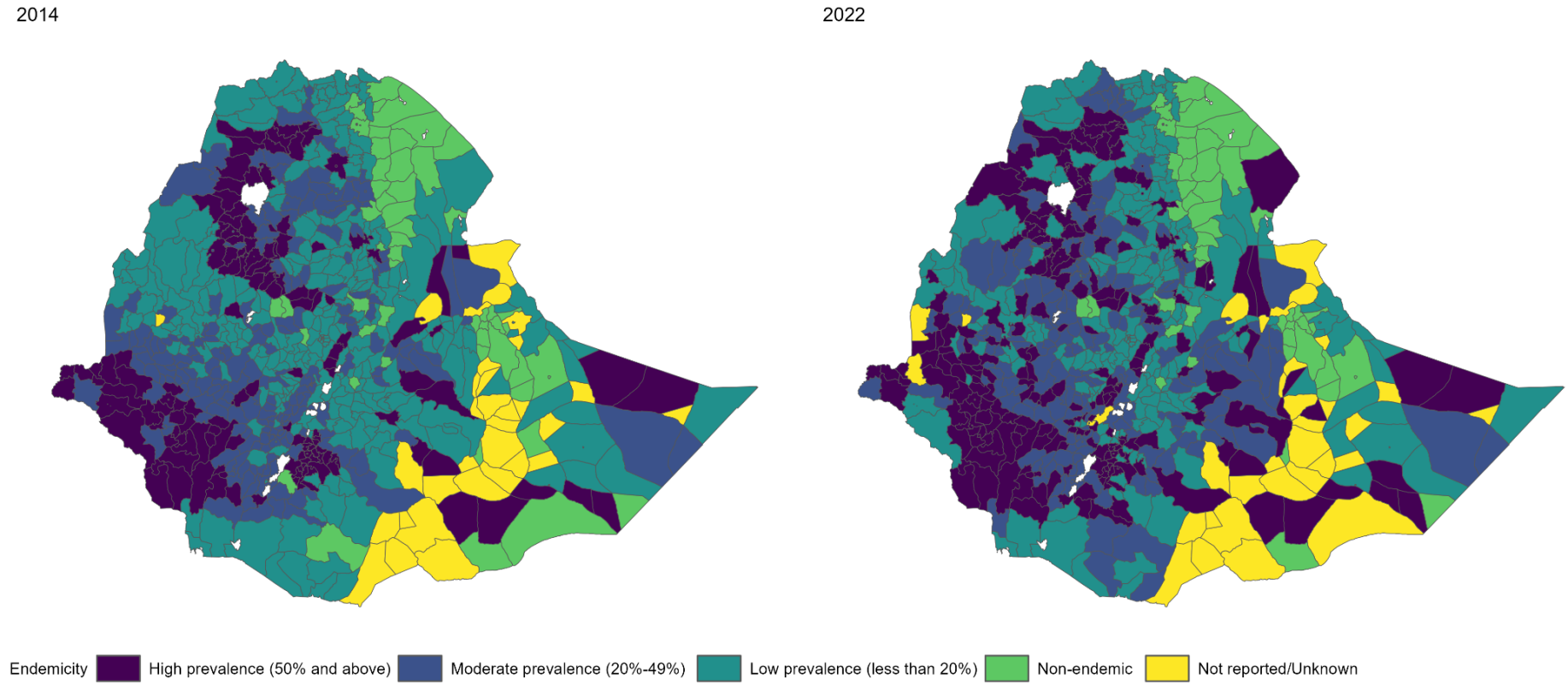


Figure 1.4: The endemicity of soil-transmitted helminths in Ethiopia in 2014 and 2022. *The endemicity of STH across Ethiopia in 2014, the year before the initiation of the national deworming program in 2015, and 2022, according to ESPEN* [85]. *The limited impact of STH control after seven years of national control is illustrated. Improvements in endemicity are seen in central-eastern and southern regions. Data is reported at the implementation unit (IU) level, defined as districts or "woredas", in Ethiopia. Endemicity in indicated in graduated blue, with green signifying non-endemic regions, yellow for unreported and unknown regions. Clear spaces indicate large waterbodies such as Lake Tana in north-western Ethiopia, and the lakes of Hawassa, and Arba Minch in the south-western regions.*

3.3. An introduction to the Geshiyaro project, 2018-2027

The Geshiyaro project was initiated in 2018, structured as a 'proof of principle' study, with the aim to assess the possibility of breaking STH transmission through the expansion and enhancement of the current national control program. This included expanding the targeted population for treatment from the national control program (sMDA) to cMDA, distributed using the existing volunteer network of health extension workers (HEW). Secondly, additional WaSH infrastructure (water points and public toilets) was constructed, enhancing that provided by the national One WaSH national program (OWNP). These interventions were delivered in parallel with community sensitisation on the importance of infrastructure utilisation and participation in cMDA campaigns for the control of STH, named behaviour change communication (BCC). As such, the project aimed to help define the most efficient intervention(s) for the control and interruption of transmission of STH in Ethiopia [45]. Project design, baseline findings, and initial analyses of project data collected to date have been previously published [60,66,84,86–89].

Funded by the Children's Investment Fund Foundation (CIFF), the project is designed as a collaborative entity between five partner organisations. Two Ethiopian governmental bodies, the Ethiopian Public Health Institute (EPHI) and the FMoH, provide essential project oversight, guidance, and expertise in program delivery. World Vision Ethiopia oversees the construction of WaSH infrastructure, and both the design and dissemination of BCC resources to ensure high uptake of MDA and community use and acceptance of WaSH infrastructure. Simprints, a spin-out company from Cambridge University, provide biometric technology used for accurate enumeration (registration and subsequent identification) of the Geshiyaro participants. Imperial College London provide collaborative epidemiological evaluation, in partnership with EPHI, of daily and annual project progress, database construction and management, epidemiological data analysis, and evaluation of intervention impact upon STH transmission interruption.

3.4. Site location

The Geshiyaro project enumerates the entire population of the Wolayita zone in South Ethiopia Regional State (SERS) (formally SNNPR), and satellite zones Tula Kifle Ketema, Wondo Genet in Sidama, and Wondo in Oromia, as shown in **Figure 1.5**. In order to collect fine-scale

data, the project enumerates at one administrative level smaller than that currently employed by the Ethiopian government, the kebele level.

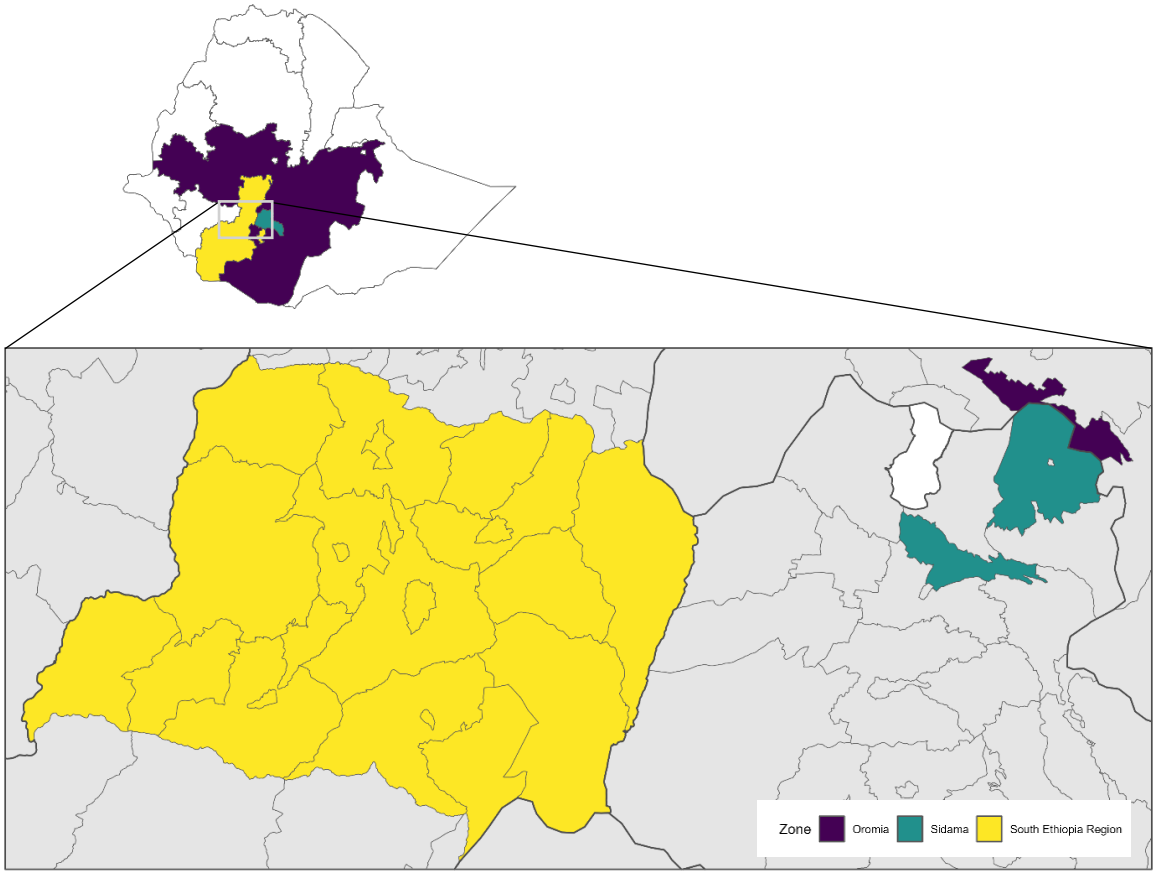


Figure 1.5: The Geshiyaro project site location in Ethiopia. *Ethiopia, shown above, is divided administratively, in decreasing size, into regions, zones, districts (woredas), and towns / villages (kebeles). The regions of Ethiopia are shown in the top left map of the country, with the three regions containing the Geshiyaro project sites highlighted: South Ethiopia Region in yellow, Sidama in green, and Oromia in navy blue. The bottom panel shows the woredas within the three regions, highlighted in the colour corresponding to their region. Thick lines denote the boundary lines of the three regions. The woredas in yellow show the Wolayita zone, which is split between Arm 1 and Arm 2. Arm 3 sites are found in Sidama and Oromia.*

The Wolayita zone has a population of just over two million people and is situated at an average altitude of 1500-1800m above sea-level. The climate remains fairly stable, with an average yearly temperature of 19.9◦C, and a bimodal rain-fall pattern averaging just over 1000mm a year, making a suitable environment for STH transmission.

According to national mapping conducted between 2013 and 2015, SNNPR (now containing SERS) reported the highest proportion of MHII for all three STH species in the country [90]. The prevalence of *A. lumbricoides* was 25.9% (5.2% MHII), *T. trichiura* was 15.3% (0.3% MHII), and hookworm was 13.5% (0.2% MHII) [90]. By the start of the Geshiyaro project in 2018, Wolayita boasted a population with a high prevalence of low intensity infections suitable for transmission break assessment as illustrated in **Figure 1.6** using baseline data.

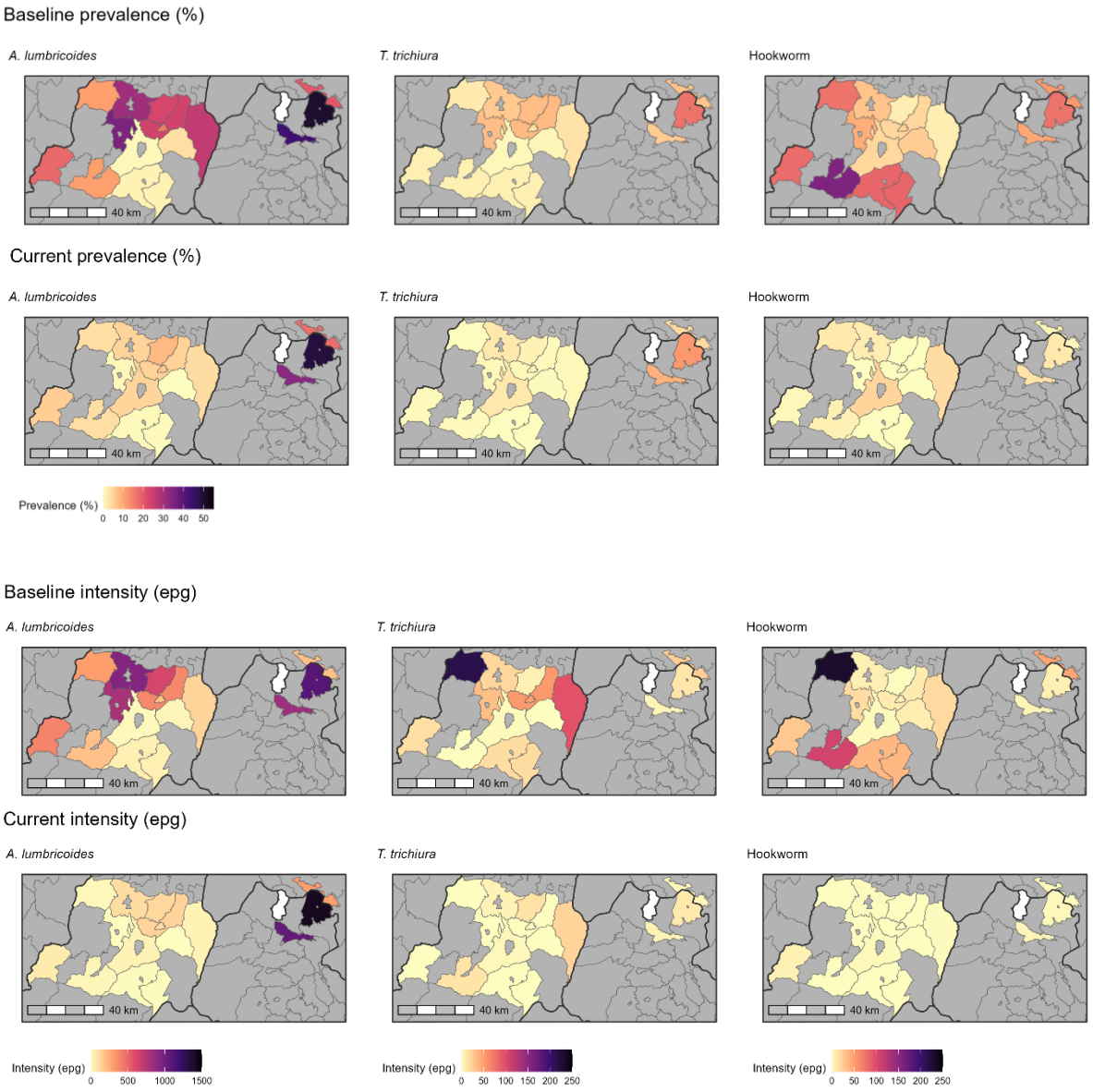


Figure 1.6: The prevalence and intensity of soil-transmitted helminths recorded at the baseline of the project, and at the latest data collection in Year 6. *Thick lines denote the administrative boundaries between the zones (Wolayita, Oromia, Sidama) of south Ethiopia. Highlighted areas show the sentinel site locations across the studied zones. Note the different legends for intensity plots due to the large discrepancy in scales. Intensity is categorised*

according to those stated by WHO, A. lumbricoides: light (1 - 4999 epg), moderate (5000 - 49,999 epg), heavy (≥50,000 epg), T. trichiura: light (1 - 999 epg), moderate (1000 - 9999 epg), heavy (≥10,000 epg), and hookworm: light (1 - 1999 epg), moderate (2000 - 3999 epg), heavy (≥4000 epg) [32].

3.5. Project intervention arms

Three intervention arms are used to enumerate the Geshiyaro project intervention delivery, and are structured as follows: Arm 1) cMDA and the construction of WaSH infrastructure implemented concomitantly with BCC; Arm 2) cMDA and the continuation of the national OWNP; and Arm 3) national sMDA and OWNP. Arm 1 and Arm 2 sites divide the Wolayita zone, whilst Arm 3 sites (the control) are situated in satellite zones neighbouring Wolayita, as illustrated in **Figure 1.5**.

3.6. Geshiyaro project timeline

The Geshiyaro project is to be completed in three phases over eight years, as outlined in the protocol [45]. Phase 1 took place in 2018 (Year 1), piloted in a single Arm 1 woreda (Bolosso Sore) whereby the population was censused, baseline parasitological mapping was conducted and the first round of cMDA took place [88] This pilot was purposed with assessing the acceptability and feasibility of using biometric technology as part of data collection. Phase 2 took place in 2019 (Year 2) and scaled-up the censusing, baseline parasitological mapping, and first cMDA distribution to the remaining woredas of Wolayita (Arm 1 and Arm 2). Through Year 3 to Year 7, annual longitudinal parasitological surveys using sentinel sites and cMDA continued. In 2025, Phase 3 will start, whereby endline parasitological mapping will take place in all intervention arms.

The proposed timeline deviated from that outlined in the protocol in three key areas. Firstly, the logistics and operations of cMDA distribution was severely disrupted by the COVID-19 pandemic (impacting project Year 3 and 4), leading to irregular distribution patterns. Secondly, biannual cMDA was incorporated into the project in Year 4, superseding the previously implemented annual rounds to compensate for the impact of COVID-19. Thirdly, Arm 3 sentinel site monitoring started a year later than planned and was initiated in Year 3. A full timeline of activities conducted to date and proposed for the future is outlined in **Figure 1.7**.

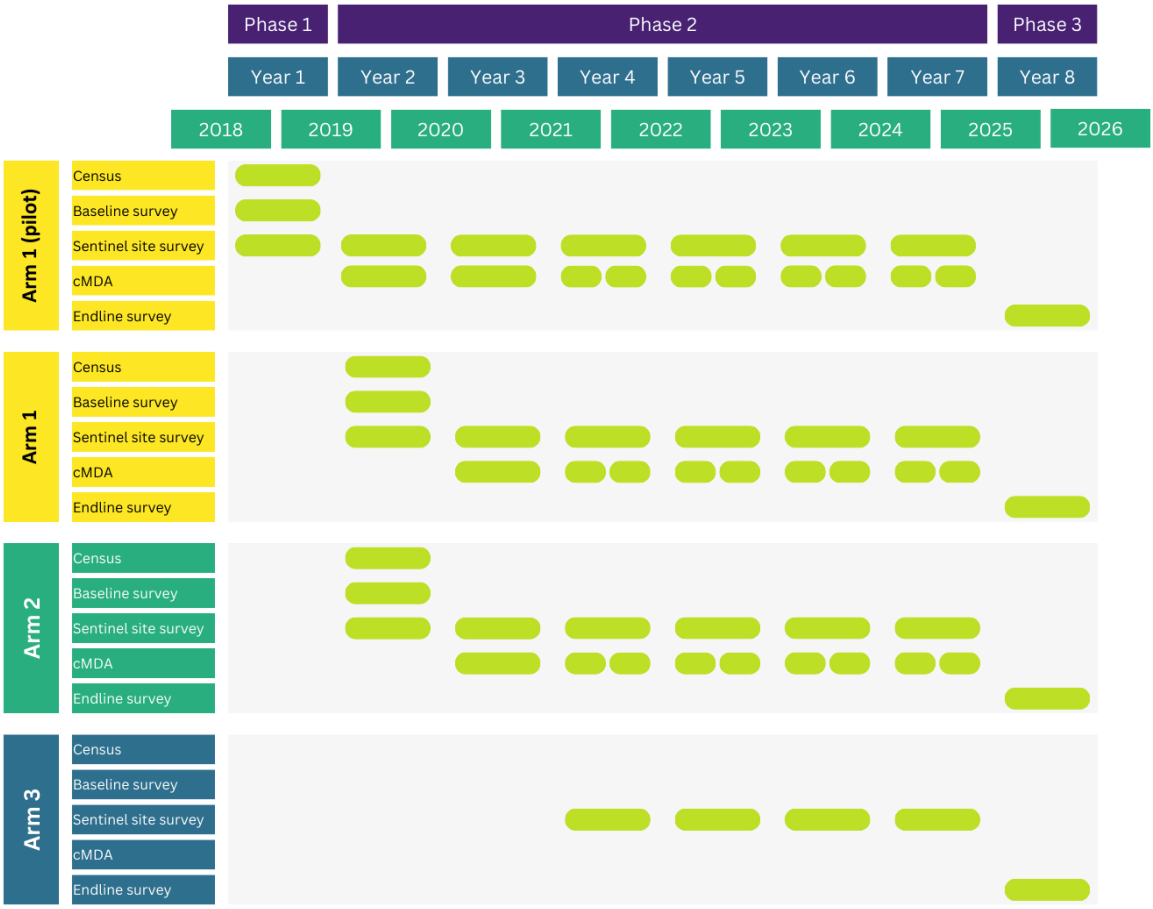


Figure 1.7: A gantt chart illustrating the Geshiyaro project timeline, 2018 to 2025. *Currently, the Geshiyaro project is concluding project Year 6. Colour coordinated activities both implemented to date, and to be conducted, are shown as categorised by project year, calendar year, and phase. The staggered nature of the project between phases is illustrated, starting first in Bolosso Sore (pilot woreda) before scaling up to the remainder of Arm 1 and all of Arm 2 sites in Year 2, and Arm 3 in Year 3. Arm 3 sMDA is not marked as this is conducted as part of the national control program, and data recording for this is inconsistent. *The baseline parasitological survey was a cross-sectional survey but a sub-section of the survey sites were selected as sentinel sites and the data used as the baseline sentinel site data.*

3.7. Measuring the impact of soil-transmitted helminth control activities implemented by the Geshiyaro project

To accurately measure the impact of the different interventions implemented within the project, a subset of woredas (five woredas, 120 kebeles) within Arm 1 and Arm 2 were censused (~ 600,000 people). This sample of the Wolayita population provided an individually linked, longitudinal dataset for M&E. Individual treatment behaviour was recorded against the census at each round of cMDA. An additional sample of 45 sentinel sites were chosen at random across the kebeles of the three intervention arms (15 sites per intervention arm). In each site, a sex-age stratified sample of the population (n = 150) were annually surveyed for STH, and each participant answered a WaSH infrastructure access questionnaire. There were 16 intersecting kebeles where the population were enumerated in both the census (cMDA behaviour recorded) and sentinel sites (parasitological data recorded). For non-censused woredas, routine Coverage Evaluation Surveys (CES) were conducted in accordance with the WHO recommendations to enumerate cMDA [86]. A minimum of six months was allowed between cMDA and sentinel site monitoring to ensure any recrudescence (parasite re-infection) could be captured, signifying continued transmission.

4. Conclusion

As discussed, there are multiple elements to consider when developing guidance for EPHP, and ultimately elimination to plan, implement and monitor attempts to eliminate STH transmission. STH dynamics and control are influenced by multiple factors that impact on the observed heterogeneities of infection in defined human host communities. Most crucially, in low-intensity settings the aggregation of STH infection within a community increases after multiple treatment rounds are administered [49,57]. Infection is sequestered in hotspots that intersects with other sources of heterogeneity such as the age-dependent distribution of infection (also modulated by MDA pressure). This increases the need for fine-scale M&E to be implemented with the power to identify these remaining pockets of infection especially in areas aiming to validate EPHP. This need is balanced by the reality of finances available within a national control budget.

Therefore, appropriate M&E strategies, chemotherapeutic pressure, sanitation infrastructure, diagnostics, and the spatial scale in which to monitor these, all require defining in accordance

with the level of infection and resources available. This tailored approach will undoubtedly incur increased programmatic costs in countries already challenged with limited national healthcare budgets and restricted philanthropic donations. The alternative, however, has been shown that continued, sub-optimal chemotherapeutic schedules will never reach transmission interruption, or EPHP, and will require MDA for the foreseeable future in an unchanging environment [8]. If drug donations taper in magnitude over the coming decade, this will almost certainly lead to an increased likelihood of STH resurgence in many communities where STH is currently endemic in the absence of any other interventions such as WaSH. Therefore, an initial higher financial and programmatic investment, increased control program intensity, and implementation of fine-scale M&E will be required for STH control, for both long-term cost-effectiveness and financial and health gains of endemic countries.

Chapter 2: Individual longitudinal compliance to neglected tropical disease mass drug administration programs, a systematic review

Dissemination

This chapter has been adapted from the paper titled, “Individual longitudinal compliance to neglected tropical disease mass drug administration programs, a systematic review”, published in 2023 by PLOS NTD [91].

Motivation

Before analysing the results of the Geshiyaro project, a systematic review was conducted to critically analyse the data available from other similar studies reporting longitudinal compliance to MDA. This highlighted the paucity of longitudinal compliance data available, thus placing the Geshiyaro project at the forefront of research as both the largest, and longest study of MDA for the control of STH.

1. Introduction

There are an estimated 1.74 billion people requiring interventions against the NTDs [4]. This has reduced by 600 million since 2010, yet considerable progress is still required to reduce the global burden of disease caused by these, predominantly parasitic, infectious diseases [4]. The recently published WHO 2030 roadmap for NTD control clearly demonstrates the link between socioeconomic status and NTD burden, highlighting the inverse relationship between increasing GDP per capita with decreasing NTD burden [4]. NTDs impart physical and financial sequalae, and infection status (often resultant from poor hygiene or living conditions due to poverty) can further reduce an individual's potential to earn, creating a downward spiral in the well-being of an infected individual. As NTDs disproportionately affect individuals of low socioeconomic status, self-funded care is not feasible for most affected, making global control of parasites predominantly reliant upon drug donations from pharmaceutical companies and implementation support of treatment programs delivery from international philanthropic organisations.

1.1. Preventative chemotherapy for neglected tropical disease (NTD) control

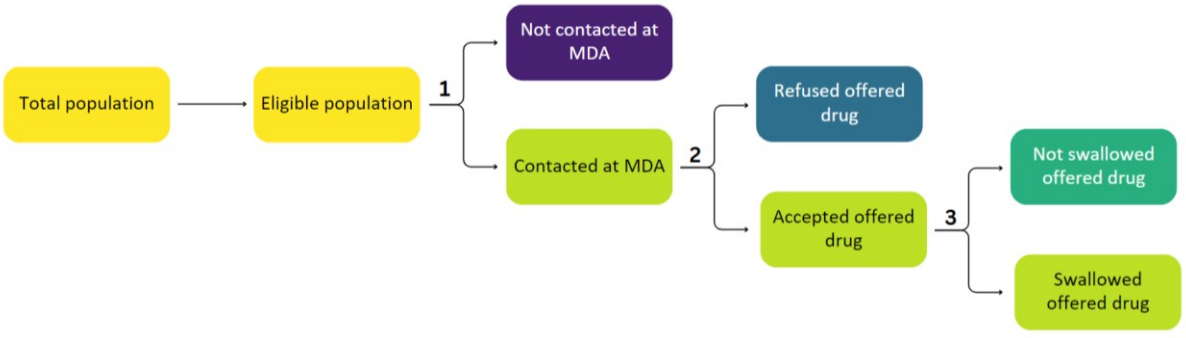
As of late 2023, there are now 21 NTDs recognised by WHO, five of which are responsible for the majority of the global NTD burden [92]. These are LF, onchocerciasis (caused by *Onchocerca volvulus* (OV)), schistosomiasis (SCH), STH, and trachoma. All these parasitic infections can be treated effectively by PC, hence providing the title (PC)-NTDs [93]. Entire endemic communities or at-risk subgroups receive MDA in an attempt to control transmission and reduce morbidity. Prior infection or treatment does not confer strong acquired immunity to any of these five parasites, and compliance (receiving and swallowing of drugs) across the targeted eligible population rarely, if ever, reaches 100%, thus repeated treatments are necessary [15]. The frequency and time interval between these repeated treatments is dependent upon prevalence levels and the life expectancy of the parasite in the human host [15,94]. Following decades of MDA, parasite prevalence levels have dropped markedly in the majority of NTD endemic communities. Currently, elimination of parasites as a public health problem has been achieved by 17 countries for LF, and 10 countries for trachoma [4].

Coverage targets are provided by WHO, however, currently no clear definitions or targeted goals exist for compliance to any of the five PC-NTDs. To avoid persistent reservoirs of

infection, MDA delivery must achieve high compliance in the total population at each round to optimise programmatic success. This is of concern in settings aiming for transmission elimination, as the coverage-compliance gap (the difference between those receiving treatment and those swallowing treatment), can sometimes reach up to 20% [95]. Control programs misconstruing coverage and compliance can therefore grossly underestimate the treated population. The recently published WHO 2030 NTD roadmap would benefit future (PC)-NTD control progress by defining distinct coverage and compliance targets for each NTD [4].

1.2. Measuring the success of preventative chemotherapy control

The key epidemiological parameters used for the M&E of control programs success can be divided into three key decision points of individual MDA behaviour as recorded in **Figure 2.1**, defining the interaction between a community drug distributor (CDD) and participant [96]. Similar decision trees have been published to help clearly define these parameters [97,98]. In this review (and in keeping with the terminology previously employed), the term *coverage* is used to refer to the proportion of the eligible population contacted by the CDD, who received the offered drugs [96,99]. *Compliance* is often confused or conflated with coverage. In this review it is defined as the proportion of the eligible population who were contacted by CDDs and swallowed the received drugs. The importance of the distinction between these two epidemiological parameters in NTD research was first highlighted by Babu and Babu (2014) in the context of reaching LF transmission break in India, but its importance has been identified in other disease areas since 1982 [55,95].



Parameter	Definition
Pprogram reach	The proportion of the eligible population contacted by CDDs during an MDA activity (decision point 1).
Coverage	The proportion of the eligible population contacted by CDDs and receiving the offered preventative chemotherapy drugs (decision point 2).
Compliance	The proportion of the eligible population contacted by CDDs and swallowing the offered preventative chemotherapy drugs (decision point 3).
Longitudinal compliance	The pattern of individual compliance behaviour over consecutive MDA treatment rounds. Patterns can be categorised into systematic treatment, random treatment, and systematic non-treatment.

Figure 2.1: Decision tree of mass drug administration treatment behaviour. *The three behavioural decision points of mass drug administration delivery and their definitions, according to these previously defined parameters by Shuford et al. (2016)* [96]*. The process demonstrates the three outcomes that can be recorded for an eligible individual during drug distribution. Abbreviations: CDD – community drug distributor.*

Rather than evaluating each MDA treatment round as a unique activity, control programs must also focus on individual longitudinal patterns of compliance to treatment over time. Ideally, this would be measured by directly observed treatment (DOT), avoiding any recall or desirability bias created from participant's recollecting past treatment. The term "longitudinal compliance" is defined in this review as the monitoring of the same individual's treatment behaviour across multiple time points. Longitudinal studies of compliance enable the identification of individuals who systematically do or do not swallow drugs over consecutive rounds of MDA, named *systematically treated* or *systematically non-treated*, respectively [100,101]. Systematic non-treatment, or the 'never treated' population has previously been referred to as non-adherence, or systematic non-compliance [96].

Pockets of 'never treated' individuals are resultant from patterns of systematic treatment, who act as an infection reservoir for re-infection. This makes the converse treatment pattern, random compliance, preferential for control as individuals swallow at least once [89,102]. The importance that this systematically non-treated proportion of the population holds in the

context of transmission elimination is dependent upon its magnitude, and the intensity of transmission in a defined locality as measured by the R_0 of the parasite. If there is a high proportion of non-treatment within a population, this is problematic for the effective control of parasites with both high and low R_0 values in defined settings [53,55].

The description of demographic associations (age and sex) of systematically non-treated populations over contiguous rounds of MDA has not been well-defined in the literature to date [96,103]. This review focuses on published studies of longitudinal compliance in defined populations, and the linkage of treatment behaviour patterns with age and sex. A systematic review of the available data published for the five (PC)-NTDs from 2016 to 2022 was conducted, updating that previously conducted by Shuford *et al.* (2016) [96]. Data is reported only from the updated review (2016-2022).

2. Methods

2.1. Search strategy

This systematic review was conducted in line with the PRISMA guidelines and is registered with PROSPERO (Registration number: CRD42022301991) [104]. Studies detailing systematic non-treatment to MDA for LF, OV, SCH, STH, and trachoma were searched using a Boolean strategy across PubMed and Web of Science databases in January 2022. The following search strategy was employed for the review, allowing for minor syntax changes between search engines, "soil-transmitted helminths" OR helminth* OR Helminthiasis OR ascari* OR hookworm OR trichur* OR strongyl* OR schistosom* bilharz* OR onchocerc* OR "river blindness" OR "elephantiasis" OR "lymphatic filariasis" OR "Wuchereria bancrofti" OR "Brugia malayi" OR wucherer* OR brugia* OR ancylostomatoidea OR Ancylostoma OR Necator OR trachoma*) AND ("compliance" OR "non-compliance" OR "adherence" OR "non-adherence" OR "refusal" OR "medication adherence" OR "systematic non-treatment" OR "systematic treatment" OR "systematic adherence" OR "systematic compliance" OR "never treated" OR "directly observed treatment" OR "mass drug administration" OR "systematic non-compliance" OR "coverage" OR "treatment coverage" OR "surveyed coverage" OR "uptake" OR "participation". The resulting PRISMA workflow is detailed in **Figure 2.2**. This is an update of the review previously conducted by Shuford *et al.* (2016), considered to be completed comprehensively. As such, studies published from 2016 up to 2022 written in English and

Spanish were considered for inclusion [96]. Minimal inclusion criteria were used due to the paucity of the relevant studies identified. These were: 1) primary compliance data reported from community or school-based control programs targeting LF, OV, SCH, STH, and trachoma infections, 2) at least two defined time points (longitudinal data), and 3) sufficiently large population sample (>100 participants). Where reported, reasons given for non-treatment were collected for subsequent meta-analyses. All data collected was thoroughly checked to be defined as compliance (swallowing of drugs). Irrespective of the term employed in papers reviewed for extraction, data reported using the compliance as defined in this review was extracted. Definitions used in the reviewed publications to incorrectly label compliance included “program / epidemiological coverage”, “uptake”, and “adherence”.

2.2. Processing of search results

Two search engines (Web of Science, PubMed) identified 3,649 studies, which were amalgamated in Excel and de-duplicated. In total, 2,529 unique studies were then transferred to Rayyan, an online software package using natural language processing and machine learning for data evaluation by the author [105]. A random selection of 10% categorised studies were checked by a second reviewer. Using this software, whilst blinded from a secondary reviewer, title and abstract screening as conducted, categorising paper themes as quantitative (n = 164) for inclusion and excluding those categorised as qualitative (n = 40), modelling (n = 45), and not relevant (n = 2280). Despite the exclusion of qualitative studies from this analysis, some themes presented in these studies were used to help interpret the data extracted in this review.

Overall, 164 quantitative studies were read in full and assessed for eligibility for data extraction. The references in these papers were screened to capture any further relevant data, generating one additional article for inclusion. From the 165 total studies identified, six studies were not publicly accessible, and a further 70 were excluded due to containing coverage data (n = 30), or irrelevant data (n = 40). The remaining 89 studies (datasets) were confirmed to report compliance data and were therefore eligible for data extraction.

Data extracted from the 89 studies included the study type, sample type (including age and sex stratifications where available), number of studied participants, length of study, geographic identifiers, drugs provided, definitions of numerator and denominator for

reported parameters, terminology used to describe parameters, and reasons for not complying with treatment. Multiple datapoints were extracted from studies when detailed stratifications such as age, regions and individual parasite species satisfied the extraction criteria. Coverage was extracted only when reported alongside compliance for comparative analyses. Due to the paucity of papers containing individual longitudinal compliance data, compliance papers were categorised in a tiered format as containing; individual compliance data (recorded by CDD), individual compliance data (self-reported), repeated cross-sectional compliance data and cross-sectional compliance. Data was analysed in R (version 4.2.2) [106] and all figures were generated using the R package ggplot2 unless specified [107].

3. Results

A total of 165 studies met the inclusion criteria for data extraction as shown in **Figure 2.2**. Of these, 46 papers were rejected from the full-text review as irrelevant due to data reported in an ineligible format e.g. averages (n = 25), the reporting of secondary data (n= 8), inability to access full-text data (n = 6), targeted treatment studies (n = 3), and reporting on sample sizes smaller than 100 (n = 2).



Figure 2.2: The PRISMA workflow of the systematic review. *The flow of data extraction is detailed from the 3,649 studies initially identified in search engine databases, through to the final selection of 89 studies for full extraction of data.*

There were 30 studies identified as reporting cross-sectional (n = 7) and longitudinal (n = 23) coverage data, not compliance data, as the abstract and title would have suggested. Removing the irrelevant studies, including studies reporting coverage data, left a total of 89 studies to be considered in the analyses. An overview of these studies is provided in **Table 2.1**.

		Cross-sectional (n (%)) (N = 32)	Longitudinal (n (%)) (N = 57)
Sample Population	preSAC	0 (0)	0 (0)
	SAC	8 (25)	6 (11)
	Adults	2 (6)	9 (16)
	Community	22 (69)	38 (67)
	Other	0 (0)	2 (4)
Stratification	Age	12 (38)	13 (23)
	Sex	13 (41)	14 (25)
	Region	18 (56)	22 (39)
	None	8 (25)	35 (44)
Species	STH	9 (28)	9 (16)
	SCH	11 (34)	6 (11)
	OV	4 (12)	18 (32)
	LF	16 (50)	29 (51)
	Trachoma	3 (9)	3 (5)

Table 2.1: Summary overview of the 89 included studies, stratified by epidemiological classification of cross-sectional or longitudinal data. *The full data extraction of the 165 studies is provided in Supporting Information 4 of Maddren et al. 2023* [91]. *Frequency and percentage of studies falling into each category is shown as "n (%)". Abbreviations: LF – lymphatic filariasis, N – number of studies, OV – onchocerciasis, preSAC – preschool-aged children, SAC – school-aged children, SCH – schistosomiasis, STH – soil-transmitted helminths.*

3.1.Stratification of compliance data

Across the 89 included studies, those stratifying compliance data by a defined region were frequent, employed by 56% and 39% of the cross-sectional and longitudinal studies, respectively. Age and sex stratifications were reported by a smaller proportion of studies. Whole communities most frequently formed the sample population, employed by 69% and 67% of cross-sectional and longitudinal studies, respectively. Sample populations categorised as 'other' used non-standard age breakdowns such as 0-14 year-olds, and 2-14 year-olds. The (arithmetic) mean sample size of cross-sectional studies ($\bar{x}$ = 4965) was considerably smaller than that of longitudinal studies ($\bar{x}$ = 1,257,386). Five of the longitudinal studies reported compliance in populations ranging from 1-400 million, reported from national control programs in Myanmar, China, Sierra Leone, and the Dominican Republic [108–112].

Within the 89 studies included in this analysis, 78 studies reported MDA data for a single NTD. An additional 30 datapoints were generated by 11 studies reporting compliance data for the treatment of two (n = 10), three (n = 12), and four (n = 8) NTDs together, totalling 108 NTD-

specific datapoints for analysis. Overall, 45, 22, 18, 17 and six studies reported compliance data for LF, OV, STH, SCH, and trachoma, respectively. The most frequently reported species combination was STH and SCH (n = 3). Trachoma studies were least common and were not reported in combination with other parasites. This is presumably due to different control methods, as only azithromycin is used for Trachoma control, unlike ivermectin, albendazole and praziquantel used in combination for the control of other PC-NTDs [113]. No trachoma compliance studies have been published since 2019.

From the 89 studies, an additional 11 geographical datapoints were generated from four studies reporting data from multiple countries, providing a total of 96 geographic datapoints. Globally, studies reporting compliance from Tanzania (n = 11) and Ethiopia (n = 9) were most prevalent, as depicted in **Figure 2.3**. Comparing the location of studies with the total population requiring treatment globally as reported by the WHO (PC)-NTD databank, highlights the geographical gaps in MDA compliance research, specifically from southern African countries for SCH and STH, and northern African countries and northern South America countries for trachoma research [114].

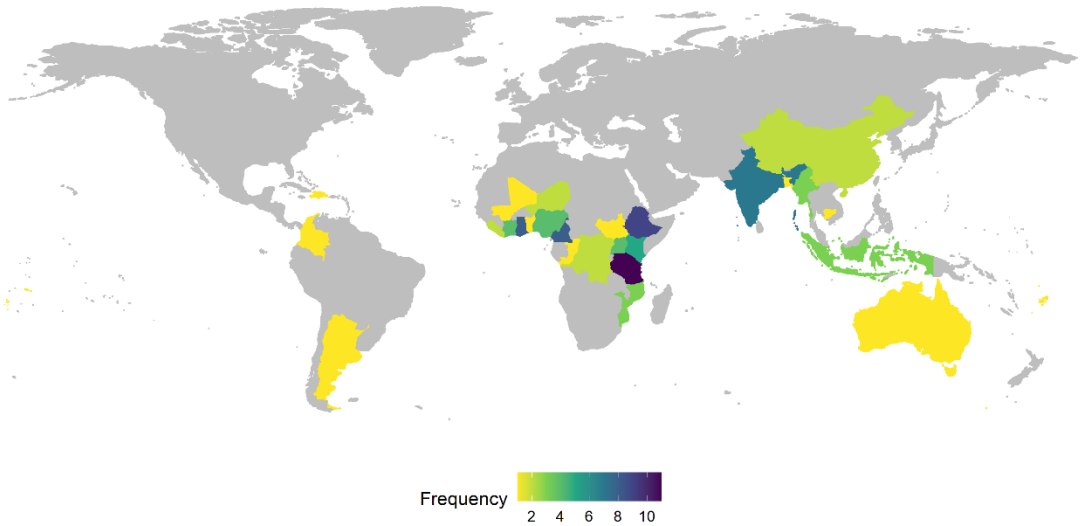


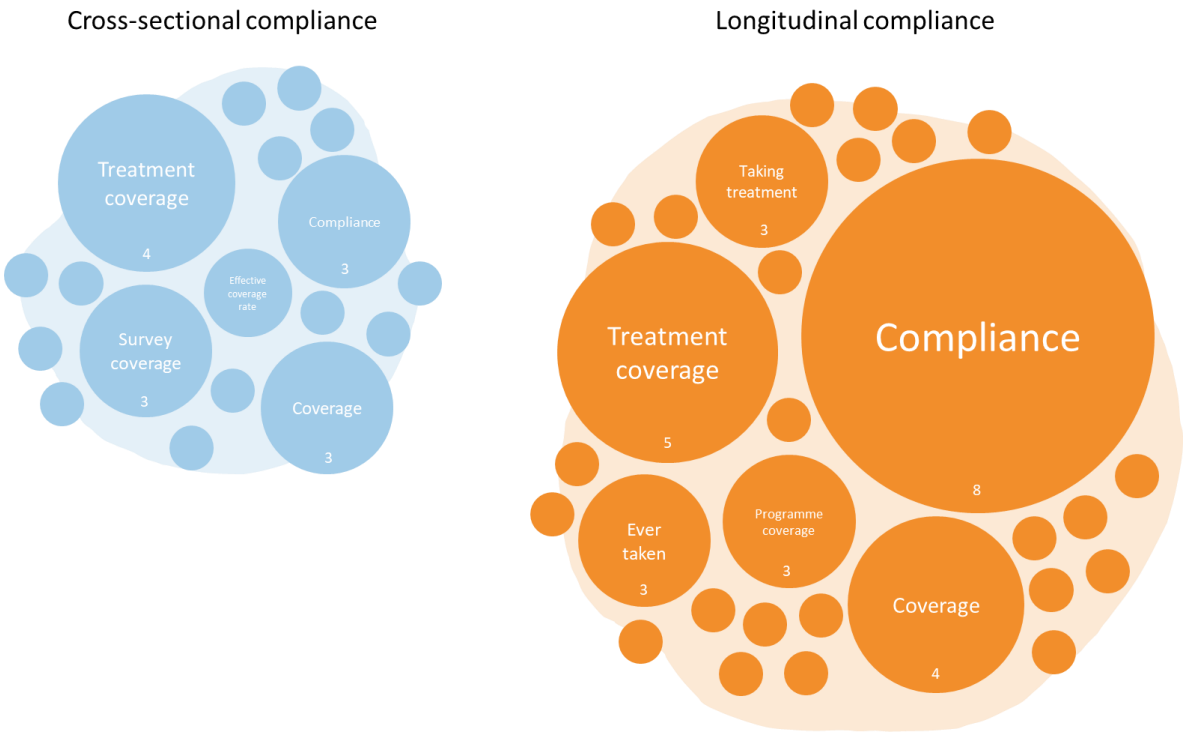
Figure 2.3: Choropleth map of compliance studies published globally from 2016 to 2022. *Countries where no papers were published are shown in grey. Four studies are represented as 11 datapoints where studies reported data for more than one country, totalling 108 datapoints from 89 studies.*

3.2. Incongruent parameter definitions

The reported numerator, denominator, and definitional calculations were carefully analysed for all reviewed studies. Where provided, these were often defined incompletely. When parameters reported did not match that used in this review, standardised parameters were assigned to the data. Often, compliance was misconstrued as coverage. The variety of parameters employed by the reviewed publications to describe cross-sectional and longitudinal compliance as defined in this review is recorded in **Figure 2.4**.

From the numerators and denominators provided, just 26 (29%) studies could be confidently identified as containing either cross-sectional or longitudinal compliance data. Compliance data defining either the correct numerator or denominator for compliance, not both, were categorised as 'assumed' (n = 12). Due to the wide variety of definitions used for the same parameter across studies (see **Figure 2.4**), publications that did not define either numerator or denominator for the parameter given were classified as undefined (n = 5). These parameters were "epidemiological coverage", "MDA participation", "treatment coverage", "MDA coverage" and "compliance".

The parameter "treatment coverage" (n = 4) was used most frequently to describe cross-sectional compliance, whereas longitudinal compliance was most frequently referred to as



"compliance" (n = 8). Compliance was only correctly used in three of the 32 cross-sectional studies where the numerator and denominator were clearly defined [98,115,116].

Figure 2.4: The variety of parameters used to describe cross-sectional and longitudinal compliance. *The number of circles represent the parameters employed (both correctly and incorrectly) to describe compliance. The frequency of parameter definition is proportional to circle size. Compliance is used most frequently to describe longitudinal compliance (n = 8), whereas treatment coverage was most frequently used to describe cross-sectional compliance (n = 4).*

3.3. Categorisation of compliance studies

Due to the paucity of the available literature detailing individual longitudinal compliance recorded by DOT, a hierarchy of studies was created, encompassing both longitudinal and cross-sectional studies as detailed in **Table 2.2**. The 57 (64%) studies containing longitudinal data were categorised as reporting individual data (recorded by data collectors (n = 3) or self-reported (n = 22)), repeated cross-sectional data (n = 32), or cross-sectional data (n = 32) (**Table 2.2**).

Compliance Data Type	Study Type	Description
Individual – annually surveyed (n = 3)	Cohort, randomised controlled trial	Longitudinal, individually linked, compliance data across >2 time points. Recorded DOT during annual surveys either by CDD, or self-reported by participant. Focus: individual level.
Individual – self-reported (time-specific or overall) summary (n = 22)	Cross-sectional	Longitudinal compliance data over defined/undefined time-period. Self-reported compliance by an individual at one time-point, looking back in time e.g., self-reported compliance to 5 available MDA rounds. Focus: individual level.
Repeated cross-sectional (n = 32)	Cross-sectional	Compliance data at each round of MDA for a set cohort (e.g., village or district), repeatedly surveyed over several time points population repeatedly sampled. Individuals not consistently present across all time points are not removed. Focus: population level.
Cross-sectional (n = 32)	Cross-sectional	Compliance data for a single round of MDA. Focus: population level.

Table 2.2: Data type and definition used to classify 57 compliance papers included in the analysis. *Compliance data was reported by both longitudinal studies (cohort, randomised controlled trials) and cross-sectional studies. The definitions of the different types of*

longitudinal and cross-sectional compliance data examined by this review are explained. Abbreviations: CDD – community drug distributor, DOT – directly observed treatment.

Of the 25 individual compliance studies, the most frequently employed method was to ask participants if they had 'ever' been treated (n = 15), either over a defined time period of five years, six years, seven years, 12 years, or the participant's lifetime. Annual and biannual studies were found at equal frequencies in the review (n = 5). Biannual studies tended to follow fewer rounds of MDA (range: 2-10 rounds), compared to annual studies (range: 4-12 rounds). Studies reporting individual longitudinal compliance increased slightly over the period 2016 to 2022, with four studies reported in 2021 compared to zero in 2016. Similarly, the number of cross-sectional compliance studies published also slightly increased, with seven studies reported in 2021.

A total of 32 studies (36%) reported cross-sectional (single time-point) compliance data. As these studies report compliance for just one time point, these studies were disregarded from any further longitudinal analysis in this review. A further 32 studies reported repeated cross-sectional compliance data over time periods ranging from a year of biannual treatment to 26 years of annual treatment. As these datasets follow compliance at a population level, these studies were not categorised as containing individual longitudinal compliance data, and were also disregarded from any further analysis.

