Development of quantitative tools and empirical approaches to aid the control and elimination of schistosomiasis in sub-Saharan Africa: from field to policy

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Declaration of originality

I declare that this is my own work produced under the supervision of Professor Maria-Gloria Basáñez, Professor Joanne Webster, Dr Martin Walker, Dr Michael French and Dr Fiona Fleming. Any collaborators or individuals who have been involved with the work have been appropriately acknowledged and all studies mentioned in this thesis have been referenced.

For Chapter 2, I supervised a MSc student and volunteer, Beatriz Calvo-Urbano, who kindly assisted by re-formatting the vast datasets from their various formats (SAS, Excel, R) and produced Figures 2.5 and 2.7 under my guidance with their first phase analyses, as well as SCI Programme Manager Elizabeth Hollenberg who kindly assisted with producing Figure 2.4.

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Abstract

Schistosomiasis is a debilitating chronic parasitic disease that occurs in the poorest regions of the world, predominantly in sub-Saharan Africa (SSA), infecting around 240 million individuals. With the vision of "a world free of schistosomiasis", the WHO and its partners have pledged to meet the ambitious goals of controlling morbidity (i.e. as currently defined, to decrease the prevalence of heavy infection intensity to less than 5% across all sentinel sites) of schistosomiasis by 2020 (in all endemic countries), achieving elimination as a public health problem (EPHP) (i.e. as currently defined, to reduce the prevalence of heavy infection intensity to less than 1% in all sentinel sites; in all endemic countries) and the interruption of transmission in selected regions by 2025. However, the guidelines that programmes follow are based predominantly on expert opinion, with limited empirical evidence. It is thus critical that we have the right tools and empirical evidence to help inform, validate or revise the WHO guidelines and help programmes achieve these ambitious goals. This work aims to do this through the following ways:

1. Generation of data: data collected from 7,500 individuals annually, from across ten different geographical sites in Uganda, varying by endemicity level and treatment history of site;
2. Understanding historical global trends towards the WHO goals: collation and analysis of national-level programmatic data from nine countries to determine if the goals have already been reached by some countries and whether the one-size-fits-all approach is useful.
3. Investigating the impact of treatment programmes: since school-aged-children (SAC) are targeted under the WHO guidelines, it is important to understand what impact this has on the wider community if we are to reach the targets.
4. Development of a quantitative tool to aid programmes: this model is aimed to be used as an addition to the monitoring and evaluation tool kits which monitor and project the reduction in prevalence (by intensity group) and can also be used as an advocacy tool.

The study begins with a coarser grain focus at country level and moves to a more detailed, finer grain study at individual host level. Results showed that the control targets were feasible and much earlier than proposed by the guidelines and that EPHP was only feasible in low endemic areas and the finer scale data highlighted the importance of spatial scales on outputs as well as heavily infected individuals present in non-treated pre-SAC and adults. Since at each level, factors have been identified that impact the epidemiology, control and feasibility of elimination, this work highlights and synthesizes possible emergent properties that cannot be understood by the study of the micro- or macro-epidemiology in isolation. This thesis presents all the different elements together to help elucidate the best approach for national control programmes to reach their goals.

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LIST OF ABBREVIATIONS AND ACRONYMS

CI: Confidence Interval

CS: Conditional State

DALY: disability-adjusted life year

DHO: District Health Officer

EPG: eggs per gram of faeces

EPHP: Elimination as a public health problem

M&E: monitoring and evaluation

MDA: mass drug administration

MMDP: Morbidity Management and Disability Prevention

MTP: Markov Transition Probability

NGO: non-governmental organization

NTD: neglected tropical disease

PC: preventive chemotherapy

PI: prediction interval

PI: prediction interval

PSAC: pre-school aged children

PZQ: praziquantel

RO: Research Objective

SAC: school-aged children

SCI: Schistosomiasis Control Initiative

SSA: sub-Saharan Africa

STH: soil-transmitted helminth

TP: transition probability

WHO: World Health Organization

INTRODUCTION

Overview of thesis aims

The aims of the PhD primarily focused on helping the schistosomiasis control community to work towards the 2020 and 2025 goals proposed in the Neglected Tropical Disease (NTD) Road Map launched by the World Health Organization (WHO) in 2012. In particular, there is a need for robust quantitative tools that will help to inform and validate or revise the WHO guidelines, for countries to progress in the path from schistosomiasis control and elimination as a public health problem to the ultimate interruption of transmission. These tools are essential to understand how a country can best achieve either control and/or elimination of schistosomiasis and determine the point at which a country should be re-mapped to assess whether they can transition from the goal of the control of morbidity to elimination of infection.

This thesis aims to achieve three main Research Objectives in order to aid schistosomiasis programmes and inform policy:

Research Objective 1. To determine where we are now in sub-Saharan Africa (SSA) and Yemen in terms of schistosomiasis transmission, and understand how historical data can inform WHO guidelines

This Research Objective aimed to provide a solid foundation to this thesis through *Chapter 1: Literature Review*, which addresses the most relevant information for the chapters that follow. Programmatic data were then used from multiple countries collected as part of the Monitoring and Evaluation (M&E) activities at the Schistosomiasis Control Initiative (SCI), to compare progress made against the WHO guidelines, for *Chapter 2: When do countries reach the aims of controlling and eliminating morbidity by schistosomiasis?* This helped determine whether the WHO guidelines are appropriate (manuscript under review).

Research Objective 2. Design, develop and evaluate a tool to aid schistosomiasis programmes for programme managers and policy makers

For this Research Objective, a Markov model was developed to predict reductions in infection prevalence over time in a programme infection using historical data from Uganda and Mali to validate and test the model (paper published in *Parasites and Vectors*). The model was parameterized and validated for a range of countries and baseline endemicities, and for intestinal schistosomiasis. Results

are shown in *Chapter 3: Development and evaluation of a Markov model to aid control programmes for schistosomiasis*. This analysis focussed on country-level to country-region (or -administrative) level compared to the global/country level analyses in Research Objective 1.

Research Objective 3. To understand age-related epidemiology at multiple scales of heterogeneity, treatment history and WHO endemicity level of sites, using data collected as part of PhD

Chapter 4 outlines the planning, budgeting, parasitological methods and data management of the field data conducted by the candidate in Uganda and which were analysed in later in the chapter, and Chapter 2 described the data collated and used in Chapter 2 for the multi-county cross-sectional historical data across multiple years, from which a subset of the latter was used to determine progress of programmes through the development and parameterisation of a model (Chapter 3). The main body of this Research Objective is addressed via *Chapter 4: What impact has over a decade of treatment had on age-infection profiles for schistosomiasis in Uganda? A descriptive study.* For this chapter, after collecting data for three treatment rounds, the data were analysed to investigate full age-infection profiles across ten sites in Uganda, which vary by treatment history and endemicity (manuscript in preparation). This enabled comparison at the individual and age-group level.

Finally, the General Discussion chapter (*Chapter 5*) brings together and summarises all the chapters in this thesis. Key findings are used to draw conclusions and propose informed modifications to, as well as support for, parts of the WHO guidelines for the control and elimination of schistosomiasis (manuscript currently being prepared for publication).

Chapter titles:

- **Chapter 1: Literature Review.**
- **Chapter 2: When do countries reach the aims of controlling and eliminating schistosomiasis-related morbidity?**
- **Chapter 3: Development and evaluation of a Markov model to aid schistosomiasis control programmes.**
- **Chapter 4: What impact has over a decade of treatment had on age-infection profiles for schistosomiasis in Uganda? A descriptive study.**
- **Chapter 5: General discussion.**

CHAPTER 1. LITERATURE REVIEW

1.1 Schistosomiasis

The "big three" diseases – the term coined for three of the world's major diseases: HIV/AIDS, malaria and tuberculosis (TB) - have long dominated media headlines, raising public awareness of their widespread and devastating impact. In 2015, there were approximately 1.1 million AIDS-related deaths (1 in 3 of those deaths due to TB co-infection), 438 000 deaths due to malaria (90% of these in the African region) and in 2014, 1.5 million deaths due to TB infection [1–4]. Consequently, these diseases have remained high on the list of priorities when addressing global health needs for governments [5–11] and donors worldwide [12–14]. Since the beginning of the new millennium, however, a relatively lesser known group of 20 communicable diseases collectively referred to as the Neglected Tropical Diseases (NTDs) have gained considerable attention [15,16], in particular the 10 diseases from this group targeted for control of morbidity and/or elimination by the year 2020 by the World Health Organization (WHO) and its global partners [17,18]. These poverty-related diseases affect billions of people in the tropical and sub-tropical regions of the world, causing substantial public health and economic burdens on these countries [19].

Schistosomiasis is one such (parasitic) NTD, predominantly occurring in sub-Saharan Africa (SSA)[20–22]. Also known as Bilharzia, the disease is caused by *Schistosoma* spp. blood flukes (flatworms) and almost exclusively occurs in the poorest regions of the world [22]. Worldwide estimates show that around 240 million individuals are currently infected by schistosomiasis [22,23], many of whom also suffer from multiple co-infections with other diseases [24]. Individuals are exposed to schistosomiasis infection in these areas due to their need to frequent infected freshwater where various daily activities are carried out such as clothes washing, bathing, playing, fishing and very commonly, drinking (drinking does not cause schistosomiasis infection, but the physical contact with water – see Section 1.1.2) [25].

1.1.1 Species characteristics

There are many species of *Schistosoma* [26], but the three major species of schistosomes responsible for human infection are *Schistosoma mansoni, S. haematobium* and *S. japonicum* (Table 1.1).

Schistosoma mansoni and S. haematobium

The two species that are responsible for the vast majority of cases in SSA and also account for the overall largest number of human cases worldwide are *S. mansoni* and *S. haematobium* [22]. *S.*

mansoni causes intestinal schistosomiasis due to the location of adult worms in the superior mesenteric veins that drain the large intestine, whereas *S. haematobium* causes urogenital schistosomiasis due to the location of the adult worms in the venous plexus of the bladder [27]. These two species are the focus of this thesis.

Schistosoma mekongi, S. intercalatum, S. guineensis and others

Schistosoma mekongi, *S. intercalatum*, and *S. guineensis* less commonly cause human infection due to being highly localised to specific regions, in particular, *S. mekongi* which is found only in the Mekong river region (on the Laos-Cambodia border) [28,29]. *S. intercalatum* is found in selected central regions in SSA and *S. guineensis* in West SSA.

Schistosoma japonicum

S. japonicum is the predominant schistosomes species infecting humans in Southeast Asia. Zoonotic transmission (between human and animal reservoirs) is especially important for this species, since its definitive host is not only humans but multiple mammal species (both domestic and wild) [28]. This poses an additional challenge to treatment programmes as animals also need to be targeted for treatment.