3.4. Individual longitudinal compliance data

A sample of the extracted columns from the review is shown below for the 12 of the 25 individual compliance studies containing both annually surveyed and self-reported individual compliance data in **Table 2.3**. A single study was identified as containing annual longitudinal compliance data recorded by CDDs, referring to the parameter as "systematic treatment" [103]. The study reported on the Kenyan project TUMIKIA, where treatment behaviour of 36,000 individuals' for four rounds of biannual MDA data for STH was digitised, linking individual treatment behaviour longitudinally via house hold occupancy [103]. In a further two studies, individuals self-reported their compliance to the previously administered round of MDA, providing data for each round of LF MDA in the Democratic Republic of the Congo and the Republic of Congo, and STH MDA in China [117,118]. These studies were categorised as 'assumed' longitudinal compliance data, due to incomplete definitions of parameter

numerators and denominators, referring to longitudinal compliance as either “treatment adherence”, or “taking treatment” [117,118].

Author	Compliance type	Stratification	NTD and drug used	Country	N	Sample Type	Terminology Used	Standardised Definition	Numerator	Denominator
Oswald *et al.* (2020) [103]	Individual: 4 biannual rounds over 2 years - recorded by CDDs.	Age, sex	STH (ALB)	Kenya	36327	whole community	Systematic treatment	Longitudinal compliance	Eligible participants swallowing	Eligible population
Campillo *et al.* (2021) [117]	Individual: 8 biannual rounds. Self-reported compliance to previous round at each subsequent round.	-	LF (ALB)	Republic of Congo, Democratic Republic of the Congo	2658	whole community	Adherence	Assumed longitudinal compliance	Not given	Not given
Liu *et al.* (2017 [118]	Individual: 2 biannual rounds. Self-reported at each time point.	-	STH (ALB)	China	10000	SAC	Taking treatment	Assumed longitudinal compliance	Not given	Eligible population
Tilahun *et al.* (2018) [119]	Individual - as previously taken: 6 annual rounds. Self-reported compliance at each round.	Age, sex	Trachoma (AZT)	Ethiopia	5826	whole community	Coverage	Longitudinal compliance	Eligible participants swallowing	Eligible population
Osue (2017) [120]	Individual - as previously taken: 10 annual rounds. Self-reported compliance to each round.	Location	OV (IVM)	Nigeria	438	adults	Taking treatment	Assumed longitudinal compliance	Not given	Not given
Wanji *et al.* (2018) [121]	Individual - as ever taken: Self-reported compliance to 1-11+ annual rounds.	Age, sex, location	OV (IVM)	Cameroon	3684	whole community	Ever treated / MDA adherence	Assumed longitudinal compliance	Not given	Eligible population

Manyeh *et al.* (2020) [122]	Individual - as ever taken: Self-reported. No limit given.	Location	LF (IVM, ALB)	Ghana	446	adults	Compliance	Longitudinal compliance	Eligible participants swallowing	Eligible population
Minetti *et al.* (2019) [123]	Individual - as ever taken: Self-reported. (Maximum median rounds – 8)	Location	LF	Ghana	924	adults	Ever treated / MDA adherence	Assumed longitudinal compliance	Not given	Not given
Manyeh *et al.* (2021) [124]	Individual - as ever taken: Self-reported. Pre- and post-intervention.	-	LF	Ghana	446	whole community	Ever taken	Assumed compliance	Not given	Not given
Aza'ah *et al.* (2020) [125]	Individual - as ever taken: Self-reported, over 5 years.	Age, sex	OV (IVM)	Cameroon	603	whole community	Compliance	Longitudinal compliance	Eligible participants swallowing	Eligible population
Forrer *et al.* (2021) [126]	Individual - as ever taken: Categorised into never, 0-50%, 50-75%, 75%+ compliance to possible rounds.	Age	OV (IVM)	Cameroon	19915	whole community	Adherence	Assumed longitudinal compliance	Not given	Eligible population
Kifle *et al.* (2021) [127]	Individual - as ever taken: 10 biannual rounds. Self-reported.	Age, sex, location	OV (IVM)	Ethiopia	553	adults	Compliance	Assumed longitudinal compliance	Not given	Eligible population

Table 2.3: Individual-level compliance data extraction. *A selection of the extracted columns for the 12 studies satisfying the criteria for individual-level compliance data. Studies reporting longitudinal compliance data (surveyed by CDD, or self-reported by participants) are highlighted in grey shading. Cross-sectional compliance data was all self-reported. Available stratifications of compliance data are shown from the possible categories of age, sex, or location. The NTD targeted by the MDA, and the drug offered is also given. The country, and the type and number of participants*

is also provided. The terminology used to describe compliance is shown, along with the 'true' definition according to this review given the numerator and denominator recorded (where given). Where there are incomplete numerator or denominators provided, compliance can only be assumed given the large heterogeneity of calculations used for the parameter. Abbreviations: ALB – Albendazole, IVM – Ivermectin, LF – lymphatic filariasis, OV – onchocerciasis, SAC – school-aged children, SCH – schistosomiasis, STH – soil-transmitted helminths.

Longitudinal compliance studies reported over a time-specific period were more common (n = 22). Two longitudinal studies asked respondents to recall their previous treatment behaviour at each round, over six annual rounds in Ethiopia for trachoma, and over 10 annual rounds in Nigeria for OV [119,120]. Three cross-sectional studies asked participants to recall their treatment behaviour during MDA for OV over a specific time period, either five annual rounds and 11+ annual rounds in Cameroon, or 10 biannual rounds in Ethiopia [121,125,127]. Two of these studies referred to compliance in line with the definitions considered for this review [125,127]. A further two cross-sectional studies asked participants to recall ever being treated during MDA for LF in Ghana [122,123]. One study in Cameroon reported longitudinal compliance as a percentage of the possible rounds per participant based upon eligibility, breaking compliance into 'never', or complying with "≤50%", "50-75%", "≥75%" of possible rounds of OV MDA [126]. One study reported the change in compliance before and after an interventional effort to increase MDA uptake for LF control in Ghana [124].

A combination of cross-sectional and longitudinal compliance was reported by 13 studies, whereby compliance to a defined or undefined number of rounds were reported, alongside compliance at the latest round of MDA [128,129,138–140,130–137]. Four of these studies defined compliance in line with the definitions considered for this review [130,136–138]. Osei *et al.* (2022, Oswald *et al.* (2016) and Krentel *et al.* (2016) provided comprehensive demographic and descriptive factors and associations with receiving, and swallowing MDA through bivariate and multivariate logistic regression analysis) [103,138,140]. This high level of descriptive detail for coverage and compliance was rarely observed in the published literature. The research landscape of MDA reporting and its impact on infection levels would greatly benefit from more studies following these detailed study designs.

3.5. Compliance versus coverage

From the 32 and 57 cross-sectional and longitudinal studies reporting compliance, 41% (n = 13) and 14% (n = 8) reported coverage data alongside compliance data. These 21 studies produced 173 datapoints of comparable coverage and compliance data for different demographic strata, namely age, sex, location, and program year. Uniquely, Chami *et al.* (2017) calculated the average marginal effects for coverage and compliance set against a variety of other variables [98]. Most commonly, coverage was reported as a proportion of the eligible population (studies = 16, datapoints = 77). Other studies reported the parameter as a raw

number (studies = 2, datapoints = 11) or as a different parameter such as epidemiological, program and geographic coverage (studies = 3, datapoints = 85).

Where reported, there was a mean average difference of 4.91% (min: 0%, max: 30.8%) between coverage and compliance figures. Similarly, there was a 11.9% (min: 7.04%, max: 21.5%) mean average percentage change between the raw number of people treated reported. A larger discrepancy of 17.7% (min: 10.3%, max: 45.9%) was noted between epidemiological / program coverage, and compliance / geographical coverage. The difference between the two parameters is shown in **Figure 2.5**.

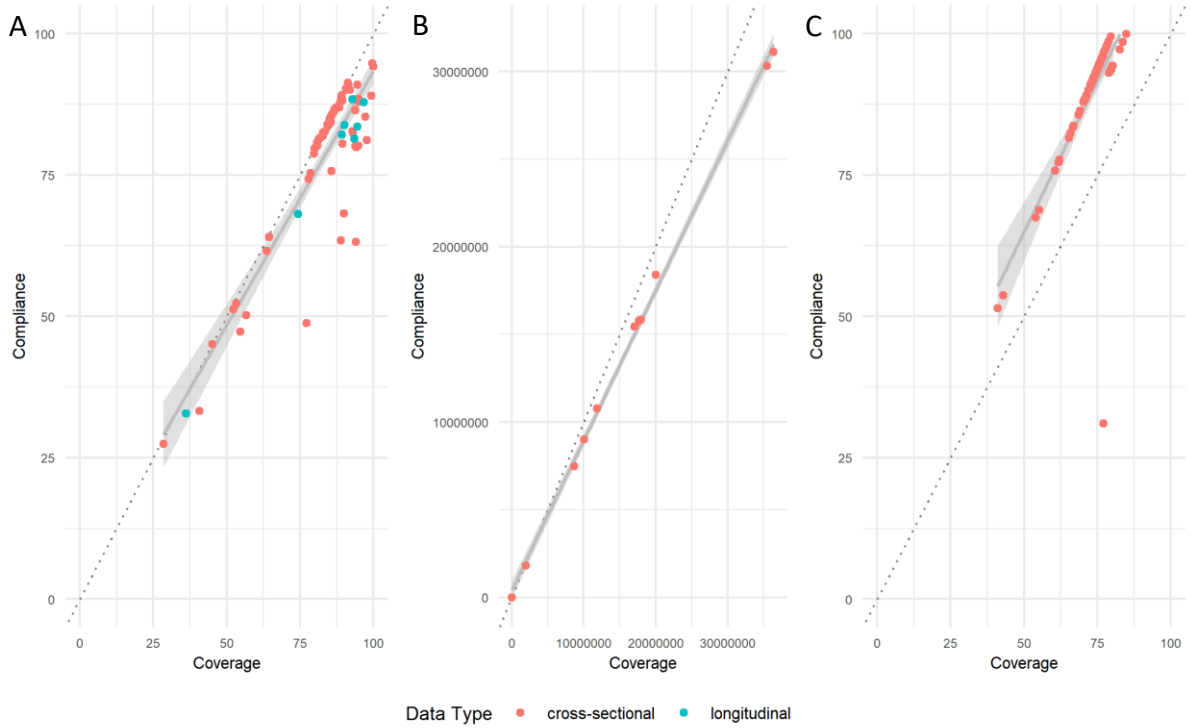


Figure 2.5: The coverage-compliance gap. *The difference between coverage and compliance figures reported by 21 studies as either proportions (**A**), raw data (**B**) or other parameters (**C**). Datapoints are coloured by the study type, either cross-sectional (13 studies, 69 datapoints) or longitudinal (8 studies, 104 datapoints). An average trendline of the reported data is shown in solid grey. The shaded line represents the conditional mean function using a linear model calculated by geom_smooth within the ggplot2 R package* [107]*. A guideline through intercept = 0 is shown to highlight the discrepancy between the two parameters.*

3.6. Stratification and analysis of compliance by demographic and behavioural factors

Stratifying the compliance data by demographic and behaviour factors helps national control programs to target groups for enhanced sensitisation and or mobilisation in MDA treatment. A total of 28 studies analysed key factors against positive and negative associations influencing compliance in the studied population. Three main methods were employed for the analysis of compliance strata: univariate, bivariate, and multivariate regression (presented as adjusted odds ratios (AOR)); Chi-squared analysis; and proportional breakdowns. Beyond the age, sex and location strata previously mentioned, further analyses were performed against enrolled/non-enrolled SAC, highest education level achieved of respondent, socioeconomic status, community type (rural/urban), marital status, occupation, ethnicity, religion, and length of stay in current village location.

Compliance increasing with age was noted by 12 studies. Specifically, compliance to treatment increasing with age was reported by Osei *et al.* (2022) (AOR 4.23 (95% CI: 0.84-21.2), adults aged >58, compared to 18-27 year olds), and Chisha *et al.* (2020) (AOR 1.45 (95% CI: 1.25-1.69), SAC aged 10–14, compared with to 5-9 year olds) [138,141]. Aza'ah *et al.* (2020) presented this phenomena via Chi-squared statistics, noting the proportion of age groups complying with MDA increased from 22.6% (95% CI: 16.3–30.4%) of 10-19 year olds, to 60.3% (95% CI: 53.1–67.1%) of participants aged ≥ 50 years ($\chi 2 = 64.1$, df = 3, $P < 0.0001$), as did Minetti *et al.* (2019), who noted MDA participation increased with age ($\chi 2 = 8.75$, df = 1, $p = 0.003$) [123,142]. Mirroring this, Kifle and Nigatu (2021) noted low compliance in young age groups, (AOR 0.68 (95% CI: 0.77-1.76) young adults aged 15-24 years, compared to >45 year olds) [127]. The variety of methods used to present age-related risk-factors with compliance prevents a subsequent meta-analysis to be conducted. This age-based trend demonstrates the requirement to include monitoring compliance by age, enabling stratified compliance data to be reviewed against the known age-dependent distribution of prevalence and enabling the direction of efforts toward under-treated groups [89].

Inconsistent conclusions were drawn for sex-related compliance behaviour. Statistical significance was noted for SAC enrolled in school, compared to those who were not

(AOR = 20.9 (95% CI: 17.4-25.1), AOR 2.29 (95% CI: 1.13–4.61) Asfaw *et al.* (2021) [141,143] . demographic groups with low compliance patterns.

Six studies noted an increased odds of compliance based upon previous compliance: systematic compliance. This was described in different ways across the reviewed publications, varying between increased compliance based upon previous compliance (AOR 10.6 (95% CI: 5.78-19.4)), willingness of future compliance (AOR 5.78 (95% CI:2.44–13.7)), and non-compliance related to previous non-compliance reported twice; (AOR 1.62 (95% CI: 1.05-2.50)) and (AOR 9.18 (95% CI: 2.43-34.7)) [119,123,135,138]. Campillo *et al.* (2021) further developed the analysis to make future predictions of drugs required based on past patterns of drug taking [117]. Consistent treatment behaviour to consecutive rounds of MDA was noted to decrease parasite prevalence.

3.7.Other factors relating to compliance

Aside from demographic factors, perceptions of both the MDA activity and the CDD delivering the treatments were also analysed in some studies. Common themes included awareness of the disease and the role of MDA, perceived individual susceptibility to the target disease, CDD dedication, health benefits, and adverse events related to drug ingestion. Prior knowledge of MDA scheduling was noted to have a significant effect on compliance in two studies. Asfaw *et al.* (2021) noted a 69% lower compliance to MDA, between prior awareness of date versus date and location of MDA activity (AOR 0.31 (95% CI: 0.12–0.82)). Krentel *et al.* (2016) noted compliance increasing with prior awareness of MDA activity (AOR 2.59 (95% CI: 1.0-6.7)) [140,143]. The perception of drugs to be beneficial to participants was also noted to be significantly associated with increased compliance; (AOR 7.33 (95% CI: 4.13–13.0)), (AOR 5.25 (95% CI: 2.55–10.8)), and (AOR 10.7 (95% CI: 5.10-22.6)) [119,138,140]. The perceived dedication and attitude of CDDs, as well as the protocols of height measurement were analysed by some authors, proving to be significant factors in increasing participant compliance. Travel time to the MDA distribution site was only collected by one study, delineating an individual's will to take MDA, with the practicality of doing so (AOR 0.22 (95% CI: 0.14–0.35) >60 minutes, AOR 0.08 (95% CI: 0.04–0.17) 30–60 minutes), reference: <30 minutes) [143]. Participant comprehension of parasitic disease (AOR 13.7 (95% CI: 1.65–113.6)), or the purpose of MDA (AOR 2.27 (95% CI: 1.44–3.59)) was noted to be significant [143,144]. Similarly, internal cues to action such as the assumption of own infection status,

susceptibility of disease and fear of disease was shown to be significant (AOR 3.63 (95% CI: 1.96–6.73)) [145]. It must be noted however, that despite these large AOR presented throughout the literature, the associated confidence intervals are very wide, reducing the reliability of this interpretation.

4. Discussion

4.1. The accurate measurement of compliance by control programs

This review highlights the paucity of individual longitudinal compliance studies available in the literature for the five (PC)-NTDs. The review aimed to compare reported individual longitudinal compliance recorded by CDDs, referred to as DOT. Despite publications dating back to 200 detailing the need for increased individual longitudinal compliance monitoring and reporting in the body of NTD research, just a single study was identified reporting individual longitudinal compliance recorded by CDDs [103,146]. The lack of publications fulfilling the review criteria resulted in the inclusion of all papers reporting compliance. As such, the review includes the analyses of very different types of compliance studies, both individual and population-level data (repeated cross-sectional studies), analysing information both recorded by CDDs and self-reported by participants.

The confidence in which these varying measures of compliance can be accepted should be interpreted with care. As previously mentioned, the gold standard to measure individual longitudinal compliance is DOT. This method avoids recall and desirability bias which may impact the compliance figures self-reported by participants when asked if they have 'ever' been treated across a defined or undefined time-period. Furthermore, participants may also confuse different MDA activities associated with different NTDs, as the MDA for different NTDs are given by the same CDD, one week apart, as they are often co-endemic. However, despite being the gold standard, it is important to note that DOT may also be subject to recording errors, since CDDs may be under pressure to report high figures.

NTD research is sometimes hindered by small budgets and limited study duration, thus the high cost of the reporting and measurement infrastructure necessary for accurately monitoring individuals over several time points to capture longitudinal compliance may not be realistic for most NTD control programs. It requires significant investment of time and

logistics to use unique identifiers (such as biometrics employed by the Geshiyaro project, or barcoded ID cards in TUMIKIA project) to accurately measure individual compliance during an MDA. This is reflected in the proportion of longitudinally recorded compliance studies (n = 3) versus cross-sectional surveys using participant recollection (n = 22) documented in this review. Conducting such cross-sectional surveys recording treatment recollection, or preferably, the number of treatment rounds attended, is more realistic for most NTD control programs in resource poor settings. Despite the decrease in accuracy of subject recall compared to DOT recorded by CDDs, a cross-sectional snapshot of compliance in the population will provide a complementary measure to coverage and will help elucidate the impact of an MDA activity upon the local parasite burden. Moreover, if such programs have failed to reach targeted prevalence and intensity levels, compliance data can accordingly be directed to the demographic groups with low compliance levels.

If a large proportion of the community is absent from the MDA survey (numerator) and this population was also absent from the baseline survey (the denominator), this will artificially inflate the population assumed to have taken treatment. For example, young male adults undertaking work away from the home setting may miss both the census and MDA activity by virtue of their occupation. The impact this 'absent population' may have on control will vary, dependent on the demographic of the population, the movement pattern, the transmission intensity in a given setting, and parasite in question [147,148].

4.2.The variation in epidemiological parameter definitions

Currently, there is much heterogeneity in the terminologies employed to define coverage and compliance including the species-specific guidelines provided by WHO. For example, in the case of LF control, two different denominators are defined for the coverage parameter in the same guideline. Drug coverage is defined as the proportion of the *eligible* (also referred to as targeted) population that *swallow* drugs. However, the programmatic drug coverage is defined as the proportion of the *total* population swallowing drugs (recommended to reach 80%). Drug CES are recommended by WHO, whereby a sub-sample of the population is questioned on their treatment behaviour, including coverage and compliance treatment behaviours [149]. This is an early example of the recommendation of detailed recording of compliance in NTD research. As such, the focus on LF compliance by the WHO (defined as coverage in the

guideline, but referred to as compliance in this review), is reflected in the number of reviewed studies, as those reporting compliance for LF control were most numerate.

In contrast, the guidance provided for STH control defines coverage as the proportion of the target population reached [34]. Systematic non-treatment (referred to as systematic non-compliance) is mentioned in the context of LF control, defined as the individuals who never ingest the medicines in any MDA round, but is absent from the analogous STH control guidelines. It would be beneficial for future editions of the WHO roadmap, and species-specific control guidelines, to clearly differentiate between coverage and compliance parameters, as current terminology use are not uniform across infections. Common definitions need to be adopted by the WHO across all NTD infections. The mismatch of parameter definitions is particularly problematic for the species recently targeted for integrated control.

The continued heterogeneity in MDA parameter definitions in NTD research highlighted in this review pertains despite the call for consistency made in the Shuford *et al*. 2016 review. Regardless of the parameter used by different studies and programs, the terminology and assumptions made in the calculation of compliance should be clearly defined within the methods section of publications to enable the scientific audience to interpret the data unambiguously.

This review reports a large difference between coverage (receiving treatment) to compliance (swallowing treatment) when comparing the data reported by studies, mirroring the 22% coverage-compliance gap previously published by Babu *et al.* (2014) and the 12.1% gap reported by Sitikantha *et al.* (2019) [95,150]. This demonstrates that a significant proportion of un-treated individuals are considered within the parameter of coverage. programs targeted with reaching coverage-based targets that conflate this parameter with compliance could therefore be under-treating unknowingly [140]. For example, if coverage reaches a defined target e.g. 75% of a population, and compliance is only 80%, then 750 will have received treatment, but only 600 will have swallowed treatment. As such, beyond the clear definition of the parameters used, a stipulation from the WHO to routinely report compliance alongside coverage would be beneficial in improving the accuracy of reporting of individuals that have been effectively treated.

Of the 89 studies included in this review, compliance stratified by location, sex, and age were rarely recorded. The importance of these co-variates is clear in many studies. Presenting compliance data at the population level will potentially aggregate important behavioural heterogeneities within communities which need programmatic attention. Future WHO guidelines to Ministries of Health would benefit from not only including coverage stratifications by age and sex, but to reflect this in compliance reporting. The collection of such data would facilitate the analysis of trends in MDA behaviour, therefore enhancing future MDA rounds through targeted sensitisation activities to improve compliance.

5. Conclusion

There is a paucity of individual longitudinal compliance monitoring of MDA treatment for the control of (PC)-NTDs. This review has shown that there has been a small increase in the number of papers published which contain clearly defined compliance measurements, from a very low baseline in 2016. This is understandable considering the cost and time demands required due to the longitudinal nature of such data collection, and the detail orientated methods required for individual-level data matching of demography to correctly employ denominators for calculating compliance. As a result, prospective cross-sectional studies interviewing participants on their treatment history at one point in time were most numerate in the reviewed literature. This is not the gold standard method of longitudinal compliance measurement, but the information that a control program or local ministry of health will gain, such as the definition of systematic or random compliance patterns in defined demographic sub-groups, will be crucial for guiding future MDA rounds to reach the goals of reducing infection to very low levels, or indeed eliminating transmission in defined populations or regions. Greater attention by WHO, Ministries of Health, and epidemiological researchers is required to unify definitions on both coverage and compliance. Furthermore, it would be beneficial for the WHO to provide detailed guidance on their measurement for the five (PC)-NTDs for improved comparability.

Chapter 3: Biometric fingerprint scanning for large-scale, individually linked, longitudinal epidemiological studies: the Geshiyaro Project in southern Ethiopia

Dissemination

This chapter has been adapted from the paper titled, “Biometric fingerprint scanning for large-scale, individually linked, longitudinal epidemiological studies: the Geshiyaro Project in southern Ethiopia”, currently in press with Transactions of the Royal Society of Hygiene and Tropical Medicine.

Motivation

The Geshiyaro project is not only the largest longitudinal study of STH epidemiology, but also employs a novel method using biometrics for participant registration, improving the quality of the data collected annually from clearly identified individuals. This enables participants to be identified at subsequent contact points throughout the project, such as MDA delivery and parasitological diagnosis. This chapter explains the data analysis methods used to collect and clean the longitudinal dataset, and assesses the value added of such fine-scale M&E with the validity of the collected data.

1. Introduction

Large-scale, longitudinal, epidemiological projects face a multitude of challenges when repeatedly identifying participants accurately in low resource settings [62]. Mobile populations, remote communities, and the high financial cost of censusing a population required for their future identification, all contribute to the rarity of such studies. Traditional paper-based censuses suffer from frequent inconsistencies in data entry and compromised accuracy when digitising data for subsequent analysis [151,152]. Electronic data capture presents an increasingly accessible method, improving the accuracy of identification. The incorporation of such technology by public health programs and research studies has significantly improved census quality [151]. Despite the gains made in electronic data capture fidelity, limitations persist at the participant identification stage. This can include the exchange, loss, or damage of study identification cards or the inconsistent self-reporting of personal identifiers (name and age), preventing subsequent matching of records between program activities. The inclusion of biometric technology, which uses individual physical characteristics as a method of unique registration and subsequent identification, aims to improve identification accuracy, helping to reduce a key inefficiency in electronic data capture [153].

Over 50% of the population in low- and middle-income countries (LMICs) are not in possession of individual identification documentation, leading to the phrase the 'invisible billion' coined by the World Bank [154]. As such, identification in LMICs public health settings is challenging. Data documenting such identification is also limited. A study in 2012 of Rwandan and Burundian health management systems found patient misidentification occurred in 65% of visits, the patients' date of birth was rarely known, and the provided name and spelling varied considerably leading to multiple records for a single person [155]. The provision of identifiable information can conversely be a confidentiality concern, especially in vulnerable populations, for example the incorporation of biometric technology in South Africa for an HIV treatment and TB case finding program, and more recently female sex workers in Zambia [156,157].

Interrupting the transmission of STH and SCH relies on a high proportion of the population consistently taking chemotherapeutics over time to reduce the prevalence and intensity of infection, as neither historic infection nor treatment confers strong acquired immunity

[15,29,89,103]. Accordingly, accurate data of a population's demographic structure (informing the calculation of the eligible population, or denominator), and subsequent interaction with an intervention (such as eligible participants swallowing drugs, the treatment compliance numerator) is crucial for evaluating the progress towards, or regress from, reaching transmission interruption. Control programs often rely upon national census data, which are conducted infrequently in most resource-poor countries, thus forcing denominators to be calculated by multiplying the latest census data by a generalised, national population growth rate.

Biometrically registering a population may greatly improve the accuracy of the denominator through the availability of high-power data cleaning intrinsic to electronic data capture. Therefore, as participants are enrolled into the database, the high fidelity of the biometric will prevent the creation of duplications in the database. Numerator accuracy is also improved through biometrically verified identification. This enhances the precision of epidemiological calculations employed for assessing progress towards transmission interruption, such as treatment coverage and compliance, or parasitological prevalence and intensity within defined demographic groups, leading to the identification of infection hotspots. Future control strategies or sensitisation methods can then attempt to address these by targeting the remaining pockets of untreated individuals. It should be noted, the description of the population will be limited, as with any survey, by the efforts to capture the whole population, enrolling households on the edge of administrative boundaries, marginalised communities, and mobile populations.

This chapter describes the benefits and challenges of implementing fingerprint scanning for registration and identification in a large-scale infection transmission interruption project, and briefly outlines the methods used to harmonise a biometrically acquired dataset. This is the first study of its kind, trialling biometric data capture for the routine M&E of NTD control. Pitfalls of biometric data collection, and proposed workflows to avoid identified problems are discussed.

2. Materials and methods

2.1. Study population

The Geshiyaro project aims to measure the impact of cMDA and improved access to WaSH infrastructure on the interruption of STH parasite transmission in Wolayita, Ethiopia. The project protocol and baseline findings have been previously published [45,60,66,84,86–89]. The impact of cMDA and construction of WaSH infrastructure upon the control of STH and SCH was measured by three study intervention arms as described in **Chapter 1**.

The entire population of the Wolayita zone received cMDA, which is divided into Arm 1 and Arm 2 (**Figure 1.5**). The population (n = 551,880 individuals) in a subsample of five of the sixteen woredas in Wolayita was biometrically enrolled in a census carried out at baseline between 2018 and 2019. This subsample provided an individually linked, longitudinal dataset for the monitoring and analysis of infection levels and cMDA treatment access across the total population of over 2 million people in Wolayita [45,158].

In this chapter, participant registration refers to the creation of the Geshiyaro census, and participant identification referring to the identification of participants during cMDA distribution against this census record. For epidemiological analysis, the population was stratified into age groups defined as infants (0-1 years old), preSAC (2-4 years old), SAC (5-14 years old), adolescents (15-20 years old), young adults (21-35 years old) and adults (35+ years olds). The definition of the infant age-group removed the ineligible population for albendazole and praziquantel from the preSAC age-group. All analysis and generation of data visualisation was conducted in R studio (version R.4.3.2) [106].

2.2. Biometric censusing

2.2.1. Non-biometric data

All non-biometric data capture was conducted using mobile phones with SurveyCTO software (Dobility, Inc; Cambridge, MA, USA). HEW and local university students recorded individual demographic data (full name (first name, father's name), age, sex, GPS location) as depicted in **Figure 3.1**. Each participant was provided with identification (ID) card, also labelled with their full name, age, sex, and location, and a unique 11-digit identification number for that

individual. A quick response (QR) code was printed on each ID card, scanning of which would retrieve participant demographics, and crucially their 11-digit identification number.

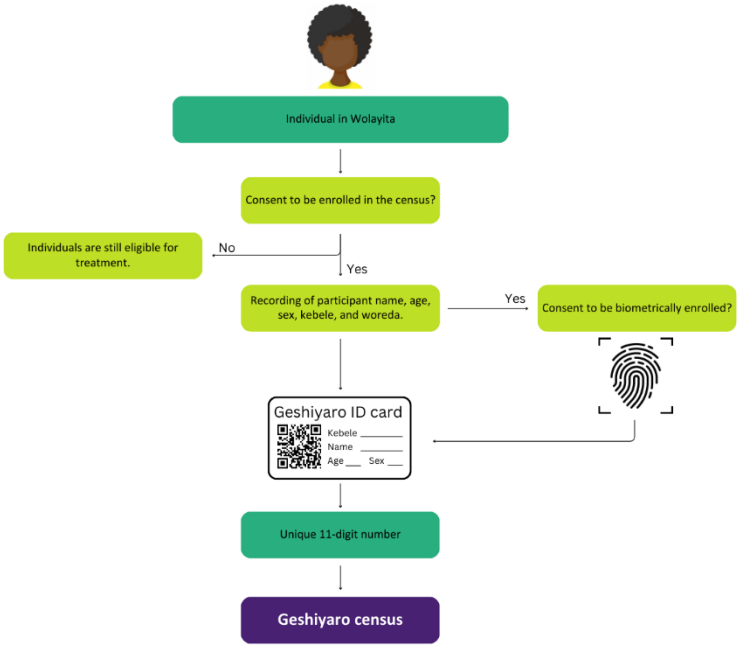


Figure 3.1: Flow diagram illustrating the process of enrolment of Wolayitian participants into the Geshiyaro census. *Demographic data for each participant is recorded on the identification (ID) card, which is linked to the census electronically through the scanning of a quick response (QR) code printed on each card. When scanned, this shows the participant's unique, 11-digit identification number. For participants that consent, this 11-digit number is also retrieved through the scanning of fingerprints collected through the Simprints mobile application* [159].

2.2.2. Biometric data

Biometric data capture was conducted using Vero fingerprint scanners and "Simprints ID" mobile application (Simprints Technology Ltd; Cambridge, UK) [159]. A biometric scan was taken of the thumb and index fingerprints of each hand for consenting participants. For participants missing a finger, the scan could be skipped. The four scanned fingerprints generated an individual's global unique identifier (GUID); numerically summarising the minutiae (ridge endings and bifurcations) of the fingerprint [159]. This GUID was linked to the participant's 11-digit identification number.

Subsequent scanning of the same four digits, in the same order, at different participant contact points in the project enabled participant identification. During identification, the biometric technology ran a matching algorithm between the current scan and the previously

registered biometric records, retrieving five GUIDs with the highest matching confidence to the active scan. The metadata associated with the five records was displayed to the HEW, allowing the selection of the correct census record if offered. If the correct record was not identified, this triggered subsequent non-biometric identification pathways such as scanning the QR code printed on a participant ID card, participant name search, or newly registering the individual. This electronic longitudinal identification of participants across project activities such as cMDA delivery, or during parasitological diagnostic surveys, enabled longitudinal linking of participants over time and across intervention arms.

2.3. Deduplication process

2.3.1. Biometric-matching process

The threshold for assessing the highest probability biometric match, both during field activities (generating the five highest probability matches), and during deduplication, was defined using a matching threshold according to methods previously described [153,157]. In brief, matching thresholds vary with populations due to fingerprint quality, requiring a bespoke threshold calibration and definition exercise to be undertaken for the population in Wolayita.

GUIDs from a random sample of 786 participants stratified by age and sex were analysed. Fingerprints were scanned, in duplicate, with a minimum of one-day separation between the scans allowing for variation between days, cleanliness, and humidity known to affect scan quality [153]. To ensure a high confidence in the two linked fingerprints, a participant photograph was taken to enhance the accuracy of the routine metadata collected, as well as the generation of a participant ID unique to the threshold activity. Informed consent was obtained from each participant. The confirmed duplicate biometrics were compared, producing a database of GUIDs pairs with an associated biometric comparison score used to determine whether the two GUIDs belonged to the same person or not. The threshold was used as an initial starting point to categorise GUID pairs into high, medium, and low confidence scores during biometric clustering and deduplication.

2.3.2. Name-matching process

A traditional Ethiopian ‘full name’ consists of a first name, father’s name, and grandfather’s name. Additionally, at birth, infants are sometimes given a generic name such as “Baby”, later

replaced by their formal name as informed by their personality that is learned with age. This tradition had a significant impact on record matching for young children presenting with different names at different activity time-points.

Commonplace name matching algorithms employing “fuzzy-matching” based on Levenshtein distances were not appropriate for accurately matching name data, using distance alone. For instance, the name ‘Elizabeth’ can intuitively be matched to ‘Liz’, ‘Lizzie’, ‘Beth’, ‘Eliza’, ‘Ellie’, and ‘Elly’ if the remaining metadata for the individual such as family name, age, and sex were consistent, but would be missed if employing fuzzy matching. A sample of 80% of the first names recorded in the Geshiyaro census were provided to native speakers to methodically provide all accepted name abbreviations and spelling variations. This was representative as Ethiopian naming convention uses the fathers first name as the family name, rather than distinct family names. The resultant matrix of names and their variations was used to confirm if similar biometric prints did indeed belong to the same individual. For the remaining names, for which there was no available data annotated by native speakers, fuzzy matching was used as a fallback.

2.3.3. Age-matching process

Less than 2% of children under the age of five have a formal registration of their birth in Ethiopia [154]. Due to the lack of formal birth registration, the self-reported nature of age was heavily influenced by recall bias and desirability bias. Thus, deduplication could not rely on the exact matching of age. Furthermore, the dynamic process of enrolment over many years was reflected by incrementally increasing ages for the same individual. Age-matching required a two-stage level of age thresholds, accepting a five-year difference in individuals ages 0-25 years old, and 15 years for individuals aged 26+ years, when all other identifying information also fell into the threshold for matching.

2.3.4. De-duplication and harmonisation of GUID database

After six years of data collection, the census data had errors and inconsistencies commonly associated with large-scale data collection, including multiple spelling variations for a single individual (abbreviations, spelling inconsistencies), poor recording or loss and replacement of ID cards, and population movement between the studied villages. Before data cleaning took place, the census data was categorised based on the name quality (number of given names,

repeated letters, alpha-numeric combinations), participant identification number (presence, absence or altered), and the quality of the biometric fingerprint scan (if consented to provide). This enabled a tiered system of deduplication for each data quality type, such that high quality biometric records were confidently analysed together, records with poor or no biometrics would rely to a greater extent on the demographic data such as age, full name and sex, and participant identification number. Records were grouped into clusters defined as a set of records likely belonging to the same person based upon the biometric-matching, name-matching and age-matching thresholds as set out below. A single record from each cluster was selected, generating a dataset with a unique participant identification number and/or GUID per participant.

Deduplication of the dataset required biometric matching of fingerprints as well as the harmonisation of the participants' 11-digit identification number, full name, age, sex, and geographical location associated with the record. Fingerprints were recorded of the HEWs who collected the cMDA data, enabling the detection and removal of self-enrolments occurring when HEW erroneously linked their own fingerprint to the record of a participant.

All biometric records were compared against one another within the village that they were enrolled, using three types of fingerprint aggregations. Each finger from one record was compared against the corresponding finger in the other record (e.g. left thumb against left thumb). The mean of these four finger-wise comparison scores was used to get the aggregate score between two sets of fingerprints. This was the predominantly used aggregation for deduplication, as it seemed to provide the least biased results such as those caused by unusual fingerprints within an individual's record, skewing their scores. Secondly, the maximum of these four finger-wise comparison scores was used to identify the special cases of self-enrolments. Finally, each finger from one record was compared against all the fingers from the other record, and the maximum of each of those comparison scores was deemed to be the aggregated comparison score for that finger (e.g. left thumb against each of left thumb, left index, right thumb, and right index, and the maximum of those four scores would be the score for the left thumb). Then, the mean of these four finger-wise aggregated scores would be the aggregated score between the sets of the fingerprints. This was used to account for any accidental swapping of hands or order of fingerprints taken.

In order to determine if two records belonged in the same cluster, a mixed strategy was used. If two records of high biometric quality matched with a high biometric comparison score, they were put in the same cluster. Else, if there was high confidence in the metadata for a participant, and a medium confidence that they matched biometrically, they were put in the same cluster based on their demographic data comparison score. The demographic data comparison score was bas based on name-matching and age-matching described above. Finally, a single record was chosen from each cluster using the thresholds mentioned above.

3. Results

3.1. Population representation by biometric registration

By the end of the sixth year of project activity and after deduplication, 92.0% of the population (n = 551,880 individuals) enrolled in the project had a biometric record. The age distribution of the Geshiyaro populations in the five censused woredas compared to the averaged estimation for the five woredas according to the international database of the United States of America (US) Census Bureau and is shown in **Figure 3.2** [160]. This comparison was used to identify if any demographic were systematically missed from the census activity.

Across all woredas, the US Census Bureau population estimated more infants (86.0% more) and pre-SAC (57.7% more), suggesting an under-sampling of both populations by the project. Conversely, according to US Census Bureau estimates, less adolescents (30.1% less) were expected, suggested a slight over-sampling by the project. Adults, young adults, and SAC were well captured. Heterogeneity in the recorded population structure can be seen between woredas, most notably the under-sampling of preSAC in Bolosso Sore (2.68%) and Damot Gale (4.09%), compared to Damot Weyide (5.99%), Bolosso Bombe (6.50%), and Abela Abaya (6.95%). Furthermore, the largest disparity between male and female recorded was observed in young adults, most notably in Abela Abaya (4.40%) and Damot Weyide (4.19%).

Within the Geshiyaro study population, biometric registration slightly favoured females (92.1% (95%CI: 91.9 - 92.3%)) compared to males (91.3% (95% CI: 91.0 - 91.5%). Biometric registration for the age groups increased from infants (4.06% (95% CI: 1.31 - 6.81%)), to preSAC (59.7% (95% CI: 59.6 - 59.9%)), adolescents (92.6% (95% CI: 92.2 - 93.0%)), young

adults (92.8% (95% CI: 92.5 - 93.2%)), SAC (93.0% (95% CI: 92.6 - 93.3%)), and through to adults (95.9% (95% CI: 95.5 - 96.2%)).

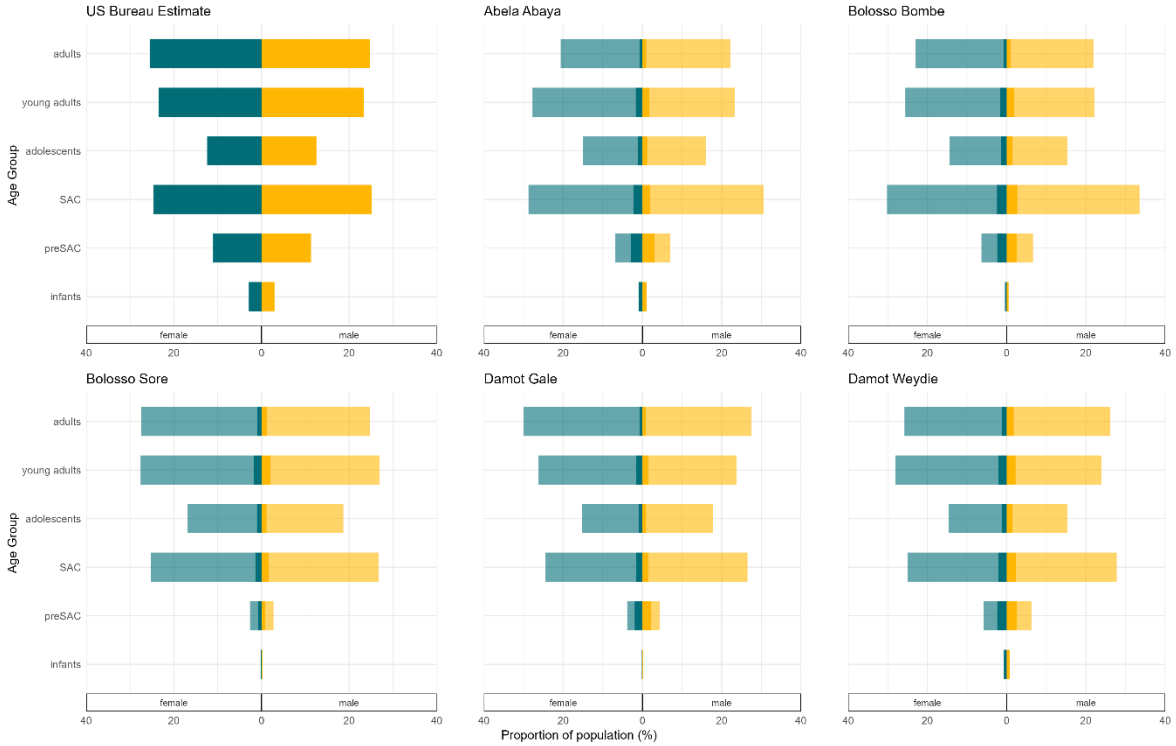


Figure 3.2: Age pyramids of the five censused woredas (districts) of the Geshiyaro project compared to the US Bureau estimates. *The breakdown of registration method (biometric: pale colour, non-biometric: strong colour) used at Year 6 of the project is demonstrated. Female participants are depicted in dark green, male in yellow. The averaged US Bureau Estimate for the five woredas for 2023 is shown for comparison. Labels: infants: 0-1 years old, preSAC: 2-4 years old, SAC: 5-14, adolescents: 15-20, young adults: 21-35, adults: 36+. Abbreviations: SAC – school-aged children.*

3.2. Identification methods employed over time

The dynamic changes in the dominance of different identification pathways used during the verification of cMDA distribution over six years of project activity is shown in **Figure 3.3**. Name search capability was not available in the first year of activity. Notably, the proportion of biometric identifications increased from 16.4% (95% CI: 16.2 – 16.6%) to 48.4% (95% CI: 48.3 - 48.5%) from Year 1 to Year 6. This remains significantly less than the overall proportion of the population registered with a biometric record (92.0%). Of the total methods used in Year 6 for identification, SAC were most frequently identified by biometric identification (54.5% (95% CI: 54.3 - 54.7%)).

A decline was seen in the use of ID card identification from 50.6% (95% CI: 50.4 - 50.9%) in Year 1 to 0.94% (95% CI: 0.92 – 0.96%). This can be attributable to either the loss, or degradation to an unidentifiable degree, of identification cards, or the increase in available biometrics to identify participants.

The proportion of new registrations decreased over time from 13.8% (95% CI: 13.6 - 13.9%) in Year 1 to 4.55% (95% CI: 4.50 – 4.59%) in Year 6. This primarily was for the enrolment of infants recently born, the enrolment of which remained high across the six years. New enrolments in other age categories shows a gradual 'mopping up' of peripheral, mobile, or remote individuals who would not be captured in a single cross-sectional census activity. By Year 6, most of the new registrations were attributed to the infant (54.8% (95% CI: 53.6 - 55.9%)) and preSAC (8.29% (95% CI: 8.04 - 8.53%)) age groups, as expected.

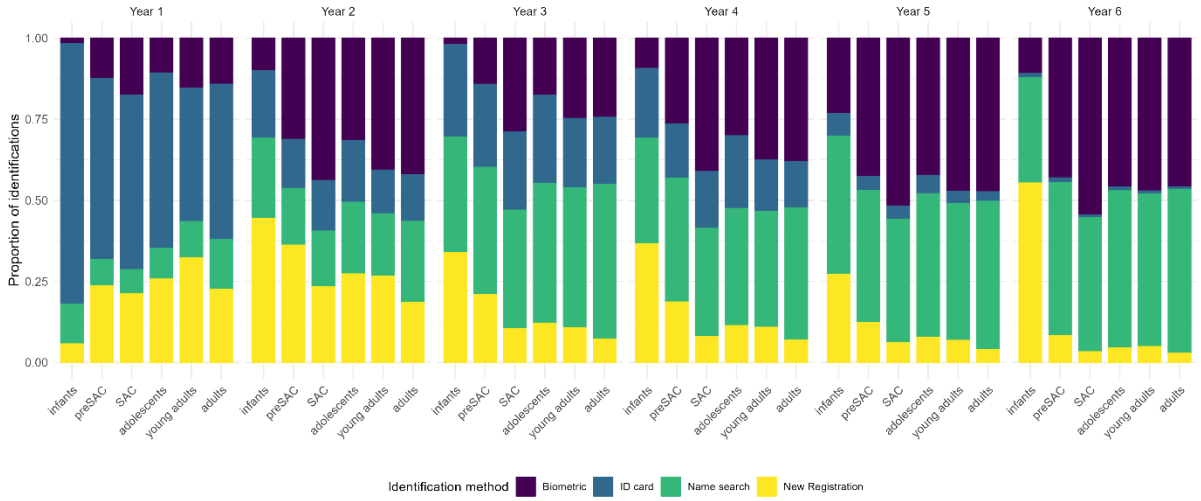


Figure 3.3: The changing proportion of identification pathways used over six years of community-wide mass drug administration (cMDA) activities. *Identification methods include biometric scanning, ID card, name searching and new registrations. Infants are not considered (aged 0-1) as this age group is not eligible for albendazole or praziquantel treatment. Note: name search capability was not available in Year 1. Labels - infants: 0-2 years old, preSAC: 2-4 years old, SAC: 5-14, adolescents: 15-20, young adults: 21-35, adults: 36+.*

4. Discussion

To achieve real-time, accurate monitoring of control program activity by measuring epidemiological variables such as drug coverage and compliance, the denominator and numerator employed by a project require frequent updating due to births, deaths, and migrations. This is of increased importance in transmission interruption programs that rely on

accurate recording of MDA compliance and identification of associated pockets of infection. Employing the deduplication algorithm as described here enables a robust clustering analysis of the censused population to be run periodically at a fraction of the time that is required for manually entering paper-based data capture information, and to a higher degree of accuracy then manually deduplicating datasets. The generation of bespoke algorithms, such as the Ethiopian-specific name-matching algorithm, further enabled the matching of census records that could not be completed manually with rigour.

The favouring of female over male biometric registration reflects both the data collection method and location- and sex- specific behaviours. The census registration was conducted door-to-door. Women were often found at home during such visits, therefore were able to provide a biometric. Men of the same age-group are often found away from the home, for economic purposes, and thus are unable to provide a fingerprint. The increase seen in biometric registration with age, with the exception of high biometric coverage in SAC, may also be a sequalae of both behaviour and technology. Infants and preSAC are challenged with providing a valid fingerprint due to size, adolescents and young adults are often found away from the home for economic reasons, with older age-groups found at home responsible for care-giving roles of infants and preSAC. Interestingly, despite the difficulty in matching a fingerprint taken of SAC in Year 1 with that taken in Year 6 due to the growth SAC demonstrated the highest proportion of biometric identification at cMDA.

4.1. Limitations

Electronic data capture using a biometrically based dataset undoubtedly resolves many of the issues faced by paper-based data capture. However, some challenges remain in data collection regardless of the methods used. These include, but are not limited to, enrolling hard to reach remote populations; absenteeism by agricultural workforces and mobile populations (often young male labourers); and resistant populations rejecting control interventions due to socio-cultural attitudes and practices.

The integration of biometric fingerprint scanning in large-scale epidemiological studies is not always straightforward. First, infants and preSAC fingerprints change rapidly with development, making accurate fingerprint identification challenging. Ethiopia has an age structure driven by a high growth rate and a young population, causing this to be a major

limitation in the context of the Geshiyaro project. Infants are disproportionately burdened with *A. lumbricoides* and *T. trichiura* infection due to age-related risk factors, therefore the reduced ability of biometric monitoring of these high infection risk populations is unfavourable.

Secondly, Wolayita has a predominantly agricultural workforce, another high infection risk-group, who often have imperfect fingerprints due to scarring and grazing as a consequence of manual labour. This impedes the reliability of biometric identification, and in the context of the Geshiyaro project, will be more likely to be enrolled by just their participant ID card, which is easily lost, again greatly reducing the confidence in the longitudinal identification of this age group. This is concerning for STH control, as agricultural workers are at higher risk of hookworm infection due to infectious larval stages found in the soil, penetrating workers bare feet. Furthermore, agricultural workers are often away from the household, travelling away from home for several weeks at a time, and consequently may miss multiple MDA activities. Refinements to fingerprint scanning technology are required to enable the inclusion of these currently systematically omitted key demographic populations such as mobile agricultural labourers and preSAC. Other biometrics, such as iris scans and facula recognition, may be a better approach in such settings. The high mobility of agricultural workers, however, will remain a challenge until synchronisation of health access is implemented in Ethiopia.

The mechanics and algorithms designed to identify an individual's fingerprint are under continued development and refinement. Although the proportion of the population biometrically identified improved year on year, less than 50% of participants in the Geshiyaro project were successfully identified by biometric fingerprint scanning during the latest cMDA activity despite 92.0% of the population having a biometric record. There are many reasons for this. In some cases, the biometric matching algorithm did not retrieve the correct GUID from the existing database at the point of identification, either because the quality of the biometric scan was poor and hence a match could not be performed accurately, or because there were errors during the biometric capturing process. Other times, the biometric matching returned the correct GUID, but existing data mismatches between the biometric data and the demographic datasets prevented the correct participant record attached to the GUID to be retrieved in real-time. Operational and training-related issues were encountered such as HEWs not selecting the participant record, even though it was correctly displayed. As

the Geshiyaro project protocol requires considerably enhanced methods for treatment due to the inclusion of participant identification compared to the routine national program of distribution only, this is to be expected. Given the span of the project of over eight years, it's also likely that the quality of the fingerprints changed in time (e.g. growth of children's fingerprints, or additional scars or marks), leading to poor matching scores, echoing limitations discussed by other longitudinal studies of fingerprint identification [153].

To improve the accuracy of the system, a stricter biometric quality threshold could be implemented. Furthermore, improvements to the workflow for the registration are also recommended, such as capturing multiple images per finger. This would have both positive and negative programmatic outcomes, both increasing the length of time taken to capture the census database, whilst also increasing the accuracy of biometric stored. In future studies, it is also recommended that the active scan used to match to the biometric database during participant identification, replaces that biometric previously stored, especially if the quality score of the newly acquired image is evaluated to be higher. This dynamic process requires evaluation of the accuracy gained in subsequent identifications, and the mistaken overwriting of inaccurately matched records. This will improve the ability to match younger children's fingerprints, as matching a year-old fingerprint will be more accurate than a five-year old print. This may also reduce the need for new registrations, which may be triggered for a child whose current print does not match the original and thus their census record cannot be found. Alternatively, the development of new biometric targets such as iris and facial scanning may help to resolve the shortcomings currently associated with fingerprint technology [161].

Socio-cultural practises and beliefs will impact the uptake of any chosen biometric technology. This applies to both participants, and the HEW implementing the technology. The early stages of the Geshiyaro project, implementation required the inclusion of several days of community sensitisation, delivered through consultations with religious leaders, village representatives, and the censused communities to ensure awareness of the technology and debunking of falsities rumoured to be associated with the data collection. Over time, the requirement and length of sensitisation lessened, and biometric records were increasingly used by the studied Geshiyaro population, which in part may be due to the global adoption of fingerprint technology used by many smartphone and electronic equipment manufacturers.

Despite the ease of integration of new registrations to the census offered by electronic data collection, predominantly capturing infants and preSAC age groups, the census remains affected by the inability to capture migration and deaths in the population. Given the length of the eight-year project, this will start to significantly affect project measurements in later years. Integrating a confirmation of participant loss data capture form may be beneficial to trial in projects of similar length, using locally recorded deaths from health-posts to aid in the maintenance of an accurate denominator. Given the considerable effort this would entail, the lack of identifiers from the individual to verify the data, and the opportunity for misuse of this system to decrease the population to subsequently inflate epidemiological coverage figures, this may not be favourable. Guided by population growth estimates, a death rate may be applied to the population before calculating epidemiological figures such as cMDA coverage or STH parasite prevalence.

The mixing of technology versions during biometric scanning proved to be problematic. Mobile application updates routinely deployed by Simprints lead to some difficulties in integration of the technology with both the smart phones used for data collection, and the Vero scanner. Furthermore, as Vero scanner technology upgraded, the clustering of biometric scans for the same person captured by 'old' and 'new' scanners were affected. As such, activities had to be conducted using the same Vero scanner version to avoid sensitivity issues created by a heterogeneous scanner deployment.

Finally, the user quality of the biometric technology varied between HEWs, from those thoroughly completing census enrolment with a full complement of data, to those recording poor biometric scans, entering abbreviated names, or inaccurate ages. This heterogeneity in HEW behaviour will shape the degree of cleaning and deduplication needed downstream and highlights the need for effective and frequent HEW training best delivered in the form of capacity building workshops.

4.2. Future recommendations

Despite the reduced proportion of the population captured by the biometric technology in infant and preSAC age groups, the success of biometric identification versus name searching or ID card identification clear in this study. By the sixth year of the project, the majority of participants had lost their ID card. For participants with an ID card, a high proportion had

faded writing, preventing the successful identification of participants by scanning the QR code. For future longitudinal projects, implementing electronic data capture for the accurate recording of program denominators and numerators is recommended. Incorporating the consensual capture of a participant's photograph to the enrolment process, as used during the threshold calibration exercise, as an alternative method for identification may be preferable to biometrics as this would evade the limitations caused by ineligible fingerprints from infant age groups or manual labourers, and is cheaper than employing biometric technology.

5. Conclusion

The Geshiyaro project has had the unique opportunity to trial the inclusion of biometric technology into a control program. The methods used and implementation experiences of the efficient collection, cleaning, and harmonisation of such biometric data have been discussed. This demonstrates that improved results can be achieved by applying a bespoke and rigorous clustering and deduplication algorithm to generate reliable denominators for epidemiological calculations. This is particularly crucial for the Geshiyaro project and more broadly any M&E assessment of infectious disease control measure impact, where cMDA coverage and compliance is a key measure of the success of the control program. This is particularly important in low parasite prevalence settings such as that of the Geshiyaro project. Therefore, this biometric technology has provided a useful procedure to improve the accuracy of the epidemiological database and has enhanced the quality of epidemiological analyses able to be achieved. This includes the investigation of individually linked longitudinal compliance patterns to drug treatment, individual predisposition to infection taking into consideration individual treatment patterns, the impact of WaSH infrastructure on individual, household and community parasite prevalence of infection, and genetic analysis based on worm expulsion studies. As biometric technology develops over time, the accuracy challenges will likely decrease, and as the technology becomes more accessible and affordable, its implementation in other epidemiological contexts holds substantial promise for improving data collection accuracy in the M&E of public health programs.

Chapter 4: Patterns of individual compliance to anthelmintic treatment for soil transmitted helminths infections in southern Ethiopia over six rounds of community-wide mass drug administration

Dissemination

This chapter has been adapted from the paper titled, “Patterns of individual compliance to anthelmintic treatment for soil transmitted helminths infections in southern Ethiopia over six rounds of community-wide mass drug administration”, published in 2023 by Transactions of the Royal Society of Tropical Medicine and Hygiene [89].

Motivation

The Geshiyaro project presents an exciting opportunity to analyse the largest, individually linked dataset recorded to date for STH treatment and re-infection. Many research groups have modelled the impact of differing treatment behaviours upon the transmission of STH, with a view to assess how patterns of compliance influence the reaching of transmission elimination. This analysis demonstrates the impact of recorded compliance patterns over six rounds of MDA, upon the probability of elimination of transmission.

1. Introduction

MDA with albendazole is the predominant intervention employed to control STH [162]. These parasites do not induce strong acquired immunity and therefore repeated treatment is required of the most susceptible age groups to reduce morbidity and transmission [6]. The global adoption of MDA has been enabled by drug donations from pharmaceutical companies, the delivery of which is often financially supported by external governmental aid agencies and philanthropic organisations. As a result of this therapeutic intervention, the number of communities globally with high prevalence of helminth infections has decreased markedly over the past decades, as documented in the WHO 2030 roadmap progress report [10]. The impact of MDA efforts is further sustained by improved WaSH infrastructure, often linked to socioeconomic development or dependent on enhanced government support or philanthropic investment [163]. Consequent to this success, national programs are increasingly evolving away from morbidity control toward EPHP, and ultimately, interruption of transmission.

1.1. Challenges facing the measurement of mass drug administration

MDA is highly efficient in significantly reducing a large proportion of community infection. However, transitioning from low prevalence to reaching EPHP, and finally to elimination of transmission, requires increased programmatic coverage of MDA and WaSH interventions across all age groups in communities with endemic STH infection. High quality M&E of MDA programs is therefore essential to record program impact and the subsequent identification of target areas or demographic groups requiring enhanced support.

The accuracy of reported treatment coverage for many NTDs is currently challenged as well demonstrated in the ESPEN database, where MDA program coverage rates are often reported above 100%, highlighting the inaccuracy in the denominator and numerators used nationally [85]. As infection levels drop, the use of accurate denominators and numerators is critical. The treatment coverage (proportion of the eligible population who receive MDA) is a common evaluation metric used by control programs, with a target of at least 75% in SAC for STH control, as recommended by the WHO [6]. However, few control programs examine compliance (proportion of the eligible population who swallow the received drugs), preferably recorded by DOT [91]. Conflating this metric with coverage thus overestimates the

interpretation of MDA impact, and is commonly seen both in the literature and the WHO guidelines [91].

1.2. The importance of recording individual longitudinal compliance

Increasingly relevant to MDA program monitoring is *individual longitudinal compliance*, defined as individually linked compliance to repeated rounds of MDA. The importance that individual longitudinal compliance patterns has upon control efforts has been demonstrated previously in studies of transmission dynamics and control impact based on individual stochastic mathematical models [102]. Hardwick *et al.* (2021) created a framework of compliance (referred to as 'adherence'), proposing the parameter ω_n to measure the strength of association of previous individual compliance behaviour at MDA with that of a future round of MDA using stochastic individual-based simulations [68]. This used the notion of conditional probability, whereby the behaviour of an individual at one round of MDA is not independent of their behaviour at a previous round (systematic behaviour). Applying this framework to the age and sex-stratified compliance dataset collected by TUMIKIA across four biannual rounds of MDA, Hardwick *et al.* showed that despite high coverage figures, past behaviour-dependent compliance (or non-compliance) lowered the potential of hookworm elimination by 43% and 23% in the two surveyed communities, respectively, compared to predictions based upon random compliance (treatment behaviour independent of that previously). Past behaviour-dependent compliance was particularly apparent in males aged over 30 years old. This conditional probability model demonstrates the impact that not only compliance, but also demographic factors, have upon reaching the goal of transmission elimination.

In the past decade, just one field epidemiological study has reported longitudinal compliance for NTDs eligible for control by PC as demonstrated in **Chapter 2** [91,103]. The study examined household longitudinal compliance to four biannual rounds of MDA over two years for STH control in coastal Kenya [103]. Evidence of non-random compliance to treatment was observed in adults aged 20–25 years, presenting as the age group with the highest odds of receiving partial (OR 1.41, 95% CI 1.22–1.63) or no treatment (OR 1.81, 95% CI 1.53–2.14) [103]. Increased studies that investigate demographic correlates with treatment behaviour are required to confirm if these reported patterns are distinct or universal. Intuitively, it would be probable that treatment taking behaviour varies greatly due to cultural, social, and personal factors. Analysing these trends against prevalence and intensity data from the same

enumerated region will inform if these patterns are significant, and thus if future MDA distribution practises would benefit from targeting key demographic groups that consistently miss or refuse treatment.

Recording individual longitudinal compliance enables the identification of systematically non-treated populations, who are consistently missed and/or who persistently do not swallow medication, over multiple rounds of MDA. This population can serve as a continued source, or reservoir, of infection to other repeatedly treated individuals, thus people may be repeatedly reinfected even after drug treatment. The importance of persistently untreated, or never treated populations has been a focus of much discussion in recent research and policy formulation on the control of helminth parasites [164]. Never treated individuals, as well as those infrequently treated, are of importance to the overall impact of an MDA program. This is especially the case for STH and SCH, which have an estimated adult worm life expectancy in the human host of one to two years in high transmission settings where reinfection is frequent. In such high transmission settings where the R_0 is large, these situations, a high frequency of MDA rounds (sometimes biannual) is required to greatly reduce levels of STH infection.

2. Methods

2.1. Mass drug administration protocol

The Geshiyaro project measures the feasibility of interrupting STH and SCH transmission by cMDA and improvements in WaSH in SERS, Ethiopia [45,60,66,84,87,88]. Starting in 2018, the project will run for eight years, completing in 2025 (**Figure 1.7**). The project protocol, and methods of evaluation are described in **Chapter 1**.

To date, seven rounds of cMDA have been delivered across six years of treatment to the pilot woreda, Bolosso Sore. This woreda has received more cMDA rounds than other woredas due to the staggered nature of project implementation (**Figure 1.7**). The remaining woredas have received five rounds of cMDA to date. Delivery methods of cMDA were adapted during the project due to the COVID-19 pandemic, including the replacement of fixed-point distribution employed prior to the pandemic by house-to-house distribution, avoiding mass congregation of individuals within the community. Anthelmintics were distributed by the existing network

of HEW, a network of care workers stationed in each kebele across Ethiopia underpinning the national healthcare system [165]. A single dose of albendazole was offered to members of the community aged one year old and above, with syrup distributed to infants aged one to four years old. From Year 4 onwards, albendazole was offered biannually in Arm 1 and Arm 2 (**Figure 1.7**).

2.2. Individual level longitudinal monitoring of community-wide mass drug administration

A sub-sample of five woredas across Arm 1 and Arm 2 were censused at baseline in 2018 using methods described in **Chapter 3**, assigning each participant with a biometric record and / or an identification card associated with an 11-digit number (**Figure 3.1**). This identification number enabled the linkage of the individual to their household demographics and WaSH infrastructure data, captured in the census, as well as parasitological data collected in concurrent sentinel site surveys [88]. Any individuals who were unable to be identified at each round of cMDA were newly registered to the census, these included new-born babies, participants that had recently moved into the woreda, and participants previously missed from the population census, ensuring the census remained updated for each cMDA round.

2.3. Recording of treatment behaviour during community-wide mass drug administration

During cMDA, each participant was identified against the census using their biometric fingerprint or ID card (see **Figure 4.1**), which linked their 11-digit participant number to their treatment behaviour. Each participant was therefore categorised as either ‘missed’ or ‘contacted’ by a HEW, with the latter further categorised as ‘accepting’ or ‘refusing’ the offered drug, and subsequently ‘refusing’ or ‘swallowing’ the accepted drug (**Figure 2.1**).

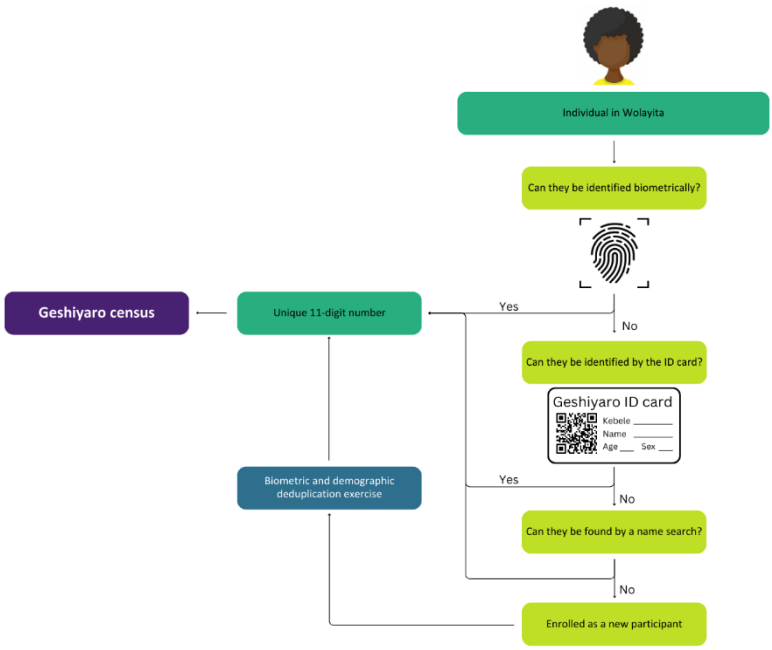


Figure 4.1: A flow diagram of the identification process of Geshiyaro participants. *Individuals are identified against a hierarchy of methods: biometric scanning, identification card, and name search. Individuals who are not identified by any of these methods are enrolled as a new participant, and added to the Geshiyaro census if satisfying deduplication criteria.*

This analysis focuses on the population in Bolosso Sore only, as the population in this woreda has received the most treatment rounds. From the total population of 210,862 individuals currently registered to Bolosso Sore by the project, the longitudinal population was defined as individuals present from baseline census to the point of analysis (present), eligible for treatment at each cMDA round. This totalled 54,659 individuals. This longitudinal population therefore was therefore unified in the number of rounds eligible for participation, removing the ambiguity created by individuals enrolled at different times, and therefore eligible for differing total number of rounds.

The eligible population for cMDA was calculated as the population aged one year old and above for albendazole, excluding all pregnant women. This eligible population is employed as the denominator for all cMDA coverage and compliance calculations. Demographic stratifications of this eligible population by age and sex were used for analysis, defining the following age groups: preSAC (aged 2-4 years), SAC (aged 5-14 years), adolescents (aged 15-20 years), young adults (aged 21-35 years) and adults (aged 36-100 years). Analysis showing age-group categories are based upon the age-group classification assigned during enrolment in Year 1 (baseline).

2.4. Data analysis

The positive binomial and beta binomial probability distributions were fitted to the observed frequency of cMDA rounds at which albendazole was swallowed. The positive binomial distribution was used as a reference point since it describes a random pattern of compliance where the probability that an individual takes treatment at any one round of cMDA is independent of their behaviour at a previous round. The compliance data was also analysed against the beta binomial distribution whereby individuals have an assigned independent probability of attendance for all rounds, drawn from a beta distribution. The coefficient of variation (a ratio of the standard deviation divided by the mean number of cMDA rounds treatment was swallowed) was calculated to provide a measure of dispersion for the frequency of treatment distribution. Low values of the coefficient of variation records a low dispersion of variation around the mean.

The Pearsons correlation coefficient was calculated to measure the degree of randomness of individual treatment behaviour on a scale from zero (entirely random) through to one (systematic behaviour, either always treated, or never treated). Multiple logistic regression was used to determine the impact of age group and sex on the never- and always treated population, the output of which was interpreted by the odds ratio (OR), calculated from the exponentiated coefficients.

The probability of transmission interruption in Bolosso Sore was forecast employing a previously detailed individual-based stochastic model of *A. lumbricoides* transmission and cMDA impact [52]. *A. lumbricoides* was chosen as this was the most prevalent STH species recorded in the Geshiyaro study. Three different treatment compliance patterns were examined with respect to the likelihood of transmission interruption: 1) the observed compliance (beta binomial), 2) random compliance (positive binomial), and 3) completely systematic non-compliance behaviour. A fraction f of population in these simulations were never treated in each scenario (non-attendance correlation: 0.21). Within a population of 2,000 people treated with albdenazole for *A. lumbricoides* infection, 1,000 simulations were undertaken. Historical cMDA compliance of the Bolosso Sore longitudinal population were used for the implemented six rounds (1: 70.0%, 2: 65.8%, 3: 77.8 %, 4: 85.1%, 5: 70.3%, 6: 67.9%), projected forward at 72.8% (average overall compliance for the six rounds) for the remaining five biannual rounds, applied uniformly across all age groups. Key epidemiological

parameters were derived from the literature and baseline data such as the baseline prevalence of *A. lumbricoides* (18%) [52]. The basic reproductive number was varied between R_0 = 1.7 – 2.9, the adult worm expectancy at one year, the density dependent parameter of worm fecundity fixed at γ = 0.08, and the negative binomial aggregation parameter for adult worms was varied between k = 0.06 – 0.18 [52]. In the simulations for systematic non-compliance, a beta distribution was employed with parameters b1 = 0.13 and b2 = 0.05. Wilson (or "plus-4") confidence intervals were calculated using the binconf() function from the Hmisc package in R [166]. This binomial probability interval differs from the normal as it is asymmetric and is not affected by overshoot or zero-value intervals.

3. Results

In Bolosso Sore, a total of 54,659 individuals were eligible for treatment at each of the six rounds between 2018 and 2023, forming the longitudinal population for analysis. The majority of this longitudinal population were able to be biometrically identified (88.7%).

An average of 21,013 (range: 23,159 – 26,844) participants were treated at each round. Albendazole was swallowed by 24,172 (Year 1), 23,159 (Year 2), 25,415 (Year 3), 26,844 (Year 4a), 24,030 (Year 4b), and 23,472 (Year 5a) participants from this longitudinal population. Coverage (proportion of eligible population receiving treatment) recorded across the six cMDA rounds reached 70.1% (95% CI: 70.5-69.7%), 66.1% (95% CI: 66.5-65.7%), 77.8% (95% CI: 78.1-77.5%), 85.1% (95% CI: 85.4-84.8%), 70.3% (95% CI: 70.7-69.9%), 67.9% (95% CI: 68.3-67.5%) from Year 1 to Year 5a. Compliance (proportion of the eligible population swallowing the received drug) varied negligibly to the recorded coverage, and similarly reached 70.0% (95% CI: 69.6-70.4%), 65.8% (95% CI: 65.4-66.2%), 77.8% (95% CI: 77.5-78.1%), 85.1% (95% CI: 84.8-85.4%), 70.3% (95% CI: 69.9-70.7%) and 67.9% (95% CI: 67.5-68.3%), as recorded by the HEW.

3.1. Frequency distributions of swallowing community-wide mass drug administration over six rounds

The frequency of rounds in which individuals swallowed treatment over the course of six rounds of cMDA increased from once (4.09%, n = 2,234), twice (7.23%, n = 3,952), thrice (12.6%, n = 6,865), four times (22.1%, n = 12,066) five times (29.4%, n = 16,088), and six times

(24.2%, n = 13,227). Only 0.42% of the study eligible population (n = 227) never attended at any of the six rounds of cMDA. Broken down for each age group, preSAC (OR: 10.1 (95% CI: 6.63 – 15.4), ref: SAC) had the highest never treated proportion of the age groups (**Table 4.1**). Conversely, adults (OR: 1.03 (95% CI: 0.98 – 1.09), ref: SAC) had the highest always treated proportion of the age groups.

The mean and variance of the treatment frequency distribution across six possible rounds, are recorded in **Table 4.1,** stratified by age and sex. Coefficient of variation (CV) values indicates a low level of dispersion around the mean, confirmed as the variance is markedly lower than the mean value. In a random distribution, the mean equals the variance. As such, the data suggests participant behaviour is not random, but more tightly constrained to a distribution with individuals highly likely to repeatedly take treatment. No change in this pattern is detectable across stratifications by age group, sex, and study population.

Age group	Sex	Population (n)	Mean	Variance	CV	PCC	Never OR (95% CI)	Always OR (95% CI)
PreSAC	female	3528	3.28	1.76	0.40	0.09	2.17 (1.91 - 2.45)	0.42 (0.39 - 0.44)
	male	3751	3.22	1.80	0.42			
SAC	female	21704	3.84	1.38	0.31	0.10	ref	ref
	male	24121	3.83	1.48	0.32			
Adolescents	female	7425	3.55	1.90	0.39	0.15	2.35 (2.14 - 2.58)	0.78 (0.75 - 0.81)
	male	8244	3.50	2.11	0.41			
Young adults	female	18158	3.71	1.79	0.36	0.17	2.59 (2.40 - 2.81)	0.89 (0.86 - 0.91)
	male	13359	3.45	2.34	0.44			
Adults	female	16747	3.99	1.29	0.28	0.13	1.35 (1.24 - 1.48)	1.34 (1.30 - 1.38)
	male	15524	3.94	1.67	0.33			

Table 4.1: Mean and variance of treatment rounds stratified by age group and sex. *Coefficient of variation is calculated for each population stratification. Pearson's correlation coefficient shown for each age bucket. Odds ratios (OR) calculated from binary logistic regression determining the impact of age grouping on the population that is either always or never treated is shown, using SAC as the reference age group. Labels: preSAC (aged 1-4 years), SAC (aged 5-14 years), adolescents (aged 15-20 year), young adults (aged 21-35 years) and adults (aged 36-100). Abbreviations: CI – confidence interval, CV – coefficient of variation, OR – odds ratio, PCC – Pearson's correlation coefficient, SAC – school-aged children.*

The beta binomial distribution (**Figure 4.2A**) described the data well for six cMDA rounds in Bolosso Sore (n = 54,659), independent of age group and sex. This fitted the observed frequency of swallowing better than the positive binomial distribution which reported a much lower log likelihood, thus demonstrating a closer goodness of fit of the beta binomial. The departure from a random distribution pattern (**Figure 4.2B**) occurs due to excesses in the frequencies of those who were always treated across six cMDA rounds (shifting the random pattern to a more uniform one with low variance). The distribution of swallowing frequency changed between age groups as shown in **Figure 4.2C**. Higher proportions of preSAC and adolescent age groups swallowed zero to four rounds of treatment. This inverts as treatment frequency increases, whereby a higher proportion of SAC, young adults and adults swallowed five and six (all) rounds of treatment. This is consistent with the Pearson's correlation coefficient in Table 1, showing the highest probability for adults (0.54), SAC (0.49) and young adults (0.42).

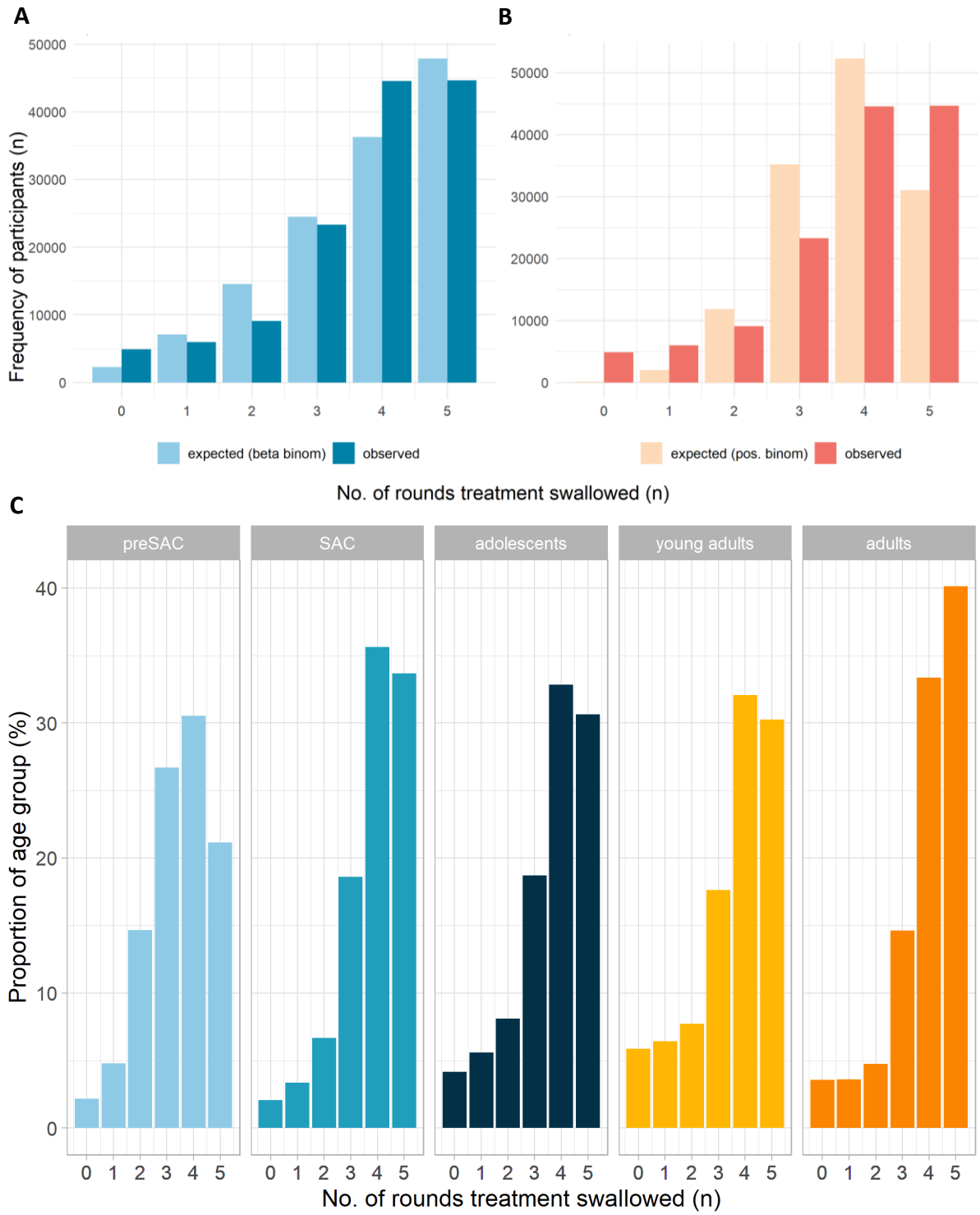


Figure 4.2: The frequency of treatments swallowed for the longitudinal population. *The treatment frequency recorded in the longitudinal population of Bolosso Sore (n = 54,659) to five rounds of cMDA. Comparison of probability distributions fitted to the observed treatment frequency data from the two populations in the Geshiyaro project. Fits of the beta binomial* ***(A)****, compared to the expected fit of the positive binomial (random)* ***(B)****, demonstrates that the beta binomial distribution records the best fit to the observed compliance data. Parameters:*

A) *mu = 0.254, sigma = 0.233, binomial denominators (bd) = 5,* ***B)*** *probability: 0.749, bd: 5.* ***C)*** *The number of treatment rounds in which drugs were swallowed, stratified by age group. Frequency shown as the proportion of each age group for comparative analysis due to the uneven distribution of age groups in the longitudinal population. Labels: preSAC (aged 1-4 years), SAC (aged 5-14 years), adolescents (aged 15-20 years), young adults (aged 21-35 years) and adults (aged 36-100).*

3.2. Probability of elimination

Using an individual based stochastic model of *A. lumbricoides* transmission and cMDA impact, the average probability of transmission interruption from 1,000 simulated trajectories is shown in **Figure 4.3**. Over 11 cMDA rounds (the total number of rounds to be delivered in Bolosso Sore by completion of the Geshiyaro project), three cMDA treatment behaviour patterns for the treated population are examined: the beta binomial distribution (that observed in the Geshiyaro population), a positive binomial distribution (random), and a population behaving entirely systematically. Assuming cMDA compliance remains at an average 72.8% (the average compliance across all six rounds to date), the model predicts by 2028 the probability of transmission elimination is approximately 65.0% (95% CI: 62.0 - 67.9%) for a population following a positive binomial (random) distribution of treatment frequency, 50.4% (95% CI: 47.3 - 53.5%) for a population following a beta binomial distribution of treatment frequency (as seen in the Geshiyaro data), and 13.1% (11.1% - 15.3%) for a population following a fully systematic fraction of non-treatment behaviour. The significant impact that compliance behaviour has upon the probability of elimination is clear in these simulations. The importance of compliance is poorly understood by policy makers where the focus has been on the never treated. These are obviously important, but so are the individuals who take few rounds out of those offered since they too can act as reservoirs of infection.

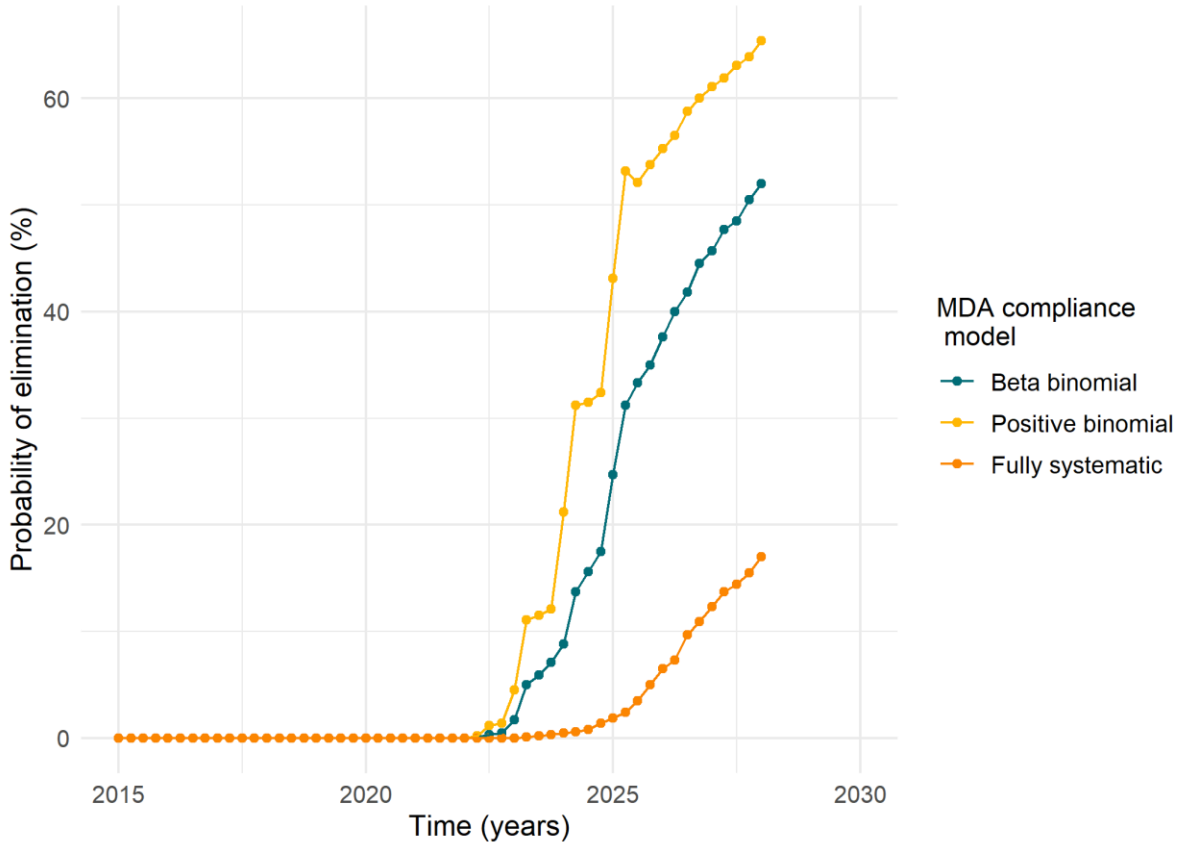


Figure 4.3: The probability of transmission interruption forecast by an individual, based stochastic model of A. lumbricoides transmission. *The impact of compliance behaviour projected forward by the beta binomial (dark green), compared to that by the positive binomial (yellow) and a simulated systematically behaving population (orange) is shown upon the probability of interrupting parasite transmission. A random treatment pattern (positive binomial) is preferable, as in this situation, individuals will be treated at least once. The beta binomial distribution is not as favourable, despite a high number of people swallowing drugs at all or most rounds of MDA. The never treated correlation was 0.21 for each simulation. The model used the average compliance value across the five past cMDA rounds (78.3%) to project behaviour after a further six future rounds of cMDA.*

4. Discussion

This analyses of compliance is based on the largest dataset of individual longitudinal compliance to cMDA for STH control as yet published, in a population of over 54,000 individuals [91]. Compliance is rarely reported accurately, if at all, for the NTDs eligible for MDA treatment [91,96]. Consequently, the detailed impact of compliance behaviours on helminth parasite control and possible transmission interruption is rarely assessed. This is

despite mathematical studies clearly showing the importance of compliance in predicting the future probability of transmission interruption [100,167]. Many of the NTDs are endemic in countries with a low GDP, therefore limiting the reality of implementing such high-cost longitudinal cohort studies as part of national programming. Considerable programmatic coordination and financial resources are required to first census the population, manage the data, and analyse longitudinally linked individual MDA behaviour recorded by DOT. Traditional paper-based methods currently employed by many national programs and research studies will struggle to complete this with minimal data entry errors. Accurate data acquisition requires a sophisticated infrastructure involving electronic data collection devices (mobile phones, tablets) and access to data collection software.

4.1. Demographic trends and systematic compliance

The highest proportion of the never treated cohort was identified in the preSAC age group (infants aged two to four years old). This age group also reported the lowest probability of swallowing treatment, likely influenced by difficulties of treating infants with tablets. This is concerning as this age group especially is most at risk of morbidity from high *A. lumbricoides* and *T. trichiura* burdens [168]. The lack of treatment in this vulnerable age group may consequently lead to the creation of a reservoir of infection in this age-group, which can continue the excretion of infectious life stages into the environment for onwards and continued transmission. In turn, this will predominantly affect mothers and caregivers such as older siblings who spend prolonged time and contact with the infant age-group. If these mothers are also pregnant (specifically in their third trimester), they will be ineligible for treatment and thus their increased exposure to infective material will remain untreated [6].

The proportion of participants who were always treated was highest for adults, SAC, and young adults age groups. An increase in compliance with age has been similarly reported by repeated cross-sectional cohort compliance studies [91]. The exception to this trend was the SAC age group, which recorded a very high probability of swallowing treatment. This may reflect the familiarity this age-group has with national deworming programs, which routinely implements sMDA. The high probability of swallowing in this age group demonstrates the importance of sensitisation of implementation activities on compliance rates.

Differing compliance rates in distinct age groups will add to the already heterogeneous distribution of infection of each STH species based upon age-dependent risk factors. For instance, preSAC were least likely to be always treated, likely affecting the reservoir of *A. lumbricoides* and *T. trichiura* infection in the community. Subsequent analysis of parasite prevalence with regards to stratified compliance behaviour is required to assess the significance of this phenomenon, at both the individual and village level.

4.2. The consequence of defined behavioural patterns of compliance

Random (positive binomial) patterns of compliance were not observed in the data. Rather, a higher fraction of always treated individuals than predicted was observed, following a beta binomial distribution of treatment frequency, whereby individuals are assigned an independent probability of swallowing at all rounds, drawn from a beta distribution. The non-random frequency of the 'always treated' population will require further research to understand the reasons influencing this behaviour. It may be a consequence of the population being part of a large study conducted over many years, where repeated participant contact from HEW and BCC strategies implemented by the Geshiyaro project may have sensitised the communities to the benefits of participation, therefore improving compliance.

4.3. Limitations

This analysis requires careful examination as to its relatability across other NTD endemic settings. Primarily, the proportion of the population who were never treated was demonstrably lower than other figures published in the limited literature available. There may be several reasons for this. Firstly, the Geshiyaro project has conducted extensive community sensitisation to encourage biometric uptake and community-wide treatment, delivered by a specialist external NGO which may have positively impacted an individual's willingness to take treatment. This sensitisation is likely more extensive than that conducted for routine sMDA as part of the national control program, which reached coverage levels ~ 50% in Arm 3. The whole community in Wolayita are offered treatment, an enhancement upon the currently implemented sMDA national standard protocol. This access to anthelmintic is not routine for adults and non-risk groups and therefore this may also trigger an increased uptake in these groups.

Secondly, this analysis is based upon the individuals that were censused at the start of the project. It can be postulated, that the population who were reached and willing to participate in the census, are similarly likely to be available for cMDA treatment. The population who were enrolled in the subsequent years, may also be absent from future rounds of cMDA, and therefore if this demographic was included in the current analysis, it may show a slightly different pattern.

5. Conclusion

Despite the most recent parasitological survey recording a very low STH prevalence in Bolosso Sore, and a compliance rate just under the WHO target of 75%, the probability of elimination remained moderate as shown in **Figure 4.3**. If the figures of never treatment are to be accepted as accurate (see Limitations), this highlights that attention is required to the whole frequency distribution of drug swallowing behaviour in the targeted population as despite representing a negligible part of the treatment frequency distribution, elimination was not projected. This clearly demonstrates the importance of fine-scale M&E of cMDA in low prevalence settings and makes a clear case for including compliance measurements in addition to coverage in cMDA evaluation. Individual longitudinal compliance behaviour has been shown to have a significant impact upon reaching transmission break, highlighting the utility of individually linked compliance in understanding community patterns to treatment. Elucidating if population behaviour is systematic or random in nature will be crucial for the evaluation of programs in low prevalence areas which require high coverage and compliance rates to reach EPHP. Furthermore, such detailed datasets allow for patterns to be delineated for defined demographic groups, enabling future targeted sensitisation prior to cMDA to improve compliance. Building upon this fine-scale monitoring of cMDA with GPS-defined infection and compliance data will, in future research studies and government run MDA evaluation programs, allow for the impact of spatial dynamics of STH transmission and control to be explored in more detail. Critically, the next key question in cMDA M&E is what spatial scale should compliance evaluation take place to assess the WHO target of EPHP, and the subsequent goal of transmission elimination?

Chapter 5: Measuring heterogeneities in soil-transmitted helminth transmission and control

Dissemination

This chapter has been adapted from the paper titled, “Measuring heterogeneities in soil-transmitted helminth transmission and control”, published in 2024 by Trends in Parasitology [44].

Motivation

The WHO recently requested enhanced MDA impact evaluation methods, and the scale-up of surveys to monitor progress toward, and consolidate guidance for, the validation of EPHP. As such, using publicly available data from ESPEN, this chapter evaluates the current WHO guidelines against the reported STH prevalence across sub-Saharan Africa. Keen interest is kept on the spatial scale used for the evaluation of EPHP, the definition of which is currently absent from guidelines.

1. Introduction

The WHO has defined EPHP as <2% of MHII STH infections diagnosed by Kato Katz [10]. A recent analysis showed 72% of IUs in sub-Saharan Africa achieved EPHP between 2000-2018, using a Bayesian space-time hierarchical model for the analysis of STH infection in children aged 5-14 years [163]. This public health success is the result of sustained MDA efforts (including the beneficial PC overlap of LF MDA programs), in combination with improved WaSH infrastructure, often linked to socioeconomic development [163]. To ensure equitable access to these public health gains, concomitant to sustained improvements in WaSH, continued investment and improved M&E of MDA programs to accurately assess impact and enhance delivery efficiency is required in endemic regions [8].

1.1. Known heterogeneities of the epidemiology of soil-transmitted helminth infection

In the recently published roadmap report on NTD control progress [10], the WHO calls for the development of thorough MDA impact evaluation methods, and the scale-up of surveys to monitor progress toward, and consolidate guidance for, the validation of EPHP. The precise framework of how this target is measured is currently undefined. Understanding the many heterogeneities observed in STH transmission dynamics will help to enable this framework to be appropriately designed across different settings, taking into consideration spatial scale, population demographics, and infection intensity. Some of these heterogeneities have been well documented, such as the non-linear relationship between intensity and prevalence of STH infection (see **Chapter 1, section 3.1**), the pre-disposition to heavy or light intensity infections by individuals, the distinct age-dependent distribution of infection, the difference in drug efficacies for the different STH species, and the impact of systematic treatment and non-treatment of individuals, or compliance patterns, over multiple MDA rounds (**Chapter 4**) [60,63,100,103,168].

Individuals infected with heavy intensity STH burdens are predisposed to this state for reasons that are poorly understood at present [60]. Post treatment these individuals are more likely, than would be expected by chance alone, to reacquire heavier infections than average in the population [60]. The reasons may be a combination of host genetics, human behaviour, cultural setting, and environmental factors linked to the spatial locations of dwellings or

schools. Most studies of this individual level of heterogeneity in worm loads derive from data in villages with endemic infection and this, combined with predisposition to heavy of light infection, creates the first tier of heterogeneity between households and families within a village.

1.2. Spatial heterogeneity of soil-transmitted helminth infection

The next tier of heterogeneity in STH transmission is that between villages or communities. Again, the reasons for this are poorly understood. Neighbouring communities with similar socioeconomic and geographic settings can report differing levels of prevalence in both treatment naïve and treated scenarios. Differences in MDA coverage and compliance levels play a key role, but are not the only source of this heterogeneity. Again behavioural, cultural, spatial, and associated environmental variables will be important determinants.

As MDA efforts intensify, the distribution of the remaining infection increases in aggregation and heterogeneity, both in relation to spatial location and demographic factors such as age and sex [49,57,169]. These remaining pockets of infection may fail to be identified in routine M&E surveys due to the aggregated nature of the STH, making it difficult to detect reservoirs of parasites at either a village or household level [49,56]. Thus, the high proportion of uninfected individuals demands large sample sizes to detect where the remaining pockets of infection lie. As such, the spatial scale chosen to confirm EPHP in such heterogeneous populations has a large impact on the accuracy of the M&E associated with measuring control impact.

Of crucial importance to the interpretation of control program impact in the face of these tiers of heterogeneity, and the focus of this review, is the question of what spatial unit and population stratification should be employed to determine if the prevalence of MHII is below the EPHP target. What spatial scale balances the sufficient granularity with budgetary realities, and should the populations measured be expanded from SAC to a representative sample of the whole community?

2. Methods

Analysis of the publicly available parasitological mapping data reported from national Ministries of Health to ESPEN can help to provide a suggested guideline for the currently

undefined spatial scale and demographic groups in which EPHP is evaluated. Unfortunately, although this database contains a large and valuable source of comparable information, mapping data is only available for SAC, and only records prevalence, not intensity. As such, it does not consider the higher burden of hookworm infection in adults, and infection levels will appear inflated for *A. lumbricoides* and *T. trichiura* due to their elevated burden in children [170].

ESPEN data is available at two spatial units, either the IU, or at a specific site defined by GPS coordinates. At the time of publication, five countries (Algeria, Comoros, Equatorial Guinea, and Namibia) do not report site data. At IU level, prevalence data is categorised in wide bandings and generalised for all STH. MDA coverage is reported as a continuous variable. Site level prevalence is reported as a continuous variable for each of the three STH species separately, alongside a categorised intensity status (high, moderate, low). No MDA coverage data is provided. Reporting prevalence alongside an intensity metric in the IU datasets would vastly improve the level and quality of analysis possible. At the time of publication, the length of longitudinal monitoring varies between IU (2013-2022) and site-level (1974-2018) data as shown in **Figure 5.1**. This data is only available for the African continent. For enhanced and comparable global monitoring, it would be beneficial to similarly access data across the Asian and South American continents where STH is endemic.

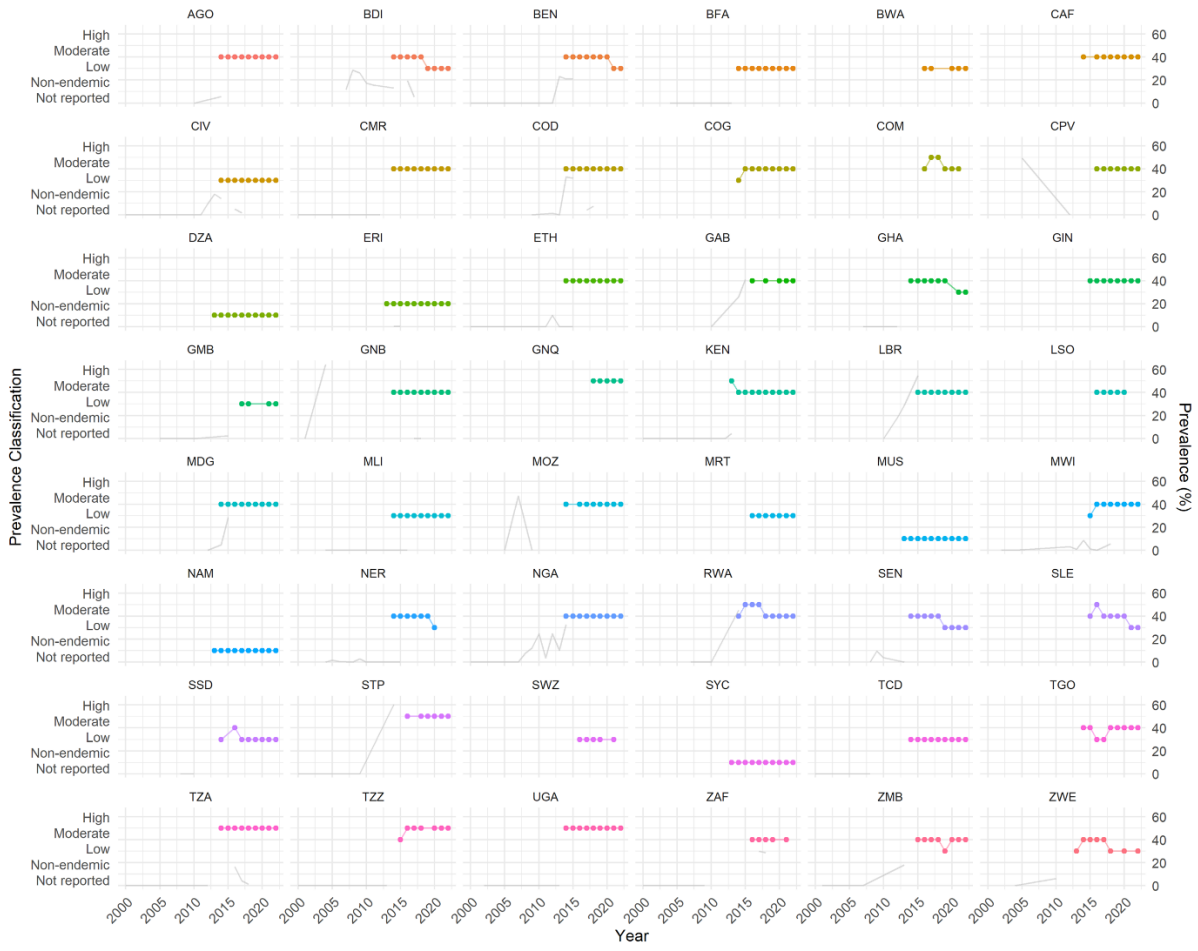


Figure 5.1: The prevalence classification and point prevalence of STH for the 48 countries reported by the Expanded Special Project for the Elimination of Neglected Tropical Diseases (ESPEN). *The prevalence for the 48 countries reported on by EPSEN from 2000 to 2020. The two measures of prevalence are shown recorded at the implementation unit level, classified into wide bandings (left-hand y-axis), and at a precise GPS defined site using point prevalence (right-hand y-axis). Data taken from the publicly available ESPEN database, accessed November 2023* [85].