Table 1.1. Schistosome species of humans and their endemic countries [30]. This is not an exhaustive list of schistosome species. Hybrids are also prevalent in these regions [31]**.**

Form of human schistosomiasis	Schistosome species	Endemic regions
Intestinal schistosomiasis	*Schistosoma mansoni*	Africa, the Middle East, the Caribbean, Brazil, Venezuela and Suriname
	Schistosoma japonicum	China, Indonesia, the Philippines
	Schistosoma mekongi	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma intercalatum and related *S. guineensis*	Rain forest areas of central Africa
Urogenital schistosomiasis	*Schistosoma haematobium*	Africa, the Middle East

1.1.2 Life cycle

Figure 1.1 shows the life cycle of human schistosomes [27]. The infectious stages to the human consist of free swimming cercariae (shed by infected snail intermediate hosts, see below) which live in freshwater (usually along shorelines); therefore, individuals living in rural areas close to infected water bodies are at highest risk of infection, where contact with freshwater (containing the freshwater snails and hence cercariae population) is common. These cercariae penetrate the human host's skin when in contact in the water (becoming "schistosomula" after entering the host), and then migrate to the portal blood in the liver over a period of 1-2 months, developing into adult schistosomes [29]. For this reason, these trematodes are also known as blood flukes since they reside in the blood stream [32]. The dioecious (separate sexes) adult worms then pair and mate, with the female worm, enveloped by the male worm, capable of producing hundreds of eggs on a daily basis [25,32] that are expelled by the host either through faeces (*S. mansoni*) or urine (*S. haematobium*). These eggs release miracidia when they hatch in fresh water, which go on to infect the intermediate snail hosts. The snail host responsible for developing the cercariae of *S. haematobium* are species of the genus *Bulinus*, and those for *S. mansoni* are species of *Biomphalaria* [25,33]. After undergoing the development stage and multiplying asexually over 4-6 weeks [25,29], the cercariae are released from the snails in their thousands, continuing the life cycle of the parasite [27,34]. The parasites have an adult life span of an estimated 3-10 years or more [29], with the larval cercarial stage having an infective life span of just 8-20 hours and the miracidia stage between 4-16 hours [34,35].

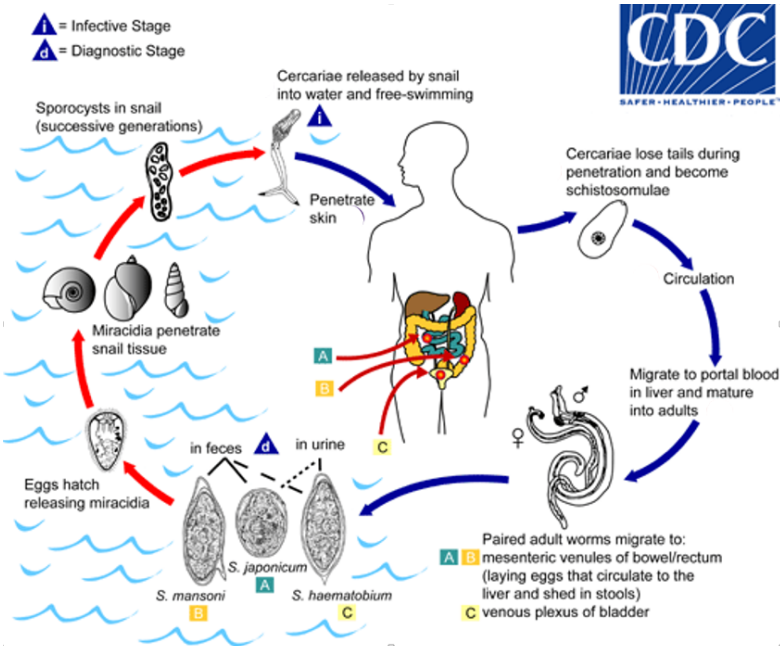

Figure 1.1. The schistosoma life cycle in humans and snails [27].

1.1.3 Pathology

Schistosomiasis results in a vast range of, often irreversible, pathological sequelae. The morbidity associated with schistosomiasis is due primarily to eggs trapped in the host's system that failed to exit the body, causing long-term tissue and organ damage where they become lodged and die within the tissue, leading to inflammatory immune reactions around them and development of granulomata (death of eggs occurs 7-14 days from the time they are laid by the female worm) [25,29]. Preventive chemotherapy (PC) aims to reduce and prevent morbidity by reducing the worm burden in individuals through regular, long-term treatment, since the most heavily infected individuals tend to experience the highest morbidity [36].

Schistosomiasis causes a plethora of morbidities, including, but not exclusive to impaired cognitive development in children as well as malnutrition and anaemia. More specifically, the morbidity related to the intestinal forms of schistosomiasis includes blood in stool, diarrhoea, abdominal pain, fatigue, impaired growth and enlargement of the liver. The latter gives rise to hepatosplenomegaly and death. Urogenital schistosomiasis is known to cause haematuria, damage to the bladder, hydronephrosis, dyspareunia, potential kidney failure and bladder cancer [32,33]. For female genital schistosomiasis (caused by *S. haematobium*), further morbidities include genital lesions, increased risk of infertility and abortion, as well as 3-4 times higher risk of infection with HIV, though unfortunately these stages are irreversible. For male genital schistosomiasis, complications are usually more easily reversed with treatment, but conditions include blood in semen (haemospermia [37]), inflammation of the testicles and prostate gland [22,29,38–40].

1.1.4 Treatment

National-scale control programmes are now in place in many SSA countries, with the majority using PC (without diagnosing individuals) by mass drug administration (MDA) with the only recommended drug at present, praziquantel (PZQ), which can be used to treat all species of schistosomes [29,41]. Experience has shown that large-scale regular PC can be successful at reducing the prevalence and intensity of infection, provided that therapeutic coverage is high [42]. Though the exact mechanism by which PZQ works is poorly known, its associated high cure rates (proportion of individuals who become parasitologically negative following treatment, of 60-90%), high egg reduction rates (proportional reduction of egg output compared to baseline of over 90%), and increased availability,

have helped dramatically to improve the global control of schistosomiasis since its first mass use over 30 years ago.[25,42,43] The recommended dose is 40mg kg^{-1} but in the field, is typically approximated using height measured with a dose pole [36].

1.2 Diagnosis

Infection with *Schistosoma* is most commonly diagnosed by the presence of schistosome eggs in stool for intestinal schistosomiasis (mainly using the Kato-Katz method [44,45]) or urine for urogenital schistosomiasis (using the urine filtration method [44]) [22]. *S. haematobium* was the only known cause of human urogenital schistosomiasis (until the acknowledgment of the existence hybrid populations [31]), whereas *S. mansoni, S. japonicum, S. mekongi, S. intercalatum* and *S. guineensis* are all causes of human intestinal schistosomiasis [22,29].

1.2.1 Prevalence and intensity metrics and age-infection profiles

The prevalence of infection, expressed as a percentage, is a measure of the proportion of individuals infected in a given population sample, irrespective of infection intensity levels. Infection intensity measurements not only provide information about the presence or absence of infection, but also provide a measure of the worm load harboured by the individual with parasites (which can be assumed to be directly related to the level of morbidity experienced by the individual). Given the difficulties inherent in measuring worm burden directly, indirect measures based on transmission stages (in this case eggs) are used. For intestinal schistosomiasis and using Kato-Katz, the units of intensity are the number of eggs per gram of faeces (epg); for urinary schistosomiasis and using urine filtration, intensity is measured as the number of eggs per 10ml of urine (eggs $10ml^{-1}$). Infection intensity categories are defined by the following WHO egg-count bins: not infected = 0 epg; infected at light intensity = 1-99 epg; infected at moderate intensity = 100-399 epg and infected at high intensity = ≥400 epg for *S. mansoni*, and not infected = 0 eggs $10ml^{-1}$; infected at light intensity = <50 eggs $10ml^{-1}$ and infected at high intensity = ≥50 eggs $10ml^{-1}$ for *S. haematobium* (note the absence of a moderate intensity category for the latter species) [36].

Age profiles of infection prevalence and intensity are used in parasitology to understand patterns of acquisition and loss of infection across age groups [46]. Figure 1.2 and 1.3 shows the age-intensity

profile for *S. mansoni* from 6 communities in Kenya where intensity information was collected from 13,000 individuals between the 1980s-1990s [47].

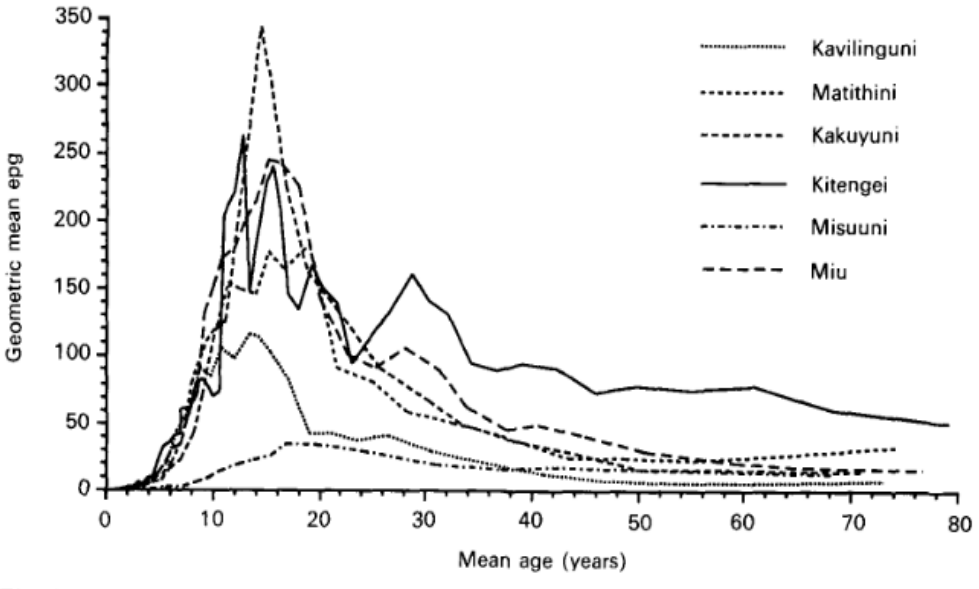

Figure 1.2. Age-intensity profiles from six communities in Kenya for *S. mansoni,* taken from Fulford et al. (1992) [47]. The y-axis is the geometric mean epg, where epg is the eggs per gram of stool sample.

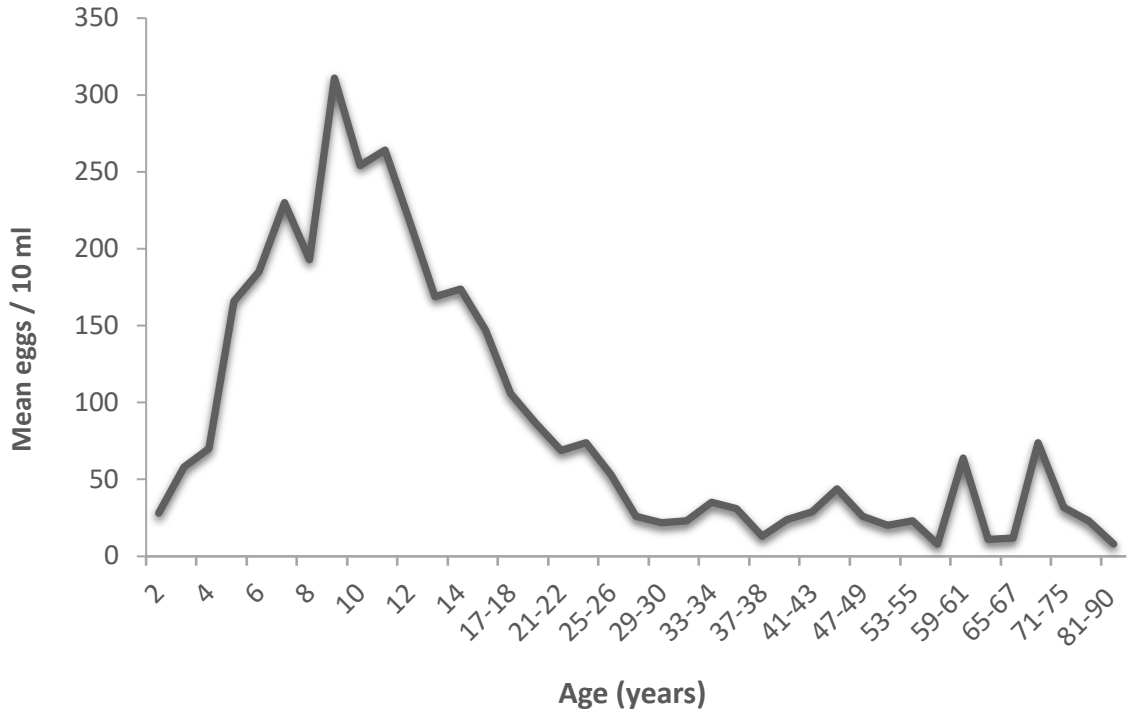

Figure 1.3. Age-intensity profile from the Misungwi Community in Tanzania for *S. haematobium*, adapted from Bradley and McCullough (1973) using the same age categorisation [48].

Young adolescents tend to harbour the heaviest levels of infection and parasite acquisition has been shown to start within the first two years of life [29]. These patterns may be due to age-related changes in exposure due to changes in behaviour (e.g. children playing with friends in the lake), age-specific changes in susceptibility (skin thickness, puberty) and/or development of acquired immunity amongst adult age groups over time [34,49,50].

1.2.2 Current diagnostic tools

Some of the currently used diagnostic tools are described below, though not all meet the ASSURED criteria list (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) [51].

UCP-LF CAA

The up-converting phosphor lateral flow circulating anodic antigen (UCP-LF CAA) test is an immunodiagnostic test that detects the presence of CAA in the urine. Though the test can be used for both *S. mansoni* and *S. haematobium,* it is more effective in detecting the latter [52]. Currently this method is not suitable for mass scale use.

POC-CCA

The point-of-care (POC) urine circulating cathodic antigen (CCA) test is another immunodiagnostic test which is used to detect *S. mansoni* infection (and is unsuitable for *S. haematobium* infection) [52,53]. It is a promising alternative to the Kato-Katz method for large-scale use and has also shown to be a more sensitive test to detect infection. However, its main limitations are that it is a semi-quantitative method of infection measurement, correlating results from traditional Kato-Katz method is a challenge and is not suitable for diagnosing soil-transmitted helminth (STH) infection.

Urine dipsticks

Urine reagent strips are used to detect haematuria (presence of blood in urine) as a presumptive diagnosis of *S. haematobium*. Hemastix® strips are dipped into a urine sample, where a colour change is observed to signify haematuria (therefore no indication of infection intensity). This test is particularly useful in areas of heavy *S. haematobium* infection, where one of the common symptoms is haematuria. Some of the drawbacks of this method are that it cannot be used for the detection of any other parasite species, it would be of limited use in areas of low infection intensities (where

infected individuals are less likely to have detectable blood in urine) and it is non-specific, since haematuria can be the symptoms of other medical conditions [54].

Urine filtration

Like the Kato-Katz method for *S. mansoni*, this is the current WHO-recommended diagnostic tool for *S. haematobium,* where both require microscopic identification of the expelled parasite eggs from host individuals. The technique involves filtering urine through a porous membrane (such as nylon, paper or a polycarbonate material), where the eggs are retained on the membrane, placed on a slide and then read by a microscopist [22]. This method is less sensitive than the CAA test but does provide a cheap, field-ready quantitative measure of infection intensity for current morbidity goals [55].

Kato-Katz

The Kato-Katz method is currently the diagnostic tool recommended by the WHO for STH and *S. mansoni* infection. Under this technique, a stool sample is pushed through a sieve to remove debris, and then placed on a slide for enumeration by a parasitologist of the number of eggs per gram of stool (this will be explained in further detail in Chapter 2, Methods) [36]. This method of diagnosis is highly specific (depending on the skill of the technician in identifying parasite eggs) since parasite eggs are very distinct by species but is not sufficiently sensitive for light infections, particularly in single slide readings. Egg output in stools varies day-to-day, so multiple slides and samples are recommended in areas of low intensity infections (when assessing morbidity, this is less of a concern since moderate and heavy infections are relatively easily detected with the Kato-Katz method) [56].

PCR

The Polymerase Chain Reaction (PCR) method involves the amplification of DNA (through PCR), with the advantage of only requiring a small sample from either stools or serum (though using stool has been shown to be more sensitive[57]), making it ideal for detecting low-intensity infections. Due to the costs, equipment and level of technical expertise required and the associated logistical challenges, this method is not ideal for large-scale use.

Other tests are also available such as formol-ether concentration (FEC), McMaster, FLOTAC, and Mini-FLOTAC [58] and the sensitive SEA (soluble egg antigen)-ELISA test for *S. haematobium* [59] or the less sensitive CCA-B [60] and CCA-L [61].

1.2.3 Challenges in diagnostics

The closest diagnostic tool, available in the current tool kit, to what can be defined as a 'gold standard' is the PCR method for its sensitivity [62]. But this still poses the question of what diagnostic to employ for large-scale, field use, particularly in areas of low-intensity infections. The tools currently recommended by the WHO for *S. mansoni* (Kato-Katz) and *S. haematobium* (urine filtration) lack the sensitivity required when the intensity of infection is low (either because of low endemicity or because of the impact of treatment), and can only detect those eggs expelled by the host (which as said, varies from day to day, within sample, and is an indirect measure of worm burden). The relationship between egg output and the number of eggs trapped and dying in host tissues (which cause the immunopathological response that leads to morbidity) is still unclear. Moreover, a clear relationship between egg output and the actual number of worms harboured by the host in humans has not been clearly established; possibly with the exception of a small historical study conducted by Cheever et al. [29,63,64] on post-mortem examinations. Recent studies have demonstrated that the density-dependent effect of fecundity may be important, because as the population of adult worms declines, remaining mature females seem to be able to produce more eggs due to decreased competition for resources, at least according to population genetic/relatedness studies in *S. mansoni*. Thus, transmission may not decline linearly with intervention (treatment) effort [65].

Some of the major challenges concerning diagnostics, infection intensity and subsequently, morbidity markers are finding a single affordable, tool with high sensitivity and specificity, which can also provide details of the level of morbidity an individual may be experiencing and that require little technical expertise to use. For *S. mansoni*, the tool that best fits these criteria is the CCA test but it has its limitations as mentioned in the previous section as well as unknown potential cross-reactions with other species, which may cause false positives, and issue with the "trace" measurement – whether this should be considered a positive or negative diagnosis (though the general consensus is that trace measurements be considered as positive).

1.3 Global and population disease burden

Schistosomiasis is a major public health problem with approximately 85% of people infected with schistosomes residing in SSA [35,41]. Figure 1.4 illustrates the global distribution of schistosomiasis [22]. Causing the second greatest human health and socio-economic burden (first being malaria),

schistosomiasis is estimated to infect over 238 million people [29,66] at a cost of 3.3-4.5 million disability-adjusted life years (DALYs) worldwide and, in SSA, causing between 15,000-280,000 deaths per year [22,23,32,35,36,41].

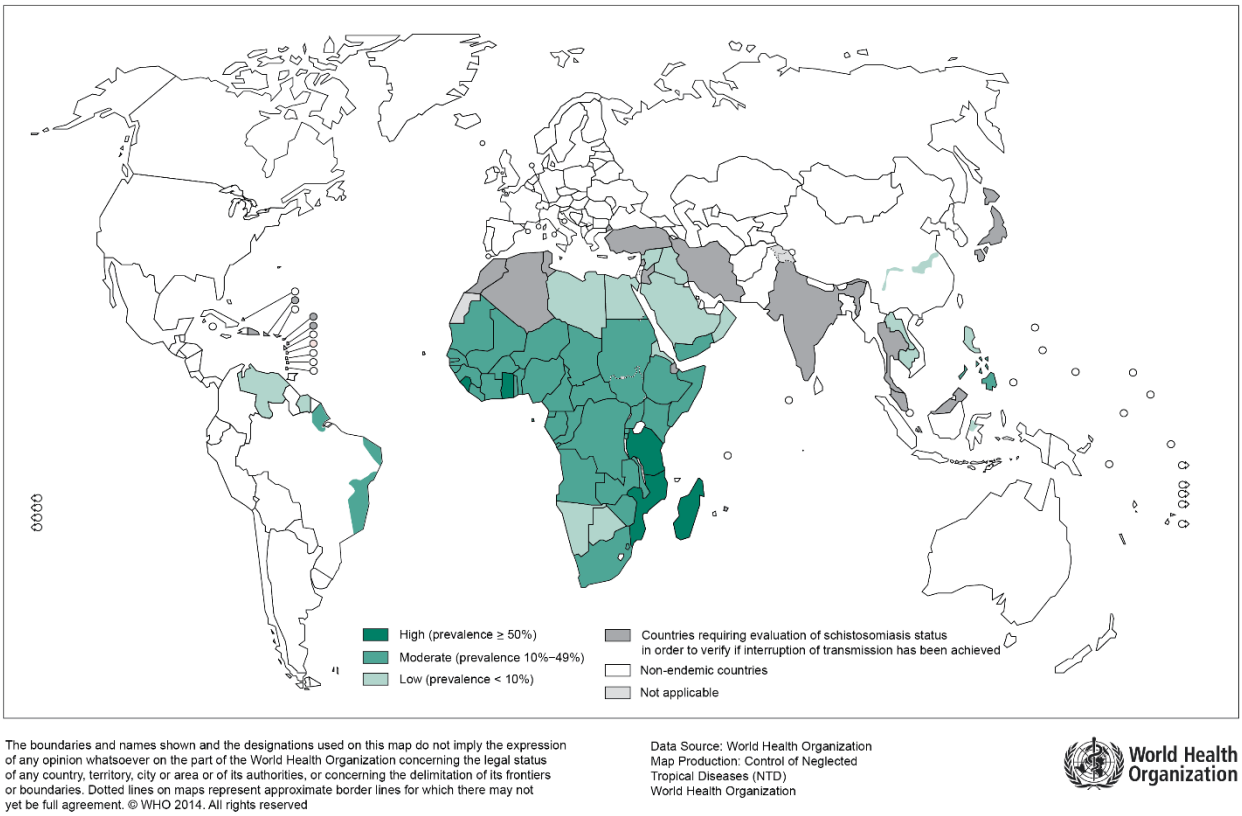

Figure 1.4. Global distribution of countries endemic for schistosomiasis [22]. The distribution of the infection is in fact highly focal.

Schistosomiasis is a highly focal disease due to the requirement of a fresh waterbody such as a lake to enable the transmission process. This, among mechanisms influencing host susceptibility, increases the heterogeneity of worm burden in the host population since all individuals are not equally exposed and/or predisposed to infection (i.e. infection is not randomly distributed). Understanding the distribution of worms amongst the host population is an important factor to consider when measuring parasite burden [67], and can be achieved by measuring the frequency distribution of worm burden (via egg counts) in the host population [68].