For health delivery or monitoring, countries are divided into administrative levels, which follow internal borders around sequentially smaller units. The four administrative levels employed by WHO and ESPEN define the following boundaries: admin level 0 = country; admin level 1 = state or region; admin level 2 = district or zone; admin level 3 = town or municipality. The admin level employed to define a country's IU varies between countries, however, most countries use admin level 2. The size of the IUs varies significantly between counties, ranging from less than 1km^2 to over 100,000km^2, as demonstrated in **Figure 5.2**. This shows an inverse

relationship between population density and IU area, where increasing population density is reflected by decreasing IU size. Despite this attempt to make IU population density comparable, a variation in population density exists between one and 10,000 people/km2.

3. Results

3.1. Prevalence measurement for soil-transmitted helminth control program stage definition

The sensitivity of STH diagnostics employed in routine program surveys (Kato Katz) has a large operational impact on control programs, as the frequency, success, and subsequent scale-down of MDA delivery is reliant upon the resultant parasitological measurements [76]. The measurement of the prevalence-dependent transition between control program phases has been recently outlined in a framework of diagnostic “use-cases” appropriate for decreasing infection (TPPs) [72,76,171]. As STH prevalence and intensity decreases, the TPP stipulates diagnostics with increased sensitivity [73,74,76]. Ideally, in parallel with the clear guidance suggested for diagnostics at differing prevalence levels, clear prevalence-specific specifications should be made for appropriate spatial scales and demographic variables, such as age and sex, for STH M&E. Lessons can also be learnt from other NTD control programs. For example, LF validation of recrudescence uses a repeated monitoring survey process for validating MDA cessation called the treatment assessment survey (TAS) [172].

3.2. The impact of population density and movement upon soil-transmitted helminth transmission

The population density within the IU is an important consideration when assessing the epidemiology and control of infectious diseases. The large variation in population density across the African continent is displayed in **Figure 5.2**, where the population density (people/km^2) is shown alongside size of the IU used to enumerate the region. In general, as population density increases, the IU size decreases. Furthermore, the geographical size of the IU will determine what radius of infectious material transmission (eggs or larvae) is being recorded. Thus, reducing the spatial unit of EPHP evaluation will improve the accuracy of M&E.

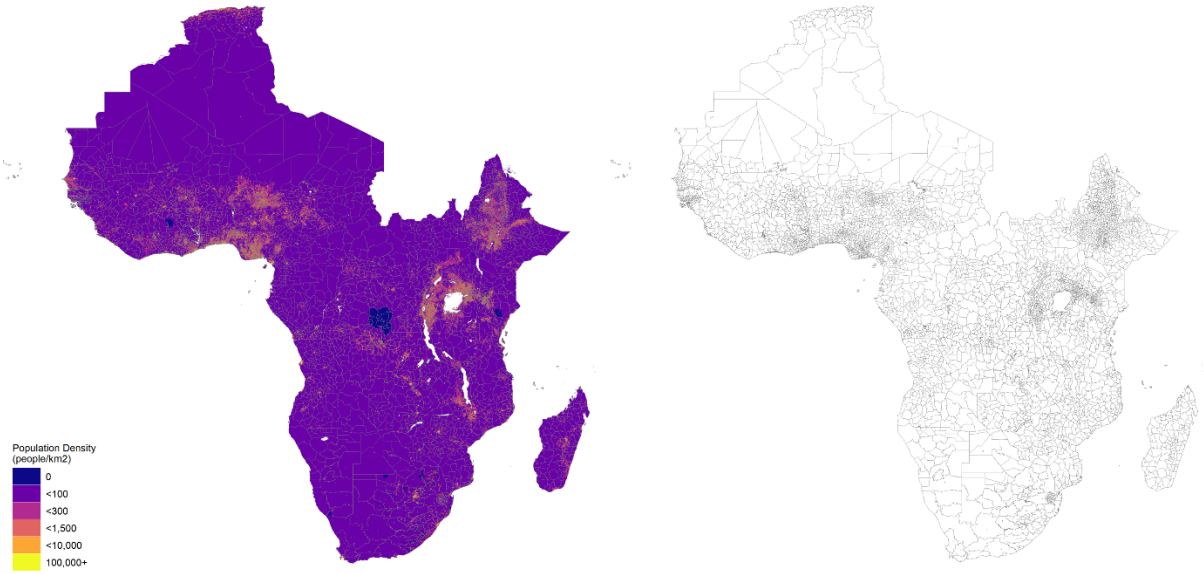


Figure 5.2. The impact of population density on implementation unit (IU) sizing. A) *The population density per km^2 in the 48 countries considered in the WHO AFRO region, showing the IU boundaries for each country. Population density pixel resolution is at 1km^2. Density is stratified into six categories, based upon population density cut-offs as defined by World Bank, whereby a rural population is < 299 people/km^2, a peri-urban population is < 1499 people/km^2, and an urban population is > 1500 people/km^2. Data taken from the WorldPop database [i]. **B)** The IU shape for reporting STH prevalence and MDA coverage used for the 48 countries considered in the WHO AFRO region according to ESPEN.*

To consider a spatial unit as a static entity fails to take into consideration the movement of populations especially from high to low prevalence regions [51]. This population mobility is common within or between countries due to economic migration, conflict, or climate related factors [51]. The spatial movement of people within and between IUs, and thus the potential exposure to reservoirs of infection or moving between low and higher prevalence areas, drives transmission and parasite persistence at larger spatial scales [173]. Recently, a fully stochastic individual-based STH mathematical model incorporating human movement patterns has clearly demonstrated the importance of movement on parasite persistence across IUs on the likelihood of achieving transmission elimination [51]. Critically, the model demonstrated the importance of considering population movement, as this significantly impacted the prediction of reaching elimination or not.

3.3. Defining appropriate spatial scales for soil-transmitted helminth control program evaluation

Hotspots of STH transmission can be identified at both individual, household and village levels. Current understanding of a sensible spatial scale over which STH transmission occurs is very poor at present. It is likely to be influenced by many factors including parasite species, local culture, WaSH infrastructure, transport access, and school distribution [51]. Molecular epidemiological studies based on parasite genome sequencing are ideally required to create an understanding of how much transmission occurs within a family, within a village and between adjacent villages. To date, these have not been conducted. For some STH species such as *A. lumbricoides* and *T. trichuria* where infection is most prevalent in younger age groups, much transmission occurs in SAC within school settings, where transmission at a single school may influence many villages.

Understanding the spatio-epidemiological factors in STH transmission that generate hotspots of infection will be crucial for any move towards targeting treatment strategies and transmission elimination. Hotspot identification is unlikely using national STH infection surveys, as these are infrequent, and aggregate the heterogeneity of infection over large spatial scales, use statistically small sample sizes, and therefore are unrepresentative (in terms of age), of the population [169]. The limited quality of M&E surveys as a component of national NTD control programs is in part a consequence of the cost implications of conducting large sample size studies at a fine spatial scale.

3.4. Selecting an appropriate spatial scale for recording soil-transmitted helminth endemicity

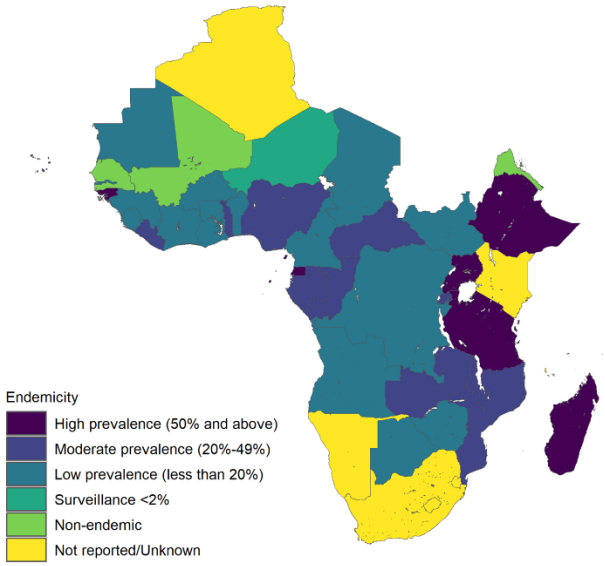
STH control activities typically piggyback onto those for SCH. Since 2022, there has been a push by the WHO to shift from district to sub-district SCH implementation and evaluation due to its focal nature. Many countries now make treatment decisions and conduct M&E at the district level for STH and sub-district for SCH. Although it is more homogeneous in nature, it is unclear whether STH should also implement at more granular level. A recent study in Cameroon highlighted the requirement of fine-scale mapping for the identification of both high endemicity sub-districts and high-risk transmission sites to implement targeted control [174]. Sub-district clustering of heavily infected children was identified, despite employing

only single Kato-Katz slides (the sensitivity of which is insufficient at low prevalence), and restricting the survey to SAC [73,175]. The ramifications of this sub-district heterogeneity of infection can result in mistreatment and misclassification of prevalence categories, as hotspots of infection can be masked when averaged at the district level.

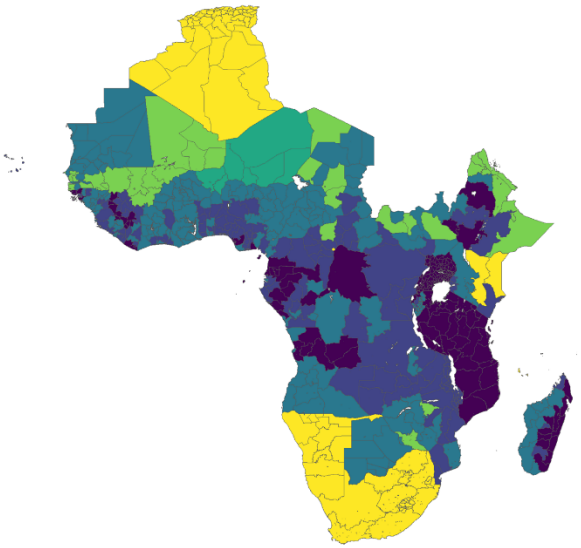
The impact of choosing too large a spatial scale for M&E for policy formulation has been previously demonstrated in MDA coverage data from Ethiopia [16]. The study employed two spatial scales (sub-district and district) [84] and clearly demonstrated that too large a scale (district, or admin level 3) would lead to premature cessation of MDA implementation in the low MDA coverage villages defined at a finer spatial scale. Mathematical models that include spatial description of STH transmission fitted to observed data show clearly that such reservoirs of infection in these fine spatial scale locations could enable infection recrudescence or 'bounce-back' where local transmission has been eliminated [51].

Using data from ESPEN, STH prevalence data in SAC is shown at the IU level specific for each country, and at increasing admin unit size in **Figure 5.3A**. The figure clearly shows smoothing of the heterogeneity when using larger admin levels for defining STH prevalence. Site level data taken from low prevalence (< 20% STH prevalence) IUs reported in the same year (**Figure 5.3B**), demonstrates a high level of heterogeneity in prevalence for 11 AFRO countries. Interestingly, despite the IU achieving the classification of low prevalence, data for Angola, Chad, the Democratic Republic of Congo, Ivory Coast, Liberia, Madagascar, Nigeria, Rwanda, South Sudan, and Togo shows SAC STH prevalence over 20%. This clearly demonstrates the requirement for wider use of such fine-scale mapping to be considered, especially at low STH prevalence levels, to increase the accuracy of IU prevalence classification. A large variation in prevalence is seen in all three species within low prevalence IUs, further demonstrating the heterogeneity between STH species.

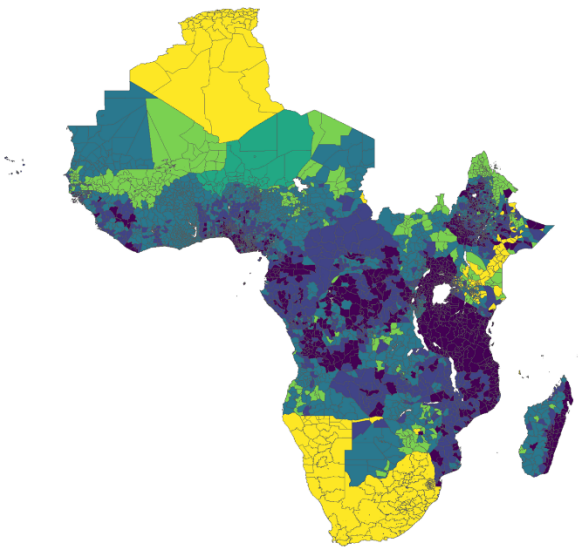
2022 STH Endemicity - Country level



2022 STH Endemicity - Admin 1 level



2022 STH Endemicity - IU level



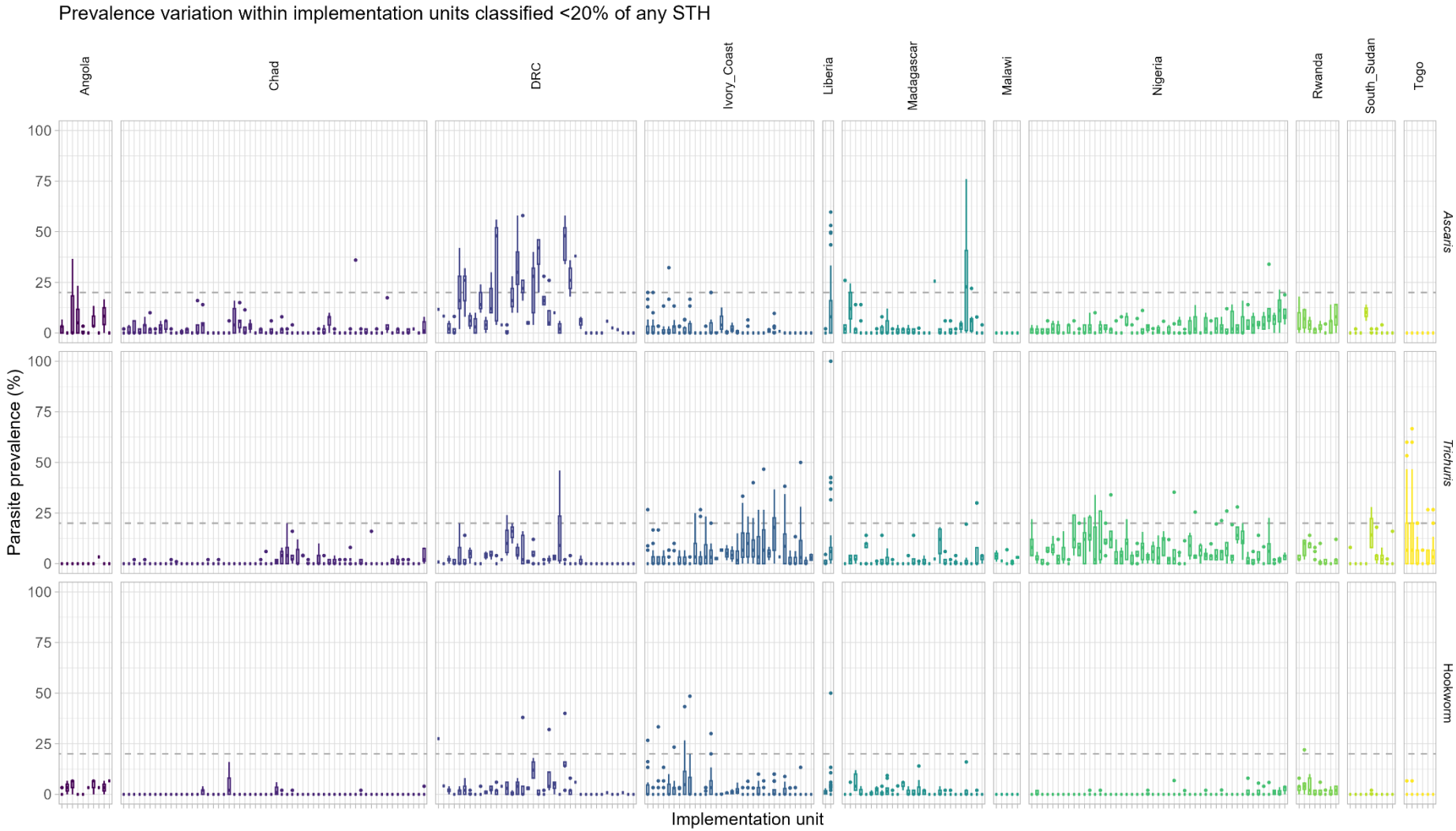


Figure 5.3: Heterogeneity in STH endemicity at national, regional, and health implementation units (IUs) in Africa. A) *Soil-transmitted helminths (STH) prevalence at the IU level demonstrate the smoothing of prevalence when using larger spatial scales, leading to under- or over-treatment.*

The administration level employed for the IU differs between countries from admin level 1, down to admin level 3. Data taken from the publicly available database Expanded Special Project for Elimination of NTDs (ESPEN), accessed Nov 2022. ***B)*** *Variation in prevalence of A. lumbricoides, T. trichiura and hookworm within IUs defined as <20% STH prevalence. Each bar represents an IU for each country, the prevalence recorded within that IU at the site level is measured against the y-axis. A prevalence of 20% is shown by a grey dashed line indicating the IUs overall endemicity label. Data taken from the publicly available ESPEN database, accessed November 2022.*

3.5. The importance of the epidemiological statistic chosen for the validation of 'elimination as a public health problem'

The current WHO guidelines defines EPHP of STH based upon the proportion of MHII [10]. The WHO treatment algorithm is, however, based on prevalence categories yet prevalence is not equal to intensity of infection, and low levels of MHII may exist in high prevalence regions which still re-seed infection in the community. Mirroring the call from the SCH research community, we encourage the replacement of reporting prevalence of MHII with average prevalence in the population in a district or sub-district, in addition to the mean intensity of infection [176]. Considering the non-linear relationship between prevalence and intensity, whereby large changes in intensity can take place when prevalence changes little, reporting intensity measures alongside prevalence will greatly improve the precision of STH monitoring in areas with low prevalence of infection.

Fine-scale parasite prevalence data is available at the site level within IUs (see **Figure 5.1 and 5.3B**), for a small proportion of the ESPEN database. According to the ESPEN site data (n = 19,817), 22.7% (max: 81.3%) of the admin level 2 (district) sites reporting <2% of MHII *A. lumbricoides* infections (i.e. has reached EPHP), also recorded an overall prevalence of infection >20% (i.e. still required annual treatment, **Figure 1.1**). This pattern was less apparent for hookworm and to much a lesser extent for *T. trichiura*, occurring in 11.9% (max: 70.9%) and 6.02% (max: 54.2%) of admin level 2 sites reporting <2% MHII. Cessation of MDA based solely upon MHII is therefore likely to result in bounce-back of STH infection, particularly *A. lumbricoides* and hookworm, due to the continual reseeding of infection by the pockets of low intensity infections.

Figure 5.4 shows the prevalence and categorisation of EPHP within admin level 2, admin level 1, and country level in differing combinations to highlight the importance of appropriate spatial scales for EPHP validation. This clearly shows the large variation in the prevalence of STH infection for different admin levels classified as either achieving EPHP or not. This variation in prevalence at different admin levels demonstrates the spatial scale for EPHP validation should be carefully defined by WHO.

In addition to the importance of spatial scale, it also shows the likelihood of achieving EPHP varies by STH species. There was a statistically significant difference ($p < 0.001$) in *A.*

lumbricoides achieving EPHP or not, when prevalence and EPHP were averaged at a country-level, and down to admin level 2. This demonstrates the suitability of the measure for this STH species. Interestingly, this was the only species where this occurs. Only when reducing the spatial scale of *T. trichuris* EPHP to admin level 1 ($p < 0.001$) and admin level 2 ($p < 0.001$), did the prevalence differ significantly between areas reaching EPHP or not, highlighting the need for finer scale analysis for this species. Similarly, hookworm prevalence only differed significantly between regions defined as reaching EPHP or not at admin level 1 and admin level 2 ($p < 0.05$). These results suggest that common spatial scales used for all the three STH species may not be an accurate approach at low prevalence levels, although it is practical. Declaring EPHP for STH at a spatial scale any larger than admin level 2 would not correctly validate a change in control strategy for hookworm infection, which is currently the most prevalent STH species in sub-Saharan Africa [163].

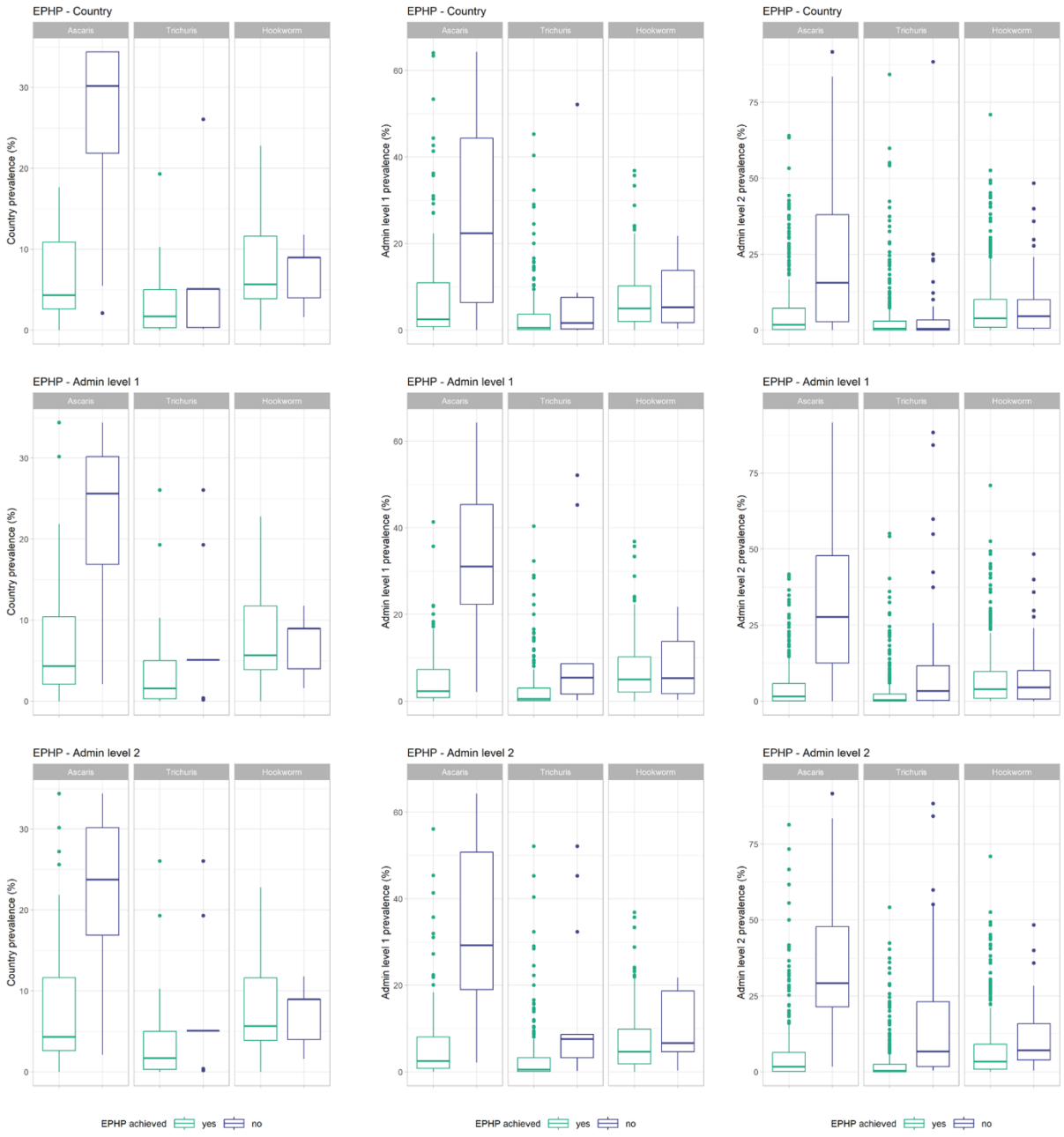


Figure 5.4: The difference in soil-transmitted helminth (STH) prevalence measured in regions labelled as achieving elimination as a public health problem (EPHP) at three varying spatial scales. *From the top panel to bottom, the spatial scale at which EPHP is declared decreases from country-level, admin level 1 (region), and admin level 2 (district). From left to right, the spatial scale in which prevalence is aggregated at decreases from country-level, admin level 1, and admin level 2. The difference between prevalence declared at different spatial scales is clear, as well as the heterogeneity at these scales between the three STH species. Data taken from the publicly available Expanded Special Project for Elimination of NTDs (ESPEN) database, accessed Nov 2022.*

3.6. Which age groups should be sampled in monitoring and evaluation (M&E) programs?

The target population for STH M&E surveys should ideally change between treatment naïve populations (baseline mapping) and those near to EPHP validation. The known difference in drug efficacies for the three major STH species will impact the age-dependent infection of the different STH species to differing degrees over time. After decades of predominantly sMDA the *A. lumbricoides* and *T. trichiura* infection reservoir in SAC will reach low levels. Untreated adults, particularly those with hookworm infection, will continuously re-seed infection, reducing the overall long-term impact of MDA. Although cMDA for LF has resulted in large numbers of adults receiving albendazole, as LF EPHP is being increasingly achieved and thus treatment scaled back, the gap in adult STH treatment is increasing. As a result, recent guidelines from the WHO included the recommendation to treat high-risk groups and WRA alongside SAC [4]. Transmission interruption for STH infection is unlikely to result from pre-SAC and SAC treatment alone as demonstrated by a wide range of mathematical modelling studies [8,50]. Including just WRA will still not eliminate the reservoirs of infection in adult males. Due to the changes in infection patterns after many rounds of MDA, and reflecting the updated recommended MDA delivery protocol, M&E surveys should include infection data from more or all age groups to enable accurate monitoring of any remaining pockets of infection aggregated in specific demographic groupings.

3.7. The accuracy of mass drug administration coverage and compliance

The epidemiological measurements entitled “coverage” and “compliance” are unfortunately used interchangeably to the detriment of comparing program monitoring in NTD research between regions and countries [91]. Relying on coverage to measure control program success may lead to premature cessation of MDA programs, enabling infection recrudescence [91,95]. Reporting the swallowing of drugs, DOT, especially in regions targeted for transmission elimination, is crucial for helping to identify untreated pockets of the targeted communities [103]. Untreated groups may arise from programmatic insufficiencies (program reach, lack of awareness, short duration), or participant refusal (adverse effects, religious and social factors, contraindications).

The importance of accurate denominators and numerators is highlighted by the ESPEN dataset, which reports 7.37% (n = 5634, range: 100-482%) of IUs reaching impossible epidemiological coverages over 100% in 2022. Furthermore, the denominator used for eligible SAC for treatment did not change year-on-year. The lack of a population growth factor applied to the data will over-estimate the coverage reported. This highlights the need for more accurate population estimates based on census data where possible. The WHO-recommended CES enumerates a representative sample of the population and relies on participant recall, the accuracy of which is known to be hampered by desirability- and recall-bias. Participant recall and DOT surveys can be linked to a national census, or to a baseline census in a study site, facilitating the accurate identification of treatment frequency. The latter denominator further enables the identification of the 'never treated' population and the calculation of the treatment frequency in a population, which enables significantly superior M&E analysis such as the accurate calculation of the probability of elimination and the targeting of treatment naïve demographic groups [177]. Financial constraints upon national programs will limit such implementation.

3.8. Heterogeneity in soil-transmitted helminth treatment

The heterogeneity in epidemiological coverage reported to ESPEN, is shown in **Figure 5.5**. Here, ESPEN define epidemiological coverage as the total number of people treated out of the total population requiring treatment. The WHO currently recommends reaching a chemotherapy coverage of above 75% in SAC at the district level. **Figure 5.5** demonstrates this should be defined at admin level 2 or smaller, as the aggregation of coverage at any higher spatial scale will lead to average infection level estimates that could result in unwarranted changes in control policy. This has also been demonstrated in an Ethiopian context where the high levels of heterogeneity in MDA coverage reported at admin level 4 (kebele), is lost when aggregated at admin level 3 (district), the IU for Ethiopia [84].

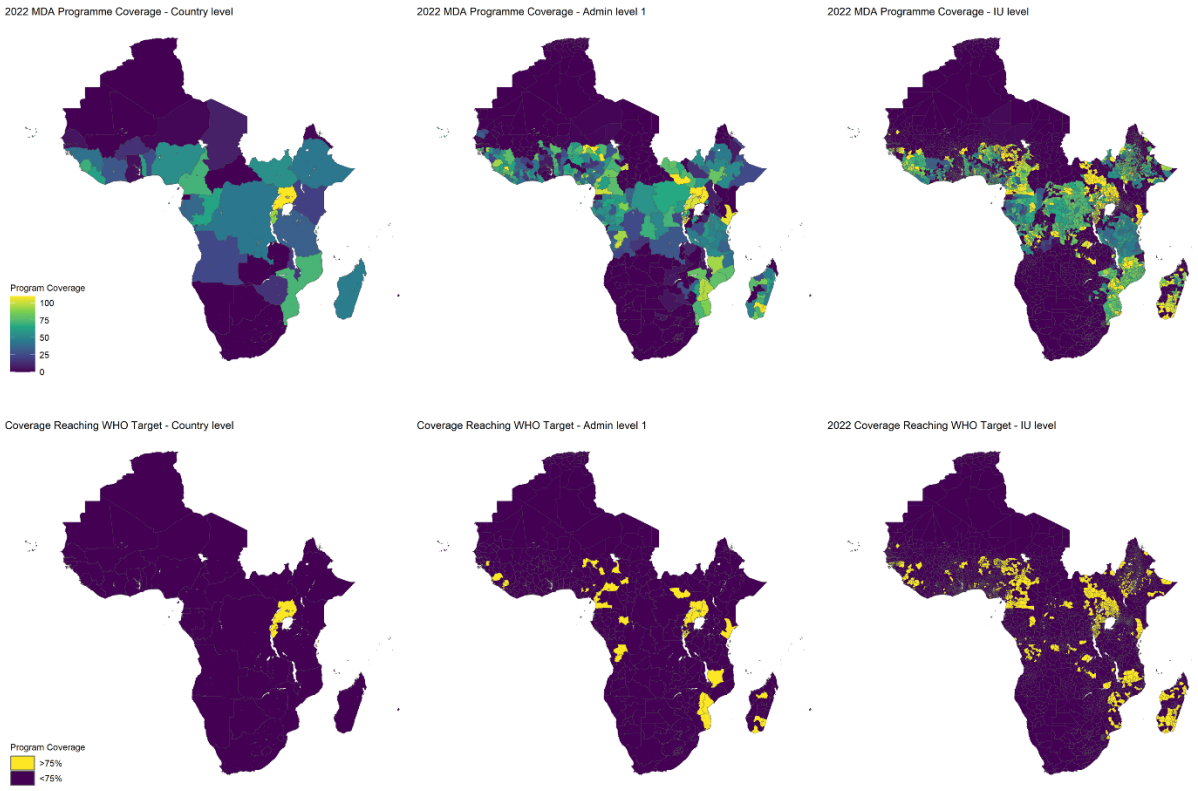


Figure 5.5: Visualising the World Health Organisation epidemiological coverage target of 75% in school-aged children (SAC). *The epidemiological coverage reported for the 48 countries considered in the AFRO region according to the Expanded Special Project for Elimination of NTDs (ESPEN). From the top panel to the bottom, epidemiological coverage is shown at increasing spatial scale from that recorded at the implementation unit, (IU) then aggregated at admin level 2 and admin level 1. The right panel shows the same data as a binary measure of regions reaching the WHO targeted 75% coverage. Data taken from the publicly available database ESPEN, accessed Nov 2022.*

4. Discussion

4.1. The future of fine-scale soil-transmitted helminth infection mapping

The call for precision spatial mapping has been made for other human helminth infections [176]. Widespread, fine-scale mapping of STH has been recently conducted as part of three large research projects; namely, DeWorm3 [29], TUMIKIA [46], and the Geshiyaro project [45]. These studies provide an opportunity to analyse hotspots of infection based on detailed demographic censuses collected at baseline, and fine scale household and village mapping of infection levels and MDA coverage. These projects are expensive, and it is unrealistic to call

for this level of detail in the routine M&E implementation within national NTD control programs. Recent development in technology, however, may help address this problem. Estimation of at-risk areas using Bayesian geostatistical modelling has been conducted using remotely sensed geographical and socioeconomic data in Nigeria [178]. Such work presents a possible low-cost alternative to fine-scale mapping, and potentially allows direct allocation of resources to high-risk areas. Broadening the scope of ESPEN beyond that of the AFRO region, and collaborating with the other WHO regional offices with endemic countries such as South America and Asia would be highly beneficial for the global coordination of NTD control and enabling such geostatistical work to be conducted for all endemic regions.

There is a need to evaluate such statistical approaches of prediction versus observation, at a fine spatial scale. In the absence of knowledge on what is an appropriate scale on which to assess the spatial scale over of STH transmission, defining the policy on what is a sensible unit of space over which to assess infection prevalence and intensity is rather difficult. This will vary by the dominant STH species in a locality and by behavioural, social, and population movement patterns. Ultimately how much M&E is done to assess progress in control will be decided on the resources available.

Using blanket recommendations on the best spatial scale for M&E of diverse parasites and communities will always be fraught with difficulties. In the light of a growing body of epidemiological evidence that spatial heterogeneity pertains in both infection levels and MDA compliance, especially as prevalence decreases, it would seem sensible for the WHO to improve the precision of advice on what is a sensible spatial sampling unit. Surveying infection at finer scales in regions declared as low prevalence would be highly desirable, although this would come with an increased cost of M&E from diagnostics consumables and human resource cost to run such surveys. Alternatively, stopping a program prematurely, and re-starting in the future after infection recrudescence may be more expensive than continuing control. Furthermore, the willingness of a community to restart their participation in control programs after a break may also wane, reducing the future efficacy possible from such a program.

Mathematical model-based studies of parasite transmission and control would be of great value in helping policy makers understand the consequences of heterogeneity in infection and control measures delivery [51]. Using the information in this review detailing the

heterogeneity that exists at low prevalence would be beneficial in demonstrating the impact of recrudescence, if any, upon the future of STH control. Improving our understanding of spatial heterogeneity at different infection levels, and how this is modulated by other factors such as population movements in defined settings, will latterly improve our comprehension of how this influences the likelihood of disease or transmission elimination. The proposed reduction of spatial scale used for elimination validation, as outlined in this review, needs much more careful consideration by bodies such as the WHO and Health Ministries in countries with endemic infection.

5. Conclusion

Much heterogeneity in STH infection is present, whether assessed at an individual, age or sex group, or spatial location level. Both the choice of control program interventions and M&E guidelines need to better reflect this heterogeneity. As STH prevalence levels continue to fall as a result of much effort over the past decade, better and more precise guidance is required from the WHO on who to treat, what diagnostic to use, and what spatial scale to employ to assess impact. A hierarchical guideline, matching M&E at differing prevalence and intensity of infections to appropriate spatial scales and population sample size would be beneficial. Monitoring can remain crude in terms of sample size and age groups targeted, and at a large spatial scale, for high prevalence areas. As regions reach lower infection levels, the M&E unit should decrease to a more granular level, enabling the infection hotspots to be identified. This implies increased cost, and paradoxically, suggests a greater M&E spend as infection levels fall. However, enhanced fine spatial scale M&E will be crucial for the accurate monitoring of STH control program impact and, concomitantly, to ensure the progress made over the past decade is sustained.

Chapter 6: The impact of soil-transmitted helminth control after multiple rounds of community-wide mass drug administration implemented in parallel with water, sanitation and hygiene interventions

Dissemination

This chapter has been adapted from the paper titled, “The impact of soil-transmitted helminth control after multiple rounds of community-wide mass drug administration implemented in parallel with water, sanitation and hygiene interventions”, currently under review with Transactions of the Royal Society of Hygiene and Tropical Medicine.

Motivation

The Geshiyaro project is the largest and longest running study of STH control, monitoring the impact of both cMDA and enhanced WaSH infrastructure access delivered with BCC (integrated control) at an individual level. Smaller studies assessing some elements of this project have been conducted before, however, this chapter is the first opportunity to report on the impact of this integrated control upon fine-scale measurements of STH prevalence and intensity. This chapter also addresses whether the gains made in control by integrated control are sufficient to warrant the recommendation to the government of Ethiopia for its inclusion in STH and SCH control programs in similar settings.

1. Introduction

The additional benefits of cMDA over sMDA, as recommended by the WHO, has been modelled by many groups showing it to be beneficial in the vast majority of epidemiological settings [8,13,14,179,180]. Despite some studies showing sMDA can help reduce the burden of infection in adult age-groups, Truscott *et al*. suggested that unless in transmission settings with R_0<2, sMDA will not be sufficient to reach transmission break without broadening the targeted population to include either pre-SAC and / or adults with treatment coverage of >80% [8,38,52,181,182]. Such high coverage figures have not been consistently evidenced as being achieved so far in either national programmes or large-scale control studies, and challenges such as systematic non-treatment remain [11,87,89]. Nevertheless, transitioning from cMDA to sMDA provides a two-fold opportunity to improve the equity of treatment. First, for hookworm infection, as adults who harbour the majority of infection burden are targeted for treatment [170,183,184]. Secondly, cMDA protocols will be more likely to treat a higher proportion of SAC than sMDA, as they reach both attending and non-school attending children [185]. Notably, the most recent estimate of enrolled children in primary and secondary school in Ethiopia reached 70.8% and 70.2%, respectively, according to households surveys in 2019 [186].

The implications of interpreting the positive findings from cMDA modelling have been discussed previously, primarily highlighting the importance of avoiding the over-extrapolation or over-generalisation of results found under specific circumstances, such as the relevance of the predominant species of STH studied, and baseline prevalence in a defined setting [187]. Furthermore, the few studies which have analysed the impact of cMDA, have not conclusively shown a significant benefit (**Table 1.1**). As such, more in-depth studies of the impact of cMDA beyond that of sMDA is required, such as that conducted by the Geshiyaro project, before the results of modelling studies can be confidently accepted, and control program guidelines changed.

1.1. Using the Geshiyaro project for the evaluation of integrated control

The control of STH via cMDA implementation in parallel to WaSH infrastructural improvements, (herein referred to as “integrated control”), has not been previously published for a sample size larger than 500 participants, or for a study spanning more than a couple of years (**Table 1.1**). This places the Geshiyaro project at the forefront to answer previously unanswered questions, such as the long-term benefit of cMDA in all age groups of the community, the possibility of reaching the interruption of transmission with cMDA, the coverage levels associated with reaching such a state, and the existence, if any, of the added benefit of WaSH improvements to cMDA. This chapter addresses each of these questions, and discusses if the change in STH infection levels is significant enough to warrant the recommendation of large-scale adoption of such methods into national control protocols globally.

1.2. Using the Geshiyaro project for the evaluation of current mass drug administration threshold targets

Currently, the WHO recommends the cessation of MDA once the prevalence of STH is <2% following an impact assessment after five years of treatment. The Geshiyaro project enumerates the population at an administration level smaller (kebele, admin level 4) than that conducted by Ethiopia currently (woreda, admin level 3). As such, the enhanced fine-scale monitoring of data available will capture more heterogeneity of the distribution of STH infection at low intensity. Due to the increased aggregation of infection seen at low prevalences after many rounds of cMDA, such as that of the Geshiyaro project sites, an increasingly smaller proportion of the community will experience high morbidity, and hotspots of infection will exist [20]. Therefore, the data from the Geshiyaro project will also shed light on the reality of STH prevalence at smaller spatial strata and how this compares to that recorded at larger spatial scales. This will enable the validation of the WHO recommendations for MDA cessation once 2% prevalence has been reached, and in turn evaluation of the EPHP target.

2. Methods

Data collected from the annual parasitological surveys (sentinel sites), drug taking behaviour (cMDA treatment records), and access to WaSH questionnaire (sentinel sites) by the Geshiyaro project, over a period of six years are evaluated. The temporal spacing of data collection is shown in **Figure 1.7**.

2.1. Enumerating the sentinel site participants

Annual parasitological mapping took place across 45 sentinel sites in 45 kebeles (**Figure 1.7**) whereby stool samples were collected, and participants answered a WaSH infrastructure access questionnaire. A demographically balanced sample of 150 participants were selected per site, consisting of 15 individuals of each sex in each age group: preSAC (aged 1-4 years), SAC (aged 5-14 years), adolescents (aged 15-20 years), young adults (aged 21-35 years) and adults (aged 36-100 years).

All participants were enrolled to the project using electronic data capture (**Figure 3.1**) fortified with biometric fingerprint technology for the registration and subsequent identification of participants using methods described in **Chapter 3**. This generated an 11-digit participant number, which could be identified either biometrically, by scanning their ID card, or searching for their name (**Figure 4.1**). Where sentinel sites existed in censused districts (n = 16 kebeles), participants could be linked to their census record and cMDA record.

2.2.Sample collection

All faecal samples collected from a participant were provided with a six-digit sample number identifiable through scanning a QR code. This code was placed on sample pots and Kato Katz diagnostic slides to reduce human errors in labelling of samples. This also allowed for anonymised diagnostics in the laboratory. Quadruple Kato Katz slides were analysed, generated from two slides prepared per sample over two consecutive days. A minimum of six months was allowed between cMDA distribution and sentinel site parasitological monitoring to ensure any recrudescence (parasite reinfection) could be captured, signifying continued STH transmission.

2.3.Statistical analysis

Summary statistics were calculated using normal confidence intervals for prevalence, and negative binomial confidence intervals for intensity using the glm.nb() function from the "MASS" package in R [188]. For intensity values that reached 0 epg, no confidence interval could be calculated. Due to the staggered nature of the project implementation, generating different number of years of data between woredas, some analysis is conducted between the baseline and latest data collection of each intervention arm, for a comparable analysis. Baseline data was collected in Year 1 (2018) for Bolosso Sore (pilot), Year 2 (2019) for the rest of Arm 1 and Arm 2 woredas, and Year 4 (2021) for Arm 3 (**Figure 1.7**). The latest collection was conducted in Year 6 (2024). As such, baseline and the current data are referred to as the 'survey type'. To account for the difference in starting prevalence and intensity of STH, relative reductions by arm and woreda are calculated as employed in previous studies of STH control [30].

Summary statistics and associations between demographic factors and WaSH covariates and STH infection were compiled for all sentinel site participants. Participants found in both sentinel sites and MDA enumerated sites were analysed for associations between treatment behaviour and STH infection.

Statistical significance was calculated using Welch's t test for continuous variables due to the unequal sample sizes and variances, and Chi square tests for categorical data. Covariates affecting the prevalence of infection at an individual level was analysed using binomial logistic regression. Exponentiated coefficients from the binomial logistic model are used to calculate the OR and AOR. Covariates affecting the intensity of infection at an individual level was analysed using negative binomial regression. Exponentiated coefficients from the model are used to calculate the ORs and AORs. Significance was considered at p value < 0.05 and are reported for significant results as either $p < 0.05$, $p < 0.01$, and $p < 0.001$.

3. Results

A total of 11,573 sentinel site participants across the three intervention arms were analysed over the course of the project, with a maximum of six years' worth of individual longitudinal data. **Table 6.2** shows the baseline distribution of the age-sex stratified participants, according to the data captured at their first point of enrolment in the project. If enrolled participants

were unable to be found at the subsequent year, a new member was enrolled for in accordance with the absentee's age-sex stratification to keep a constant and balanced sample size. This explains why larger population were enrolled in Arm 1 and Arm 2 compared to Arm 3, due to the longer period of follow-up in Arms 1 and 2.

Age Group (years)		Intervention arm		
	Sex	Arm 1 (cMDA, WaSH intervention)	Arm 2 (cMDA, national OneWaSH)	Arm 3 (sMDA, national OneWaSH)
preSAC (0-4 years)	Male	208	215	148
	Female	245	226	170
SAC (5-14 years)	Male	519	434	428
	Female	420	341	363
Adolescents (15-20 years)	Male	187	264	215
	Female	219	241	226
Young adults (21-35 years)	Male	278	238	257
	Female	393	295	323
Adults (36+ years)	Male	364	266	234
	Female	353	289	259
Missing demographics		939	2038	295
Total		4054	4604	2915

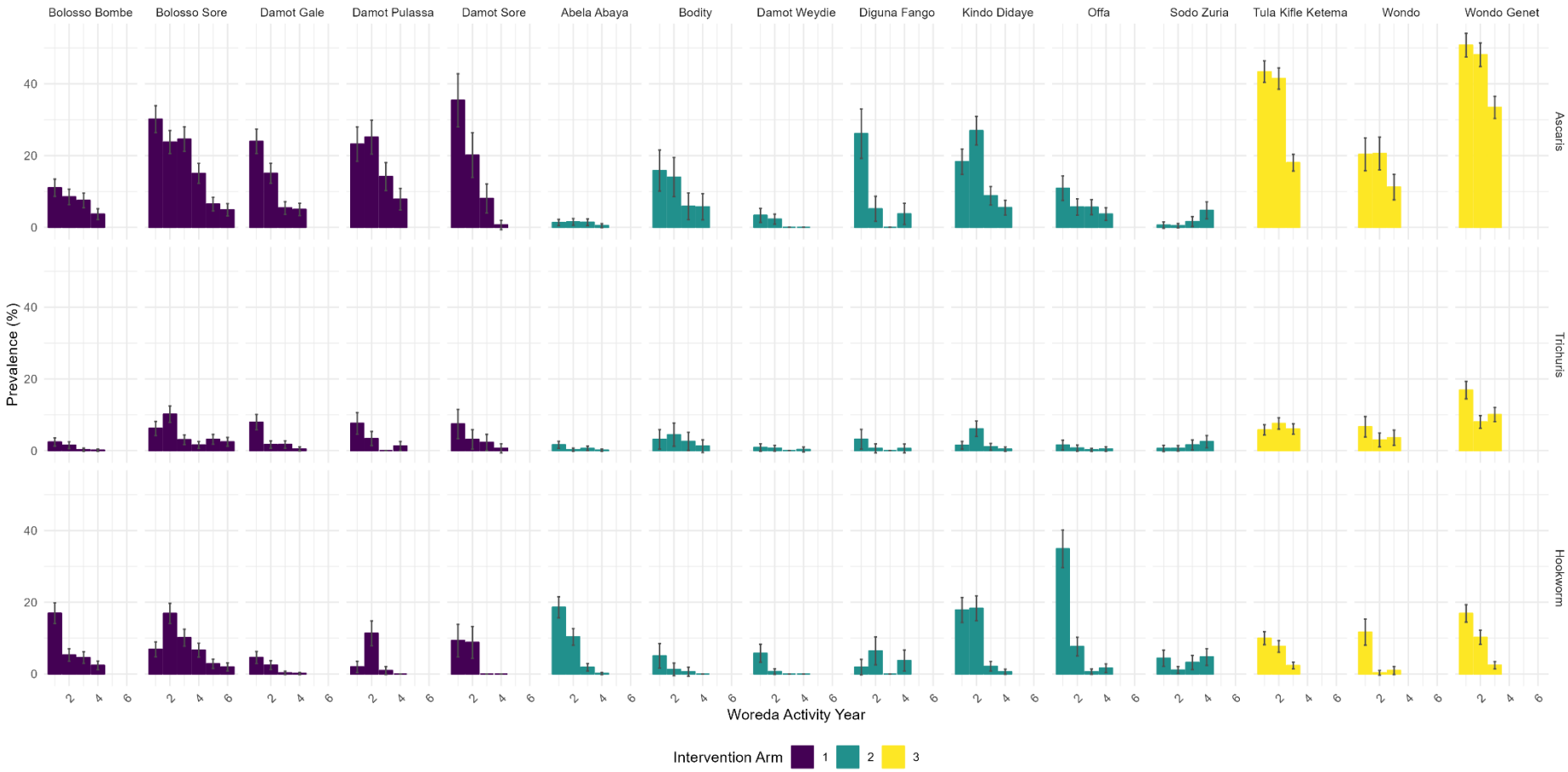
Table 6.2: The baseline distribution of the 11, 573 Geshiyaro participants enrolled across the 45 sentinel site locations. *Age grouping is shown based on the characteristic recording during enrolment. The participants missing demographic data and are removed from age-sex stratified analysis.*

3.1. Overview of prevalence and intensity of infection over time

The distribution of prevalence and intensity over time, by intervention arm and species is shown in **Figure 6.1**. The prevalence at baseline was highest in intervention Arm 3 for both *A. lumbricoides* (Arm 3: 43.3% (95% CI: 41.2 - 45.3%), Arm 1: 22.6% (95% CI: 20.9 - 24.3%), Arm 2: 8.65% (95% CI: 7.53 - 9.78%)) and *T. trichiura* (Arm 3: 10.4 (95% CI: 9.09 - 11.6%), Arm 1: 5.84% (95% CI: 4.88 - 6.80%), Arm 2: 1.57% (95% CI: 1.08 - 2.07%)), whilst hookworm was recorded highest at baseline in Arm 2 (Arm 2: 15.0% (95% CI: 13.6 - 16.5%), Arm 3: 13.0% (95% CI: 11.6 - 14.4%), Arm 1: 8.69 (95% CI: 7.55 - 9.84%)).