Studies have shown that the distribution of worm burden is highly overdispersed (i.e. that the variance is much greater than the mean), in which the majority of hosts harbour light infection or are uninfected and a small proportion harbour a heavy burden and are likely to play a major role in transmission [50,69,70]. This is further demonstrated by an individual's tendency to re-acquire heavy infection post-treatment (and likewise those with lighter infections pre-treatment are predisposed to lighter infections post-treatment). The pattern of parasite distribution amongst hosts is often approximated by the negative binomial distribution, which is defined by *m*, the mean worm burden, and *k*, the aggregation parameter (which inversely measures the degree of overdispersion) [34,50,67,71]. Since individuals with the heaviest burden likely experience the highest morbidity and contribute most to transmission, these groups should (even in the presence of density-dependent fecundity their 'net' contribution would be greater) be monitored closely when measuring the impact of a programme [36]. This characteristic could also be harnessed if programmes were to opt for targeted treatment of the most heavily infected individuals [50,70–73].

1.4 Modelling

Disease models are useful in programme monitoring and evaluation (M&E), outbreak analysis and predictions and informing intervention policy, where they have often been employed [74–76]. Statistical models (such as logistic regression models, generalised linear models, etc.) are routinely used in M&E for schistosomiasis programmes to measure the impact of the treatment intervention (Chapter 2). Mechanistic mathematical models, which explicitly model the life cycle and transmission of schistosomiasis often through a series of differential equations are used to determine the feasibility of schistosomiasis elimination, disease predictions as well as informing future international guidelines and national policy [77–79]. However, due to the technical expertise required to develop, understand or run these models and the important underlying assumptions these models make (which are sometimes based on simulated data), policy makers and Ministry of Health programme managers have rarely utilised these powerful tools. Therefore, historically, intervention strategy and policy have been based mainly on expertise and experience rather than data or models (Section 1.6) [80–82].

This reluctance to readily employ mathematical modelling outputs to programme policy stems partly out of the knowledge that schistosomiasis is highly focal and that relatively few specifics are known about the schistosomiasis life cycle (with a high level of uncertainty surrounding certain parameters). For example, the egg output is an indirect measure of worm burden and little is known about the

relationship between the two. Another example is that the snail stage of the life-cycle is difficult to parameterise as there is so few data available to provide reliable estimates. However, many models have been developed despite these hurdles [79,83–86].

A Markov model is a type of stochastic model that models the sequence of states with a random probability, and is a 'memoryless' process, i.e. where each subsequent state only depends on the current state and not any past states. The main appeal of the Markov approach compared to mechanistic mathematical modelling approaches resides in its simplicity, whereby the underlying transmission dynamics are not modelled explicitly but are captured empirically using a purely statistical approach based on estimated transition probabilities (TP) [34,87]. The model can be used to track progress and to identify deviations from expected programme performance where observed values fall outside predicted uncertainty intervals (e.g. 95% prediction intervals [PIs]). Markov models have been more commonly employed in health economics cost-effectiveness analyses and in chronic diseases [88–90]

1.5 Activities of a control programme

1.5.1 Overview of activities

More than 80 million individuals out of 258.8 million at risk who required preventive treatment actually received treatment in 2016, reaching a global coverage of 54% in school-aged children (SAC) (Figure 1.5) [22,91–93]. One of the major partners responsible for facilitating the distribution of PZQ is Merck KGaA, for their donation of over 290 million tablets of PZQ to the WHO since 2008 and have committed up to a further 250 million tablets per year from 2016 [94,95]. The tablets are distributed by the Ministries of Health of endemic countries, where in some, non-governmental organizations such as the Schistosomiasis Control Initiative (SCI) provide technical support and assistance (and in some cases purchasing and supplying additional PZQ) [32,96–98].

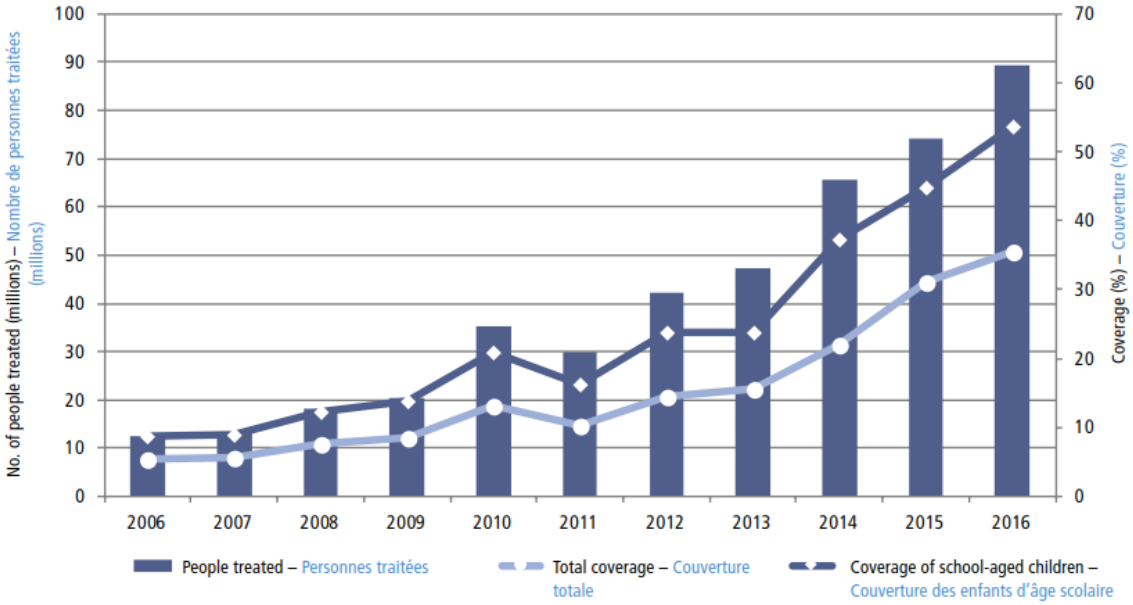

Figure 1.5 Global treatment coverage between 2006 – 2016 for schistosomiasis. Taken from reference [93].

Since its establishment, the SCI, based at Imperial College London, has helped to provide over 200 million treatments with praziquantel to those in need [98]. SCI provides technical support and financial assistance to the Ministries of Health of endemic countries; thus the programmes are run and owned by the countries themselves [35]. Amongst other activities, the programmes involve collecting sentinel site data from randomly selected schools and students as part of the monitoring and evaluation (M&E) process, to help understand programme impact and inform programme design.

The primary aim of most schistosomiasis control programmes at inception is to reduce the morbidity in the population. As previously mentioned, this is done by reducing the intensity of infection (number of parasites in an individual) through regular PC of the population with PZQ [22]. Managing and preventing heavy infections are particularly important in these control programmes, since the higher the intensity, the greater the degree of morbidity experienced by the individual.

School-aged children (SAC, 5-15 years) are often the primary target for PC programs to avert the long-term damage caused by these parasites. The highest values of infection prevalence and intensity are found in this age bracket and resources are often too limited for treatment on a wider scale to "less prioritised" age groups [34]. In addition, the school system provides a convenient platform for effective programme delivery since the majority of the children in a community can be treated at one time and high coverage and compliance can potentially be achieved. Adult populations at high risk

such as fishermen are also targeted for PC in those communities where overall community prevalence is high (i.e. >50%) [22,99].

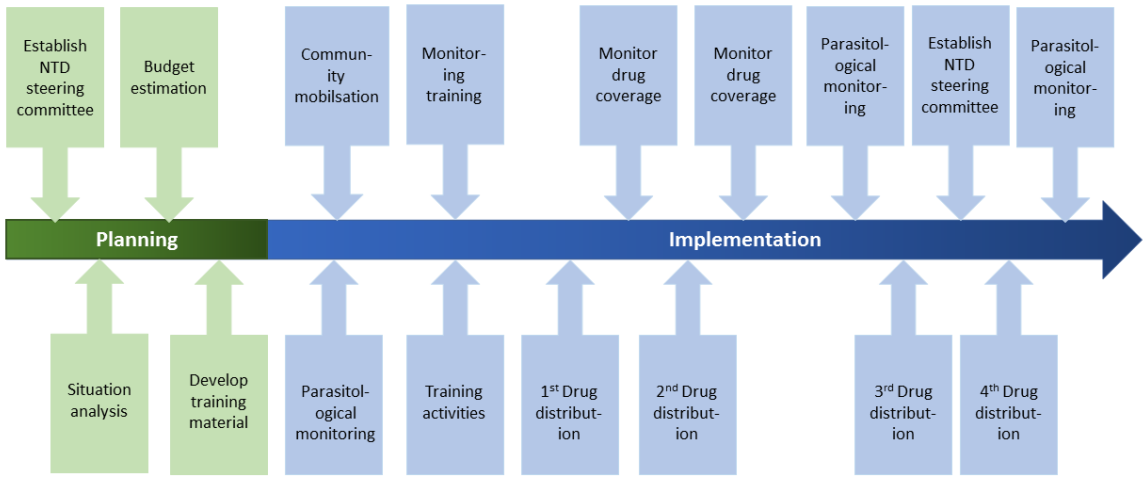

Figure 1.6 Processes involved in a deworming programme, adapted from [36].

Figure 1.6 illustrates the activities involved in the planning of control programme. These activities can be summarised into three general groups, focussing on activities relevant to the thesis [36]:

1. **Planning**: which includes (among other activities, Figure 1.6) the collection of data to map the region and determine prevalence by ecological zone in order to select the best WHO intervention strategy [99] in each area;
2. **Implementation**: this includes training and drug distribution;
3. **Monitoring and Evaluation**: this includes monitoring MDA coverage at each round in selected sites after each drug administration and assessing the impact of the control programme (at baseline and every 2-3 years). Impact assessment is through indicators such as the prevalence and intensity of infection and morbidity, etc.

The aim of a control programme is to: a) reduce the overall burden of infection; and b) to keep the burden low in the population [36,99]. The distribution of infection in a country is initially mapped prior to MDA campaigns to gain information on the geographical distribution of infection prevalence and to determine the appropriate treatment regimen applicable to these implementation units, using

the WHO endemicity categories and guidelines [100]. National baseline mapping is an intensive and costly process in terms of finance and logistics, but plays a vital role in determining the intervention requirements for the next several years. After several rounds of treatment have been implemented, the WHO recommends re-evaluation of schistosomiasis infection and to determine plans for the next stages of the programme [36].

1.5.2 Monitoring and Evaluation

Following baseline mapping, routine parasitological data are collected by programmes from school sentinel-site as part of the M&E , which are less costly and provide a more general idea of the impact of the programme (through estimates at a sentinel site level, powered to infer at the national level, for example), since nationwide mapping on an annual basis may not be an efficient use of already limited resources. M&E activities also include treatment impact surveys, treatment coverage surveys (performance monitoring), process monitoring and the prevalence mapping previously mentioned. Thus M&E is an essential component of control programmes to assess and improve performance, which is of high interest to all stakeholders (affected communities, national ministries of health, donors, etc.).

1.6 WHO guidelines and recommendations for control programmes

1.6.1 Brief history of the WHO guidelines

The schistosome parasite was first officially discovered in 1852 by Theodor Maximilian Bilharz and Carl Theodor Ernst, with records of historical infections dating as far back as 6000 years ago, and has since been the subject of tens of thousands of studies [101,102]. However, the first World Health Organization's World Health Assembly (WHA) for schistosomiasis took place in 1950 (WHA3.26 resolution[103]) and remained in place for 25 years until the WHA28.53 resolution in 1975 when it was recognised that the disease still remained largely uncontrolled and that new guidelines concerning food and water sources needed to be implemented [81]. This was soon followed by WHA29.58 in 1976, urging further research and for "priority to be given to the control of schistosomiasis in accordance with the importance this disease presents as a public health problem"[104]. It was not until 2001 for the next WHA resolution, WHA54.19, that treatment was

urged for the high-risk individuals and ensuring access to PZQ in all endemic areas, setting the goal to reach 75% (100% of all at-risk SAC) by 2010 [81]. This subsequently led to the development of the WHO's "Helminth control in school-age children: a guide for managers of control programmes (First edition)" in 2002 and "Preventive Chemotherapy in Human Helminthiasis" guidelines for control programme managers in 2006 [105,106]. However, these targets were not reached by 2010 and second editions of the guidelines were published in 2011 (see Section 1.5.2), which did not differ significantly from the 2006 treatment guidelines. These were closely followed up by the 2012 Elimination of Schistosomiasis WHA65.21 [107]. The WHA65.21 resolution led to new targets in 2013 and were published in the WHO's Progress report 2001–2011 and strategic plan 2012–2020 (Section 1.5.3). Although resolutions on elimination were established, no changes were made to recommendations for treatment on achieving these goals, nor the M&E to demonstrate that the goals had been reached [99,108].

1.6.2 Current WHO guidelines

The current WHO treatment guidelines for control programmes use the prevalence determined through situational analyses or mapping of the country, which are: prevalence of infection less than 10% requires PC once every three years, between 10% and 49% requires biennial treatment and 50% or greater requires annual treatment. These thresholds were based predominantly on expert opinion and limited empirical evidence. The WHO recommended diagnostic tools are Kato-Katz for *S. mansoni* and urine filtration for *S. haematobium.* The impact of the control programme in reducing morbidity is recorded as part of M&E activities through impact surveys conducted at baseline (i.e. before the first MDA) and at set follow-up times, usually before each MDA. Impact surveys collect epidemiological data from a selected number of schools (i.e. sentinel schools) and, in some cases, from selected communities. Following several rounds of treatment, the impact of the control programme is likely to have positively changed the infection status of the area. The WHO therefore recommends re-evaluation of the country after 5-6 years in order to appropriately modify the treatment strategy for the subsequent years [36,109], though again, this time-range is based largely on expert opinion. Figure 1.7 illustrates a decision tree for control programmes with the recommended guidelines.

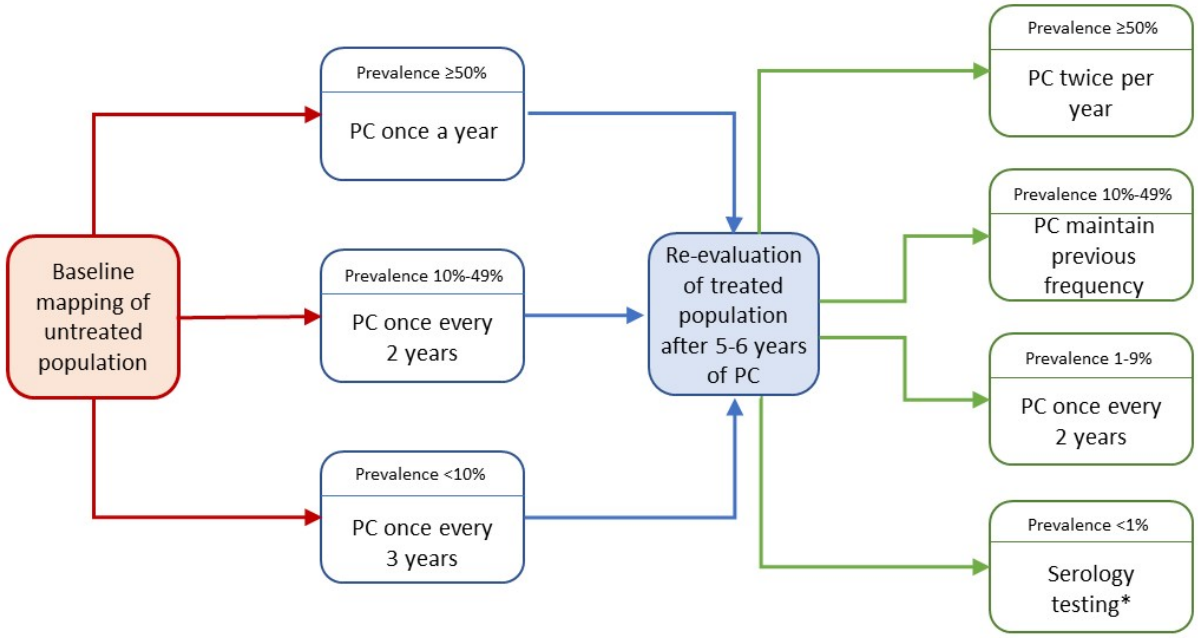

Figure 1.7. Treatment guidelines for schistosomiasis preventive chemotherapy (PC) control programmes [36]. *if positive, PC once every two years; if negative then no PC required.

Many countries have progressed from control to elimination. For a control programme to progress to the elimination targets, they must first reach the targets or "threshold points" set by the WHO (see Figure 1.8). These will be discussed in further detail in Section 1.5.3.

1.6.3 WHO Roadmap and the London Declaration on NTDs

With the vision of "a world free of schistosomiasis", the WHO and its partners have pledged to meet the ambitious goals of controlling morbidity (i.e. as currently defined, to decrease the prevalence of heavy infection intensity to less than 5% across all sentinel sites) of schistosomiasis by 2020 (in all endemic countries), achieving elimination as a public health problem (EPHP) (i.e. as currently defined, to reduce the prevalence of heavy infection intensity to less than 1% in all sentinel sites; in all endemic countries) and the interruption of transmission in selected regions by 2025 [99,108].

A roadmap for control and elimination of 10 prioritised NTDs for the period 2012-2020 was developed by the WHO's Strategic and Technical Advisory Group (STAG) for NTDs in April 2011. The Strategic Plan's goals were to: a) control schistosomiasis-induced morbidity by 2020; b) eliminate schistosomiasis as a public health burden by 2025; and c) interrupt transmission in selected countries by 2025[99]. The five strategies for the NTDs recommended by the WHO are: 1) preventive chemotherapy (PC, for helminthiases and trachoma); 2) intensified disease management (for other

NTDs); 3) vector and intermediate-host control; 4) veterinary public health at the human–animal interface; and 5) provision of safe water, sanitation and hygiene. This roadmap was launched by the then Director-General, Dr Margaret Chan at the same time of the London Declaration on NTDs in January 2012, which aim to support and coordinate efforts towards the targets [17,18,99]. In addition, the 8 Millennium Development Goals (MDGs) stemming from the UN Millennium Declaration, where the NTDs fall under the "other diseases" category of MDG 6 ("combating HIV and AIDS, malaria and other diseases") and subsequently, the more recent 17 Sustainable Millennium Goals (SDGs), where NTDs fall under SDG 3 (SDG 3.3: "by 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases") [5,16,17,99,110], complement and further add to the momentum towards the 2020 targets and beyond.

The London Declaration on NTDs in January 2012 endorsed the ambitious targets set by the WHO for the control and elimination of many NTDs, including schistosomiasis, with the elimination 'as a public health problem' from most WHO regions and by selected African countries by 2020 (i.e. reducing prevalence of heavy infection to < 1% in all sentinel sites) [17,18,99]. In some local settings, interruption of transmission is also anticipated, thereby accelerating elimination of the disease [17].

Figure 1.8 summarises the WHO guidelines for the progression of countries from the control to eventual elimination of schistosomiasis (a list of countries and their stages can be found in [99]). These guidelines are based largely on expert opinion and use the number of treatment implementation years as progression thresholds for transition to the next stage of control or elimination.

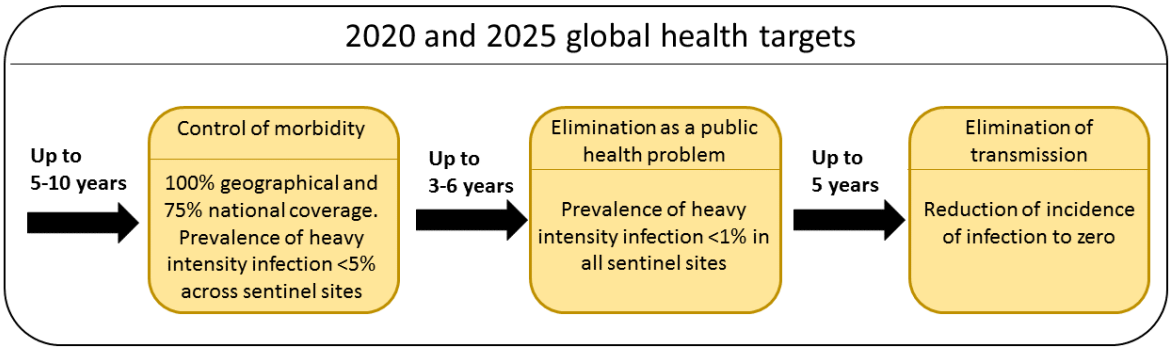

Figure 1.8 Proposed timelines towards schistosomiasis control and elimination (as a public health problem as well as transmission) targets [99]. Recommended interventions for Elimination as a public Health Problem: adjusted PC and complementary interventions; essential interventions for interruption of transmission: intensified PC and complementary interventions.

It is worth noting here that the term elimination is somewhat ambiguously used in the literature because it may be interpreted as elimination of the public health burden or as elimination of the infection reservoir [111]. Most programmes aim initially at the former, and as they progress become more ambitious towards the latter. It is also important to note that interruption of transmission is not strictly equivalent to elimination of infection, because even if the force of infection (the rate of acquisition of new worms per unit time [34]) were reduced to zero, the long lifespan of the adult stages of some of these helminthiases [112] would mean that the presence of the adults and of transmission stages would remain for some time until the parasite populations dwindle due to natural attrition.

CHAPTER 2. MULTI-COUNTRY ANALYSIS OF CONTROL AND ELIMINATION THRESHOLDS

This chapter is based on a publication that has recently been submitted and reviewed (pending final decisions) by Arminder K. Deol, Fiona M. Fleming, Beatriz Calvo-Urbano, Martin Walker, Victor Bucumi, Issah Gnandou, Edridah M. Tukahebwa, Samuel Jemu, Upendo J. Mwingira, Abdulhakeem Alkohlani, Mahamadou Traoré, Wendy Harrison, Schistosomiasis Control Initiative, Maria-Gloria Basáñez, Michael D. French and Joanne P. Webster. "Schistosomiasis - Assessing Progress towards 2020 & 2025 Global Goals".

This Chapter represents the first multi-country and multi-year empirical study, comparing epidemiological data with WHO threshold criteria on morbidity control, elimination as a public health problem (EPHP) and elimination of transmission, to assess whether a one-size-fits-all approach is appropriate for guiding schistosomiasis treatment strategies.

2.1 Introduction

Schistosomiasis prevalence levels at specific administrative levels are usually determined at the mapping stage of the country programme, which then determine the treatment strategy. The current WHO treatment guidelines state: prevalence of infection less than 10% requires triennial preventive chemotherapy (PC, once every three years), between 10% and 49% requires biennial treatment and 50% or greater requires annual treatment (see Chapter 1 and Figure 2.1). The impact of the control programme in reducing morbidity (using prevalence and/or intensity as a proxy) is recorded as part of monitoring and evaluation (M&E) activities through impact surveys conducted at baseline (i.e. before the first round of PC) and at set follow-up times, usually before each subsequent PC round. Impact surveys collect epidemiological data from a selected number of schools (i.e. sentinel schools) and, in some cases, from selected communities. The prevalence and intensity of infection are re-evaluated after 5-6 years of treatment from baseline, through re-assessment mapping (also referred to as 'remapping' and 're-evaluation') of the country, in order to assess the progress of the programme and determine the treatment strategy for subsequent years (Figure 2.1 taken from Chapter 1) [36,109].