All STH infections were classified as low intensity at baseline according to the WHO guidelines [189] (**Figure 6.1**). *A. lumbricoides* recorded the highest epg across all arms, reaching 561.0 epg (95% negative binomial CI: 437.8 -719.0 epg) in Arm 1, 140.6 epg (95% negative binomial CI: 140.1 - 141.1 epg) in Arm 2, and 858.1 epg (95% negative binomial CI: 732.2 - 1005.7 epg)

in Arm 3. *T. trichiura* was recorded at very low intensities of 84.5 epg (95% negative binomial CI: 50.6 - 141.0 epg) in Arm 1, 17.6 epg (95% negative binomial CI: 17.4 - 17.8 epg) in Arm 2, and 10.8 epg (95% negative binomial CI: 7.9 - 14.9 epg) in Arm 3. Hookworm was also recorded at very low intensities of 72.2 epg (95% negative binomial CI: 48.3 - 108.0 epg) in Arm 1, 33.2 epg (95% negative binomial CI: 25.5 - 43.1 epg) in Arm 2, and 11.2 epg (95% negative binomial CI: 8.5 - 14.7 epg) in Arm 3.


Bolosso Bombe
Bolosso Sore
Damot Gale
Damot Pulassa
Damot Sore
Abela Abaya
Bodity
Damot Weydie
Diguna Fango
Kindo Didaye
Offa
Sodo Zuria
Tula Kifle Ketema
Wondo
Wondo Genet
Ascaris
Trichuris
Hookworm
Prevalence (%)
0
20
40
2
4
6
Woreda Activity Year
Intervention Arm
1
2
3

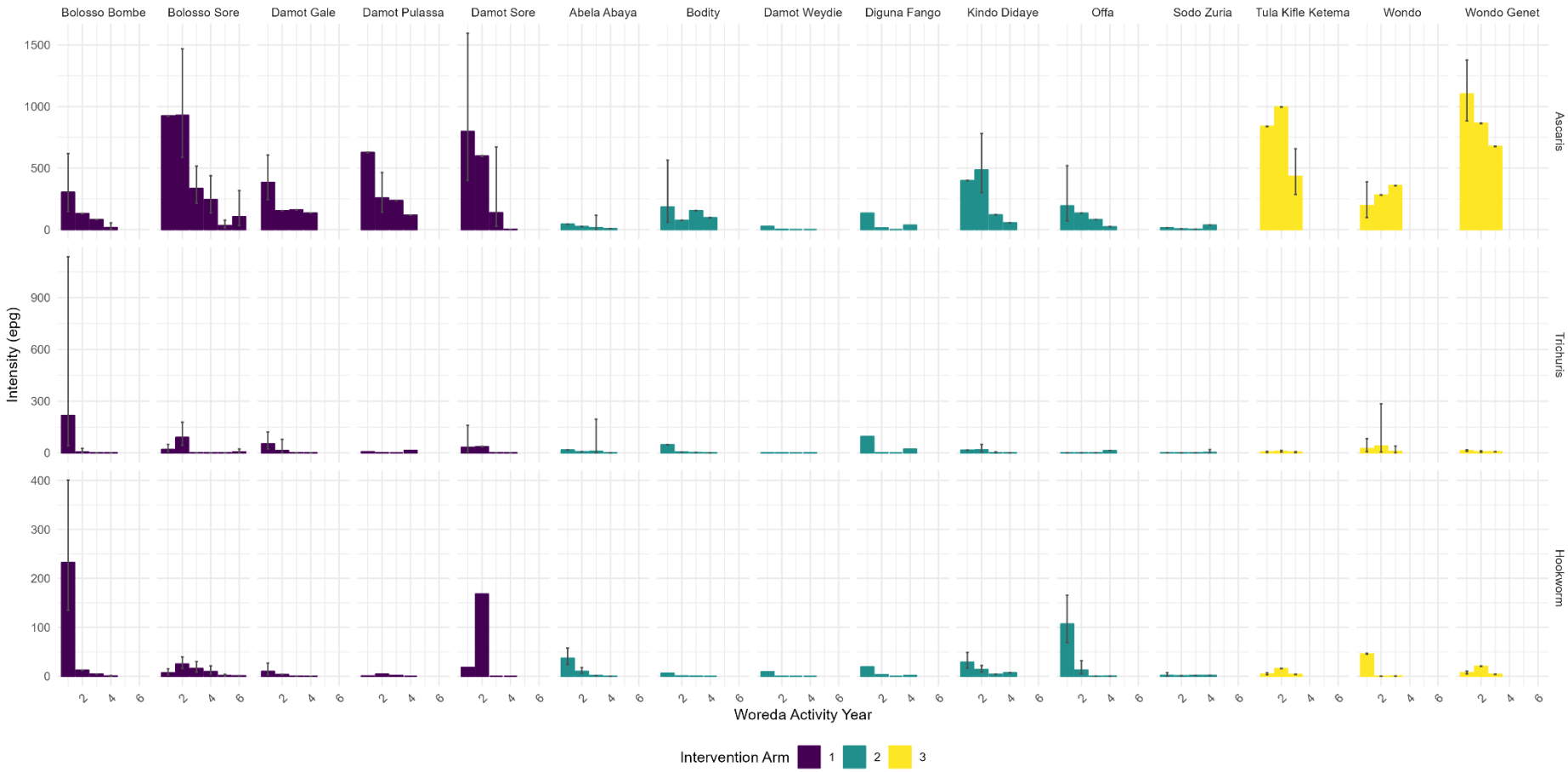


Figure 6.1: The prevalence and intensity of soil-transmitted helminths (STH) by woreda (district) and year. *Prevalence error bars were calculated using normal 95% confidence intervals, whereas intensity error bars were calculated using negative binomial 95% confidence intervals. Erro bars were not possible when woreda's reached 0% prevalence at any of the years. Colours indicate the classification of each woreda (district) into the*

project's three intervention arms. Bolosso Sore, the pilot woreda, (Arm 1) has two extra data collection activities compared to the remainder of Arm 1 and Arm 2 due to the staggered nature of the project implementation.

3.2. Prevalence change over time, by age and sex

A change in the age-dependence of infection can be seen between survey types (baseline and the latest data collection) when comparing participants receiving cMDA (Arm 1 and Arm 2) compared to sMDA (Arm 3) as displayed in **Figure 6.2**. Most notable, is the decrease in hookworm infection from baseline to the current status in adult age groups receiving cMDA.

The population enumerated by the Geshiyaro project were not treatment naïve, and had received annual sMDA treatment since 2015 delivered through the national STH control program [190]. Despite this, a defined age-dependent prevalence distribution was still noted. The odds of infection in SAC compared to other age groups was 29% and 43% higher for *A. lumbricoides* and *T. trichiura* infection, respectively (AOR: 1.29 (95% CI: 1.16 - 1.44), $p < 0.001$), (AOR: 1.43 (95% CI: 1.20 - 1.70) $p < 0.001$), when compared to other age groups, controlling for survey type (baseline or most recent survey). As expected, the odds of hookworm infection were 29% lower in SAC (AOR: 0.71 (95% CI: 0.60 - 0.84), $p < 0.001$) compared to other age groups, controlling for survey type. This captures the higher proportion of hookworm burden known to infect adults at baseline, which is significantly reduced in the population received cMDA, showing the increase in equity gained by this distribution method.

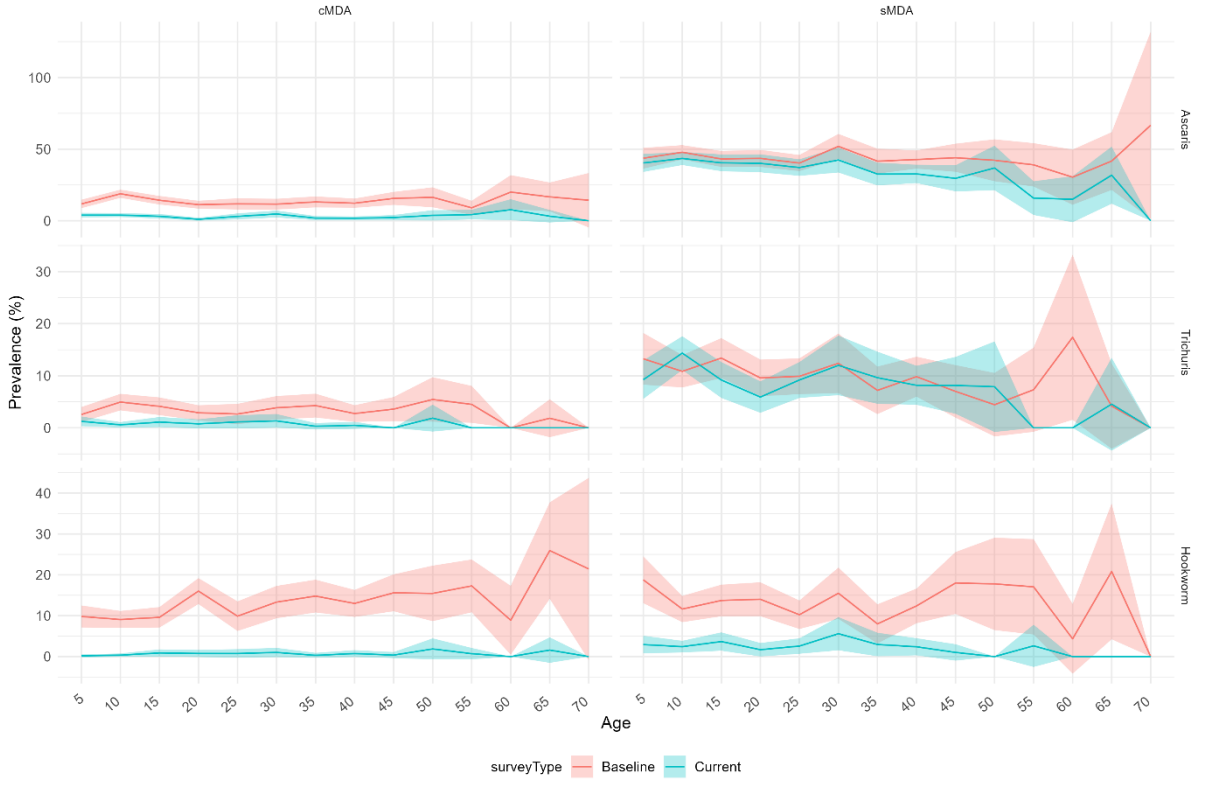


Figure 6.2: A comparison of the age-distribution of soil-transmitted helminth (STH) prevalence between populations receiving community-wide MDA (cMDA) and school-based MDA (sMDA) at baseline and the most recent survey. *Participant age is divided into 5-year age bandings, and cut at 70 years due to the lack of complete bandings after this age point for all species and survey types. A shaded ribbon shows the 95% confidence of reported prevalence. Note the difference in y-axis scale between STH species due to varying data ranges.*

3.3. Relative reduction in prevalence and infection intensity

Due to the variation in starting prevalence and intensities (**Figure 6.1**) between intervention arms, the relative reduction in intensity and prevalence (**Figure 6.3**) was analysed [30]. The relative reduction of *A. lumbricoides* intensity was statistically significant across all arms (Welch's t-test, $p < 0.001$). The relative reduction for *T. trichiura* and hookworm intensity was significant for arm 2 only (*T. trichiura*: Welch's t-test, $p < 0.05$, hookworm: Welch's t-test, $p < 0.001$). The relative reduction in prevalence was statistically significant for all species (all species χ^2 $p < 0.001$ (exception *T. trichiura* $p < 0.01$).

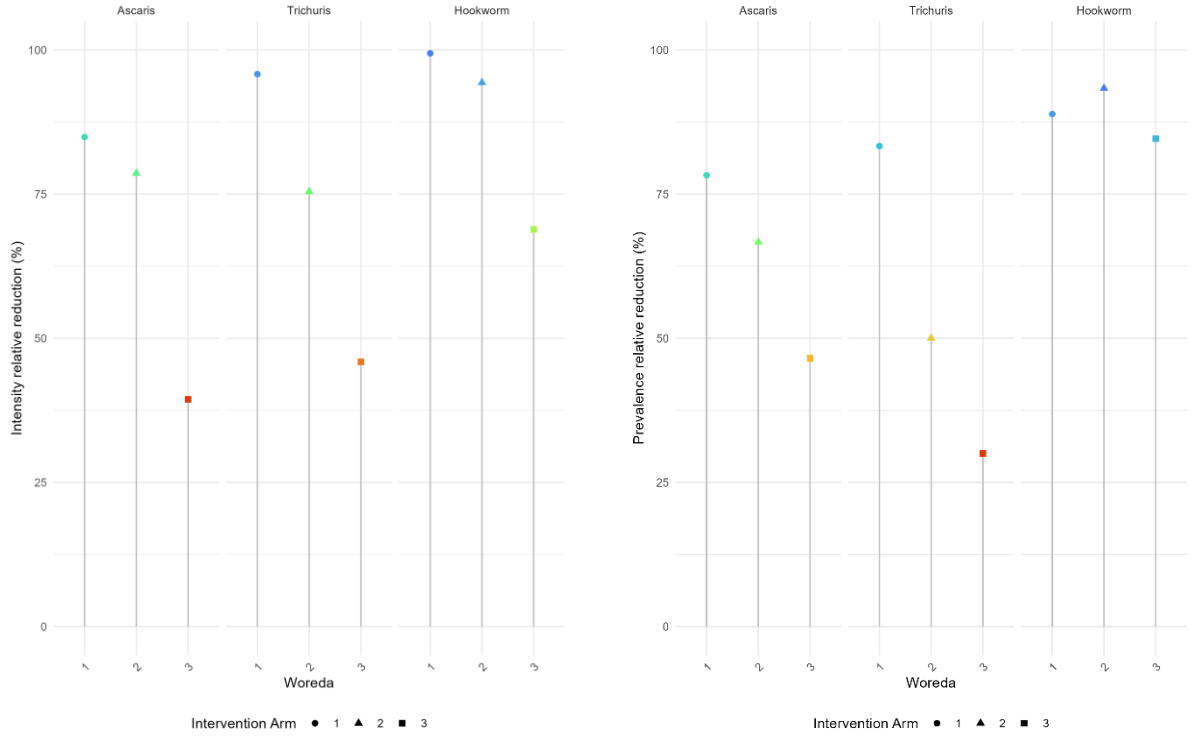


Figure 6.3: The relative difference in infection intensity and prevalence for the three studied soil-transmitted helminth species. *Points are coloured by the magnitude of the change, large decreases are shown in blue, small decreases are shown in red. The point shape is determined by the intervention arm.*

The largest relative reduction in intensity and prevalence was seen in hookworm infection in Arm 1 (98.7% in intensity, 93.3% in prevalence) and Arm 2 (94.3% in intensity, 88.9% in prevalence). This may be attributed to the newly implemented cMDA schedule in these intervention arms which includes the treatment of adults who currently remain untreated under sMDA protocols as conducted in Arm 3 (control arm).

The results of binomial logistic regression models assessing the change in prevalence between arms showed an 237%, 174%, and 61% increased odds of infection in Arm 3 compared to Arm 1 for *A. lumbricoides* (AOR: 3.37 (95% CI: 3.03 - 3.76), $p < 0.001$), *T. trichiura* (AOR: 2.74 (95% CI: 2.28 - 3.32), $p < 0.001$), and hookworm (1.61 (95% CI: 1.35 - 1.92), $p < 0.001$), respectively, holding survey type at a constant value. There was a 62% and 68% decrease in the odds of infection of *A. lumbricoides* (AOR: 0.38 (95% CI: 0.33 - 0.45), $p < 0.001$) and *T. trichiura* (AOR: 0.32 (95% CI: 0.23 - 0.43), $p < 0.001$) in Arm 2, compared to Arm 1. Contrastingly, there was a 75% increase in the odds of infection of hookworm (AOR: 1.75 (95% CI: 1.47 - 2.07), $p < 0.001$) in Arm 2 compared to Arm 1, suggesting the importance of WaSH measures and cMDA delivery implemented in Arm 1 on the control of the skin penetrator.

3.4. Validating the use of community-wide mass drug administration

The substantial beneficial impact of cDMA over sMDA on the reduced prevalence of STH is clear as displayed in the AOR in **Figure 6.4**, generated by multivariate binomial logistic (prevalence) and negative binomial (intensity) regression models. Due to the different length of time each woreda has been analysed (**Figure 1.7, Figure 6.1**), the difference between baseline and the most recent survey (survey type) was analysed.

Holding age group, sex, and survey type at a constant value, the odds of a participant being infected by *A. lumbricoides*, *T. trichiura*, and hookworm in a community only receiving sMDA was 483% higher (AOR: 5.83 (95% CI: 5.26 - 6.46%, $p < 0.001$)), 329% higher (AOR: 4.29 (95% CI: 3.59 - 5.14%, $p < 0.001$)), and 16% higher (AOR: 1.16 (1.00 - 1.34%, $p < 0.05$)), respectively, compared to participants receiving cMDA. This clearly demonstrates the enhanced impact of cMDA for STH infection control. Holding age group, sex, and survey type at a constant value, the change in intensity of infection was only significant for *A. lumbricoides* (AOR: 5.81 (95% CI: 4.46 - 7.61%, $p < 0.001$)) and hookworm (AOR: 1.54 (95% CI: 1.09 - 2.20%, $p < 0.05$)) in communities receiving sMDA. The observed low prevalence, intensity, and focal distribution

of *T. trichiura* and consequent low statistical power are likely explanations for the absence of a similarly significant impact observed by the different MDA protocols.

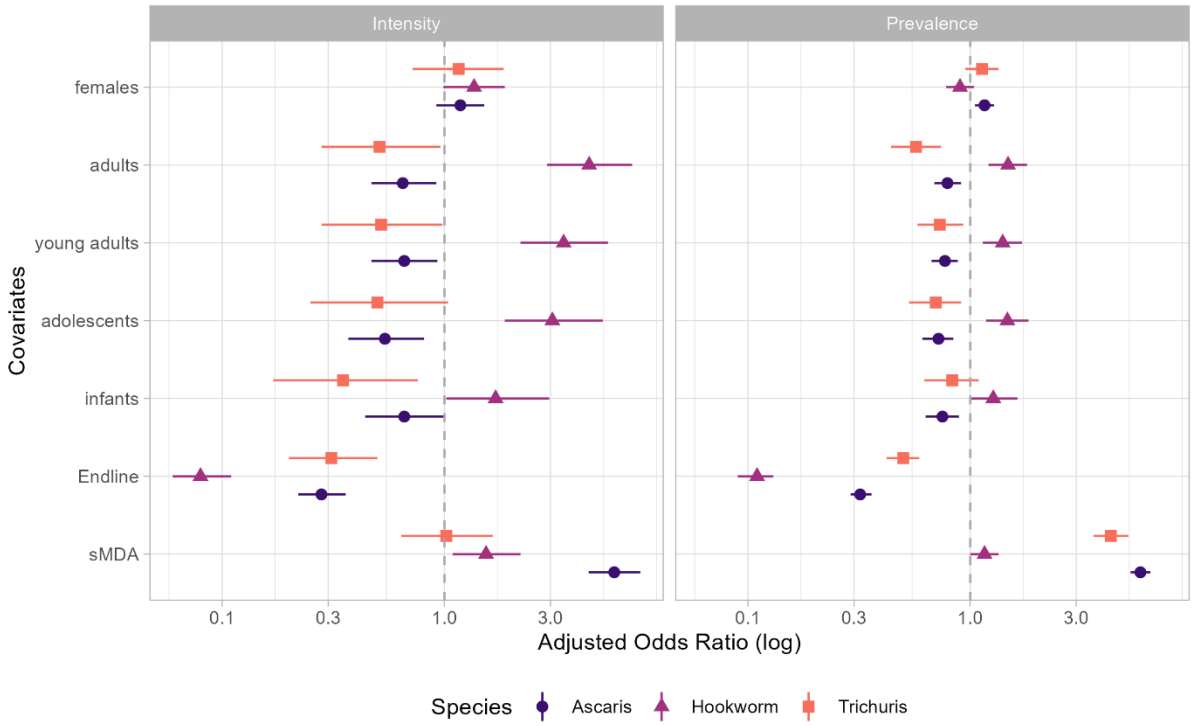


Figure 6.4: The results of multivariate binomial logistic (prevalence) and negative binomial (intensity) regression models. *The impact om prevalence and intensity of soil-transmitted helminths (STH) after years of control with community-wide mass drug administration (cMDA) or school-based MDA (sMDA). Points are coloured and shaped dependent on STH species. The dashed line at 1 indicates no effect, confidence intervals crossing this line is indicative of no statistical significance. Comparators for sex are male participants, and for age groups are school-aged children.*

There was a reduced odds of infection at the latest data collection compared to baseline for all species. Holding all other variables constant, the odds infection by *A. lumbricoides*, *T. trichiura*, and hookworm at the latest data collection point reduced by 68% (AOR: 0.32 (0.29 - 0.36%), p < 0.001), 50% (AOR: 0.50 (0.42 - 0.59%), p < 0.001), and 89% (AOR: 0.11 (0.09 - 0.13%), p < 0.001), respectively, when compared to the baseline. Similarly, the reduction in intensity at the latest data collection point reduced by 72% (AOR: 0.28 (95% CI: 0.22 - 0.36%), p < 0.001), 69% (AOR: 0.31 (95% CI: 0.20 - 0.50%), p < 0.001), and 92% (AOR: 0.08 (95% CI: 0.06 - 0.11%), p < 0.001), respectively, when compared to the baseline.

The difference in age distribution of the STH species is apparent. Holding all other covariates constant, the odds of hookworm infection was found to be higher in all age groups, when compared to SAC, maintaining the trend seen in the bivariate analysis above. The only significant effect of sex was seen in the increased odds of *A. lumbricoides* prevalence in female participants (AOR: 1.16 (95% CI: 1.05 - 1.28%, $p < 0.01$)).

3.5. Prevalence and intensity of infection

The non-linear relationship between prevalence and intensity is well described by the negative binomial distribution as shown in **Figure 6.5**. The aggregation parameter, *k*, inversely measures the degree of aggregation of infection within individuals in the host population. The smaller the value of *k*, the higher the level of aggregation. In other words, infection is sequestered in increasingly smaller pockets in the community.

The change in aggregation between baseline and the latest data collection is clearly demonstrated in infection data recorded for *A. lumbricoides*, as *k* falls from 0.030 at baseline to 0.011 at the latest data collection. A similar reduction between survey type is recorded for *T. trichiura* (0.007 to 0.004) and hookworm (0.017 to 0.002). These results show that with the decrease of prevalence in the community, aggregation has increased, corroborating results previously published by other studies [49]. At low intensity levels (below 1,000 epg), such as those recorded in the figure for *A. lumbricoides*, the prevalence changes dramatically from ~60% to 0%, whilst intensity decreases more gradually. This is well aligned with Figure 1B reported by Anderson *et al* [14].

This prompts the need to validate the spatial scale that should be employed to enumerate such low prevalence levels, corroborating the arguments made in **Chapter 5**. As aggregation increases at low prevalence, there will be a need for fine-scale monitoring during transmission interruption studies as this enhanced granularity will be required to identify the remaining pockets of infection aggregated in individuals, households, and kebeles.

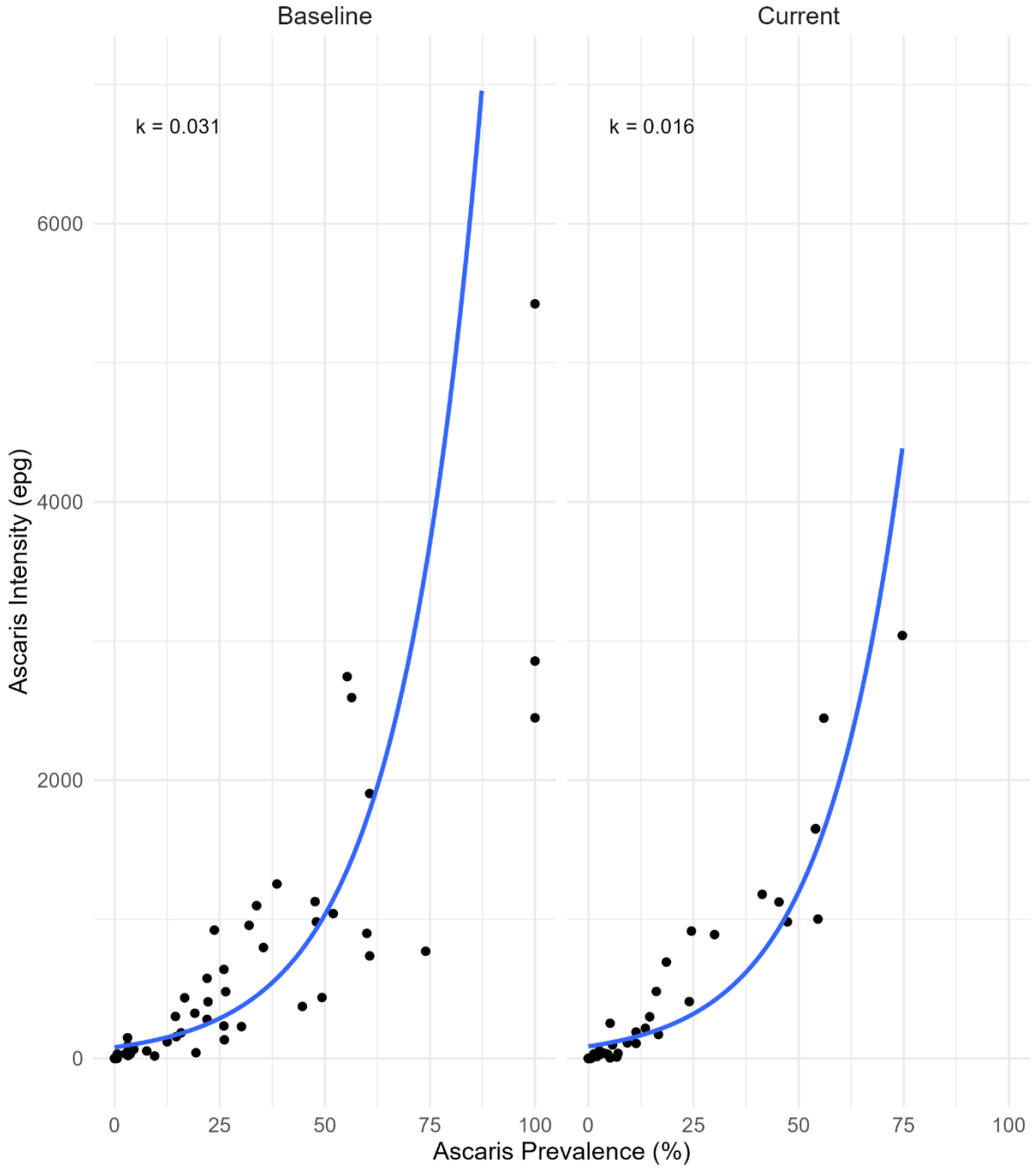


Figure 6.5: The non-linear relationship recorded between A. lumbricoides prevalence and intensity. *Panels show data collected at baseline and the latest data collection (survey type). The negative binomial distribution well describes the relationship between the two measurements, as displayed in the blue line. The degree of aggregation, defined by the aggregation parameter (k), is shown for each survey type, and decreases from baseline to the latest data collection, showing an increase in parasite aggregation caused by cMDA pressure.*

3.6. Relative reduction of intensity and treatment compliance

The relationship between the MDA strategy and the reduction in STH is clear. There was a non-significant positive correlation between the relative reduction in kebele level prevalence and treatment compliance. **Figure 6.6** compares the mean average compliance to the relative reduction in infection prevalence between baseline and latest data collection for each kebele where both MDA and sentinel site data exist (n = 16 kebeles). There is an increase in the relative reduction of prevalence as demonstrated by the Pearson's R statistic, but this is not significant for any of the STH species. Indeed, negative binomial regression of the relative reduction and compliance was non-significant for all STH species as demonstrated by the wide confidence bounds. The relative reduction of intensity at the kebele level was not appropriate for analysis due to the small number of positive samples at this fine-scale aggregation.

The absence of a significant association between compliance and prevalence may be due in part of the nature of the low prevalence setting. Pre-disposition to infection is known to exist in the population, as recorded by a previous study in the Geshiyaro population [60]. Therefore, at these low prevalence levels, treatment may not show such a strong association as individuals who can be treated are, and the remaining infection is maintained in the population that will always be predisposed. This effect of pre-disposition will be masked at higher prevalence levels as they will make up a smaller proportion of the infected population. Further investigation into the association between predisposition and treatment frequency is required.

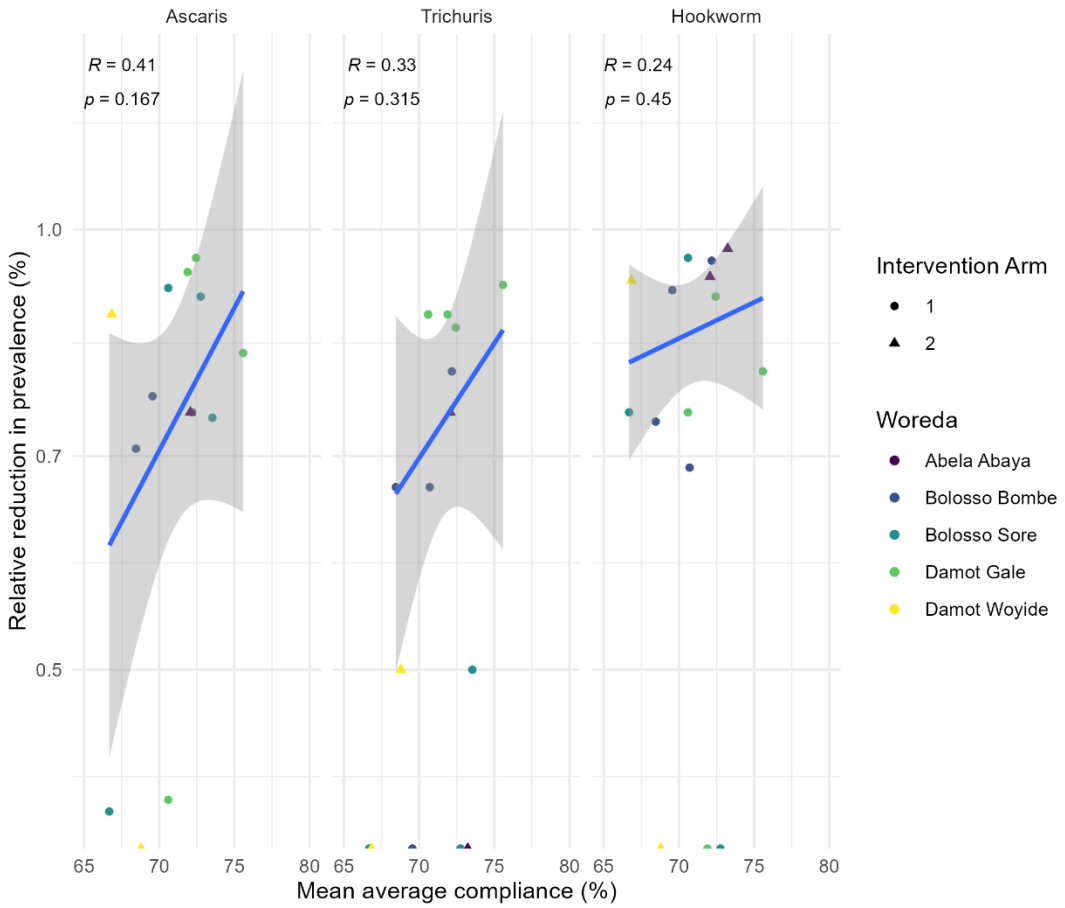


Figure 6.6: The relative reduction in prevalence of infection between the baseline and latest data collection, relative to the mean average compliance recorded for the kebele. *Pearson's R statistic and corresponding p value is shown for each soil-transmitted helminth species. Points are coloured by species, and shape has been guided by intervention arm.*

There was, however, a significant difference in the infection status of the individuals enrolled in the sentinel sites when compared to whether they were treated at the latest available round of cMDA. The average prevalence of any STH infection in participants who were treated in the latest round was 4.58% (95% CI: 3.35 - 5.81). Participants who were not treated at the latest round had a higher average prevalence of 7.77% (95% CI: 4.72 - 10.83). Participants who were recorded as swallowing treatment at the latest available round were 43% less likely to be infected (OR 0.57 (95% CI: 0.35 - 0.96), $p < 0.05$), compared to those who were not.

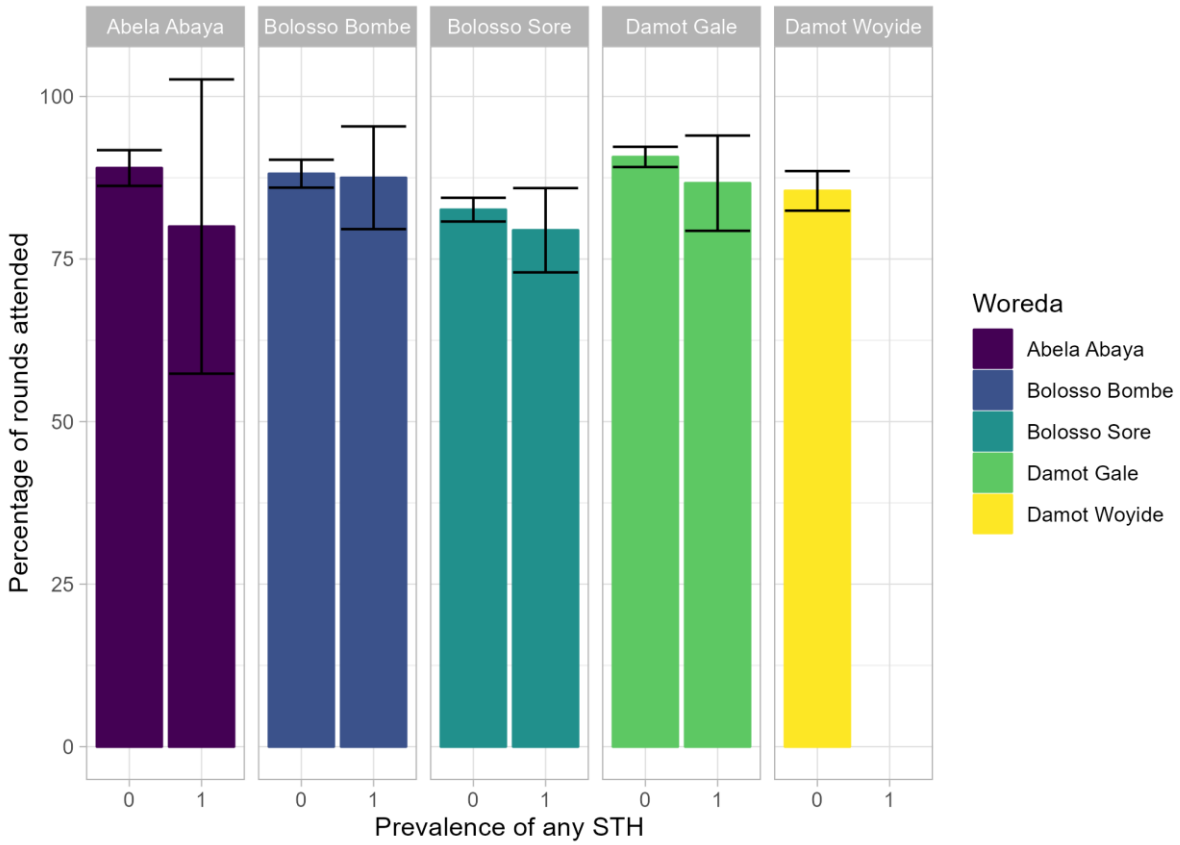


Figure 6.7: The relationship between the prevalence of any soil-transmitted helminth (STH) recorded at the latest parasite survey, against the proportion of rounds attended in the sentinel site population. *The longitudinal population is comprised of individuals who have been present in the census since baseline census collection, and eligible for treatment at each distribution. Error bars for the prevalence of any STH are shown, and overlap for all woredas, showing the lack of significance. Note, there was no infection in Damot Weydie at the latest round of data collection.*

The comparison in the percentage of rounds attended in the longitudinal population (calculated using methods applied in **Chapter 4**, as those eligible since the start of data collection in each woreda) to the prevalence of any STH infection is shown in **Figure 6.7**. No significant relationship between percentage of rounds attended and infection status was found. This may be due to the quick re-infection time for STH, and the lack of immunity acquired from natural infection (or indeed treatment), pre-disposition to infection, or the incomplete recording of MDA compliance by the project [51,60]. The difference in prevalence in groups recently treated or not was not significantly associated with age or sex.

The longitudinal population was used in an attempt to the reduce potential confounders in the data collection such as incomplete matching of participant records over time. However, the longitudinal population also has its own biases. For example, individuals that have been recorded since the baseline may be more likely to participate in all activities as they were easily found at the first round of data collection. There was a negligible increase in the percentage of rounds attended, as demonstrated by the overlapping error bars, in individuals without any infection in the latest round of data collection. The lack of statistical significance may be due to incomplete treatment records for participants, incomplete recording of treatment behaviour, the result of the small sample size used for the analysis (n = 1009 participants), or other confounding covariates on the prevalence of STH infection.

3.7. Characteristics of kebeles reaching <2% prevalence

By the latest data collection in Year 6 (2024), a total of 35 (77.8%), 33 (73.3%), and 20 (44.4%) kebeles had reached prevalence <2% for hookworm, *T. trichiura*, and *A. lumbricoides*, respectively, out of the 45 kebeles surveyed. The distribution of these kebeles across the project sites is shown in **Figure 6.8**. These kebeles were found across all three arms for *T. trichiura* and hookworm, but only in Arm 1 or Arm 2 for *A. lumbricoides*.

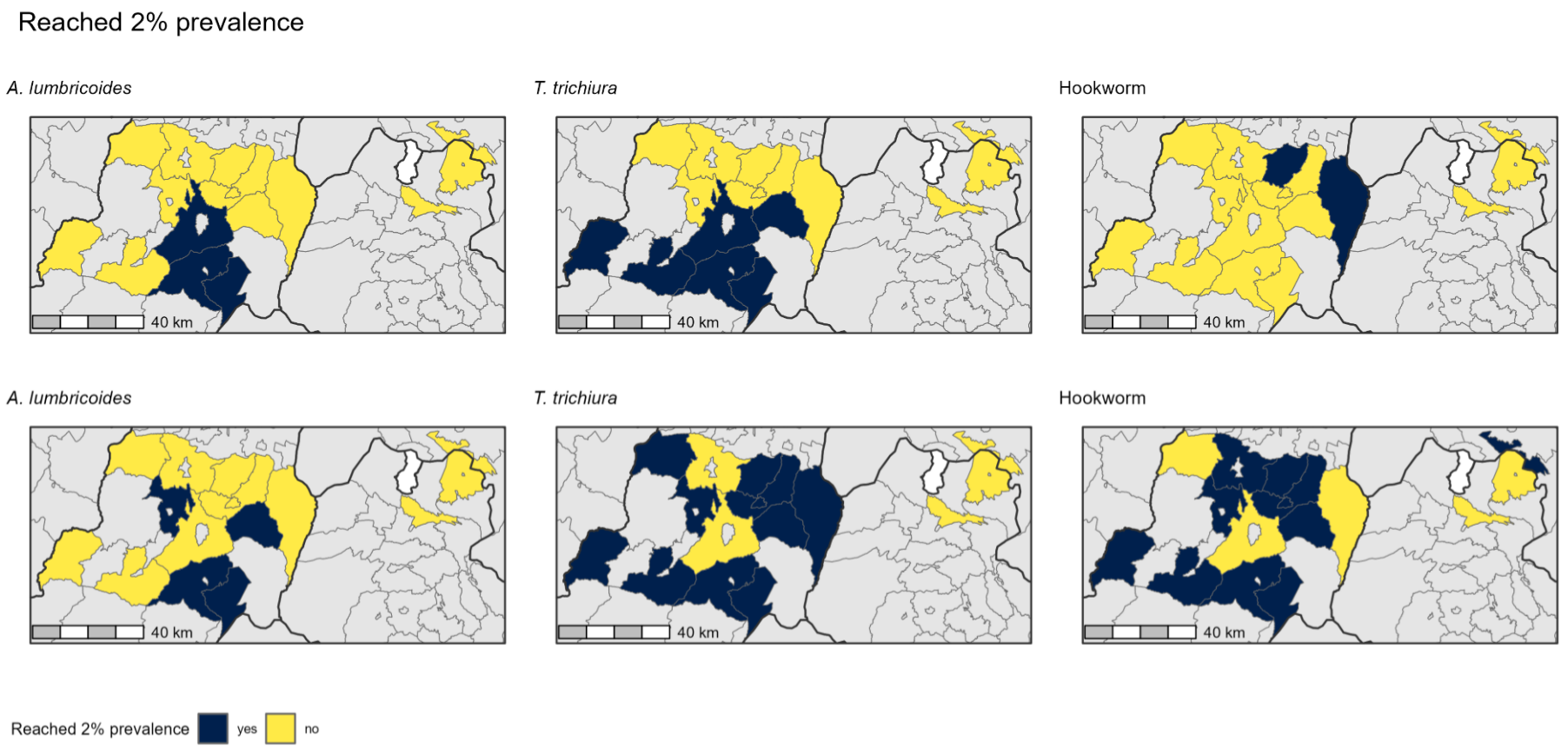


Figure 6.8: The location of woredas reaching the threshold prevalence of < 2% across the studied Geshiyaro sites. *All woredas enumerated by the project are coloured, grey woredas are those not enumerated by the project. Top panel: the baseline prevalence of the three soil-transmitted (STH) species. Bottom panel: the STH prevalence at the latest data collection. Bold lines indicate the administrative boundaries of the zones in south Ethiopia.*

The difference in the progression of prevalence over time between kebeles eventually reaching 2% prevalence (as targeted by the WHO for stopping MDA) by Year 6 are shown below in **Figure 6.9A**. The maximum prevalence recorded in kebeles eventually reaching the target was 20.5% (95% CI: 14.2 - 26.9%) for *A. lumbricoides*, 5.70% (95% CI: 3.65 - 7.76%) for *T. trichiura*, and 14.1% (95% CI: 11.0 - 17.1%) for hookworm. All kebeles recording a prevalence <2% have remained below the target for the last two years.

There was a significant difference in the treatment behaviour between participants in kebeles which reached the 2% threshold (*A. lumbricoides*: $X^2 = 933.30$, $p < 0.001$, *T. trichiura*: $X^2 = 99.93$, $p < 0.001$, hookworm: $X^2 = 69.22$, $p < 0.001$). As revealed by bivariate binomial logistic regression, participants in kebeles that had reached the threshold had a significantly higher odds of swallowing treatment (*A. lumbricoides* OR: 1.19 (95% CI: 1.17 - 1.20), $p < 0.001$, *T. trichiura* OR: 1.04 (95% CI: 1.03 - 1.05), $p < 0.001$, hookworm OR: 1.04 (95% CI: 1.03 - 1.05), $p < 0.001$). This association at the individual level was not found when looking at average coverage achieved aggregated at the kebele level. The trend of coverage in the kebeles achieving the target are shown in **Figure 6.9B**.

From the 12 WaSH covariates collected by the project (**Chapter 7, Table 7.1**), two variables were found to be significantly associated with the kebeles reaching the 2% threshold target; access to a year-round permanent (one that did not fluctuate between rainy and dry seasons, ($p < 0.01$, **Figure 6.9C**)) fresh water source and decreased access to an improved toilet ($p < 0.01$, **Figure 6.7D**). The term 'fresh water' source in this context means a source of water from the environment, one that is not piped, or from a deep well. As such, this water source can dry out in dry seasons. It is intuitive that ability to access 'fresh water' year-round is associated with reduced infection as individuals are not forced to access alternative, potentially higher-risk, water sources in the dry season. Such a plentiful supply may also encourage the use of water for many WaSH practises such as hand washing after toilet use and before eating or food preparation which reduces the risk of STH transmission as there is no requirement for water conservation.

The relationship between kebeles reaching 2% prevalence, and decreased access to an improved toilet, is unintuitive. This association is discussed in **Chapter 7**. In brief, this variable may be confounded by another WaSH variable, or the interpretation of the provided answer and / or question. If the access to an improved toilet is indeed associated with an increased

risk of infection, this will require further investigation into the root cause. Possible explanations include cleanliness of infrastructure, the timely removal of collected waste, and availability of hand washing near the facility.

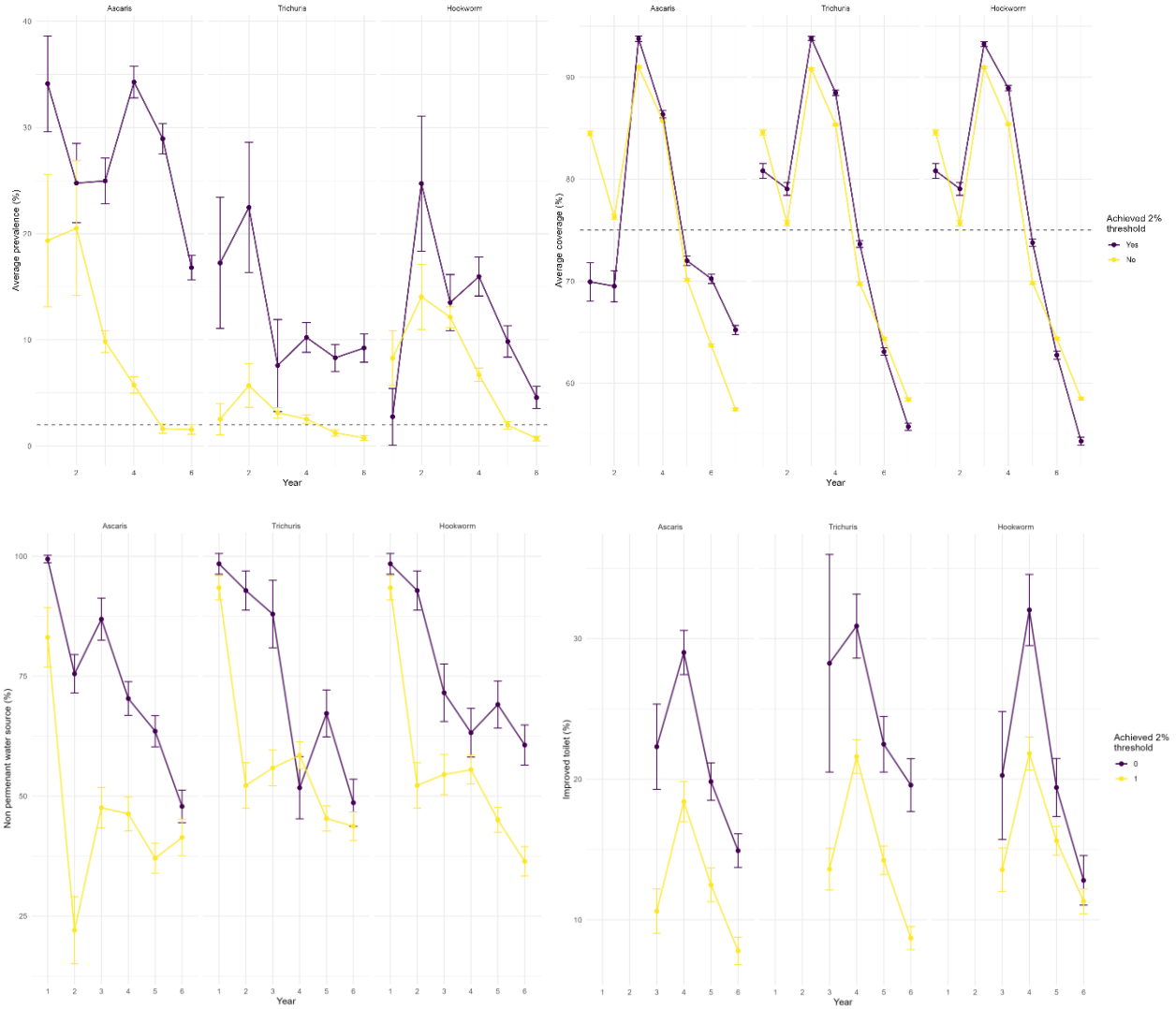


Figure 6.9: The difference in the longitudinal recording of covariates between kebeles that did and did not reach the World Health Organisation (WHO) target of <2% soil-transmitted helminth (STH) prevalence. A) *The difference in prevalence between kebeles that do and don't reach the target, shown as a dashed line at 2%.* ***B)*** *The difference in treatment compliance between kebeles reaching the targeted prevalence. A dashed line at 75% shows the coverage target as defined by WHO.* ***C)*** *and* ***D)*** *The significant water, sanitation, and hygiene (WaSH) covariates associated with a difference in prevalence between kebeles reaching the target.*

3.8. The spatial scale used to measure soil-transmitted helminth prevalence within a population

The Geshiyaro project data presents the opportunity for large sample sized analyses at different spatial scales. The smallest spatial scale enumerated by the project is one administrative unit smaller than that used by the WHO (i.e. admin level 3 for Ethiopia). As such, the data collected by the project can be used to validate if the spatial units used by the WHO in this low prevalence setting is appropriate, or does it hide heterogeneity in prevalence and MDA coverage levels as posited in **Chapter 5**. As previously discussed, a reduction in prevalence, through many cMDA rounds for example, is associated with a higher level of parasite burden aggregation in the community (**Figure 6.5**) [49]. Therefore, this may increase the chance of hotspots of infection detectable at small spatial scales but not at larger ones. Too large a spatial scale will aggregate prevalence over many tiers of heterogeneity, loosing the power to detect the local prevalence in a kebele or household.