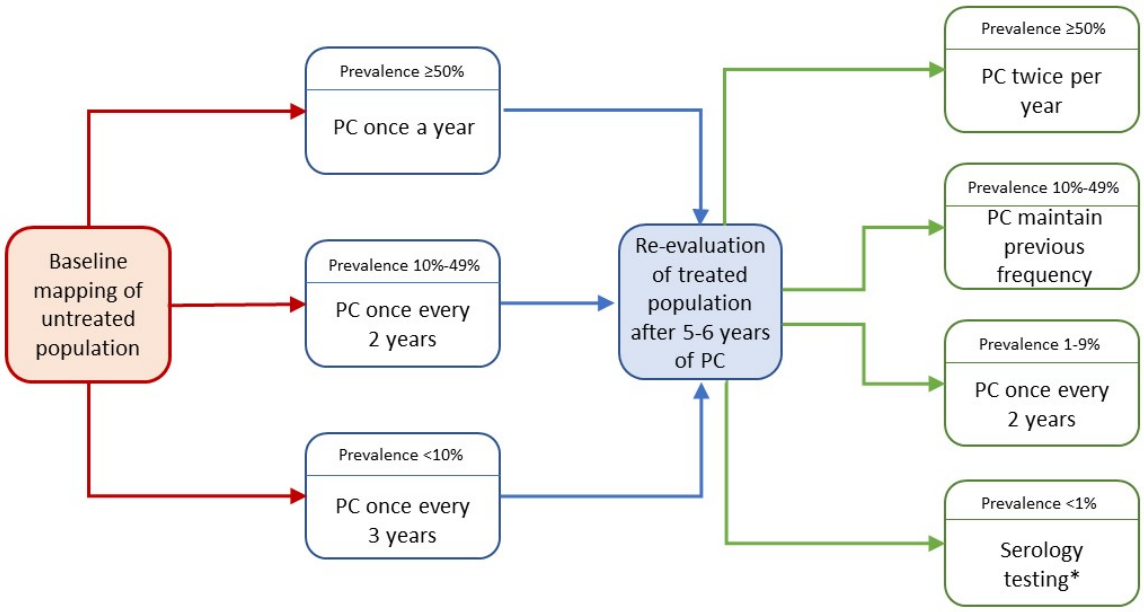

Figure 2.1. Treatment guidelines for schistosomiasis preventive chemotherapy (PC) control programmes [36]. *if positive, PC once every two years; if negative then no PC required.

Morbidity control at a national scale has been generally successful in many endemic countries [113] and this has led, in part, to a revision of the WHO's strategic plan and towards an elimination strategy (Chapter 1, section 1.5.3)[99]. In particular, the WHO has set the ambitious goals of controlling morbidity (i.e. prevalence of heavy-infection intensity <5% aggregated across sentinel sites) of schistosomiasis by 2020 and achieving elimination as a public health problem (EPHP, i.e. elimination of morbidity where prevalence of heavy-infection intensity <1% in all sentinel sites) in all endemic countries by 2025. Complete interruption of transmission is also a target in selected regions by 2025 (i.e. the regions of the Americas, Eastern Mediterranean, Europe, South-East Asia, Western Pacific and selected countries in the African Region, Figure 2.2 taken from Chapter 1) [17,99,108].

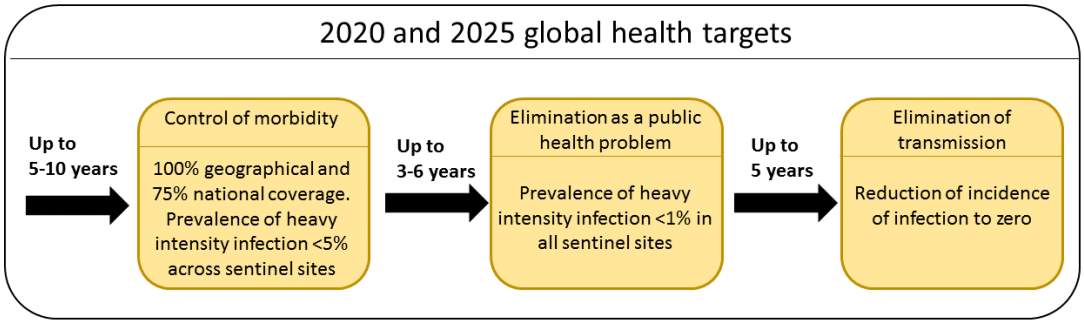

Figure 2.2. Proposed timelines towards schistosomiasis control and elimination (as a public health problem as well as transmission) targets [99].

The WHO has published guidance on how programmes can progress from control of schistosomiasis to EPHP and to a more limited extent, interruption of transmission [99]. However, the time required for transitions between goals is unlikely to be uniform for all countries due to the variability between them (Figure 2.3). When the original guidelines were first developed (Figure 2.1), there were limited epidemiological data available. Consequently, the guidelines were likely based on the little empirical evidence available and largely on expert opinion. Hence, there exists a pressing need to analyse quantitative evidence, captured through programme monitoring, to validate or update these guidelines to aid countries to reach these goals.

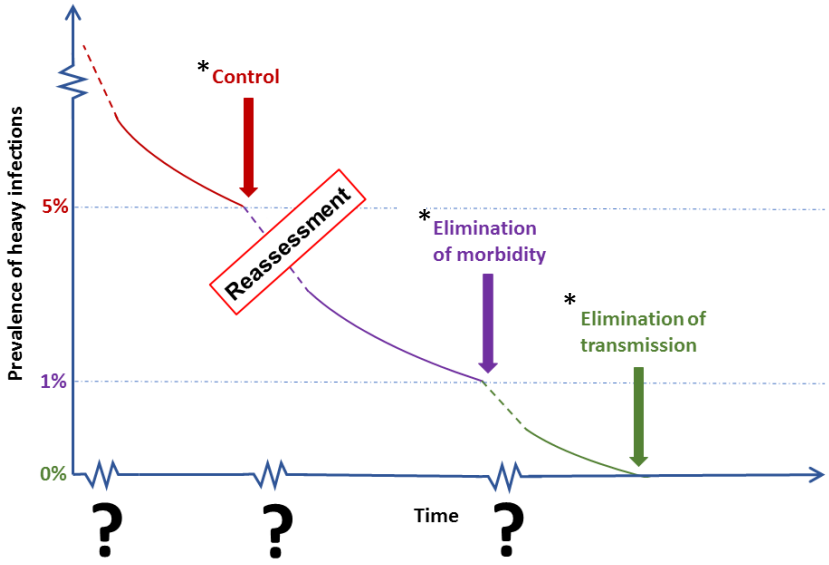

Figure 2.3. Schematic representation of programme progression towards elimination of schistosomiasis. *Recommended World Health Organization strategies: control (of morbidity) by preventive chemotherapy (PC) and complementary interventions where possible; elimination of morbidity (i.e. elimination as a public health problem) by adjusted PC and complementary interventions strongly recommended; elimination of transmission by intensified PC in residual areas of transmission and complementary interventions essential [99]. Note that guidelines on the definition of "intensified PC" is currently lacking as are specifics on "complementary interventions".

Many countries, through the Ministries of Health and/or non-government organisations (NGOs) such as the SCI have been implementing control programmes for a sufficient number of years to enable assessing adherence to WHO targets and timeframes [96]. Therefore, the questions we now face include: i) when do countries reach the WHO and 2020/2025 targets (if at all); and ii) how best to use routinely collected sentinel site M&E data to determine this? To address these questions, the extensive historical datasets from SCI-derived M&E activities in endemic countries were analysed and compared to assess progress made thus far on reaching the WHO control and/or elimination operational threshold(s). Recent theoretical mathematical modelling work projects that the 2020 goal of control of morbidity is likely obtainable for low-prevalence and moderate settings, but will be missed in high-intensity settings under current treatment guidelines [114]. The aims of this Chapter were to: (1) provide the first empirical multi-country comparison of programmatic data with WHO threshold criteria on morbidity control and EPHP; (2) assess whether a one-size-fits-all approach is appropriate for guiding schistosomiasis treatment strategies; (3) investigate other possible metrics to define thresholds for control and EPHP; and (4) determine the relationship between prevalence of heavy-infection intensity and overall prevalence across treatment rounds and countries.

2.2 Materials and methods

2.2.1 Data Collation and analyses

Impact surveys (also referred to as sentinel-site surveys) are an essential component of monitoring and evaluation (M&E) activities, which determine how a programme is performing in terms of reducing prevalence and intensity of infection, usually in the target population (school-aged children, SAC). Typically schools, number of sentinel sites and total sample size depend on the country administrative level at which the survey is aiming to represent, determined in the survey protocol development.

For these historical data from SCI-supported programmes used in this thesis, data sharing agreements were shared and signed between SCI and the Ministries of Health of endemic countries. Raw egg count data were collated and formatted (which were stored in various formats and software) from the historical impact surveys conducted in nine countries one month (or less) prior to the following treatment round as per standard protocol.

Table 2.1 shows the final list of countries from which data were analysed and the information available of the programmes, obtained either from the datasets directly or from the programme reports and protocols. Inclusion criteria for data analyses were:

i) programmes that were supported by the SCI;
ii) having more than two years of impact survey data; and
iii) cross-sectional data comprising SAC.

These data represent a unique collection from multiple country programmes, which enable the comparison of outcomes between country programmes as well as with the global WHO targets.

The term "country programme" is used throughout this chapter rather than "country", since some countries had programmes that could not be combined for the analysis, as was the case in Mali and Burundi (see also footnote to Table 2.1). The Burundi programme had begun with a large 'pilot' study in 2007 combining data from 12 sentinel sites, which then continued alongside the Burundi 'national' study that began a year later, with data from 19 additional sentinel sites. The two Mali programmes represented a different scenario where surveys, treatment dates and treatment frequency were not consistent between three regions (Koulikoro, Bamako, and Segou). In Segou region, three annual treatment rounds had been conducted from 2004; in in Bamako and Koulikoro, two annual treatment rounds had taken place from 2005. Thus, for Burundi and Mali, these data were not combined for the analysis.

The methods used to calculate sample sizes per impact survey were as currently employed at the SCI, as mentioned above. This provided the number of sentinel sites (schools) and children to be sampled within each site, powered to detect a difference in prevalence over time at a given administrative level, accounting for clustering at the sentinel site level (i.e. the phenomenon that individuals from the same sentinel site/cluster are more alike than individuals from a different sentinel site/cluster). Participants in the survey were sampled through randomisation and survey methods were standardised across countries. Standard Kato-Katz and Urine Filtration methods were used to detect *S. mansoni* and *S. haematobium* infection, respectively (see references contained in Table 2.1 for specific country information).

The prevalence by infection intensity category, i.e. the proportion of individuals with a given number of schistosome eggs per gram of faeces (epg) for *S. mansoni* or per 10 ml of urine for *S. haematobium* (Table 2.2), and 95% confidence intervals (95% CIs), were calculated by treatment round, schistosome species, and country by the candidate. Mean prevalence and 95% CIs were calculated to account for the clustering of the data at sentinel site level, using the R *survey* package [115]. The point prevalence

estimates were used for the comparison against the WHO guidelines, since the guidelines do not suggest calculations of 95% CIs. However, the 95% CIs were calculated for reference as using the upper limits to determine treatment category may be a more conservative approach in further studies.