Figure 6.10 shows the variation of kebele level prevalence (admin level 4) within woredas that have been classified against the WHO threshold targets of <2% prevalence in SAC (the threshold for MDA cessation), and <10% prevalence (sMDA every two years). The mean (dashed box plot line) and median (solid box plot line) prevalence of kebeles within each respective woreda classification all fell under the targeted threshold. Nevertheless, there were 15.6% (maximum prevalence: 26.7%), 13.0% (maximum prevalence: 6.92%), and 16.9% (maximum prevalence: 7.33%) kebeles recording an average prevalence higher than the 2% averaged at the woreda level for *A. lumbricoides* and *T. trichiura* and hookworm, respectively. There were a further 14.0% (maximum prevalence: 73.5%), 14.6% (maximum prevalence: 22.5%), and 9.68% (maximum prevalence: 22.6%) kebeles recording an average prevalence higher than the 10% averaged prevalence at the woreda level for *A. lumbricoides* and *T. trichiura* and hookworm, respectively. The number of outliers is to be expected given the increased level of aggregation seen at baseline for these species (**Figure 6.5**).

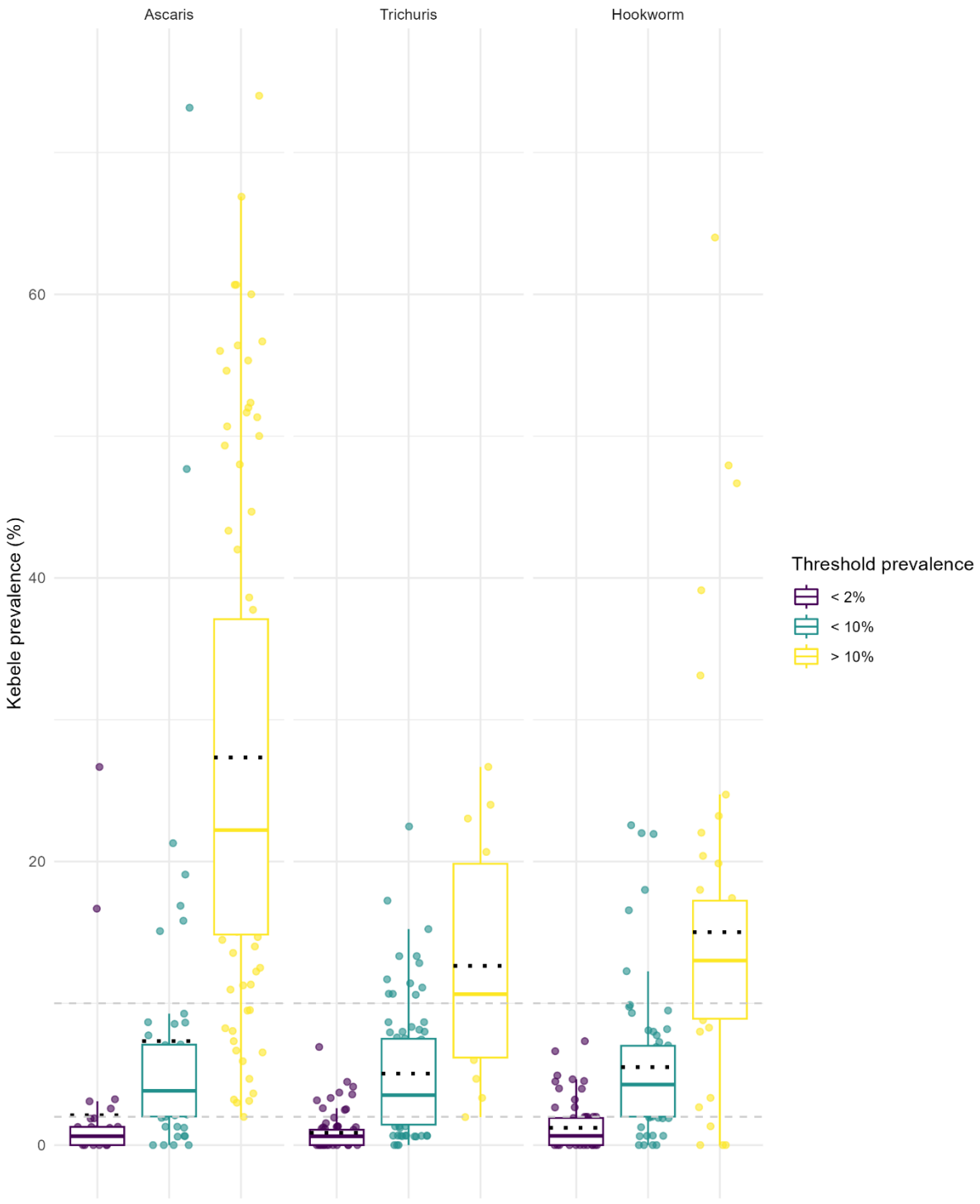


Figure 6.10: The variation in kebele prevalence within woredas respectively classified as reaching less threshold targets for each species. *The variation of prevalence that is aggregated when using woreda (district) level statistics is shown, using the fine-scale data from the Geshiyaro sentinel site data. Woredas are classified against the prevalence threshold for changing MDA treatment frequency as guided by WHO: MDA cessation at < 2% STH prevalence in SAC; <10% MDA biennial treatment frequency. Dashed grey lines show these*

thresholds. Prevalence is calculated from school-aged children (SAC) prevalence only in keeping with the WHO recommendations. The median value (solid line) and mean value (dashed line) of kebele prevalence is shown in each box plot.

4. Discussion

4.1. The significance of community-wide mass drug administration for the control of soil-transmitted helminths

To date, this is the largest and longest running study investigating the impact of implementing cMDA, over the routinely implemented sMDA. Similar studies investigating cMDA are detailed in **Table 1.1**, however this is the first study to conclusively show a statistically significant reduction in the prevalence of STH due to multiple rounds of cMDA compared to sMDA in low prevalence settings. Despite baseline measurements reporting a higher prevalence of infection in Arm 3, a greater relative reduction prevalence was observed in Arm 1, and Arm 2 to a lesser extent, compared to Arm 3. Despite the significance of the relative reduction in intensity for *A. lumbricoides*, this was only significant in Arm 2 for *T. trichiura* and hookworm. The observed low prevalence, intensity, and focal distribution of *T. trichiura* and hookworm (**Figure 6.1**) and consequent low statistical power recorded by the Geshiyaro project are likely explanations for the absence of a similarly significant impact.

The integrated control of STH showed a differing impact on the control of faecal-orally transmitted species (*A. lumbricoides* and *T. trichiura*) compared to skin penetrator species (hookworm). Faecal-orally transmitted species were less likely to be found in Arm 2, whereas skin penetrator species were more likely to be found in Arm 2, when compared to Arm 1. This may be due to differences in the access to WaSH infrastructure between the two intervention arms. A more extensive analysis into the variation of WaSH available between the intervention arms is presented in **Chapter 7**, which addresses the question if the difference in the odds of infection reported is significantly associated to the access of WaSH infrastructure.

The results of the Geshiyaro project have shown the value of using cMDA over of sMDA in this setting. The implications of this work on the future of STH control are reliant upon realistic evaluation of the resources available to implement changes to national control programs. Implementing a solely MDA-focused strategy for the control of STH is arguably more

achievable than accomplishing universal access to improved WaSH infrastructure. The World Bank recently estimated there is an annual $140 billion spending gap to achieving universal WaSH coverage [191]. Transforming programmes from sMDA into cMDA would also require significant investment, and key barriers to implementation would need addressing. These include the availability of human resources and high-quality sensitisation resources, an increase in drug stocks either from enhanced pharmaceutical company pledges or in-country purchases, and the impact of extra logistical pressure on existing governmental infrastructure and budgets [192].

The results of this project should also be interpreted in the context of which they were delivered. The participants receiving cMDA in Arm 1, also benefitted from the construction of WaSH infrastructure. This may have influenced the individual willingness to partake in cMDA, enhancing drug taking behaviour. Furthermore, there was a constant presence of project representatives in the districts of Arm 1 and Arm 2 to conduct the sentinel site data collection. This visual reinforcement of the project, the interest in individual parasite loads presence would have served as a reminder of the importance of taking part.

The impact of cMDA distributed by the project is compared to the national sMDA program, which has been reported to achieve much lower coverage rates (~50%). This significant difference in coverage achieved between arms will impact control efficiency. A follow-up study of comparable coverage rates achieved for sMDA and cMDA would be beneficial. Such studies may indeed show that high coverage of sMDA is not possible, due to a high proportion of non-attending SAC, therefore reinforcing the importance of cMDA, or at least community-based methods of MDA delivery to SAC, rather than school-based methods.

4.2. Covariates affecting the impact of community-wide mass drug administration on the control of soil-transmitted helminths

The recorded age distribution of infection showed the expected relationship with age and infecting species, as has been well documented previously. Aside from corroborating with previous studies, this demonstrates the importance of measuring infection across the whole community at low prevalence levels. The increased odds of infection seen in non-SAC age groups for hookworm infection suggest that programs enumerating only SAC may pre-

emptively stop or slow control efforts, as demonstrated in **Figure 6.10**. Furthermore, it demonstrates the increase in equity of treatment if cMDA protocols are implemented.

There was a significant association between recent drug swallowing behaviour of participants and their infection status, as has been shown in previous studies, and more broadly to kebeles reaching the 2% prevalence target, compared to those that did not [170]. This positive association at the individual level was not observed when assessing the compliance and prevalence or intensity aggregated at a kebele level. This loss of significance with aggregation of data is interesting. It may highlight flaws in the data recording cMDA in Arm 1 and Arm 2, or it may simply be a reflection of the high variability in parasite loads between individuals (the negative binomial distribution of parasite number person) linked to high aggregation patterns (low *k* values).

It is unintuitive that treatment and prevalence are not positively correlated, due to the multiple studies reporting otherwise. Although the biometrically enhanced monitoring of the population provides the opportunity to longitudinally follow the population with assumed high-fidelity year-on-year, the Geshiyaro census may be missing segments of the population as suggested in **Figure 3.2**. As such, the project may be recording the behaviour of participants who do readily take medication, and are likely to interact with such a program. The census may not have fully captured the population who routinely miss MDA activities, the population who do not trust the control program, and those who did not wish to consent to taking part. The latter response does not prevent the participant from receiving MDA, the first and second eventuality is likely that the participant will never comply with such control programs.

Secondly, the MDA treatment recording may not have accurately recorded all the treatments given. For example, HEW may have distributed some medication without recording the participant against the census, or the data quality for that individual may have been classified as too poor to be included in the dataset, and was removed as part of the deduplication process. As such, it is intuitive that if the denominator or numerator is incorrect, assessing the individual level associations between treatment and prevalence in a short time frame (was the person treated at the last available treatment round), that the expected positive association is found between treatment and prevalence of infection.

Alternatively, if the data is accurate, perhaps prevalence is significant at the individual level, and the increased heterogeneity in the distribution of infection seen in low prevalence settings then aggregated in a larger population, such as a kebele or woreda, mute this effect. For example, it seems likely that predisposition to infection (due to behavioural, cultural, environmental of genetic factors) 'trumps' treatment as the driver for reinfection post treatment. This explanation requires further study.

4.3. Validating the spatial scale used to enumerate the impact of community-wide mass drug administration

The increase in aggregation (measured inversely by the aggregation parameter, *k*) after multiple treatment rounds for all species (**Figure 6.5**) translates to the existence of hotspots of infection within individuals, household or small villages. This highlights the importance of fine-scale monitoring and increasing sample sizes at low prevalence levels to accurately measure the prevalence of infection. This aggregation of infection was demonstrated in the variation in kebele level prevalence within woredas (**Figure 6.10**).

In woredas classified as reaching <2%, the high number of outliers falling above the threshold cut-off for MDA program cessation is indicative that even when a community has reached EPHP and has a woreda aggregated prevalence in SAC <2%, there is still a considerable amount of infection remaining in the community. These kebeles reporting higher prevalence will likely sustain the transmission of STH within and between communities, leading to recrudescence of infection back to levels requiring treatment again if MDA ceases as stipulated by the WHO guidelines.

The Geshiyaro data highlights elements of STH control policy which would benefit from change, in particular, areas of low prevalence. Following the recommendation of the WHO, the woredas reporting <2% prevalence would cease to receive national deworming. As the data in **Figure 6.10** demonstrates, this would be detrimental to control, as within woredas labelled as <2% are kebeles reporting high prevalence, which would re-seed infection in an uncontrolled manner in the absence of routine de-worming. Although the number of people still infected in these woredas is small, their impact on the rest of the woreda's prevalence is disproportionate as just one infected individual can seed infection to the whole community. Instead of treatment cessation, the participants in woredas with <2% prevalence would

benefit from a trial of fine-scale mapping. Introducing fine-scale mapping once 2% prevalence has been reached within a district would enable kebele-level treatment and therefore targeting of remaining hotspots of infection. In the context of Ethiopia, the existing infrastructure of health posts managed by the volunteer network of HEW within each kebele would provide a suitable foundation for this to be managed. Furthermore, utilising additional networks such as antenatal care which interact with some of the highest burdened population (preSAC, WRA) may provide an additional avenue for both diagnosis and subsequent treatment.

4.4. Validating the definition of elimination as a public health problem (EPHP)

The definition of EPHP is <2% prevalence of MHII in SAC, as diagnosed by Kato Katz. It should be noted that the prevalence of MHII infections recorded by the project has satisfied the EPHP criteria at the woreda level. However, the prevalence of infection reached above 50% in one woreda and fell consistently between 10-40% at baseline. Therefore, using the WHO treatment guide, these communities would receive annual deworming treatment. This data highlights the fact that much infection persists even when the EPHP target has been met. A considerable proportion of the population are still infected, and although low average intensity of infection is reflected by reduced morbidity, the continued low levels of infection act to sustain transmission in the long term.

4.5. Limitations

Due to the low prevalence and intensity found in the project population, this analysis would be enhanced by the use of higher sensitivity molecular methods of parasitological diagnosis such as qPCR [74]. This enhanced sensitivity method will be implemented as part of the endline analysis in Year 8 (**Figure 1.5**). At the low prevalence levels currently reported, there is a fair chance that infection may be missed during diagnosis based on Kato Katz, despite the use of quadruple slides. Repeating this analysis when qPCR results are available is recommended.

5. Conclusion

This is the largest and longest study of the impact of integrated control on STH to date. It has shown clearly that cMDA is highly beneficial for the reduction of STH prevalence and intensity,

most notably and consistently for *A. lumbricoides*. The cMDA implemented as part of the Geshiyaro project, has been achieved through the utilisation of an existing network of HEW employed by the Ethiopian FMoH, who underpin the healthcare delivery in the country. The HEW are already mobilised for the distribution of the national sMDA. Despite utilising this existing network, it should be noted, that cMDA incurs a greater cost. Economic analysis of the project is planned upon completion, and it would be prudent to assess if the gains in prevalence and intensity reductions of STH are enough to warrant the increased costs required to implement such control.

Once prevalence is very low (and hence highly aggregated), such as that recorded currently by the Geshiyaro project, a change in control strategy may be desirable based on targeted treatment or even test-and-treat, providing diagnostic costs are not prohibitive. Pooled sampling strategies have been trialled by small studies in this vein, as a method to reduce such costs. Individuals identified as being predisposed to infection could be continually treated. This population may be the final barrier for reaching transmission interruption of STH, further research into this subset of the population is recommended and highly anticipated.

Chapter 7: Evaluating the impact of water, sanitation, and hygiene upon the transmission of soil-transmitted helminths over six years of the Geshiyaro project in southern Ethiopia

Dissemination

This chapter has been adapted from the paper titled, “Evaluating the impact of water, sanitation, and hygiene upon the control of soil-transmitted helminths over six years of the Geshiyaro project in southern Ethiopia”, currently under review with Transactions of the Royal Society of Hygiene and Tropical Medicine.

Motivation

The provision of functional WaSH infrastructure is essential for sustaining the immediate gains provided by MDA, ensuring control is maintained in the long term by reducing the pool of infectious material from the environment. However, many studies and meta-analyses of WaSH impact on STH control have failed to conclusively show significant effect. This chapter analyses the data collected annually from the sentinel sites of the Geshiyaro project, whereby participants are asked to answer a questionnaire on their WaSH access and usage, alongside coprological diagnosis of their stool.

1. Introduction

The transmission of STH is dependent on a host coming into contact with an infectious lifecycle stage of the parasite. Infectious life cycle stages develop from eggs expelled in faeces, excreted from an infected host, which then mature over a period of weeks in the environment before reaching their infectious state. As such, the transmission of STH is common in areas of low hygiene, and infection with STH acts to perpetuate the link between poverty and poor health [193]. The method of transmission used by helminths divides STH species into two categories: those using the faecal-oral pathway or those relying on skin penetration [5]. Infectious *A. lumbricoides* and *T. trichiura* eggs are ingested from contaminated fingers, food, or water, whilst the infectious free-living hookworm larval stage penetrate exposed skin, often bare feet and hands, in contact with soil contaminated with larvae [1].

The mainstay of STH control is the distribution of chemotherapeutic drugs to SAC, regardless of infection status, referred to as MDA [6]. This broad-strokes approach has been successful in controlling morbidity, and global trends have shown a general decrease in the proportion of heavy intensity infections [163]. The success of treatment is short-lived however, as neither infection or treatment induces active immunity against the parasites, thus making re-infection from reservoirs of infection common [55,194]. As such, large improvements in access to and quality of WaSH infrastructure is an important and necessary addition to MDA for the sustained control of STH.

1.1. Difficulties in measuring water, sanitation, and hygiene covariates

Although the correlation between decreasing STH prevalence and increasing use of WaSH infrastructure is epidemiologically logical, many research studies and meta-analyses have failed to conclusively show a positive association [68,195]. There are many reasons for this. WaSH research is fraught with issues in accurately recording infrastructure use. Participants may bias their answers to questionnaires (social desirability bias), and recording the presence of infrastructure cannot be conflated with its use or functionality. The definition and choice of questions that can be used to measure WaSH variables via interview is challenged by the level of specificity requested (binary responses vs. the definition of differing levels or quality of access). These questions are subject to interpretation by the data collectors and participant, and the consequent answers in turn are subject to interpretation during analysis.

Heterogeneity in access to differing qualities of infrastructure, or contradictory behaviours will impact the analysis of a single variable either measured at the community-level, household, or individual level. Individuals will undoubtedly be heterogeneous in their exposure to risk factors due to their different behavioural characteristics. For example, a child may attend a school with poor toilet facilities, play in unprotected rivers socially, and eat and drink water collected from a protected water source. Each behaviour carries either a low or high risk of STH infection, and therefore an individual's exposure to infectious material is resultant upon the combination of multiple variables. The risk factor variation will impact the analysis attempted of a single WaSH covariate. Until the spatial kernel of STH transmission is defined (over what spatial scale does transmission occur and at what frequency), presumably dependent on the level of behavioural, and infrastructure access heterogeneity in the community, the relevant spatial scale at which to measure the WaSH use for the control of STH is difficult to define.

Finally, the length of time in which WaSH data is collected can hinder the opportunity to record any impact. Often studies are short, due to financial constraints, and yet the impact of WaSH upon the community burden of infection is enacted over a longer period. This is due to the lead time required to account for construction and implementation, community acceptance of the infrastructure, and then the impact of continuous infrastructure use time to significantly reduce exposure to infection and thus impact parasitological monitoring.

1.2. Using the Geshiyaro project to measure the impact of water, sanitation, and hygiene covariates

The Geshiyaro project is designed to explore the impact of improvements in cMDA implemented in parallel with the construction of WaSH infrastructure and BCC, referred to as integrated control. The baseline WaSH covariates recorded by the project have been previously published [66]. The design of the study, and epidemiological analyses of the data collected to date have been published [45,60,84,86–89]. The project provides a valuable opportunity to measure the control of STH over a period of eight years, and as such, a large data repository of STH infection in relation to cMDA, and WaSH infrastructure use has been collected [45]. This data is individually-linked, and longitudinally follows participants in southern Ethiopia, forming the longest and largest epidemiological dataset of STH control

published to date. This chapter reports the change in prevalence from baseline to Year 6 of the project, and details associations of infection prevalence and intensity with the survey measured WaSH covariates.

2. Methods

2.1. The Geshiyaro project

The Geshiyaro project enumerates the population of the Wolayita zone in SERS, as illustrated in **Figure 1.5**. To accurately assess the impact of the expanded MDA protocol sMDA to cMDA, and the impact of improved WaSH infrastructure and community sensitisation to it, the Geshiyaro project enumerates populations divided into three intervention arms as described in **Chapter 1**. Stool samples were collected from participants enrolled in the sentinel sites, using methods described in **Chapter 6**, which were biometrically verified and linked to the census (**Figure 4.1**) using methods described in **Chapter 4**.

2.2. Water, sanitation, and hygiene data collection

During the annual collection of faecal samples for sentinel site coprological diagnosis, participants enrolled in the sentinel sites were systematically asked the same questions pertaining to their access to and use of WaSH infrastructure. The 11 questions are shown in **Table 7.1**, which generated 12 variables for analysis. Of note, three variables (hand washing with water and soap, attendance at school, and drying up of water sources) analysed were resultant upon a previous answer, as demonstrated in **Table 7.1**. Just under half the questions (n = 5), were recorded privately as the data collector's observation instead of asking the participant. Responses are coded as improved or not improved according to the WHO Joint Monitoring program (JMP) guidelines [196].

Question	Choice of answer	Categorisation according to JMP guidelines	Variable name
What is the main source of drinking water for your household?	Piped directly into the home with a tap in the household	Improved	improvedWaterSource
	Piped into the property and maybe shared with other households	Improved	
	Piped to a neighbour	Improved	
	Public tap (standpipe)	Improved	
	Shallow well with hand pump	Improved	
	A hand dug well with lid (protected)	Improved / fresh water	
	A hand dug well without lid (unprotected)	Not improved / fresh water	
	Rainwater collected by the household	Improved / fresh water	
	Surface water (river/stream/lake/canal)	Not improved / fresh water	
	Water collected from a protected spring	Improved / fresh water	
	Water collected from an unprotected spring	Not improved / fresh water	
	Cart with small tank or drum	Improved	
	Other	NA	
	Don’t know	NA	
How long does it take for you to reach your water source, wait, collect, and return?	0-15 minutes	Improved	timeWaterJourney
	15-30 minutes	Improved	

	30-45 minutes	Not improved	
	45-60 minutes	Not improved	
	60+ minutes	Not improved	
If improvedWaterSource categorised as 'freshwater', does this water source dry up during the dry season?	Yes / No	NA	nonPermenantWaterSource
Where do you normally bathe yourself?	At home with water collected from community water supply (borehole/tap etc)	Improved	safeBathingWater
	At home with rainwater	Improved	
	At home with water collected from a fresh water source (river/lake/spring)	Not improved	
	In the community at protected water sources (covered spring/hand dug well/community standpipe)	Improved	
	In the community at unprotected water sources (river/lake/spring)	Not improved	
	Other	NA	
	Don't know	NA	
What kind of toilet facility do members of your household normally use?	Pour flush	Improved	improvedToilet
	Ventilated	Improved	
	Pit latrine with slab	Improved	
	Pit latrine without slab	Not improved	
	Composting toilet	Improved	
	Bucket	Not improved	
	No facility	Not improved	
Where is the toilet facility located? (Observation)	In own house	Private	privateToilet
	In own property	Private	
	Elsewhere	Not private	

Is this toilet facility shared with other households?	Yes / No	NA	sharedToilet
Are there handwashing facilities within three meters of a toilet? (Observation)	Yes / No	NA	Handwashing
If yes to 'handwashing', is there water available at this facility? (Observation)	Yes / No	NA	HandwashingWater
If yes to 'handwashing', is there soap or detergent available at this facility? (Observation)	Yes / No	NA	HandwashingSoap
Is the individual wearing shoes? (Observation)	Yes / No	NA	Shoes

Table 7.1: Questions asked annually to sentinel site participants pertaining to WaSH infrastructure access. *The questions, available choices, and their subsequent categorisation used for the analysis of WaSH infrastructure access and use in association with soil-transmitted helminth prevalence. Note three questions are dependent on a previous response, and thus were not asked to all participants. The categorisation column shows the relevant categorisation of the answer against the Joint Monitoring program (JMP) guidelines* [196].

2.3. Data analysis

The STH species were grouped according to their transmission pathways for the analysis of prevalence against WaSH infrastructure access and use. Individual level associations between the binary variable of prevalence and WaSH variable use were analysed using binomial logistic regression. Kebele level associations between the aggregated prevalence and access to WaSH variable were analysed using linear regression. The glm() function of the "stats" package was used for both regression models. Both regression methods were controlled for intervention arm and project year. Collinearity was assessed, and covariates with a variance score above 10 were excluded. The ORs were calculated from the exponentiated logistic and linear regression models. Bivariate and multivariate models were used to assess WaSH variables.

The heterogeneity of an individual's behaviour was classified into consistent low-risk or high-risk. The responses used to classify such behaviour included the use of an improved water source, the ability to access water in less than 30 minutes, shoe wearing, access to an improved toilet facility, access to safe bathing water, and a toilet located within the household compound that is not shared with other families.

Significance levels are reported against the following thresholds, $p < 0.05$, $p < 0.01$, and $p < 0.001$, with significance considered $p < 0.05$. All analysis was conducted in R studio (version 4.3.2). The three questions dependent upon a previous answer were removed from the multivariate analysis as limiting it to individuals answering all the available questions would have significantly limited sample size.

3. Results

3.1. The change in soil-transmitted helminth prevalence

The prevalence of STH at baseline (see **Figure 1.7**), and the latest round of sentinel site data collection in Year 6 shown below in **Figure 7.1**. In general, STH decreased in prevalence over the six years of project interventions. Overall, the baseline prevalence of faecal-oral and skin penetrator species was respectively 24.4% (95% CI: 22.7 – 26.2%) and 8.71% (95% CI: 7.55 – 9.86%) in Arm 1, 9.24% (95% CI: 8.09 – 10.4%) and 15.0% (95% CI: 13.6 – 16.5%) in Arm 2, and 46.0% (95% CI: 43.9 – 48.0%) and 13.0% (95% CI: 11.6 – 14.4%) in Arm 3. By the latest data collection, prevalence had dropped to 5.27% (95% CI: 4.36 – 6.18%) and 1.21% (95% CI: 0.76

– 1.66%) in Arm 1, 3.50% (95% CI: 2.77 – 4.23%) and 1.30% (95% CI: 0.85 – 1.75%) in Arm 2, and 25.5% (95% CI: 23.7 – 27.3%) and 2.21% (95% CI: 1.61 – 2.82%) in Arm 3. This equated to a 78%, 62%, and 44.5% decrease in faecal-oral species prevalence and an 86%, 91%, and 83% reduction in skin penetrator species across Arm 1, Arm 2, and Arm 3, respectively. A markedly reduced impact was seen in the reduction of faecal-oral species in Arm 3, which received sMDA and no further WaSH intervention by the Geshiyaro project.

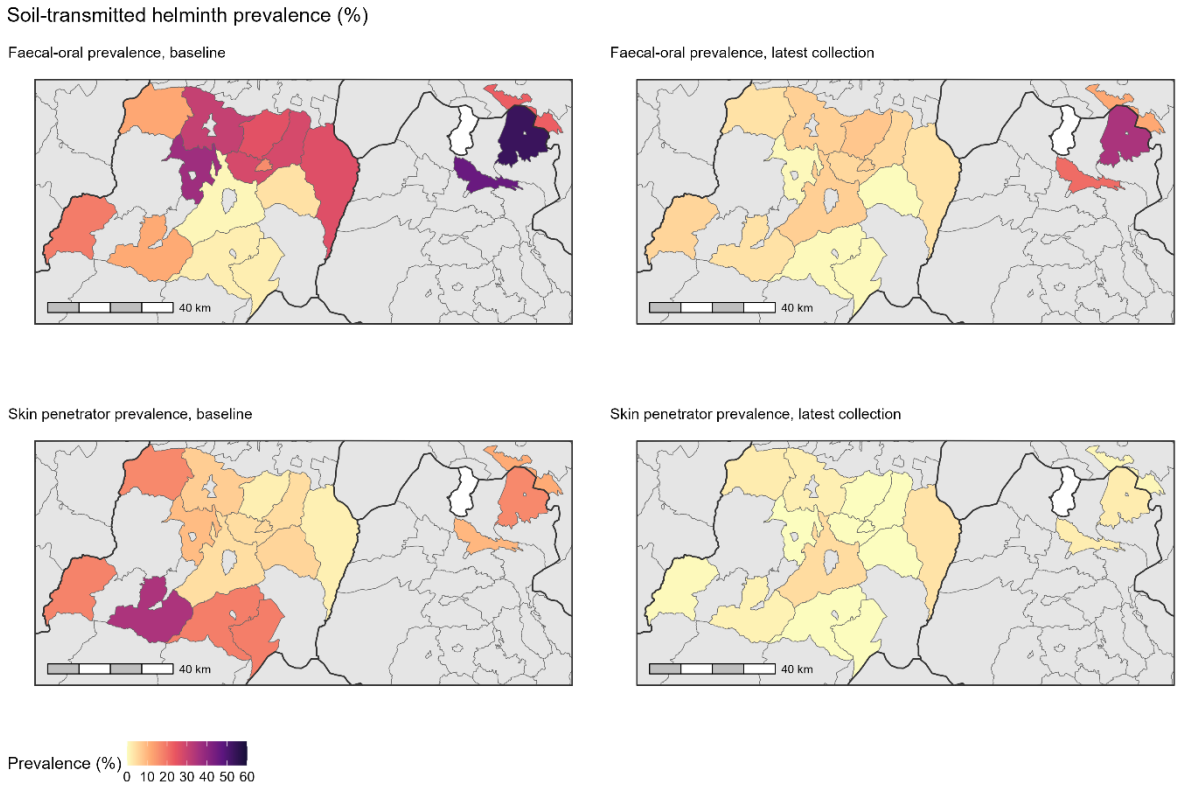


Figure 7.1: The prevalence of faecal-orally transmitted and skin penetrator soil-transmitted helminths at baseline and project Year 6 (2024). *The left-hand cluster of districts (woredas) fall into Arm 1 and Arm 2 of the project, which divides the Wolayita zone. The right-hand cluster of woredas are those of Arm 3, or the control arm. Bold lines denote the boundaries of administrative zones of south Ethiopia.*

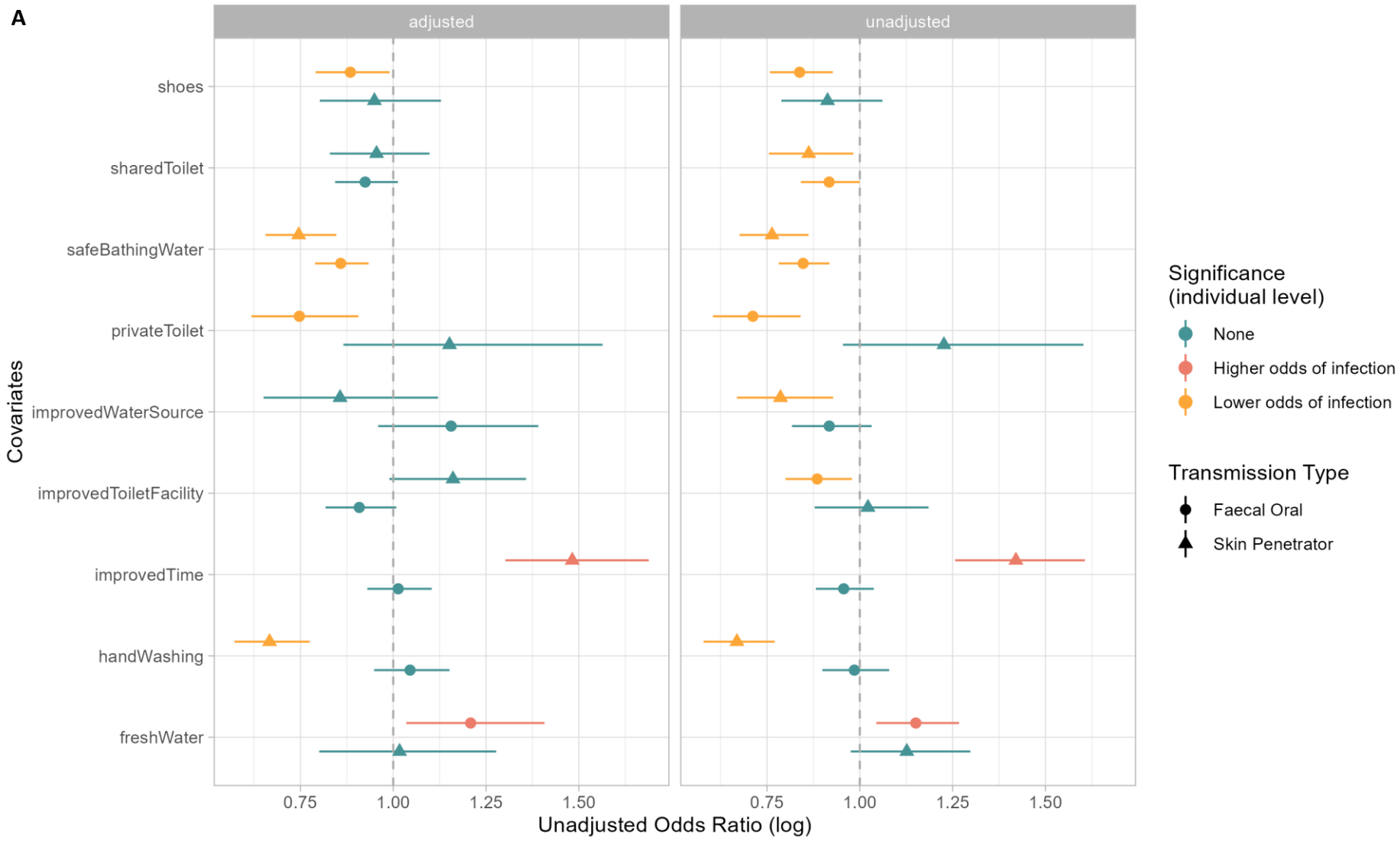
3.2. The change in the odds of infection in relation to water, sanitation, and hygiene infrastructure access

The results of the bivariate (OR) and multivariate (AOR) analysis of STH infection and WaSH infrastructure access available at an individual and kebele level is shown in **Figure 7.2**. In general, the significant associations between prevalence and WaSH infrastructure coverage that are seen at the individual level are lost when aggregated at the kebele level. This is true

for the protective association between shoe-wearing, accessing safe bathing water, using a private toilet, and the presence of a handwashing station near a toilet facility. The coverage of these WaSH variables is shown in **Figure 7.3**. This demonstrates the importance of ubiquitous and consistent usage of WaSH infrastructure by a whole community to reduce community wide STH transmission, and subsequently reach transmission break; where the R_e of the helminth parasites falls below unity in value [15]. Individually, there is a protective effect, but this progress or protection from transmission is lost when variation in behaviour of the community is included in the analyses when aggregated across the larger population size of a kebele.

3.3. Water access and soil-transmitted helminth infection

The only variable associated with an increased odds of infection at both the individual and kebele level, was the ability to access water in trip that totalled less than 30 minutes (inclusive of time to source, queuing, and returning), which increased the likelihood of skin penetrator species infection by 48% at the individual level (AOR: 1.48 (95% CI: 1.30 - 1.69), $p < 0.001$), and 11% at the kebele level (AOR: 1.11 (95% CI: 1.03 - 1.19), $p < 0.01$). This is a somewhat surprising relationship of an improved WaSH indicator with increased prevalence. However, access to water in less than 30 minutes is indicative of the presence of either a close waterbody or water collection point. Indeed, 88.9% of individuals that could collect their water in less than 30 minutes accessed an improved water source. This is further indicative of a consistent water table, and thus could indicate soil with an increased moisture content. As the water source is close, it could be presumed that frequent trips are made to the source. Thus, increased walking routes to access water on moist terrain could increase the chance of infection from infective larvae which favour moist soil conditions.


A
adjusted
unadjusted
shoes
sharedToilet
safeBathingWater
privateToilet
improvedWaterSource
improvedToiletFacility
improvedTime
handWashing
freshWater
Covariates
0.75
1.00
1.25
1.50
Unadjusted Odds Ratio (log)
Significance (individual level)
None
Higher odds of infection
Lower odds of infection
Transmission Type
Faecal Oral
Skin Penetrator

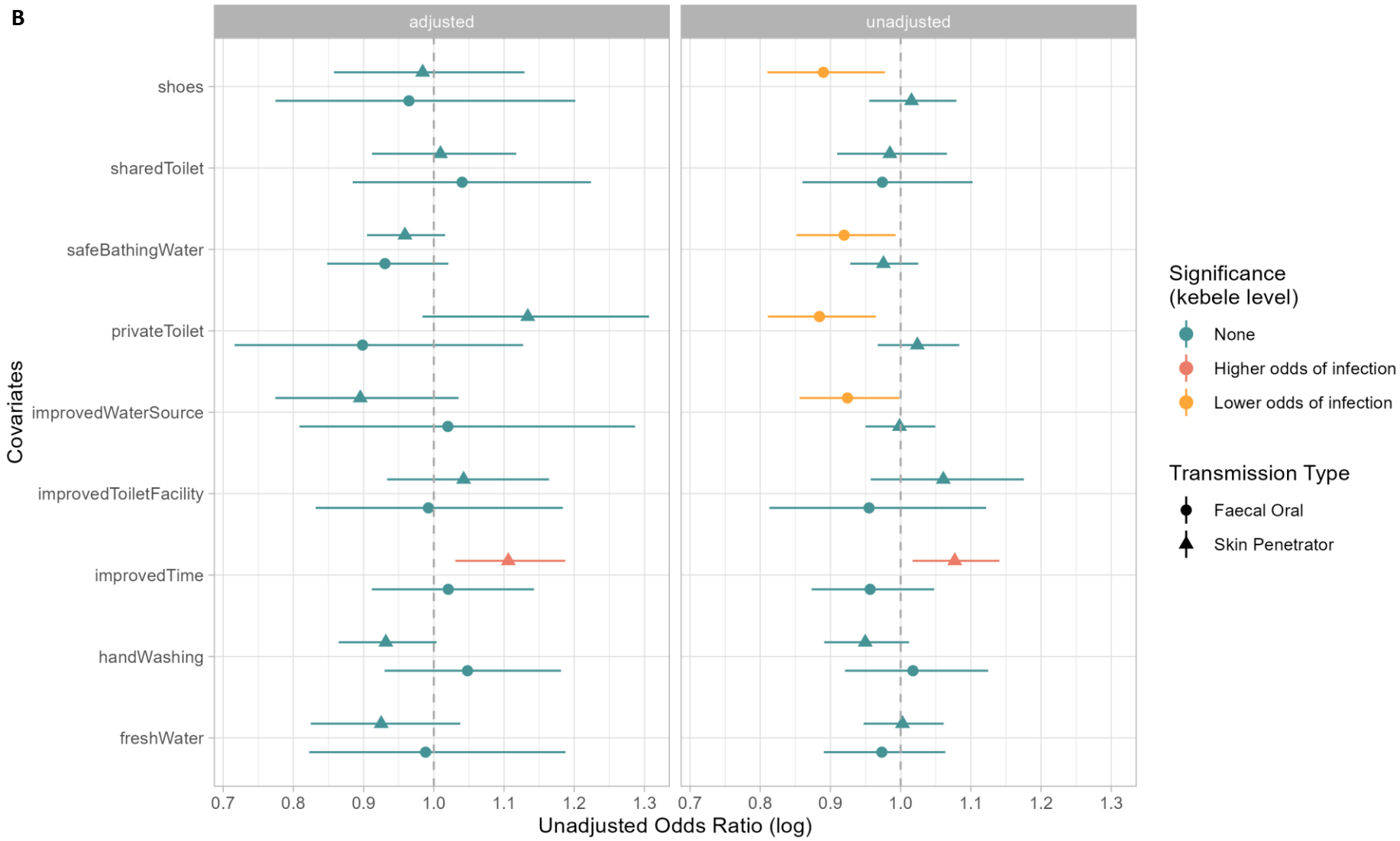

B
adjusted
unadjusted
shoes
sharedToilet
safeBathingWater
privateToilet
improvedWaterSource
improvedToiletFacility
improvedTime
handWashing
freshWater
Covariates
0.7
0.8
0.9
1.0
1.1
1.2
1.3
Unadjusted Odds Ratio (log)
Significance (kebele level)
None
Higher odds of infection
Lower odds of infection
Transmission Type
Faecal Oral
Skin Penetrator

Figure 7.2: The association of access to different WaSH infrastructure with STH infection at the individual level (A) and aggregated at the kebele level (B). *The transmission pathways divide the STH species into those that are transmitted by the faecal-oral route (A. lumbricoides, T. trichiura) or via skin penetration (hookworm). The left-hand panel shows the effect of all displayed WaSH variables, adjusted for intervention arm and project year. The right-hand panel demonstrates the effect of a single WaSH variable, adjusted only for the effects of intervention arm and project year. The non-permanent water source and hand washing with water variables are removed from the individual-level adjusted analysis as this question was a follow-up to a previous question, therefore limiting the full analysis to only those who responded to these questions would be under-powered.*

Access to safe bathing water was significantly associated with a 15% and 24% reduction in faecal-oral (AOR: 0.85 (95% CI: 0.78 - 0.92), $p < 0.001$) and skin penetration species (AOR: 0.76 (95% CI: 0.68 - 0.86), $p < 0.001$), respectively, at an individual level. An association was seen at a kebele level in bivariate analysis, but the significance of the association was lost in the multivariate analysis. The majority of participants (29.7%) answered as either bathing in water collected from an unprotected fresh water source (river/lake/spring), whilst 26.2% used water collected from a borehole or tap (protected source).

The access of fresh water (water from a hand dug well, surface water (river, lake, stream), rainwater, or spring) was associated with 21% increased odds of infection by faecal-orally transmitted species at an individual level (AOR: 1.21 (95% CI: 1.04 - 1.41), $p < 0.05$). These unprotected water sources are prone to contamination by toilet waste-water run-off and open defecation, which may be causing this association.

3.4.Sanitation access and soil-transmitted helminth infection

Overall, access to an improved toilet facility was inconclusive across all transmitter types. Access to improved toilet infrastructure was only associated with an 11% reduction in faecal-orally transmitted species (0.89 (95% CI: 0.80 - 0.98), $p < 0.05$) at an individual level. This relationship was observed only in the bivariate analysis and was lost when holding all other WaSH variables constant in the multivariate analysis, showing the reduction of effect against the heterogeneity in other WaSH behaviour. Interestingly, when toilets infrastructure was assessed against a simpler, binomial, metric (structure on private property or shared with

other families), an important and intuitive relationship was seen whereby a private toilet facility (within the household, or within the household compound) was associated with a 25% reduction in the odds of faecal-orally transmitted infection at an individual level (AOR: 0.75 (95% CI: 0.62 - 0.91), $p < 0.01$)).

The access to handwashing facilities near a toilet was associated with a 33% reduction in skin penetrator species (AOR: 0.67 (95% CI: 0.57 - 0.78), $p < 0.001$) at an individual level. This question was posed to individuals that answered that they had access to a toilet within their household compound.

Most surprisingly, shoe-wearing was not associated with a protective effect against hookworm infections at either the individual level or aggregated at a kebele level. A reduced AOR and OR was observed for skin penetrator infections, however this was not significant as the confidence intervals crossed the value of 1 (no effect) as shown in **Figure 7.3**. It was, however, associated with a 12% reduction in the risk of infection by faecal-orally transmitted species at an individual level (AOR: 0.88 (95% CI: 0.79 - 0.99), $p < 0.05$). Some reasoning for the lack of association includes participants who would ordinarily not wear shoes, doing so to greet the interviewer as a function of social desirability bias. Alternatively, hookworm penetration may not only occur through the soles of the feet, as such, children who wear shoes may lie down or play on the ground for prolonged periods of time, allowing larvae to penetrate the skin.

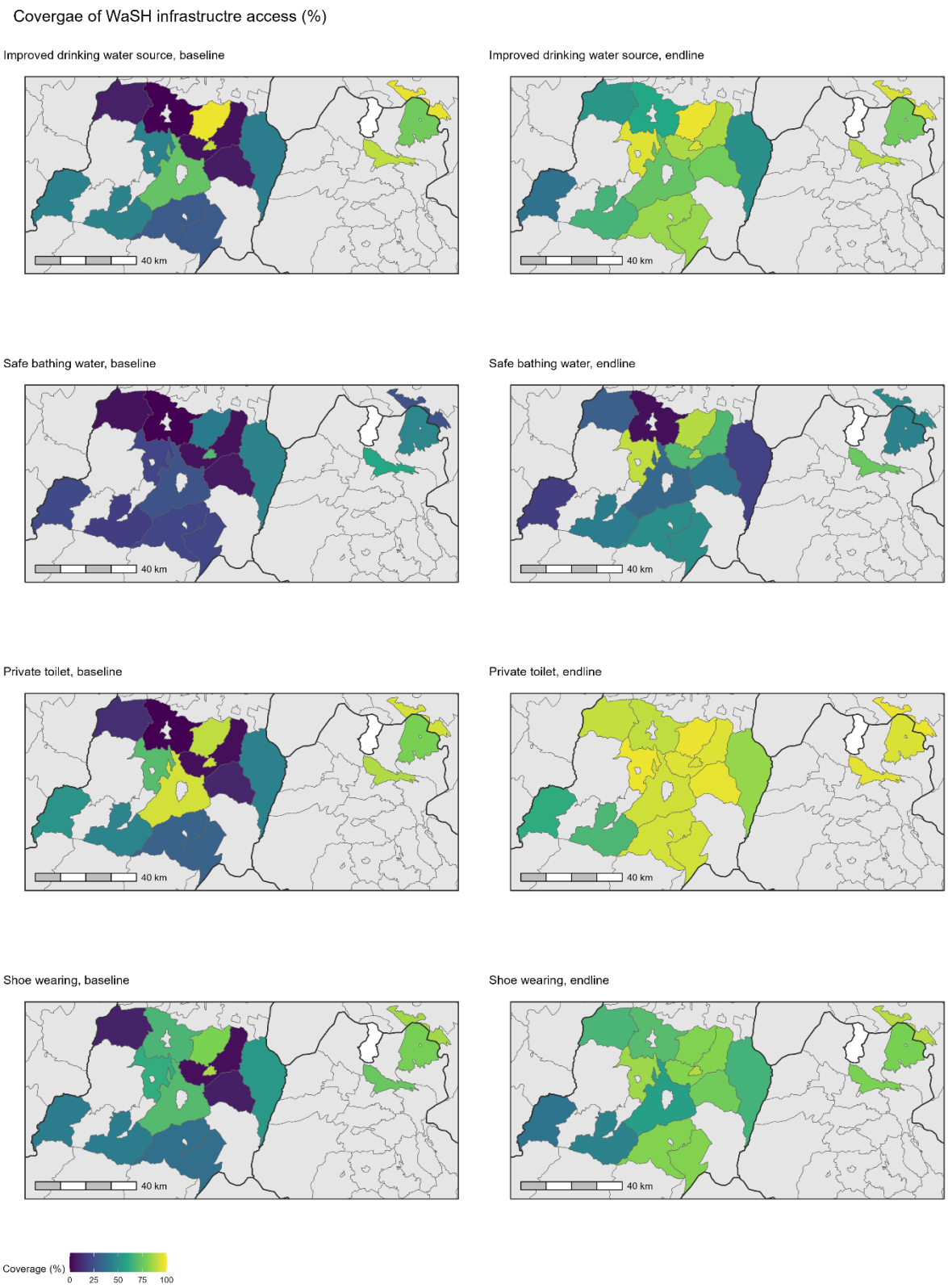


Figure 7.3: The coverage of WaSH variables reported at baseline and the latest data collection. Spatial heterogeneity is seen across the woredas (districts) of southern Ethiopia. *Bold lines show the boundaries between the administrative zones in south Ethiopia.*

3.5. The change in water, sanitation, and hygiene coverage with time

There was a distinct improvement in the coverage of WaSH access over time, which is clearly illustrated in **Figure 7.4**. As the points cluster closer to the higher values of WaSH coverage with time (depicted in the changing point colour), the heterogeneity in the prevalence of STH species across the sentinel sites can be seen to decrease.

There is also a distinct difference between the impact of the improved WaSH infrastructure (implemented in Arm 1) and intervention arm. Participants in both Arm 1 and Arm 2 receive cMDA, whilst participants in Arm 3 (the control arm) receive the national standard program of sMDA. The combined effect of the enhancement in MDA strategy and WaSH variable therefore is clear in Arm 1. The proportion of children who attend school was the only variable associated with a near significant change in STH prevalence in Arm 3. The data used for this analysis was filtered by school age eligibility. In Arm 3, only SAC are treated as stipulated by the national control efforts. The three panels in the plot of school attendance therefore reflects individuals that have access to treatment, similar to that of Arm 1 and Arm 2 in the remaining plots, further demonstrating the positive effect of routine deworming.

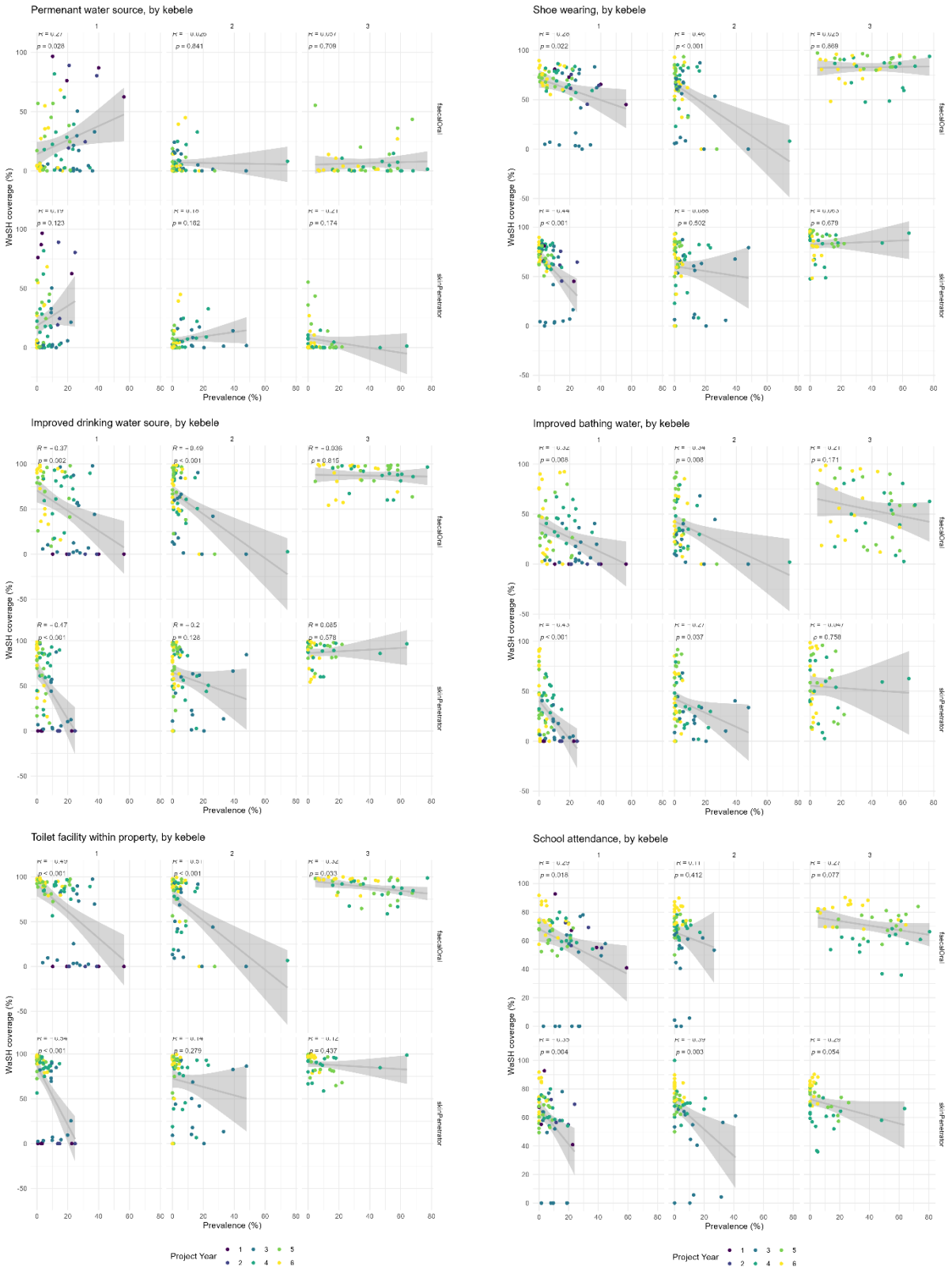


Figure 7.4: The change in prevalence of faecal-orally transmitted and skin penetrator soil-transmitted helminth (STH) species with change in WaSH coverage averaged at the kebele.

A change in the coverage of WaSH covariates can be seen over time, as demonstrated with

the change in point colour. Pearson's R statistic and associated significance value are shown for each plot.

3.6. The difference between homogeneous and heterogeneous individual behaviour

Many studies have shown the importance of the distribution of individual behaviour at MDA activities over time on the probability of STH elimination in a community [89,102,103,197]. In the same vein, the consistency of using and accessing improved WaSH infrastructure at an individual level is assessed in **Figure 7.5**. When examining many WaSH variables, assuming the participant has answered honestly, the response can still be influenced by heterogeneity in risk-taking behaviours. Marking participants as either behaving homogeneously (consistently conducting low risk behaviours, n = 591) or heterogeneously (a mix of low- and high-risk behaviours, n = 20,961), their associated infection levels are recorded in **Figure 7.5**. Only three individuals' behaviour were classified as homogeneously high-risk.

A significant 23% reduction in prevalence was seen for faecal-orally transmitted STH infections only when assessing individual behaviour through binary multivariate regression of heterogeneity (AOR: 0.77 (95% CI: 0.62 - 0.96), $p < 0.05$), holding intervention arm and project year constant. The significance of homogeneous behaviour was lost at both the kebele level and woreda level when using multivariate linear regression. No association was seen for skin penetrating species. The difference in the reduction of prevalence year-on-year is seen (**Figure 7.5**), where individuals with consistent low-risk behaviour reach low-levels of prevalence by Year 5 in both Arm 1 and Arm 2. The homogeneous participants in Arm 2, Year 5 had a combined prevalence of 0% ((95% CI: 0.00 - 0.00), n = 86), increasing only to 2.56% in Year 6 ((95% CI: -2.46 - 7.59%), n = 39). Similarly, homogeneous participants in Arm 1 recorded a low prevalence of 7.14% ((95% CI: -6.86 - 21.14), n = 14) in Year 5, which reached 0% in Year 6 ((95% CI: 0.00 - 0.00), n = 18). Comparatively, the lowest the prevalence reached in the heterogeneous participants was 5.26% ((95% CI: 4.33 - 6.19%), n = 2,205) and 2.51% ((95% CI: 1.82, 3.19), n = 1,996), respectively for Arm 1 and Arm 2 in Year 6.

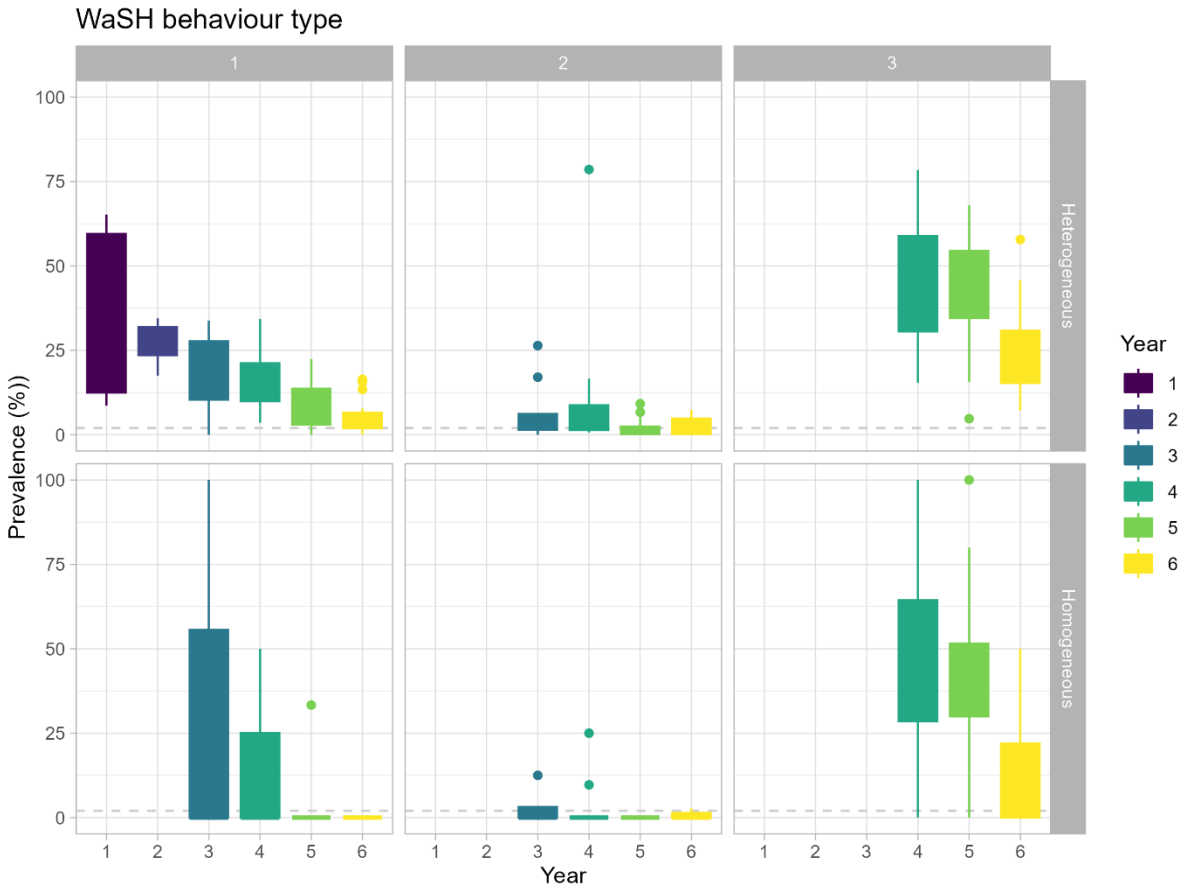


Figure 7.5: The difference in A. lumbricoides prevalence between participants reporting consistent low-risk WaSH behaviour (homogeneous), compared to those who were heterogeneous. *The change in prevalence year-on-year is shown between arms. Participants behaving homogeneously (lower panel) reach prevalence levels below 2%, whereas participants behaving heterogeneously do not. A dashed line indicates the 2% prevalence threshold targeted for STH control.*

4. Discussion

Despite the challenges and ambiguity which faces the analysis of associations between WaSH infrastructure access and the prevalence of STH species, this chapter details some interesting correlations. Prior to the Geshiyaro project, it could be suggested that the answers to WaSH questionnaires often deployed to research infrastructure use and access is flawed by the lack of analytical power. Here, the Geshiyaro project analyses were able to link individual answers to multiple questionnaires over time, in relation to individual parasitological data, showing statistical significance at the individual level.

4.1. The importance of homogeneous low-risk behaviour

The results of this analysis show two key findings. First, there was a significant association found between WaSH access and STH prevalence at the individual level, that was lost when the data was aggregated at the kebele level. This shows the danger of individuality within a community, and future programs should therefore focus on community-based sensitisation and ownership to ensure a unanimous and consistent utilisation of infrastructure provided. Second, individual-based analysis showed that consistently accessing improved WaSH infrastructure (homogeneous behaviour) was associated with a maintained reduction in prevalence to levels at or below 2%, which was lost when a differing quality of infrastructure was used (heterogeneous behaviour). This demonstrates again the importance of consistent behaviour, at the individual level this time, as the interaction with one high-risk activity undoes the infection prevention from any low-risk activity. Both relationships between WaSH activity and prevalence are intuitive, but neither have not been reported in the literature to date.

In Nepal, WaterAid embedded WaSH educational sessions within routine infant immunisation visits, which reported an increase from 2-53% in key hygiene behaviours after one year and an increase in immunisation coverage [198]. Integration of health services across different touchpoints may help with the promotion of consistent WaSH use in the community, therefore improving the sustained control of STH within endemic populations.

4.2. Significant associations found between water, sanitation, and hygiene infrastructure access and usage

The protective effect of shoe wearing (faecal-oral species only), accessing safe bathing water (both transmission types), accessing a private toilet (faecal-oral species only), and the availability of a handwashing station (skin penetrator species only) were all associated with a reduced individual risk of STH infection. This corroborates the results of an Indian study, which similarly found an absence of a protective effect of shoe-wearing, and a protective effect on the availability of handwashing stations for skin-penetrator species [170]. Conversely, the ability to access water in less than 30 minutes and the access to water from a hand dug well, surface water (river, lake, stream), rainwater, or spring, was associated with an individual increase in skin penetrator species and faecal-orally transmitted species, respectively.

The reduction in the prevalence of STH with access to safe bathing water, and in the same vein, the increase of faecal-orally transmitted species with access to unprotected water are indicative of the importance of a safe water supply and the reduction of STH infection. When a household's water supply is limited, an assumed hierarchy of needs can be postulated, whereby water for drinking and food preparation may be prioritised. Therefore, when water supply is plentiful enough to be used at multiple WaSH infrastructure points, it can be suggested that households are more likely to have enough water to facilitate a handwashing station, which was associated with a reduced risk of skin penetrator species infection.

The lack of statistical association between WaSH variables and prevalence measures such as access to an improved toilet facility, may be explained by the contextual analysis. If a toilet was built in the first year of the project, initially this infrastructure will have acted appropriately to remove infectious material from the environment. After several years, if this infrastructure is not maintained, i.e. the collected waste is not removed appropriately, the infrastructure will act as a reservoir of infection. Participants therefore may respond positively to be able to access improved infrastructure, yet this infrastructure made to reduce the risk of infection may be increasing it.

4.3. Limitations

Due to the very low recorded prevalence and intensity of hookworm, and consequent low statistical power, strong associations were less likely to be found in the analyses of associations with WaSH variables. At the low prevalence levels seen in the Geshiyaro project after multiple rounds of cMDA, parasite burden is known to increase in aggregation as measured inversely by the negative binomial aggregation parameter, *k* [49]. The highly aggregated infection at low prevalence means a very few individuals harbour parasites in the total population. The observed aggregation may be a consequence of predisposition to heavy infection by a few individuals (for poorly understood reasons) recorded in the Geshiyaro project [57,60]. The small number of infected individuals may result in difficulties in finding a significant association with the recorded WaSH variables. *A. lumbricoides* and *T. trichiura* infections were more prevalent and were additionally grouped together due to their similar transmission pathways, therefore increasing the power of finding a statistically robust association with WaSH variables. By the latest data collection in year six, all species were recorded at very low prevalence levels. Thus, finding a significant association between this increasingly zero-

inflated dataset (uninfected) is challenging. It is also important to note the transmission dynamics of each STH species will also impact the effect reported. *A. lumbricoides* has a higher R_0 than *T. trichiura* and hookworm, and therefore has a faster time to reinfection compared to the other infections. As such, the effect of the WaSH interventions will be more apparent for *A. lumbricoides* infections compared to the others.

The results of this WaSH analysis are open to different avenues of interpretation due to the imprecise and subjective nature of individual responses to questionnaires. As previous studies have detailed, the answers provided by participants may have been subject to desirability bias. The answers are also subject to the data collector's interpretation and consequent labelling. The questions may also be interpreted differently between participants.

If the questions were answered as objectively as possible, multiple confounding factors remain which may further impact an individual's infection status. The answers provided may have been that which associated with the most common use of infrastructure. For example, an individual may have an improved toilet at home, but their place of work has an unimproved facility where they became infected. As such, it may be prudent in the future to ascertain the different range of facility types used, and rank in order of proportional use. This will also present a challenge, as the individual and data collector may not be as motivated to answer a more detailed questionnaire this as accurately.

Some of the questions were recorded as an observation made by the data collector rather than asking the participant. It should be noted however, that the data collector recording the presence of facilities does not necessarily equate to their use. Furthermore, as with other variables, the facilities will need to be used consistently and kept clean, as it will require just one instance of contact with a contaminated source to enable STH transmission. For example, as previously discussed an individual may have access to improved facilities in their home, but when away at school, work, retail, or leisure they may not.

5. Conclusion

The analyses presented in this chapter have shown for the first time that improved WaSH infrastructure reduces the likelihood of STH infection when longitudinal data is analysed at the individual level, and that consistent WaSH behaviour over time impacts the likelihood of reaching and maintaining low (or no) infections in individuals. Kebele-level associations are

lost when aggregating data at larger spatial and demographic scales of analysis, presumed to be consequent to the high level of heterogeneity in WaSH facilities available to use, and thus resulting in heterogeneity of individual behaviour. This highlights the importance of ensuring consistent behaviour across a community, leading to the relevance of community-wide sensitisation and mobilisation to use improved infrastructure. The progress of control will be as fast as the 'worst' behaving individuals. Also of significance was the marked improvement in access to improved WaSH infrastructure over time, augmented by the increase in infrastructure coverage consequent to planned construction and behaviour change sensitisation implemented by the project. These impacts took time to mature in the project sites, and the WaSH impact was not apparent until a number of years passed. This highlights the importance of increasing the period of time between baseline and endline of studies employed to measure WaSH impact in similar future studies, which are ordinarily limited to a short follow-up period.

Chapter 8: Lessons learnt from the Geshiyaro project

1. Introduction

The steady global progress in the control of STH is an impressive feat, both in terms of the sheer volume of donated anthelmintics, and the scale of international collaboration required between Ministries of Health and NGOs to deliver them [17]. As the socioeconomic status of a country increases, so will the population's access to improved WaSH infrastructure, removing infectious life stages from the environment and thus breaking the transmission cycle and the subsequent need for treatment (**Figure 8.1**). In lieu of improved socioeconomic status consequent of financial developments however, control of STH will require constant therapeutic pressure to counter the continued transmission of infection.

With this in mind, the novel, epidemiological analysis conducted by the Geshiyaro project data has provided the opportunity to use a large-scale, longitudinal, biometrically verified, dataset to assess enhancements to Ethiopia's national STH control strategies, namely the additional impact gained from integrated control (cMDA, additional WaSH infrastructure, and BCC). The data has also enabled a deeper understanding of the key heterogeneities and dynamics of STH transmission and control in low prevalence areas complementing and furthering the work previously published. This, in turn, has generated data-led conclusions to be drawn upon the validation of EPHP and transmission break, which may be added to the body of evidence used for future policy formulation of STH control, specifically in low prevalence areas. Although funding for this study cannot realistically be expected in the implementation of a long-term national strategy, it has provided the opportunity to trial novel strategies that can be recommended or rejected based on performance and cost effectiveness. Furthermore, the implications of this research has challenged some WHO recommendations, and provided a validation of others.

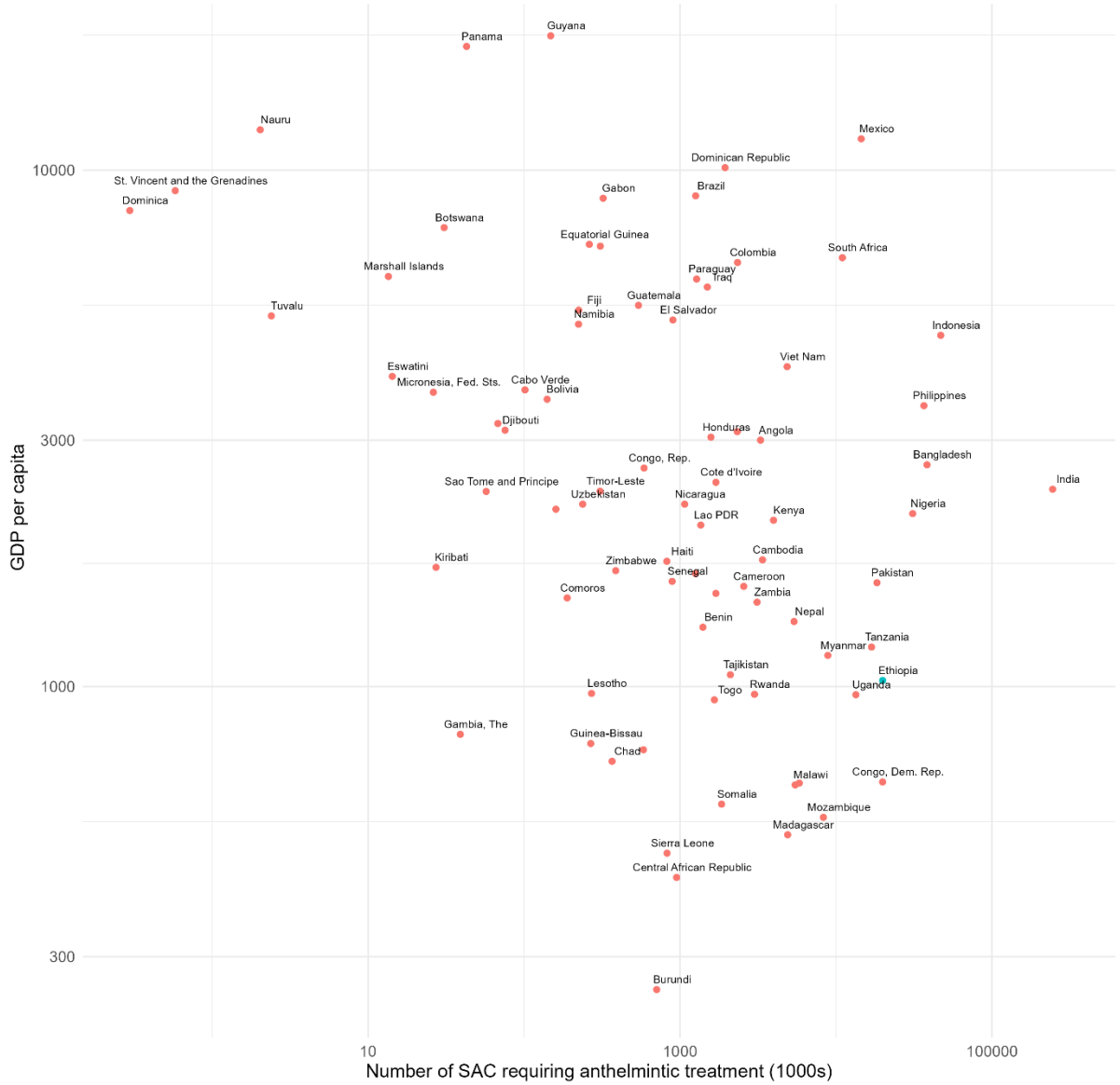


Figure 8.1: The relationship between gross domestic product (GDP) per capita and school-aged children (SAC) requiring treatment for soil-transmitted helminths. *The correlation between the economic output and the magnitude of STH treatment required for countries endemic with STH, illustrating the inverse link between low socioeconomic status and high STH burden. Ethiopia is highlighted in blue. Note the log scale on both axes. Data taken from the WHO* [199] *and WorldBank* [200].

2. Summary of motivations and resultant research chapters

This thesis has answered the following three key questions:

i. How informative are unique individual identifiers such as biometrics in measuring the impact of STH control programs?

ii. What spatial scale and demographic sample is appropriate for accurate M&E of STH control program impact in low prevalence settings?

iii. What is the magnitude of difference in STH control between sMDA versus cMDA, and to what extent is that further enhanced by the construction of WaSH infrastructure and BCC?

2.1. The importance of individual level data collection using biometric identifiers

2.1.1. The challenges

Associations between prevalence, treatment compliance, and access to WaSH infrastructure were significant at the individual level, yet this was often lost at larger spatial aggregations. This can help explain why, for example, other WaSH studies have struggled to find strong associations with infection. It has chiefly highlighted the heterogeneity of individual behaviour and how this impacts STH control, and thus the importance of employing individual level M&E in STH programs, especially in low prevalence settings. In recognition of the additional cost that individual level data requires to implement, alternatives have been suggested where possible.

The Geshiyaro project has benefited from this individual-level M&E, however, challenges remain within the fine-detail dataset. As highlighted by comparisons to other population estimates such as the US Census Bureau of Statistics, the population enumerated by the project was not representative of all age-groups, suggesting subsets of the population denominator were underestimated (**Figure 3.2**). Furthermore, the statistically significant association expected between treatment compliance and prevalence was not seen. Individual treatment compliance at the most recent cMDA round was the only significant variable, as aggregating compliance at a kebele level for example, lost this relationship. This further suggests the numerator reported for this activity is not accurate. It is therefore hard to recommend such intensive data collection strategies when the data is not completely reliable.

The collection of individual level data is a highly costly process. First, a baseline census activity is required to define the population denominator. This requires dedicated effort to reach all members of the community, in particular capturing who might be routinely missed such as mobile subsets of the population, marginalised members of the community, and those in

geographically hard-to-reach areas. Matching these enrolled individuals is almost impossible using paper-based methods, and is greatly improved through electronic collection, although this comes at a significant cost. Furthermore, the use of biometrics was shown to be partially successful, as key demographic groups such as young infants and young male adults, struggled to provide viable biometric prints. These groups are coincidentally some of the most important for close follow-up due to their higher risk to STH infection.

The implementation of electronically and biometrically enhanced data collection is therefore not realistic for many programs. Replacing the incorporation of biometric identifiers with a photograph for high fidelity matching, for example, may present a cost-effective alternative to biometric technology?

2.1.2. The triumphs

Despite the challenges in the data collected, the power of analysis gained from the resulting individual level, longitudinal dataset has enabled some novel conclusions to be drawn. For instance, the importance of measuring compliance behaviour over time to assess the probability of interrupting transmission. Using a subset of the Geshiyaro population, named the longitudinal population, the difference in elimination probability for a population following a positive binomial (random) distribution (65.0% (95% CI: 62.0 - 67.9%)), a beta binomial distribution (50.4% (95% CI: 47.3 - 53.5%)), or fully systematic distribution (13.1% (95% CI: 11.1% - 15.3%)) of treatment frequency (as seen in the Geshiyaro data), assuming the same coverage was achieved, was demonstrated (see **Figure 4.3**). This concept builds upon the importance of the 'never treated' population, but also highlights the relevance of recording the full treatment frequency distribution of the number of MDA rounds taken by each individual in the population.

The importance of elucidating such treatment behaviour in the population is clearly demonstrated, however, this was financially expensive. Therefore, the recommendation of conducting a questionnaire on a subset of the population regarding their treatment behaviour (e.g. how many rounds attended, their last treatment) would still be beneficial in gaining a deeper understanding of the impact the delivered MDA will have upon the population.

2.2. What is a spatially appropriate scale for measuring the control of soil-transmitted helminths, and latterly the validation of transmission break?

Choosing an appropriate spatial scale for the evaluation of control programs must balance the accuracy of measurement with the reality of financial constraints of collecting such data. Analysis of STH prevalence data submitted by the AFRO country's Ministries of Health to the ESPEN portal suggested the high level of variation in STH prevalence may mean that the spatial scales currently used for validation of low STH prevalence are inappropriately large. There were severe limitations to this dataset due the nature of the reported data, requiring a more detailed analysis with fine-scale data.

Using the fine-scale monitoring of prevalence employed by the Geshiyaro project the M&E of the Ethiopian national control program was assessed. The kebele level data recorded by the project revealed significant heterogeneity within the spatial unit (woreda level) currently employed to evaluated STH control. As these prevalence metrics are used to define the transition between the WHO guidance for STH control (**Figure 1.1**), such measurement at a spatial scale too large may create downstream problems. In woredas that were classified as reaching 2% prevalence, the prevalence at which the WHO recommends MDA cessation, there was a high degree of heterogeneity of prevalence at the kebele level (**Figure 6.10**). As such, if MDA was indeed stopped in these woredas, then the kebeles reporting higher prevalence may re-seed infection within the woreda leading to STH recrudescence.

In addition, collection of prevalence and intensity data for individuals has enabled the calculation of the degree of parasite aggregation (measured by the parameter, k) within communities before and after intervention with integrated control as shown in **Figure 6.5**. This analysis has shown an increased aggregation of infection, which, in reality, means the generation of hotspots of infection and therefore increase heterogeneity of infection. This further shows the importance of reporting prevalence at smaller spatial scales when low prevalence is recorded at the woreda level currently implemented.

2.3. The magnitude of difference in soil-transmitted helminth control when employing integrated control strategies

2.3.1. Is there an added benefit to employing a community-wide mass drug administration strategy?

Analysis presented in **Chapter 6** showed the clear benefit in control gained through cMDA beyond that of sMDA in the low prevalence context of SERS, Ethiopia. Despite the variation in starting prevalence between intervention arms, the odds of a participant being infected by *A. lumbricoides*, *T. trichiura*, and hookworm in a community receiving sMDA was 483% higher (AOR: 5.83 (95% CI: 5.26 - 6.46%, $p < 0.001$)), 329% higher (AOR: 4.29 (95% CI: 3.59 - 5.14%, $p < 0.001$)), and 16% higher (AOR: 1.16 (1.00 - 1.34%, $p < 0.05$)), respectively, than participants receiving cMDA (see **Figure 6.4**). This clearly demonstrates the additional control gained from cMDA strategies of STH. These results validate the conclusions drawn from published mathematical model-based studies of cMDA impact on parasite transmission [37].

Furthermore, the age-stratified data also showed that SAC were 29% (AOR: 1.29 (95% CI: 1.16 - 1.44), $p < 0.001$) and 43% (AOR: 1.43 (95% CI: 1.20 - 1.70) $p < 0.001$) more likely to be infected by *A. lumbricoides* and *T. trichiura*, respectively, when compared to all other age groups. As expected, the odds of hookworm infection were 29% lower in SAC (AOR: 0.71 (95% CI: 0.60 - 0.84), $p < 0.001$). Therefore, as previously shown by other large STH control studies, the increase in treatment equity achieved when including adult age-groups in cMDA strategies is even greater for hookworm control. Therefore, consideration should be taken as to which is the dominant STH species, and therefore if a sMDA strategy is appropriate for the infection setting.

2.3.2. What impact, if any, does water, sanitation, and hygiene infrastructure add to the control of soil-transmitted helminths with community-wide mass drug administration?

The analysis of WaSH infrastructure access upon the control of STH transmission signified the statistical importance of this at an individual level, as most associations were lost when aggregated at lager scales such as the kebele. This may explain why other studies of WaSH infrastructure access have failed to draw statistically significant associations, as most published analyses are evaluated at a larger spatial scale.

Most notably, as demonstrated in **Figure 7.2**, was the protective impact of access to safe bathing water, which was associated with a 15% and 24% reduction in faecal-oral (AOR: 0.85 (95% CI: 0.78 - 0.92), $p < 0.001$) and skin penetration species (AOR: 0.76 (95% CI: 0.68 - 0.86), $p < 0.001$), respectively, at an individual level. In addition, access to a private toilet facility (within the household, or within the household compound) was associated with a 25% reduction in the odds of faecal-orally transmitted infection at an individual level (AOR: 0.75 (95% CI: 0.62 - 0.91), $p < 0.01$)).

Enhancing the bivariate analysis between a single WaSH infrastructural intervention and STH control, the idea of participants who homogeneously report low-risk behaviours was developed. This highlighted a key failing in WaSH analysis: analysing each variable as a distinct entity. In reality, individuals will have access to a range of different WaSH infrastructures, and some poor hygiene practises may negate the benefits of others classified as improved. As such, when analysing the difference between participants reporting the use of homogeneously low-risk behaviours and access, a 23% significant reduction in prevalence was seen for faecal-orally transmitted STH infections (AOR: 0.77 (95% CI: 0.62 - 0.96), $p < 0.05$). Furthermore, participants reporting homogenous access to improved WaSH infrastructure reached and maintained prevalence levels below 2%, which was not achieved in those reporting heterogenous WaSH access.

The data from the Geshiyaro project have shown a significant association between STH control and WaSH, which sustains the gains made by cMDA. WaSH data is often challenged with showing such a positive association. Despite this, it makes epidemiological sense for improved WaSH infrastructure access to reduce STH prevalence, as this helps to reduce the infection reservoir in the community which would otherwise enable the continued transmission in the community. The intrinsic link between poverty and STH prevalence is consequent of this (**Figure 8.1**). Therefore, regardless of the conclusions drawn from this project, the importance of WaSH is accepted, as an integral component of STH control alongside PC.

2.3.3. Implementation of the Geshiyaro project through existing healthcare system structures

The setting in which the success of integrated control was delivered should be noted and considered before making any future recommendations of its suitability for implementation

in national programs. The Geshiyaro project was implemented using the existing network of HEW which currently underpins the Ethiopian health delivery service. The integration of the project within existing systems helped ground the project is reality as the enhanced integrated protocol was able to be tested using the national infrastructure. Positively, this project has showed that sMDA protocols can be expanded to cMDA with a high coverage. It should be noted, however, that this was implemented using additional infrastructure created by the project, privately funded by CIFF, that would not be routinely available if implemented as part of a national control strategy due to budgetary constraints. This includes the daily reporting of cMDA coverage enabled by the electronic data capture methods used, enhanced supervision of HEW by EPHI staff, and additional sensitisation strategies provided by non-governmental partners. Nevertheless, woredas that were not followed electronically, and thus without daily analytics of progress, also showed consistent, high coverage when measured using CESs [86]. The overinflation of CES data has been noted as the results may be affected by small sample sizes, social desirability bias, and recall bias [84].

3. Discussion

The data collected by the Geshiyaro project provides a rich source to analyse the multiple heterogeneities of STH transmission and control, and their impact upon reaching elimination. Consequently, the results of each chapter are summarised with the view to any relevant policy implications to enhance current guidance.

3.1. Implications of implementing community-wide mass drug administration in national control programs

The Geshiyaro data has shown a marked improvement in the control of STH by cMDA and WaSH, compared to the standard national program. Despite this decrease in prevalence, widescale implementation of cMDA would be prohibitively expensive and as such it is unrealistic to expect universal and unanimous adoption of this enhanced treatment schedule by all national programs. By proxy, STH is a disease of poverty, and therefore endemic countries will have many competing priorities for limited public health budgets. The current target of 75% coverage of sMDA is not currently reached unanimously across Ethiopia, let alone globally. Therefore, before the implementation of cMDA over sMDA is recommended,

efforts should be placed on reaching these sMDA targets in a smaller target population before stretching infrastructure and resources to reach the whole community.

3.2. Development of enhanced WHO guidelines for soil-transmitted helminth control

The reduction in prevalence by integrated control (cMDA, WaSH, BCC), as well as the coverage of cMDA and WaSH infrastructure access was shown to be heterogeneous, which was elucidated only through individual-based monitoring, and lost at larger spatial aggregations.

If similar fine-scale monitoring is to be implemented in future control programs, either through an increased number of sites sampled per spatial unit for fine-scale mapping, or increased sample size representation within a population, this will be dependent on the development of high-sensitivity, practical, cheap, point-of-care diagnostics for STH. Currently available methods would not be cost effective if employed in a such a strategy [62]. Molecular techniques such as qPCR provide a high-sensitivity diagnostic solution, yet are highly logistical and financially expensive, and require training of human resources to build and manage.

In the absence of new diagnostic enhancements or developments, standard coprological techniques such as Kato Katz can be optimised, presenting a realistic option for most control programs. Increasing the number of slides used per sample increases the sensitivity of the diagnostic without the need for any further infrastructure, requiring only an increase in human resources for slide-reading. The Geshiyaro project employed quadruple Kato Katz slides, enhancing the routinely implemented double slides as recommended by WHO. As Kato Katz equipment can be washed and reused, the only increased expenditure required for this was the increased human resources to read the additional two slides per sample. Furthermore, recent developments in diagnostic methods include AI powered technology to read Kato Katz slides [77]. This increases the sensitivity of slide reading even in low prevalence areas, as determinants of such low sensitivity such as human error removed. Furthermore, species-specific morphological nuances of excreted eggs will be reported with high confidence. For example, reporting the presence of unembryonated or embryonated *A. lumbricoides* eggs will be highly informative for control. The presence of unembryonated eggs is indicative that reproductively viable female worms are present, without a reproductively

viable male. This is a key indicator that transmission break point may be reached, as no onward excretion of infectious eggs will occur from that host.

As such, rather than changing STH control guidelines, enhancements can be suggested. A proportion of unembryonated eggs could be added to the WHO targets, as confirmed by modelling transmission studies, which would indicate the interruption of transmission. A community with 2% prevalence, but 100% embryonated eggs would be less likely to reach transmission break, than one with 75% of unembryonated eggs. Additionally, levels of MDA and WaSH coverage achieved should be taken into consideration. A community with 2% prevalence yet only 30% community access to clean water is more likely to see recrudescence of infection, compared to a community with 75% coverage. This would enhance the awareness of the multiple aspects of control required for STH.

3.3.A community-led solution to soil-transmitted helminth control

The analysis of the Geshiyaro project has shown the importance of a unified community response to the control of STH, both in terms of the acceptance of anthelmintics through compliance behaviour analysis, and utilisation of WaSH infrastructure. The best designed interventions will not be successful if not adopted by a significant proportion of the community, and as the WaSH analysis highlighted, the progress in control of STH within a community will be as slow as the worst adopter of hygiene behaviours. This is a positive conclusion, as more expensive interventions are not necessarily required, but rather the impact of existing interventions currently targeted to endemic communities can be enhanced through better community engagement, sensitisation of the importance of participation, empowering communities through ownership of their collective response. Such community-wide engagement with deworming has shown to be successful. One notable example is India's annual National Deworming Day, which treats hundreds of millions of children in a single day [201].

Due to the characteristics of worm aggregation in a community, at low prevalence levels the infection will be sequestered in increasingly small pockets of the community which will be hard to identify without expanding the sample size analysed parasitologically. Individuals who remain infected may be predisposed to this state, and therefore will need constant re-treatment. As such, patient-lead treatment, or access to anthelmintics to supplement national

control programmes may be necessary and beneficial to control the final stages of STH transmission. Alternatively, utilising existing infrastructure to enhance the reach of treatment may be plausible, for example using antenatal care pathways to reach mothers and young children which were shown to be under-treated and represented in the Geshiyaro dataset. Such 'surround sound' implementation of STH control has been achieved in Nepal for example, where WaSH educational programs were integrated into infant immunisation programs with success measured both in WaSH and immunisation coverage. Such clinics will provide another opportunity for the health service to contact high-risk mothers and infants, both for treatment and WaSH education.

3.4. Using the Geshiyaro data in a wider context

The Geshiyaro project has shown the power of analysis conducted at the individual level, however, implementing the expensive methods used to collect this data is unrealistic for many national control programs. For programs who are unable to collect such fine-scale data to benefit from that collected by the project, the analysis presented here can instead to be used to infer or extrapolate upon regularly collected data, such as prevalence in SAC as recommended by the WHO. Knowing that in the Geshiyaro population, for example, that *A. lumbricoides* and *T. trichiura* infections were 29% and 43% more likely to be infected, respectively, this routinely collected data can be used to estimate that in adult populations (as calculated using country-specific age structures) that are currently unmonitored. Including this estimation in calculations of STH prevalence of the whole community may help to better guide control strategies.

The fine-scale data collected by the project, in reference to other routinely collected geospatial data inferred from satellite mapping (temperature, soil type, vegetation index) could also be used to predict the transmission of infection using Bayesian geospatial modelling. As such, future programs can input routinely collected data such as SAC prevalence or treatment compliance into an interface such as a web or mobile application powered by Shiny R for instance, linked to the geospatial model defined using Geshiyaro data. The output of these routine inputs, specified by locally defined, and publicly available geospatial data, can then be used to estimate infection levels at a much finer scale. This could indicate hotspots of infection requiring treatment, which may otherwise have been underestimated due to the aggregation of heterogeneous prevalence at spatial scales inappropriately large for the local

prevalence. The use of such methods will increase the equity in M&E available to other programs, as national programs will be able to access finer-scale data.

3.5. Suggested future work

Many of the analyses presented in this thesis have generated further questions which should be addressed in future research to completely understand the data collected in the Geshiyaro project. Of importance, is the relationship between treatment frequency and infection. The lack of association between compliance and prevalence reduction is surprising. It can be suggested that at such low prevalence levels, this lack of reduction in STH prevalence is due to the effect of predisposition being larger in magnitude than the effect of chemotherapeutics. As such, the remaining infection in the population will be difficult to eliminate in the long-term as these individuals are predisposed to infection. Elimination in such individuals will depend on the whole population reaching $R_0<1$ [20,48,53]. A deeper analysis into treatment frequency, prevalence, and intensity of infection over time at an individual level will help to elucidate this relationship. If this does indeed show that the last reservoir of infection in a low prevalence community are those who are predisposed to infection, this will be highly valuable for the design of control policies in low prevalence settings. Characteristics of the predisposed population in the Geshiyaro project can be described using the data-rich census records, and if distinct, may help other control programs identify the predisposed population in other communities. Test-and-treat protocols for communities with <2% prevalence would seem highly desirable to ensure predisposed individuals do not push communities from a stable elimination state, via the unstable equilibria of transmission break, back to one of endemicity.

4. Conclusion

The data collected by the Geshiyaro project has enabled the description of many heterogeneities in the transmission and control of STH. Some of these are novel, such as the description of the treatment compliance behaviour and its impact upon the probability of transmission elimination, the positive association between homogeneous low-risk WaSH behaviour and STH prevalence, and the heterogeneity of fine-scale prevalence measurements missed at larger spatial scales. Other analyses have confirmed patterns previously described by smaller studies or suggested by modelling results such as the additional impact of STH control gained by cMDA strategies compared to sMDA, and the distribution of infection across

distinct demographic groups. The project is also the first of its kind to implement biometrically verified, individual level monitoring of a large population. It is hoped that the conclusions drawn from this data-rich project and lessons learnt from this novel project will be utilised in the body of research used to develop future policy recommendation for the control of STH globally, and ultimately improve the efficacy of interventions aimed to reduce the burden of worms in resource poor, endemic settings.

References

1. World Health Organsiation. Soil-transmitted helminth infections. In: World Health Organsiation [Internet]. 2023 [cited 18 Mar 2024]. Available: https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections#:~:text=Transmission,these eggs contaminate the soil.

2. Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396: 1204–1222. doi:10.1016/S0140-6736(20)30925-9

3. World Health Organisation. WHO guideline on preventive chemotherapy for public health control of strongyloidiasis. Geneva; 2024. Available: https://www.who.int/publications/i/item/9789240094024

4. World Health Organisation. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Ntuli DMM, editor. Geneva; 2021.

5. Echazú A, Bonanno D, Juarez M, Cajal SP, Heredia V, Caropresi S, et al. Effect of Poor Access to Water and Sanitation As Risk Factors for Soil-Transmitted Helminth Infection: Selectiveness by the Infective Route. PLoS Negl Trop Dis. 2015;9: e0004111. doi:10.1371/JOURNAL.PNTD.0004111

6. World Health Organisation. Guideline: Preventive Chemotherapy To Control Soil-Transmitted Helminth Infections In At-Risk Population Groups. Geneva; 2017. Available: http://apps.who.int/bookorders.

7. Maizels RM, Smits HH, McSorley HJ. Modulation of Host Immunity by Helminths: The Expanding Repertoire of Parasite Effector Molecules. Immunity. 2018;49: 801. doi:10.1016/J.IMMUNI.2018.10.016

8. Truscott JE, Hollingsworth TD, Brooker SJ, Anderson RM. Can chemotherapy alone eliminate the transmission of soil transmitted helminths? Parasites Vectors 2014 71. 2014;7: 1–8. doi:10.1186/1756-3305-7-266

9. World Health Organisation. 2030 targets for soil-transmitted helminthiases control programmes. Geneva; 2019. Available: https://iris.who.int/bitstream/handle/10665/330611/9789240000315-eng.pdf?

10. World Health Organisation. Global report on neglected tropical diseases 2023. World Health Organization, editor. Geneva; 2023. Available: https://www.who.int/publications/i/item/9789240067295

11. World Health Organisation. Schistosomiasis and soil-transmitted helminthiases: progress report, 2022. Geneva; 2023 Dec. Available: https://www.who.int/publications/i/item/who-wer9851-667-676

12. Bundy DAP, Schultz L, Antoninis M, Barry FBM, Burbano C, Croke K, et al. A positive consequence of the COVID-19 pandemic: how the counterfactual experience of school closures is accelerating a multisectoral response to the treatment of neglected tropical diseases. Philos Trans R Soc B Biol Sci. 2023;378: 1–13. doi:10.1098/RSTB.2022.0282

13. Anderson RM, Turner HC, Truscott JE, Hollingsworth TD, Brooker SJ. Should the Goal for the Treatment of Soil Transmitted Helminth (STH) Infections Be Changed from Morbidity Control in Children to Community-Wide Transmission Elimination? PLoS Negl Trop Dis. 2015;9: e0003897. doi:10.1371/journal.pntd.0003897

14. Anderson RM, Truscott JE, Pullan RL, Brooker SJ, Hollingsworth TD. How Effective Is School-Based Deworming for the Community-Wide Control of Soil-Transmitted Helminths? PLoS Negl Trop Dis. 2013;7: e2027. doi:10.1371/JOURNAL.PNTD.0002027

15. Anderson R, Truscott J, Hollingsworth TD. The coverage and frequency of mass drug administration required to eliminate persistent transmission of soil-transmitted helminths. Philos Trans R Soc B Biol Sci. 2014;369. doi:10.1098/RSTB.2013.0435

16. DeWorm T, Team T. Baseline patterns of infection in regions of Benin, Malawi and India seeking to interrupt transmission of soil transmitted helminths (STH) in the DeWorm3 trial. [cited 12 Sep 2023]. doi:10.1371/journal.pntd.0008771

17. Bundy DAP, Appleby LJ, Bradley M, Croke K, Hollingsworth TD, Pullan R, et al. 100 Years of Mass Deworming Programmes: A Policy Perspective From the World Bank's Disease Control Priorities Analyses. Adv Parasitol. 2018;100: 127–154.

doi:10.1016/BS.APAR.2018.03.005

18. Stoll NR. This Wormy World. J Parasitol. 1947;33: 1–18. Available: http://www.jstor.org/stable/3273613

19. Anderson RM, Schad GA. Hookworm burdens and faecal egg counts: an analysis of the biological basis of variation. Trans R Soc Trop Med Hyg. 1985;79: 812–825. doi:10.1016/0035-9203(85)90128-2

20. Anderson RM, May R. Infectious diseases of humans: Dynamics and control. Trends Ecol Evol. 1991;6: 340–341. doi:10.1016/0169-5347(91)90048-3

21. Anderson RM, May RM. The invasion, persistence and spread of infectious diseases within animal and plant communities. Philosophical transactions of the Royal Society of London. Series B, Biological sciences. The Royal Society London; 1986. pp. 533–570. doi:10.1098/rstb.1986.0072

22. Chan MS, Guyatt HL, Bundy DAP, Medley GF. The development and validation of an age-structured model for the evaluation of disease control strategies for intestinal helminths. Parasitology. 2009/04/06. 1994;109: 389–396. doi:DOI: 10.1017/S0031182000078422

23. Molyneux DH, Asamoa-Bah A, Fenwick A, Savioli L, Hotez P. The history of the neglected tropical disease movement. Trans R Soc Trop Med Hyg. 2021;115: 169–175. doi:10.1093/trstmh/trab015

24. World Health Organisation. London Declaration On Neglected Tropical Diseases. In: World Health Organisation [Internet]. 2012 [cited 26 Jul 2023]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/67443/NTD_20Event_20-_20London_20Declaration_20on_20NTDs.pdf

25. Miguel E, Kremer M. Worms: identifying impacts on education and health in the presence of treatment externalities. Econometrica. 2004;72: 159–217.

26. Taylor-Robinson DC, Maayan N, Soares-Weiser K, Donegan S. Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin

and school performance (Review). Cochrane database Syst Rev. 2015;7.

27. Welch VA, Ghogomu E, Hossain A, Awasthi S, Bhutta Z, Cumberbatch C, et al. Deworming and adjuvant interventions for improving the developmental health and well-being of children in low-and middle-income countries: A systematic review and network meta-analysis. Campbell Syst Rev. 2016;12: 1–383.