For programmes where the point prevalence of heavy-infection intensity fell below <1%, an analysis was conducted to verify whether this was the case in all sentinel sites (indicative of EPHP) or only an aggregate result across sentinel sites (indicative of morbidity control). The candidate evaluated trends in the prevalence of heavy infection through time from cross-sectional data for both *S. mansoni* and *S. haematobium*, in line with WHO guidelines [99]. The guidelines do not specify whether treatment round or calendar year should be used as timelines for their targets. Since PC may not be annual, treatment round was considered the most appropriate time scale. Additional data on overall prevalence and prevalence of moderate combined with heavy-intensity infection (*S. mansoni* only) were also evaluated and compared with trends of heavy-intensity infection prevalence.

Table 2.1. Data used in this chapter from SCI assisted programmes within sentinel sites

Country programme	Start year	Endemic parasite species	Baseline endemicity (*spp.*)	Treatment frequency	Number of sentinel sites	Average number of individuals per sentinel site (SD)	Ref.
Burkina Faso	2004	*S. m.* *S. h.*	Low (*S. m.*) High (*S. h.*)	Biennial	16	94 (48)	[116]
Burundi National*	2008	*S. m.*	Low (*S. m.*)	Annual	19	307 (78)	[117]
Burundi Pilot*	2007	*S. m.*	Low (*S. m.*)	Annual	12	319 (65)	[117]
Malawi	2012	*S. m.* *S. h.*	Low (*S. m.*) Low (*S. h.*)	Annual	22	110 (15)	*(Pers. Comm.)*
Mali-Segou*	2004	*S. m.* *S. h.*	Moderate (*S. m.*) High (*S. h.*)	Annual	10	103 (26)	[118,119]
Mali-Bamako/ Koulikoro*	2004	*S. m.* *S. h.*	Moderate (*S. m.*) High (*S. h.*)	Mixed	11	76 (24)	[118,119]
Niger	2004	*S. h.*	High (*S. h.*)	Annual	8	285 (83)	[35]
Rwanda	2008	*S. m.*	Low (*S. m.*)	Annual	6	254 (103)	*(Pers. Comm.)*
Tanzania	2005	*S. m.* *S. h.*	Moderate (*S. m.*) Moderate (*S. h.*)	Annual	21	124 (62)	[35]
Uganda	2003	*S. m.*	Moderate (*S. m.*)	Annual	39	80 (45)	[120]
Yemen	2010	*S. m.* *S. h.*	Low (*S. m.*) Moderate (*S. h.*)	Biennial	136	34 (49)	*(Pers. Comm.)*

S. m. = *Schistosoma mansoni*; *S. h.* = *Schistosoma haematobium*; Pers. Comm. = personal communication. *Burundi and Mali were split into two segments in this study: 'Burundi Pilot' (containing data from twelve sentinel sites) and 'Burundi National' (data from nineteen sentinel sites), where the surveys began in different years, and 'Mali-Segou' (one sentinel region, ten sentinel site schools) and 'Mali-Bamako/Koulikoro' (two regions, eleven sentinel site schools) where different treatment strategies were implemented. SD = standard deviation.

While the WHO guidelines use prevalence of heavy-intensity infection as an indirect measure of morbidity (assuming morbidity is proportional to infection intensity), the combined measure of prevalence of moderate- plus heavy-intensity infection was included, due to uncertainty in the appropriateness of the current egg count thresholds for intensity (Table 2.2) and because some degree of morbidity is likely to be caused by the presence of any number of eggs in the host (whether or not an individual is symptomatic) [121]. Information on the relationship between infection intensity and severity of morbidity for *S. haematobium* is scarce and there is no empirical reason for the choice of the prevalence thresholds proposed or for the lack of a moderate intensity category (Table 2.2).

Table 2.2. Infection intensity categories for schistosomiasis and corresponding egg count cut-offs [36].

Parasite	Light intensity	Moderate intensity	Heavy intensity
Schistosoma mansoni	1-99 epg	100-399 epg	≥ 400 epg
Schistosoma haematobium	1-50 eggs/10 ml	Not defined	> 50 eggs/10 ml

Epg = eggs per gram of faeces

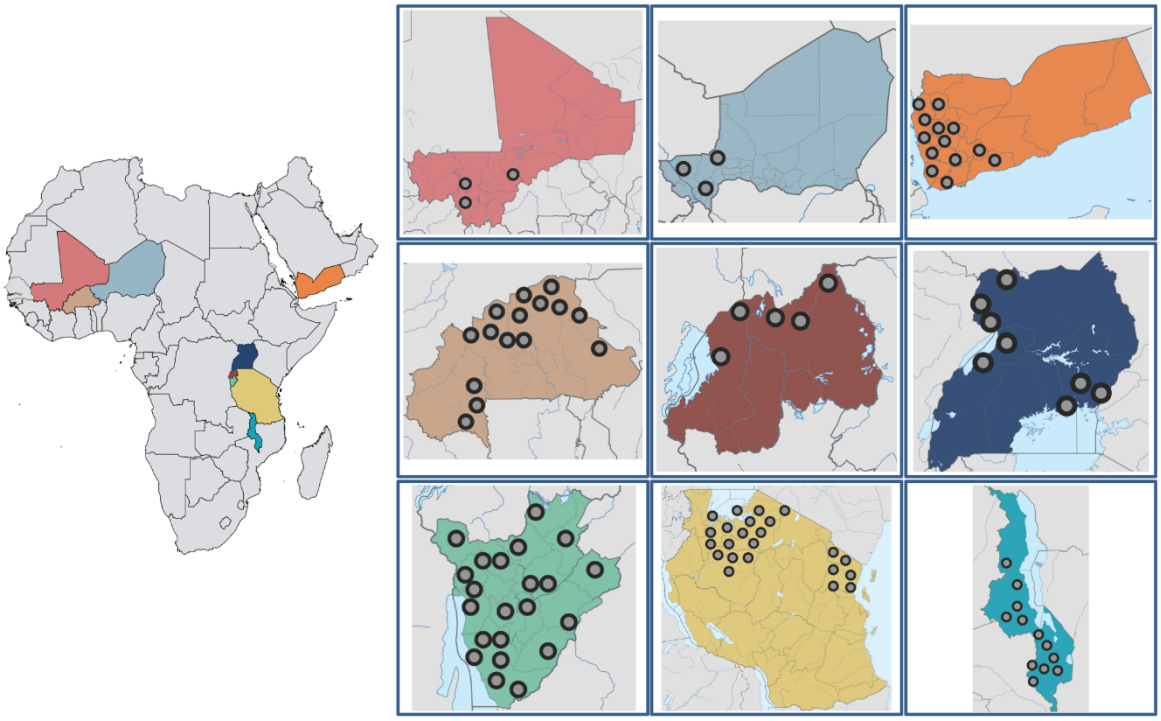

Figure 2.4. Countries from which data were analysed. The left-hand map shows country locations within Africa, and Yemen. Dots on the right-hand maps indicate the location of the sentinel sites. From left to right, starting in the top left square (number of sentinel sites in total in brackets): Mali (21), Niger (8), Yemen (136), Burkina Faso (16), Rwanda (6), Uganda (39), Burundi (31), Tanzania (21) and Malawi (22).

2.3 Results

The baseline endemicities of infection for both species of *Schistosoma* greatly varied. Baseline prevalence of *S. haematobium* ranged from 9.8% [95% CI: 8.7-11.0] in Malawi (a low endemicity country) to 82.1% [95% CI: 79.8-84.3] in Mali-Segou (a high endemicity country) [36]. Prevalence for *S. mansoni* varied from 1.9% [95% CI: 1.2-2.9] in Malawi (low endemicity) to 45.4% [95% CI: 44.0-46.9] in Uganda (moderate endemicity). Despite this heterogeneity, infection intensities in all countries fell in response to the programmes' first round of treatment to below, or within 0.8% of the <5% prevalence of heavy intensity threshold for control for *S. mansoni* infection and within 3.3% for *S. haematobium* (Figures 2.5 to 2.7).

For both schistosome species, treatment successfully reduced the prevalence of heavy-intensity infection to below 5% in all countries except Niger for *S. haematobium* (5.4% [95% CI: 4.6-6.3]), which only marginally missed the control of morbidity metric in the first treatment round (Figures 2.5 to 2.7 and Tables 2.3 and 2.4). The more ambitious target of EPHP (Figures 2.6 and 2.8) was only achieved for *S. mansoni* infection, and only in half of the country programmes. Moreover, Malawi had already reached EPHP for *S. mansoni* at baseline.

2.3.1 *Schistosoma mansoni*

All ten country programmes reached the control of morbidity threshold after two rounds of treatment (Figures 2.5 and 2.6 and Table 2.3). This included Uganda which had a high baseline prevalence. However, a subsequent gradual increase in the prevalence of heavy-intensity infection to just over the 5% threshold was observed in Uganda after the third and fourth treatment rounds. Burkina Faso, Burundi (pilot and national programme) and Rwanda reached the EPHP threshold after three treatment rounds or fewer (but note that these sites had a baseline prevalence of heavy-infection intensity already below the 5% morbidity control threshold).

When using the more conservative criterion of <1% and <5% prevalence of moderate- plus heavy-intensity infection to represent morbidity control (*S. mansoni* only), six country programmes were shown to be already below this threshold at baseline and one further country programme (Mali-Segou) met this target after one round of treatment. Three country programmes achieved EPHP after the third treatment round (Burkina Faso) or after just one treatment round (Malawi and Rwanda). The remaining country programmes failed to reach any target in the relatively short time-span of the data currently available.