28. Pullan RL, Halliday KE, Oswald WE, Mcharo C, Beaumont E, Kepha S, et al. Effects, equity, and cost of school-based and community-wide treatment strategies for soil-transmitted helminths in Kenya: a cluster-randomised controlled trial. 2019;393. doi:10.1016/S0140-6736(18)32591-1

29. Ásbjörnsdóttir K, Ajjampur S, Anderson R, Bailey R, Gardiner I, Halliday K, et al. Assessing the feasibility of interrupting the transmission of soil-transmitted helminths through mass drug administration: The DeWorm3 cluster randomized trial protocol. PLoS Negl Trop Dis. 2018;12: e0006166. doi:10.1371/JOURNAL.PNTD.0006166

30. Dyer CEFF, Ng-Nguyen D, Clarke NE, Hii SF, Nguyen HQ, Nguyen V-AAT, et al. Community-wide versus school-based targeted deworming for soil-transmitted helminth control in school-aged children in Vietnam: the CoDe-STH cluster-randomised controlled trial. Lancet Reg Heal - West Pacific. 2023;41. Available: http://www.thelancet.com/article/S2666606523002389/fulltext

31. Clarke NE, Clements ACA, Amaral S, Richardson A, McCarthy JS, McGown J, et al. (S)WASH-D for Worms: A pilot study investigating the differential impact of school- versus community-based integrated control programs for soil-transmitted helminths. Mackenzie CD, editor. PLoS Negl Trop Dis. 2018;12: e0006389. doi:10.1371/journal.pntd.0006389

32. World Health Organisation. Eliminating soil-transmitted helminthiases as public health problem in children: progress report 2001–2010 and strategic plan 2011–2020. Geneva; 2012. Available: https://iris.who.int/bitstream/handle/10665/44804/9789241503129_eng.pdf?sequence=1&isAllowed=y

33. World Health Organisation. Prevention and control of schistosomiasis and soil-

transmitted helminthiasis. Geneva; 2002. Available: https://pubmed.ncbi.nlm.nih.gov/12592987/

34. World Health Organsiation. Helminth control in school age children: a guide for managers of control programmes. Geneva; 2011. Available: http://www.who.int/neglected_diseases/en

35. Becker SL, Liwanag HJ, Snyder JS, Akogun O, Belizario V, Freeman MC, et al. Toward the 2020 goal of soil-transmitted helminthiasis control and elimination. PLoS Negl Trop Dis. 2018;12: e0006606. doi:10.1371/JOURNAL.PNTD.0006606

36. Werkman M, Wright JE, Truscott JE, Easton A V, Oliveira RG, Toor J, et al. Testing for soil-transmitted helminth transmission elimination: Analysing the impact of the sensitivity of different diagnostic tools. PLoS Negl Trop Dis. 2018;12: e0006114. doi:10.1371/journal.pntd.0006114

37. Truscott JE, Werkman M, Wright JE, Farrell SH, Sarkar R, Ásbjörnsdóttir K, et al. Identifying optimal threshold statistics for elimination of hookworm using a stochastic simulation model. Parasit Vectors. 2017;10: 1–12. doi:10.1186/S13071-017-2256-8/TABLES/2

38. Werkman M, Toor J, Vegvari C, Wright JE, Truscott JE, Ásbjörnsdóttir KH, et al. Defining stopping criteria for ending randomized clinical trials that investigate the interruption of transmission of soil-transmitted helminths employing mass drug administration. PLoS Negl Trop Dis. 2018;12: e0006864. doi:10.1371/journal.pntd.0006864

39. Brooker SJ, Nikolay B, Balabanova D, Pullan RL. Global feasibility assessment of interrupting the transmission of soil-transmitted helminths: A statistical modelling study. Lancet Infect Dis. 2015;15: 941–950. doi:10.1016/S1473-3099(15)70042-3

40. Hasegawa M, Pilotte N, Kikuchi M, Means AR, Papaiakovou M, Gonzalez AM, et al. What does soil-transmitted helminth elimination look like? Results from a targeted molecular detection survey in Japan. Parasit Vectors. 2020;13: 1–11. doi:10.1186/s13071-019-3875-z

41. Hong ST, Chai JY, Choi MH, Huh S, Rim HJ, Lee SH. A successful experience of soil-transmitted helminth control in the Republic of Korea. Korean J Parasitol. 2006;44:

177–185. doi:10.3347/KJP.2006.44.3.177

42. Qian MB, Utzinger J, Li SZ, Montresor A, Zhou XN. Towards elimination of soil-transmitted helminthiasis in China. Lancet Reg Heal West Pacific. 2022;22: 100455. doi:10.1016/J.LANWPC.2022.100455

43. Xu Y, Wang Y, Wang L, Kong X, Yan G, Li Y, et al. The prevalence of soil transmitted helminths and its influential factors in Shandong Province, China: an analysis of surveillance data from 2016 to 2020. Infect Dis Poverty. 2023;12: 1–13. doi:10.1186/S40249-023-01100-4/TABLES/7

44. Maddren R, Anderson RM. Measuring heterogeneities in soil-transmitted helminth transmission and control. Trends Parasitol. 2024;40: 45–59. doi:10.1016/j.pt.2023.11.003

45. Mekete K, Ower A, Dunn J, Sime H, Tadesse G, Abate E, et al. The Geshiyaro Project: a study protocol for developing a scalable model of interventions for moving towards the interruption of the transmission of soil-transmitted helminths and schistosome infections in the Wolaita zone of Ethiopia. Parasit Vectors. 2019;12: 1–12. doi:10.1186/s13071-019-3757-4

46. Brooker SJ, Mwandawiro CS, Halliday KE, Njenga SM, McHaro C, Gichuki PM, et al. Interrupting transmission of soil-transmitted helminths: a study protocol for cluster randomised trials evaluating alternative treatment strategies and delivery systems in Kenya. BMJ Open. 2015;5. doi:10.1136/BMJOPEN-2015-008950

47. Anderson RM. Depression of host population abundance by direct life cycle macroparasites. J Theor Biol. 1980;82: 283–311. doi:10.1016/0022-5193(80)90104-6

48. Hardwick RJ, Werkman M, Truscott JE, Anderson RM. Stochastic challenges to interrupting helminth transmission. Epidemics. 2021;34: 100435. doi:10.1016/j.epidem.2021.100435

49. Kura K, Truscott JE, Collyer BS, Phillips A, Garba A, Anderson RM. The observed relationship between the degree of parasite aggregation and the prevalence of infection within human host populations for soil-transmitted helminth and schistosome infections. Trans R Soc Trop Med Hyg. 2022;116: 1226–1229.

doi:10.1093/TRSTMH/TRAC033

50. Anderson R, Hollingsworth TD, Truscott J, Brooker S. Optimisation of mass chemotherapy to control soil-transmitted helminth infection. Lancet. 2012;379: 289–290. doi:10.1016/S0140-6736(12)60120-2

51. Collyer BS, Truscott JE, Mwandawiro CS, Njenga SM, Anderson RM. How important is the spatial movement of people in attempts to eliminate the transmission of human helminth infections by mass drug administration? Philos Trans R Soc B. 2023;378. doi:10.1098/RSTB.2022.0273

52. Truscott JE, Turner HC, Farrell SH, Anderson RM. Soil-Transmitted Helminths: Mathematical Models of Transmission, the Impact of Mass Drug Administration and Transmission Elimination Criteria. Adv Parasitol. 2016;94: 133–198. doi:10.1016/BS.APAR.2016.08.002

53. Anderson RM, May RM. Helminth Infections of Humans: Mathematical Models, Population Dynamics, and Control. Adv Parasitol. 1985;24: 1–101. doi:10.1016/S0065-308X(08)60561-8

54. Chong NS, Hardwick RJ, Smith SR, Truscott JE, Anderson RM. A prevalence-based transmission model for the study of the epidemiology and control of soil-transmitted helminthiasis. PLoS One. 2022;17. doi:10.1371/JOURNAL.PONE.0272600

55. Anderson RM, May RM. Population dynamics of human helminth infections: control by chemotherapy. Nature. 1982.

56. Werkman M, Wright JE, Truscott JE, Oswald WE, Halliday KE, Papaiakovou M, et al. The impact of community-wide, mass drug administration on aggregation of soil-transmitted helminth infection in human host populations. Parasites and Vectors. 2020;13: 1–12. doi:10.1186/S13071-020-04149-4/FIGURES/5

57. Mayer J, Collyer, Benjamin S. Maddren R, Abtew B, Firdawek Liyew E, Chernet M, Tollera G, et al. Patterns of soil-transmitted helminths aggregation in the human host population after many years of intensive mass drug administration [IN REVIEW]. Trans R Soc Trop Med Hyg. 2024.

58. Hardwick RJ, Vegvari C, Truscott JE, Anderson RM. The 'breakpoint' of soil-transmitted helminths with infected human migration. J Theor Biol. 2020;486: 110076. doi:10.1016/J.JTBI.2019.110076

59. Collyer BS, Anderson RM. Probability distributions of helminth parasite burdens within the human host population following repeated rounds of mass drug administration and their impact on the transmission breakpoint. J R Soc INTERFACE. 2021;18. doi:10.1098/rsif.2021.0200

60. Rayment Gomez S, Maddren R, Liyew EF, Chernet M, Anjulo U, Tamiru A, et al. Predisposition to soil-transmitted helminth reinfection after four rounds of mass drug administration: results from a longitudinal cohort in the Geshiyaro project, a transmission elimination feasibility study in the Wolaita zone of southern Ethiopia. Trans R Soc Trop Med Hyg. 2023 [cited 19 Apr 2023]. doi:10.1093/TRSTMH/TRAD007

61. Bundy DAP, Appleby LJ, Bradley M, Croke K, Hollingsworth TD, Pullan R, et al. Mass Deworming Programs in Middle Childhood and Adolescence. Dis Control Priorities, Third Ed (Volume 8) Child Adolesc Heal Dev. 2017; 165–182. doi:10.1596/978-1-4648-0423-6_CH13

62. Chami GF, Bundy DAP. More medicines alone cannot ensure the treatment of neglected tropical diseases. Lancet Infect Dis. 2019;19: e330–e336. doi:10.1016/S1473-3099(19)30160-4

63. Moser W, Schindler C, Keiser J. Efficacy of recommended drugs against soil transmitted helminths: systematic review and network meta-analysis. BMJ. 2017;358. doi:10.1136/BMJ.J4307

64. Davis EL, Danon L, Prada JM, Gunawardena SA, Truscott JE, Vlaminck J, et al. Seasonally timed treatment programs for Ascaris lumbricoides to increase impact—An investigation using mathematical models. PLoS Negl Trop Dis. 2018;12: e0006195. doi:10.1371/JOURNAL.PNTD.0006195

65. Cooper AJ, Déirdre Hollingsworth T. The impact of seasonality on the dynamics and control of Ascaris lumbricoides infections. J Theor Biol. 2018;453: 96–107. doi:10.1016/J.JTBI.2018.05.025

66. Phillips AE, Ower AK, Mekete K, Liyew EF, Maddren R, Belay H, et al. Association between water, sanitation, and hygiene access and the prevalence of soil-transmitted helminth and schistosome infections in Wolayita, Ethiopia. Parasit Vectors. 2022;15: 410. doi:10.1186/s13071-022-05465-7

67. Nery SV, Traub RJ, McCarthy JS, Clarke NE, Amaral S, Llewellyn S, et al. WASH for WORMS: A Cluster-Randomized Controlled Trial of the Impact of a Community Integrated Water, Sanitation, and Hygiene and Deworming Intervention on Soil-Transmitted Helminth Infections. Am J Trop Med Hyg. 2019;100: 750–761. doi:10.4269/AJTMH.18-0705

68. Vaz Nery S, Pickering AJ, Abate E, Asmare A, Barrett L, Benjamin-Chung J, et al. The role of water, sanitation and hygiene interventions in reducing soil-transmitted helminths: Interpreting the evidence and identifying next steps. Parasites and Vectors. 2019;12: 1–8. doi:10.1186/S13071-019-3532-6/TABLES/1

69. World Health Organization. Safely managed drinking water - thematic report on drinking water 2017. Geneva; 2017.

70. Easton A V., Oliveira RG, O'Connell EM, Kepha S, Mwandawiro CS, Njenga SM, et al. Multi-parallel qPCR provides increased sensitivity and diagnostic breadth for gastrointestinal parasites of humans: Field-based inferences on the impact of mass deworming. Parasites and Vectors. 2016;9: 1–12. doi:10.1186/S13071-016-1314-Y/FIGURES/7

71. Bundy DAP, Thompson DE, Golden MHN, Cooper ES, Anderson RM, Harland PSE. Population distribution of Trichuris trichiura in a community of Jamaican children. Trans R Soc Trop Med Hyg. 1985;79: 232–237. doi:10.1016/0035-9203(85)90343-8

72. World Health Organisation. Diagnostic target product profile for monitoring and evaluation of soil-transmitted helminth control programmes. Montresor DA, editor. Geneva; 2021. Available: https://apps.who.int/iris/handle/10665/342539

73. Dunn JC, Papaiakovou M, Han KT, Chooneea D, Bettis AA, Wyine NY, et al. The increased sensitivity of qPCR in comparison to Kato-Katz is required for the accurate assessment of the prevalence of soil-transmitted helminth infection in settings that have received

multiple rounds of mass drug administration. Parasites and Vectors. 2020;13: 1–11. doi:10.1186/S13071-020-04197-W/TABLES/3

74. Papaiakovou M, Littlewood DTJ, Gasser RB, Anderson RM. How qPCR complements the WHO roadmap (2021–2030) for soil-transmitted helminths. Trends Parasitol. 2021;37: 698–708. doi:10.1016/j.pt.2021.04.005

75. Ullah H, Tian Y, Arbab S, Li K, Khan MIU, Rahman SU, et al. Circulatory microRNAs in helminthiases: Potent as diagnostics biomarker, its potential role and limitations. Front Vet Sci. 2022;9: 1018872. doi:10.3389/FVETS.2022.1018872/BIBTEX

76. Cools P, Vlaminck J, Albonico M, Ame S, Ayana M, Antonio BPJ, et al. Diagnostic performance of a single and duplicate Kato-Katz, Mini-FLOTAC, FECPAKG2 and qPCR for the detection and quantification of soil-transmitted helminths in three endemic countries. PLoS Negl Trop Dis. 2019;13: e0007446. doi:10.1371/JOURNAL.PNTD.0007446

77. Ward PK, Roose S, Ayana M, Broadfield LA, Dahlberg P, Kabatereine N, et al. A comprehensive evaluation of an artificial intelligence based digital pathology to monitor large-scale deworming programs against soil-transmitted helminths: a study protocol. medRxiv. 2023 [cited 2 Nov 2023]. doi:10.1101/2023.09.28.23296266

78. Nations U. UN Population Division Data Portal: Interactive access to global demographic indicators. In: Data Portal Population Division [Internet]. Available: https://population.un.org/dataportal/home?df=eb630975-5af6-454d-a16d-72d6ade30700

79. Ethiopia M of H. The Third National Neglected Tropical Diseases Strategic Plan 2021-2025. Addis Ababa; 2021. Available: https://espen.afro.who.int/system/files/content/resources/Third NTD national Strategic Plan 2021-2025.pdf

80. Bank TW. Poverty headcount ratio at national poverty lines (% of population) - Ethiopia. In: World Bank, Poverty and Inequality Platform [Internet]. Available: https://data.worldbank.org/indicator/SI.POV.NAHC?locations=ET

81. UNCATD. World Investment Report 2020. New York; 2020.

82. WorldBank. GDP growth (annual %) - Ethiopia. [cited 20 Jun 2024]. Available: https://data.worldbank.org/indicator/NY.GDP.MKTP.KD.ZG?end=2022&locations=ET&start=2000

83. Seife F. Combating Parasitic Worms in Ethiopia. In: PLOS Neglected Tropical Diseases [Internet]. 2021. Available: https://yoursay.plos.org/2021/03/combating-parasitic-worms-in-ethiopia/

84. Rayment Gomez S, Maddren R, Liyew EF, Chernet M, Anjulo U, Tamiru A, et al. Spatial heterogeneity in mass drug administration from a longitudinal epidemiological study assessing transmission interruption of soil transmitted helminths in the Wolaita zone of southern Ethiopia (Geshiyaro Project). PLoS Negl Trop Dis. 2024;18: e0011947. doi:10.1371/JOURNAL.PNTD.0011947

85. ESPEN. Soil-transmitted helminths. Available: https://espen.afro.who.int/diseases/soil-transmitted-helminthiasis)

86. Liyew EF, Chernet M, Belay H, Maddren R, Landeryou T, Kalahasti S, et al. Coverage evaluation surveys following soil-transmitted helminthiasis and schistosomiasis mass drug administration in Wolaita Zone of Ethiopia—The Geshiyaro project. PLoS One. 2021;16: e0260722. doi:10.1371/JOURNAL.PONE.0260722

87. Landeryou T, Maddren R, Gomez SR, Kalahasti S, Liyew EF, Chernet M, et al. Longitudinal monitoring of prevalence and intensity of soil-transmitted helminth infections as part of community-wide mass drug administration within the Geshiyaro project in the Bolosso Sore district, Wolaita, Ethiopia. PLoS Negl Trop Dis. 2022;16: e0010408. doi:10.1371/JOURNAL.PNTD.0010408

88. Phillips AE, Ower AK, Mekete K, Liyew EF, Maddren R, Mengistu B, et al. Baseline soil-transmitted helminth and schistosome infection in the Geshiyaro project, Ethiopia: A unique transmission interruption project using biometric fingerprinting for longitudinal individual analysis. PLoS Negl Trop Dis. 2023;17: e0011589. doi:10.1371/journal.pntd.0011589

89. Maddren R, Collyer B, Phillips AE, Rayment Gomez S, Abtew B, Anjulo U, et al. Patterns of individual compliance with anthelmintic treatment for soil-transmitted helminth

infections in southern Ethiopia over six rounds of community-wide mass drug administration. Trans R Soc Trop Med Hyg. 2023 [cited 24 Nov 2023]. doi:10.1093/TRSTMH/TRAD079

90. Leta GT, Mekete K, Wuletaw Y, Gebretsadik A, Sime H, Mekasha S, et al. National mapping of soil-transmitted helminth and schistosome infections in Ethiopia. Parasites and Vectors. 2020;13: 1–13. doi:10.1186/S13071-020-04317-6/TABLES/4

91. Maddren R, Phillips A, Rayment Gomez S, Forbes K, Collyer BS, Kura K, et al. Individual longitudinal compliance to neglected tropical disease mass drug administration programmes, a systematic review. Reithinger R, editor. PLoS Negl Trop Dis. 2023;17: e0010853. doi:10.1371/JOURNAL.PNTD.0010853

92. World Health Organisation, WHO media team. WHO officially recognizes noma as a neglected tropical disease. WHO Geneva; Dec 15, 2023. Available: https://www.who.int/news/item/15-12-2023-who-officially-recognizes-noma-as-a-neglected-tropical-disease

93. West SK. Blinding trachoma: Prevention with the safe strategy. Am J Trop Med Hyg. 2003;69: 18–23. doi:10.4269/ajtmh.2003.69.18

94. Farrell SH, Anderson RM. Helminth lifespan interacts with noncompliance in reducing the effectiveness of anthelmintic treatment. Parasites and Vectors. 2018;11. doi:10.1186/s13071-018-2670-6

95. Babu B V., Babu GR. Coverage of, and compliance with, mass drug administration under the programme to eliminate lymphatic filariasis in India: a systematic review. Trans R Soc Trop Med Hyg. 2014;108: 538–549. doi:10.1093/trstmh/tru057

96. Shuford K V., Turner HC, Anderson RM. Compliance with anthelmintic treatment in the neglected tropical diseases control programmes: A systematic review. Parasites and Vectors. 2016;9: 1–16. doi:10.1186/S13071-016-1311-1/FIGURES/8

97. Willis GA, Mayfield H, Kearns T, Naseri T, Thomsen R, Gass K, et al. A community survey of coverage and adverse events following country-wide triple-drug mass drug administration for lymphatic filariasis elimination, Samoa 2018. PLoS Negl Trop Dis. 2020;14. doi:10.1371/journal.pntd.0008854

98. Chami GF, Kontoleon AA, Bulte E, Fenwick A, Kabatereine NB, Tukahebwa EM, et al. Community-directed mass drug administration is undermined by status seeking in friendship networks and inadequate trust in health advice networks. Soc Sci \& Med. 2017;183: 37–47. doi:10.1016/j.socscimed.2017.04.009

99. Krentel A, Fischer PU, Weil GJ. A Review of Factors That Influence Individual Compliance with Mass Drug Administration for Elimination of Lymphatic Filariasis. PLoS Negl Trop Dis. 2013;7. doi:10.1371/journal.pntd.0002447

100. Farrell SH, Truscott JE, Anderson RM. The importance of patient compliance in repeated rounds of mass drug administration (MDA) for the elimination of intestinal helminth transmission. Parasit Vectors. 2017;10: 1–12. doi:10.1186/s13071-017-2206-5

101. Brieger WR, Okeibunor JC, Abiose AO, Ndyomugyenyi R, Wanji S, Elhassan E, et al. Characteristics of persons who complied with and failed to comply with annual ivermectin treatment. Trop Med \& Int Heal. 2012;17: 920–930. doi:10.1111/j.1365-3156.2012.03007.x

102. Hardwick RJ, Truscott JE, Oswald WE, Werkman M, Halliday KE, Pullan RL, et al. Individual adherence to mass drug administration in neglected tropical disease control: A probability model conditional on past behaviour. PLoS Negl Trop Dis. 2021;15. doi:10.1371/journal.pntd.0009112

103. Oswald WE, Kepha S, Halliday KE, Mcharo C, Safari T, Witek-McManus S, et al. Patterns of individual non-treatment during multiple rounds of mass drug administration for control of soil-transmitted helminths in the TUMIKIA trial, Kenya: a secondary longitudinal analysis. Lancet Glob Heal. 2020;8: e1418–e1426. doi:10.1016/S2214-109X(20)30344-2

104. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Int J Surg. 2010;8: 336–341. doi:10.1016/J.IJSU.2010.02.007

105. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5: 1–10. doi:10.1186/S13643-016-0384-

4/FIGURES/6

106. RCoreTeam. R: A language and environment for statistical computing. Vienna: R Core Team; 2022. Available: https://www.r-project.org/.

107. Wickham H. ggpolt2: Elegant Graphics for Data Analysis. Use R! series. New York: Springer-Verlag; 2016. Available: http://ggplot2.org

108. Koroma JB, Sesay S, Conteh A, Paye J, Bah M, Sonnie M, et al. Progress on elimination of lymphatic filariasis in Sierra Leone. Parasites and Vectors. 2018;11: 1–10. doi:10.1186/S13071-018-2915-4/FIGURES/2

109. Koroma JB, Sesay S, Conteh A, Koudou B, Paye J, Bah M, et al. Impact of five annual rounds of mass drug administration with ivermectin on onchocerciasis in Sierra Leone. Infect Dis Poverty. 2018;7: 1–12. doi:10.1186/S40249-018-0410-Y/FIGURES/2

110. Aye NN, Lin Z, Lon KN, Linn NYY, Nwe TW, Mon KM, et al. Mapping and modelling the impact of mass drug adminstration on filariasis prevalence in Myanmar. Infect Dis Poverty. 2018;7: 1–11. doi:10.1186/S40249-018-0420-9/TABLES/4

111. Mao FZ, Chen YY, Xu XZ, Ni BX, Jin XL, Dai Y, et al. Multi-intervention integrated deworming strategy for sustained control of soil-transmitted helminths infections: a case study in Jiangsu Province, China. Infect Dis Poverty. 2021;10. doi:10.1186/S40249-021-00903-7

112. Gonzales M, Noland GS, Mariano EF, Blount S. Lymphatic filariasis elimination in the Dominican Republic: History, progress, and remaining steps. PLoS Negl Trop Dis. 2021;15: e0009590. doi:10.1371/JOURNAL.PNTD.0009590

113. Tian L, Wang N-L. Trachoma control: the SAFE strategy. Int J Ophthalmol. 2018;11: 1887–1888. doi:10.18240/ijo.2018.12.01

114. World Health Organisation. Control of Neglected Tropical Diseases | PCT Databank. 2022 [cited 23 Mar 2023]. Available: https://www.who.int/teams/control-of-neglected-tropical-diseases/data-platforms/pct-databank

115. Kulkarni P, Thomas JJ, Dowerah J, Murthy MRN, Ravikumar K. Mass drug administration programme against lymphatic filariasis-an evaluation of coverage and compliance in a

northern Karnataka district, India. Clin Epidemiol Glob Heal. 2020;8. doi:10.1016/j.cegh.2019.04.013

116. Kulkarni P, Dowerah J, Thomas JJ, Murthy MRN, Ravikumar K. Exploring effectiveness of mass drug administration program against lymphatic filariasis in Raichur district, Karnataka. Int J Heal ALLIED Sci. 2019;8: 268–272. doi:10.4103/ijhas.IJHAS_46_19

117. Campillo JT, Awaca-Uvon NP, Missamou F, Tambwe J-P, Kuyangisa-Simuna G, Weil GJ, et al. Results From 2 Cohort Studies in Central Africa Show That Clearance of Wuchereria bancrofti Infection After Repeated Rounds of Mass Drug Administration With Albendazole Alone Is Closely Linked to Individual Adherence. Clin Infect Dis. 2021;73: E176–E183. doi:10.1093/cid/ciaa1232

118. Liu C, Lu L, Zhang L, Luo R, Sylvia S, Medina A, et al. Effect of Deworming on Indices of Health, Cognition, and Education Among Schoolchildren in Rural China: A Cluster-Randomized Controlled Trial. Am J Trop Med Hyg. 2017;96: 1478–1489. doi:10.4269/AJTMH.16-0354

119. Tilahun Z, Fenta TG. Coverage of azithromycin mass treatment for trachoma elimination in Northwestern Ethiopia: A community based cross-sectional study. BMC Ophthalmol. 2018;18: 1–9. doi:10.1186/S12886-018-0868-1/TABLES/3

120. Osue HO. Field-Based Evidence of Single and Few Doses of Annual Ivermectin Treatment Efficacy in Eliminating Skin Microfilaria Load after a Decade of Intervention. Ethiop J Health Sci. 2017;27: 129–138. doi:10.4314/ejhs.v27i2.5

121. Wanji S, Chounna Ndongmo WP, Fombad FF, Kengne-Ouafo JA, Njouendou AJ, Longang Tchounkeu YF, et al. Impact of repeated annual community directed treatment with ivermectin on loiasis parasitological indicators in Cameroon: Implications for onchocerciasis and lymphatic filariasis elimination in areas co-endemic with Loa loa in Africa. PLoS Negl Trop Dis. 2018;12: e0006750. doi:10.1371/journal.pntd.0006750

122. Manyeh AK, Ibisomi L, Ramaswamy R, Baiden F, Chirwa T. Exploring factors affecting quality implementation of lymphatic filariasis mass drug administration in Bole and Central Gonja Districts in Northern Ghana. PLoS Negl Trop Dis. 2020;14: e0007009. doi:10.1371/journal.pntd.0007009

123. Minetti C, Tettevi EJ, Mechan F, Prada JMJM, Idun B, Biritwum N-KK, et al. Elimination within reach: A cross-sectional study highlighting the factors that contribute to persistent lymphatic filariasis in eight communities in rural Ghana. PLoS Negl Trop Dis. 2019;13: e0006994. doi:10.1371/journal.pntd.0006994

124. Manyeh AK, Chirwa T, Ramaswamy R, Baiden F, Ibisomi L. Evaluating context-specific evidence-based quality improvement intervention on lymphatic filariasis mass drug administration in Northern Ghana using the RE-AIM framework. Trop Med Health. 2021;49. doi:10.1186/s41182-021-00305-3

125. Aza'ah RA, Sumo L, Ntonifor NH, Bopda J, Bamou RH, Nana-Djeunga HC. Point prevalence mapping reveals hotspot for onchocerciasis transmission in the Ndikinimeki Health District, Centre Region, Cameroon. Parasites and Vectors. 2020;13: 1–8. doi:10.1186/S13071-020-04387-6/FIGURES/2

126. Forrer A, Wanji S, Obie ED, Nji TM, Hamill L, Ozano K, et al. Why onchocerciasis transmission persists after 15 annual ivermectin mass drug administrations in South-West Cameroon. BMJ Glob Heal. 2021;6: e003248. doi:10.1136/bmjgh-2020-003248

127. Kifle B, Nigatu M. Compliance to a Five-Year Biannual Ivermectin Treatment for Onchocerciasis Elimination and Its Determinants among Adults in the Bench Maji Zone, Southwest Ethiopia: A Community-Based Cross-Sectional Study. J Parasitol Res. 2021;2021. doi:10.1155/2021/8866639

128. Nath TC, Padmawati RS, Murhandarwati EH. Barriers and gaps in utilization and coverage of mass drug administration program against soil-transmitted helminth infection in Bangladesh: An implementation research. J Infect Public Health. 2019;12: 205–212. doi:10.1016/j.jiph.2018.10.002

129. Kamga G-RR, Dissak-Delon FN, Nana-Djeunga HC, Biholong BD, Ghogomu SM, Souopgui J, et al. Audit of the community-directed treatment with ivermectin (CDTI) for onchocerciasis and factors associated with adherence in three regions of Cameroon. Parasit Vectors. 2018;11: 1–16. doi:10.1186/s13071-018-2944-z

130. Kamga G-RR, Dissak-Delon FN, Nana-Djeunga HC, Biholong BD, Mbigha-Ghogomu S, Souopgui J, et al. Still mesoendemic onchocerciasis in two Cameroonian community-

directed treatment with ivermectin projects despite more than 15 years of mass treatment. Parasit Vectors. 2016;9: 1–12. doi:10.1186/s13071-016-1868-8

131. Dickson BFR, Graves PM, Aye NN, Nwe TW, Wai T, Win SS, et al. The prevalence of lymphatic filariasis infection and disease following six rounds of mass drug administration in Mandalay Region, Myanmar. PLoS Negl Trop Dis. 2018;12. doi:10.1371/JOURNAL.PNTD.0006944

132. Kamga G-RR, Dissak-Delon FN, Nana-Djeunga HC, Biholong BD, Ghogomu SM, Souopgui J, et al. Important progress towards elimination of onchocerciasis in the West Region of Cameroon. Parasit Vectors. 2017;10. doi:10.1186/s13071-017-2301-7

133. Jones C, Ngasala B, Derua YA, Tarimo D, Reimer L, Bockarie M, et al. Lymphatic filariasis transmission in Rufiji District, southeastern Tanzania: Infection status of the human population and mosquito vectors after twelve rounds of mass drug administration 11 Medical and Health Sciences 1117 Public Health and Health Services. Parasites and Vectors. 2018;11: 1–8. doi:10.1186/S13071-018-3156-2/TABLES/4

134. Coutts SP, King JD, Pa'au M, Fuimaono S, Roth J, King MR, et al. Prevalence and risk factors associated with lymphatic filariasis in American Samoa after mass drug administration. Trop Med Health. 2017;45. doi:10.1186/S41182-017-0063-8

135. Dickson BFRR, Graves PM, Aye NN, Nwe TW, Wai T, Win SS, et al. Risk factors for lymphatic filariasis and mass drug administration non-participation in Mandalay Region, Myanmar. Parasit Vectors. 2021;14: 1–14. doi:10.1186/s13071-021-04583-y

136. Akinsanya B, Adewale B, Adenusi A, Lawal AdD, Rahman O. Infectivity of Simulium damnosum s.l. and therapeutic coverage of ivermectin distribution 10 years post treatment around Owena Dam, Ondo state, Nigeria. Brazilian J Infect Dis. 2019;23: 410–418. doi:10.1016/j.bjid.2019.10.003

137. Lupenza ET, Gasarasi DB, Minzi OM. Lymphatic filariasis elimination status: Wuchereria bancrofti infections in human populations and factors contributing to continued transmission after seven rounds of mass drug administration in Masasi District, Tanzania. PLoS One. 2022;17: e0262693. doi:10.1371/JOURNAL.PONE.0262693

138. Osei FA, Newton S, Nyanor I, Osei-Yeboah E, Amuzu EX, Mensah NK, et al. Mass drug

administration targeting Onchocerca volvulus in Owabi catchment area in Ashanti Region, Ghana: Determinants of drug coverage and drug uptake. Parasite Epidemiol Control. 2022;16: e00235. doi:10.1016/J.PAREPI.2021.E00235

139. Dissak-Delon FN, Kamga G-RR, Humblet PC, Robert A, Souopgui J, Kamgno J, et al. Adherence to ivermectin is more associated with perceptions of community directed treatment with ivermectin organization than with onchocerciasis beliefs. PLoS Negl Trop Dis. 2017;11. doi:10.1371/journal.pntd.0005849

140. Krentel A, Damayanti R, Titaley CR, Suharno N, Bradley M, Lynam T. Improving Coverage and Compliance in Mass Drug Administration for the Elimination of LF in Two 'Endgame' Districts in Indonesia Using Micronarrative Surveys. PLoS Negl Trop Dis. 2016;10: e0005027. doi:10.1371/JOURNAL.PNTD.0005027

141. Chisha Y, Zerdo Z, Asnakew M, Churko C, Yihune M, Teshome A, et al. Praziquantel treatment coverage among school age children against Schistosomiasis and associated factors in Ethiopia: a cross-sectional survey, 2019. BMC Infect Dis. 2020;20: 872. doi:10.1186/s12879-020-05519-0

142. Aza'ah RA, Sumo L, Ntonifor NH, Bopda J, Bamou RH, Nana-Djeunga HC, et al. Point prevalence mapping reveals hotspot for onchocerciasis transmission in the Ndikinimeki Health District, Centre Region, Cameroon. Parasit Vectors. 2020;13: 1–8. doi:10.1186/s13071-020-04387-6

143. Asfaw MA, Hailu C, Beyene TJ. Evaluating Equity and Coverage in Mass Drug Administration for Soil-Transmitted Helminth Infections among School-Age Children in the Hard-to-Reach Setting of Southern Ethiopia. Pediatr Heal Med Ther. 2021;12: 325. doi:10.2147/PHMT.S316194

144. Annashr NN, Amalia IS, Phuong Dinh HT, Dinh HTP. Low Knowledge and Unawareness of the Health Promotion as the Determinant Factors in Non-Compliance to the Mass Drug Administration Program. KESMAS-NATIONAL PUBLIC Heal J. 2021;16: 39–44. doi:10.21109/kesmas.v16i1.3271

145. Widjanarko B, Saraswati LD, Ginandjar P. Perceived threat and benefit toward community compliance of filariasis' mass drug administration in Pekalongan district,

Indonesia. Risk Manag Healthc Policy. 2018;11: 189–197. doi:10.2147/RMHP.S172860

146. Babu B, Kar SK. Coverage, compliance and some operational issues of mass drug administration during the programme to eliminate lymphatic filariasis in Orissa, India. Trop Med \& Int Heal. 2004;9: 702–709. doi:10.1111/j.1365-3156.2004.01247.x

147. Shintouo CM, Shey RA, Mets T, Vanhamme L, Souopgui J, Ghogomu SM, et al. Onchocerciasis Fingerprints in the Geriatric Population: Does Host Immunity Play a Role? Trop Med Infect Dis 2021, Vol 6, Page 153. 2021;6: 153. doi:10.3390/TROPICALMED6030153

148. Brooker S, Bethony J, Hotez PJ. Human Hookworm Infection in the 21st Century. Adv Parasitol. 2004;58: 197–288. doi:10.1016/S0065-308X(04)58004-1

149. World Health Organisation. Monitoring and epidemiological assessment of mass drug administration in the global program to eliminate lymphatic filariasis: a manual for national elimination programmes. Ichimori DK, editor. Geneva; 2011. Available: https://www.who.int/publications/i/item/9789241501484

150. Banerjee S, Bandyopadhyay K, Khan MF, Akkilagunta S, Selvaraj K, Tripathy JP, et al. Coverage of mass drug administration for elimination of lymphatic filariasis in urban Nagpur, Central India: A mixed method study. J Fam Med Prim CARE. 2019;8: 3009–3014. doi:10.4103/jfmpc.jfmpc_503_19

151. Oswald WE, Kennedy DS, Farzana J, Kaliappan SP, Atindegla E, Houngbégnon P, et al. Development and application of an electronic treatment register: a system for enumerating populations and monitoring treatment during mass drug administration. Glob Health Action. 2020;13. doi:10.1080/16549716.2020.1785146

152. King JD, Buolamwini J, Cromwell EA, Panfel A, Teferi T, Zerihun M, et al. A novel electronic data collection system for large-scale surveys of neglected tropical diseases. PLoS One. 2013;8: e74570. doi:10.1371/journal.pone.0074570

153. Roberts C h, Stott C, Shawe-Taylor M, Chaudhry Z, Lal S, Marks M. Biometric linkage of longitudinally collected electronic case report forms and confirmation of subject identity: An open framework for ODK and related tools. medRxiv. 2022; 2022.10.13.22280647. doi:10.1101/2022.10.13.22280647

154. World Bank. Inclusive and Trusted Digital ID Can Unlock Opportunities for the World's Most Vulnerable. 2019 [cited 31 Jul 2023]. Available: https://www.worldbank.org/en/news/immersive-story/2019/08/14/inclusive-and-trusted-digital-id-can-unlock-opportunities-for-the-worlds-most-vulnerable

155. Nyssen M, Van Bastelaere S, Verbeke F, Karara G, Van Bastelaere S, Nyssen M, et al. Patient Identification and Hospital Information Management Systems in sub-Saharan Africa: a Prospective Study in Rwanda and Burundi. Rwanda Med J / Rev Médicale Rwandaise RMJ. 2012;69. Available: https://www.researchgate.net/publication/269222217

156. Kranzer K, Lawn SD, Meyer-Rath G, Vassall A, Raditlhalo E, Govindasamy D, et al. Feasibility, Yield, and Cost of Active Tuberculosis Case Finding Linked to a Mobile HIV Service in Cape Town, South Africa: A Cross-sectional Study. PLOS Med. 2012;9: e1001281. doi:10.1371/JOURNAL.PMED.1001281

157. Wall KM, Kilembe W, Inambao M, Chen YN, Mchoongo M, Kimaru L, et al. Implementation of an electronic fingerprint-linked data collection system: A feasibility and acceptability study among Zambian female sex workers. Global Health. 2015;11: 1–11. doi:10.1186/S12992-015-0114-Z/TABLES/2

158. Central Statistics Agency. Population Size by Sex, Region, Zone and Wereda: July 2021. Addis Ababa; 2021.

159. Matthew D, Storisteanu L, Norman TL, Grigore A, Norman TL. Biometric Fingerprint System to Enable Rapid and Accurate Identification of Beneficiaries. Glob Heal Sci Pract. 2015;3. doi:10.9745/GHSP-D-15-00010

160. United States Census Bureau. Population Clock: World. 2023 [cited 9 Mar 2023]. Available: https://www.census.gov/popclock/world/et

161. Corby PM, Schleyer T, Spallek H, Hart TC, Weyant RJ, Corby AL, et al. Using Biometrics for Participant Identification in a Research Study: A Case Report. J Am Med Informatics Assoc. 2006;13: 233–235. doi:10.1197/JAMIA.M1793

162. Webster JP, Molyneux DH, Hotez PJ, Fenwick A. The contribution of mass drug administration to global health: past, present and future. Philos Trans R Soc B-

BIOLOGICAL Sci. 2014;369. doi:10.1098/rstb.2013.0434

163. Sartorius B, Cano J, Simpson H, Tusting LS, Marczak LB, Miller-Petrie MK, et al. Prevalence and intensity of soil-transmitted helminth infections of children in sub-Saharan Africa, 2000–18: a geospatial analysis. Lancet Glob Heal. 2021;9: e52–e60. doi:10.1016/S2214-109X(20)30398-3

164. Boatin BA, Basanez M-G, Prichard RK, Awadzi K, Barakat RM, Garcia HH, et al. A Research Agenda for Helminth Diseases of Humans: Towards Control and Elimination. PLoS Negl Trop Dis. 2012;6: e1547. doi:10.1371/journal.pntd.0001547

165. Assefa Y, Gelaw YA, Hill PS, Taye BW, Van Damme W. Community health extension program of Ethiopia, 2003-2018: Successes and challenges toward universal coverage for primary healthcare services. Global Health. 2019;15: 1–11. doi:10.1186/S12992-019-0470-1/FIGURES/4

166. Rollin Brant, Frank Harrell, Brad Biggerstaff. R: Confidence Intervals for Binomial Probabilities. In: R Documentation [Internet]. [cited 29 Apr 2024]. Available: https://search.r-project.org/CRAN/refmans/Hmisc/html/binconf.html

167. Anderson R, Turner H, Farrell S, Truscott J. Studies of the Transmission Dynamics, Mathematical Model Development and the Control of Schistosome Parasites by Mass Drug Administration in Human Communities. Adv Parasitol. 2016;94: 199–246. doi:10.1016/BS.APAR.2016.06.003

168. Vegvari C, Giardina F, Malizia V, De Vlas SJ, Coffeng LE, Anderson RM. Impact of Key Assumptions About the Population Biology of Soil-Transmitted Helminths on the Sustainable Control of Morbidity. Clin Infect Dis. 2021;72: S188–S194. doi:10.1093/CID/CIAB195

169. Hatherell HA, Simpson H, Baggaley RF, Hollingsworth TD, Pullan RL. Sustainable Surveillance of Neglected Tropical Diseases for the Post-Elimination Era. Clin Infect Dis. 2021;72: S210–S216. doi:10.1093/CID/CIAB211

170. Ajjampur SSR, Kaliappan SP, Halliday KE, Palanisamy G, Farzana J, Manuel M, et al. Epidemiology of soil transmitted helminths and risk analysis of hookworm infections in the community: Results from the DeWorm3 Trial in southern India. PLoS Negl Trop Dis.

2021;15: e0009338. doi:10.1371/JOURNAL.PNTD.0009338

171. Lim MD, Brooker SJ, Belizario VY, Gay-Andrieu F, Gilleard J, Levecke B, et al. Diagnostic tools for soil-transmitted helminths control and elimination programs: A pathway for diagnostic product development. PLoS Negl Trop Dis. 2018;12: e0006213. doi:10.1371/JOURNAL.PNTD.0006213

172. Ramzy RMR, Rabiee A, Abd Elaziz KM, Campbell CH, Kittur N, Colley DG, et al. Test, Treat, Track, Test, and Treat Active Surveillance toward Elimination of Schistosomiasis: A Feasibility Study. Am J Trop Med Hyg. 2020;103: 1572–1577. doi:10.4269/AJTMH.20-0156

173. Hardwick RJ, Vegvari C, Collyer B, Truscott JE, Anderson RM. Spatial scales in human movement between reservoirs of infection. J Theor Biol. 2021;524: 110726. doi:10.1016/J.JTBI.2021.110726

174. Nguemnang Kamdem C, Arnol Zebaze Tiofack A, Mezajou Mewamba E, Yangea Tchounkeu E, Rostand Atiokeng Tatang J, Loic Tekeu Mengoue E, et al. Fine mapping of Ascaris lumbricoides, Trichuris trichiura and hookworm infections in sub-districts of Makenene in Centre Region of Cameroun. Sci Rep. 2022;12: 1–17. doi:10.1038/s41598-022-18285-7

175. Nikolay B, Brooker SJ, Pullan RL. Sensitivity of diagnostic tests for human soil-transmitted helminth infections: a meta-analysis in the absence of a true gold standard. Int J Parasitol. 2014;44: 765–774. doi:10.1016/J.IJPARA.2014.05.009

176. Wiegand RE, Fleming FM, de Vlas SJ, Odiere MR, Kinung'hi S, King CH, et al. Defining elimination as a public health problem for schistosomiasis control programmes: beyond prevalence of heavy-intensity infections. Lancet Glob Heal. 2022;10: e1355–e1359. doi:10.1016/S2214-109X(22)00287-X

177. Maddren R, Collyer B, Phillips A, Rayment Gomez S, Mengistu B, Anjulo U, et al. Patterns of individual compliance to anthelmintic treatment for soil transmitted helminths infections in southern Ethiopia over many rounds of community-wide mass drug administration. Lancet Infect Dis. 2023;IN REVIEW.

178. Mogaji HO, Johnson OO, Adigun AB, Adekunle ON, Bankole S, Dedeke GA, et al.

Estimating the population at risk with soil transmitted helminthiasis and annual drug requirements for preventive chemotherapy in Ogun State, Nigeria. Sci Rep. 2022;12: 1–12. doi:10.1038/s41598-022-06012-1

179. Truscott J, Hollingsworth TD, Anderson R. Modeling the interruption of the transmission of soil-transmitted helminths by repeated mass chemotherapy of school-age children. PLoS Negl Trop Dis. 2014;8: e3323. doi:10.1371/journal.pntd.0003323

180. Asbjornsdottir KH, Means AR, Werkman M, Walson JL, Ásbjörnsdóttir KH, Means AR, et al. Prospects for elimination of soil-transmitted helminths. Curr Opin Infect Dis. 2017;30: 482–488. doi:10.1097/QCO.0000000000000395

181. Bundy DAP, Wong MS, Lewis LL, Horton J. Control of geohelminths by delivery of targeted chemotherapy through schools. Trans R Soc Trop Med Hyg. 1990;84: 115–120. doi:10.1016/0035-9203(90)90399-Y

182. Anderson R, Farrell S, Turner H, Walson J, Donnelly CA, Truscott J. Assessing the interruption of the transmission of human helminths with mass drug administration alone: optimizing the design of cluster randomized trials. Parasit Vectors. 2017;10. doi:10.1186/s13071-017-1979-x

183. Keiser J, Utzinger J. Community-wide soil-transmitted helminth treatment is equity-effective. Lancet. 2019;393: 2011–2012. doi:10.1016/S0140-6736(18)32981-7

184. Avokpaho EFGA, Houngbégnon P, Accrombessi M, Atindégla E, Yard E, Means AR, et al. Factors associated with soil-transmitted helminths infection in Benin: Findings from the DeWorm3 study. PLoS Negl Trop Dis. 2021;15: e0009646. doi:10.1371/JOURNAL.PNTD.0009646

185. Mupfasoni D, Montresor A, Mikhailov A, King J. The Impact of Lymphatic Filariasis Mass Drug Administration Scaling Down on Soil-Transmitted Helminth Control in School-Age Children. Present Situation and Expected Impact from 2016 to 2020. PLoS Negl Trop Dis. 2016;10: e0005202. doi:10.1371/JOURNAL.PNTD.0005202

186. Statistics UI for. Number of students and enrolment/attendance rates by level of education. Available: https://data.uis.unesco.org/Index.aspx

187. Turner HC, Bundy DAP. Programmatic implications of the TUMIKIA trial on community-wide treatment for soil-transmitted helminths: further health economic analyses needed before a change in policy. 2020 [cited 8 Nov 2021]. doi:10.1186/s13071-020-3977-7

188. Venables W, Ripley B. Modern Applied Statistics with S. Fourth. New York: Springer; 2002. Available: https://www.stats.ox.ac.uk/pub/MASS4/.

189. Organization WH. Prevention and control of intestinal parasitic infections. WHO Technical Report. Geneva: World Health Organization; 1987. Available: https://iris.who.int/handle/10665/41298

190. Federal Ministry of Health. National Neglected Tropical Diseases Master Plan Federal Democratic Republic of Ethiopia Ministry of Health, 2nd Ed. Addis Ababa; 2016.

191. Joseph G, Rong Hoo Y, Wang Q, Aroha B, Andres L. Funding a Water-Secure Future : An Assessment of Global Public Spending. Washington D.C; 2024.

192. Roll A, Saxena M, Orlan E, Titus A, Juvekar SK, Gwayi-Chore M-C, et al. Policy stakeholder perspectives on barriers and facilitators to launching a community-wide mass drug administration program for soil-transmitted helminths. Glob Heal Res Policy. 2022;7: 47. doi:10.1186/s41256-022-00281-z

193. Gall S, Müller I, Walter C, Seelig H, Steenkamp L, Pühse U, et al. Associations between selective attention and soil-transmitted helminth infections, socioeconomic status, and physical fitness in disadvantaged children in Port Elizabeth, South Africa: An observational study. PLoS Negl Trop Dis. 2017;11. doi:10.1371/JOURNAL.PNTD.0005573

194. Jia T-W, Melville S, Utzinger J, King CH, Zhou X-N. Soil-Transmitted Helminth Reinfection after Drug Treatment: A Systematic Review and Meta-Analysis. PLoS Neglected Top Dis. 2012;6. doi:10.1371/journal.pntd.0001621

195. Coffeng LE, Vaz Nery S, Gray DJ, Bakker R, de Vlas SJ, Clements ACA. Predicted short and long-term impact of deworming and water, hygiene, and sanitation on transmission of soil-transmitted helminths. PLoS Negl Trop Dis. 2018;12: e0006758. doi:10.1371/JOURNAL.PNTD.0006758

196. Rakotomanana H, Komakech JJ, Walters CN, Stoecker BJ. The WHO and UNICEF Joint Monitoring Programme (JMP) Indicators for Water Supply, Sanitation and Hygiene and Their Association with Linear Growth in Children 6 to 23 Months in East Africa. Int J Environ Res Public Health. 2020;17. doi:10.3390/ijerph17176262

197. Dyson L, Stolk WA, Farrell SH, Hollingsworth TDD. Measuring and modelling the effects of systematic non-adherence to mass drug administration. Epidemics. 2017;18: 56–66. doi:10.1016/j.epidem.2017.02.002

198. WaterAid. Hygiene promotion through immunisation. Available: https://washmatters.wateraid.org/projects/hygiene-promotion-through-immunisation

199. Soil transmitted helminthiases | World Health Organization. [cited 20 Jun 2024]. Available: https://apps.who.int/neglected_diseases/ntddata/sth/sth.html

200. GDP per capita (current US$) | Data. In: World Bank [Internet]. [cited 20 Jun 2024]. Available: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD

201. World's largest deworming campaign targets 270 million children in one day. In: World Health Organisation [Internet]. Geneva; 2016. Available: https://www.who.int/news/item/10-02-2016-world-s-largest-deworming-campaign-targets-270-million-children-in-one-day#:~:text=World's largest deworming campaign targets 270 million children in one day,-10 February 2016&text=An estimated 270 million children