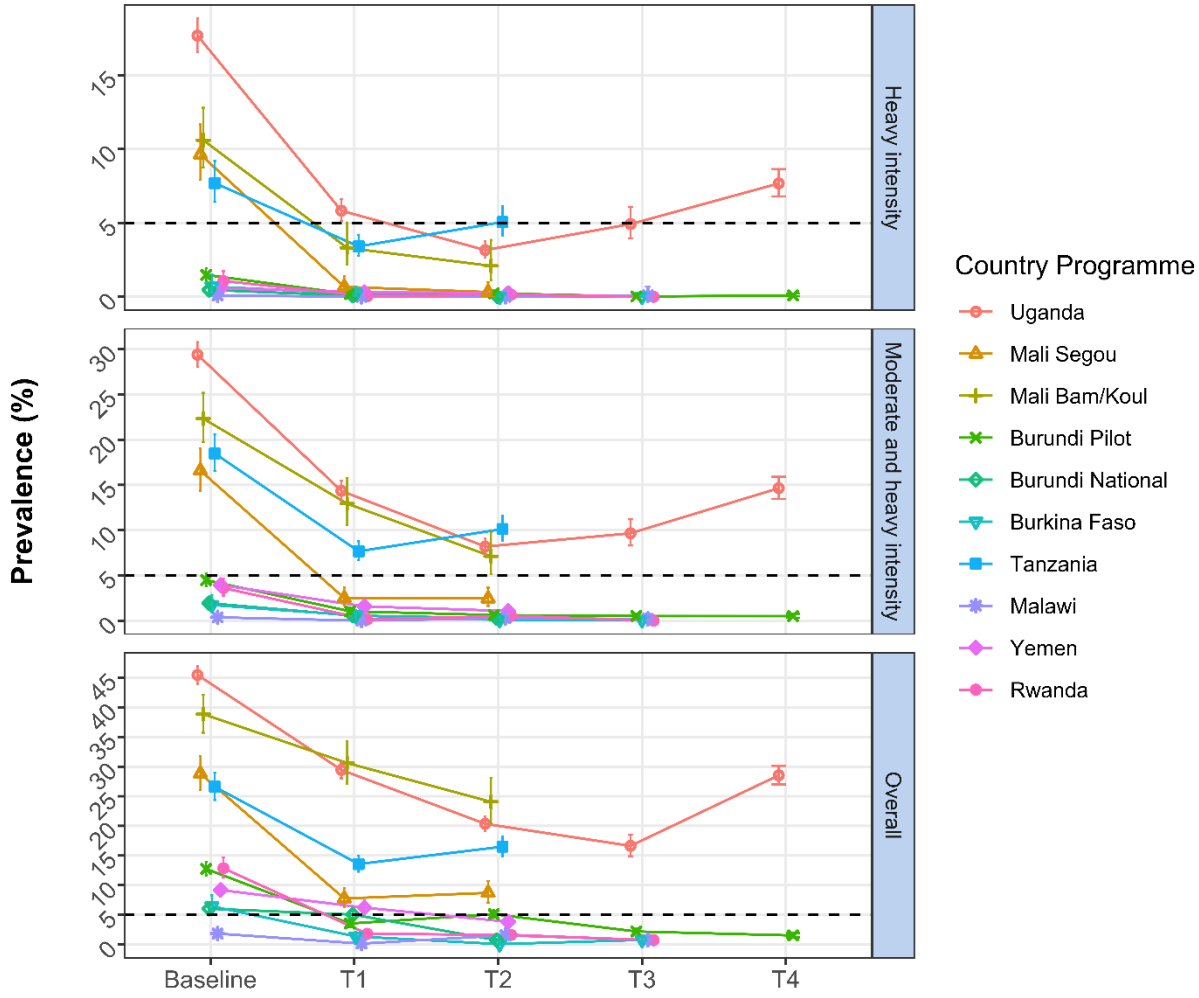

Figure 2.5. Temporal changes in prevalence of *Schistosoma mansoni* infection in school-aged children (SAC) aggregated across sentinel sites from each country. The dashed lines show the 5% and 1% cut-offs for prevalence of heavy-intensity infection control of morbidity and EPHP, respectively. Panels from top to bottom show: the prevalence of high-intensity infection; the prevalence of moderate- plus high-intensity infection and the overall prevalence of infection respectively. The error bars show the 95% confidence intervals, accounting for clustering of the data at the level of the sentinel sites.

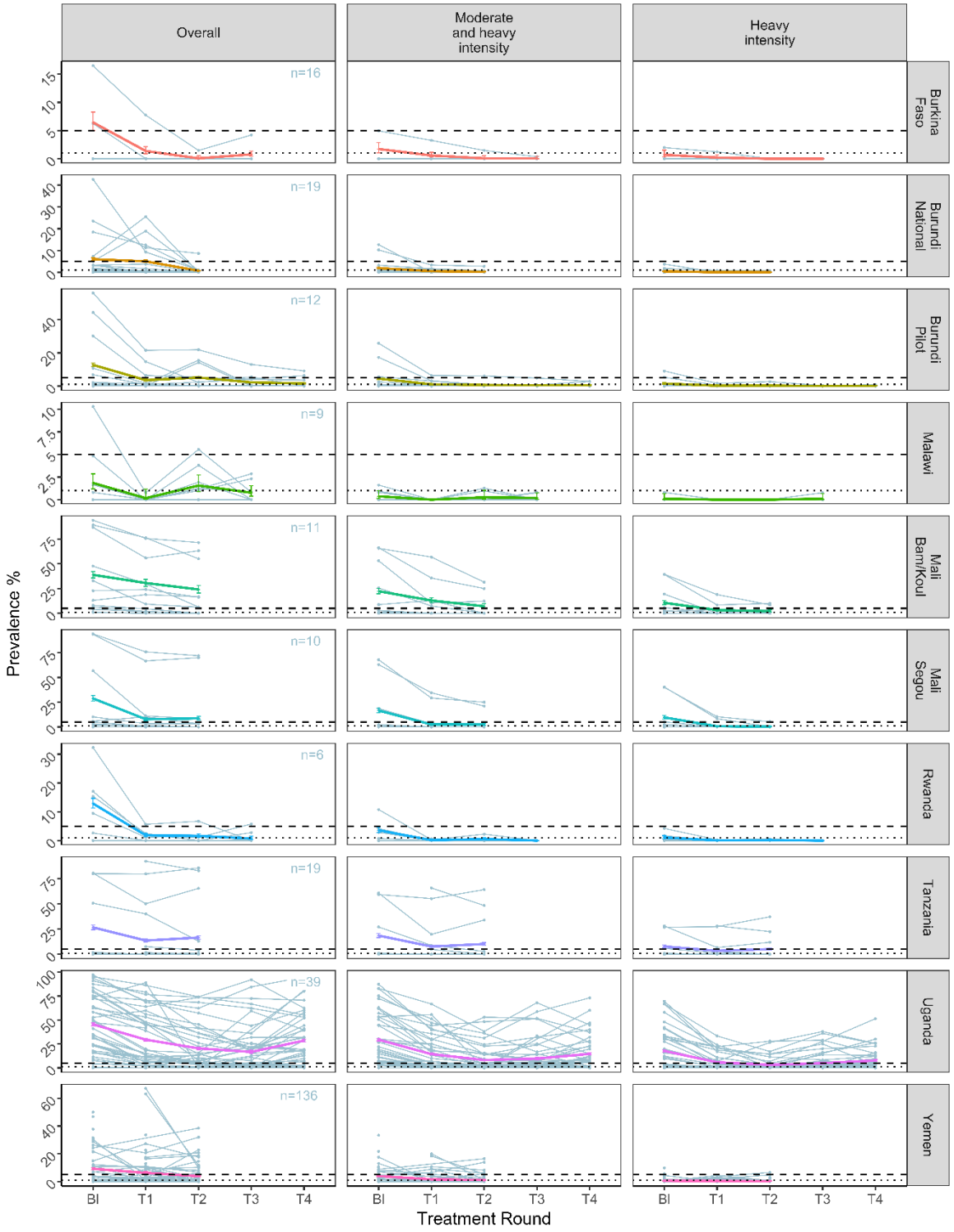

Figure 2.6. Temporal changes in prevalence of *Schistosoma mansoni* infection in school-aged children (SAC) by sentinel site for each country (light blue lines) and aggregated across sentinel sites from each country (coloured lines), where n= number of sentinel sites. The black dashed lines show the 5% cut-offs for prevalence of heavy-intensity infection indicating control of morbidity (for mean prevalence, coloured lines) and the black dotted lines show the 1% cut-offs for prevalence of heavy-intensity infection indicating elimination as a public health problem (EPHP, referring to the light blue lines for sentinel sites in each country). Columns represent overall prevalence, moderate- plus heavy-intensity infection and heavy intensity infection prevalence. 95% confidence intervals were calculated accounting for clustering of the data by sentinel site. Note the different y-axes scales.

Table 2.3. Rounds of treatment required to reduce *Schistosoma mansoni* infection to reach the World Health Organization's (WHO's) goal of morbidity control (<5% prevalence of heavy-intensity infection, aggregated across all sentinel sites) and elimination as a public health problem (EPHP, <1% prevalence of heavy-intensity infection in all sentinel sites). Baseline endemicity levels refer to the WHO prevalence category at country level, accounting for clustering of the data at the level of the sentinel sites.

Baseline endemicity levels	**Mean baseline prevalence % (95% CI)**	**Baseline prevalence of heavy-intensity infection % (95% CI)**	**Country**	**Frequency of treatment**	**Goal/s reached§**	**No. of treatment rounds (post-baseline)**	***No. of treatment rounds for moderate- plus heavy-intensity prevalence***
Low	6.5 (5.0-8.3)	0.7 (0.3-1.5)	Burkina Faso	Biennial	Control	0	*0*
					EPHP	2	*3*
Low	6.0 (5.4-6.7)	0.5 (0.3-0.7)	Burundi National	Annual	Control	0	*0*
					EPHP	2	*Not yet reached*
Low	12.7 (11.7-13.9)	1.5 (1.1-2.0)	Burundi Pilot	Annual	Control	0	*0*
					EPHP	3	*Not yet reached*
Low	1.9 (1.2-2.9)	0.1 (0.0-0.7)	Malawi	Annual	Control	0	*0*
					EPHP	0	*1*
Low	12.9 (11.3-14.7)	1.1 (0.7-1.7)	Rwanda	Annual	Control	0	*0*
					EPHP	1	*1*
Low	9.2 (8.4-10.0)	0.6 (0.4-0.8)	Yemen	Biennial	Control	0	*0*
					EPHP	*Not yet reached*	*Not yet reached*
Moderate	28.8 (26.0-31.8)	9.6 (7.9-11.7)	Mali-Segou	Annual	Control	1	*1*
					EPHP	*Not yet reached*	*Not yet reached*
Moderate	38.8 (35.7-42.1)	10.6 (8.7-12.8)	Mali-Bamako/ Koulikoro	Annual/ Biennial	Control	1	*Not yet reached*
					EPHP	*Not yet reached*	*Not yet reached*
Moderate	26.6 (24.4-28.9)	7.7 (6.4-9.2)	Tanzania	Annual	Control	1	*Not yet reached*
					EPHP	*Not yet reached*	*Not yet reached*
Moderate	45.4 (44.0-46.9)	17.7 (16.6-18.9)	Uganda	Annual	Control	2	*Not yet reached*
					EPHP	*Not yet reached*	*Not yet reached*

§ For programmes that reached 1% heavy/moderate- plus heavy intensity infection prevalence across all sentinel sites, further analyses were conducted to verify whether this was reached in all sentinel sites for EPHP (results shown in this table).

Table 2.4. Rounds of treatment required to reduce *Schistosoma haematobium* infection to reach the World Health Organization's (WHO's) goal of control (<5% prevalence of heavy-intensity infection aggregated across all sentinel sites) and elimination as a public health problem (EPHP, <1% prevalence of heavy-intensity infection in all sentinel sites). Baseline endemicity levels refer to the WHO prevalence category at country level, accounting for clustering of the data at the level of the sentinel sites.

Baseline endemicity levels	Mean baseline prevalence % (95% CI)	Baseline prevalence of heavy intensity % (95% CI)	Country	Frequency of treatment	Goal/s reached§	No. treatment rounds (post-baseline)
Low	9.8 (8.7-11.0)	2.2 (1.7-2.8)	Malawi	Annual	Control	0
					EPHP	*Not yet reached*
Moderate	24.1 (22.4-25.8)	6.9 (6.0-8.0)	Tanzania	Annual	Control	1
					EPHP	*Not yet reached*
Moderate	10.6 (9.8-11.5)	3.6 (3.2-4.2)	Yemen	Biennial	Control	0
					EPHP	*Not yet reached*
High	56.2 (53.8-58.5)	25.2 (23.2-27.3)	Burkina Faso	Biennial	Control	1
					EPHP	*Not yet reached*
High	75.9 (73.8-77.9)	21.3 (19.4-23.3)	Niger	Annual	Control	*Not yet reached*
					EPHP	*Not yet reached*
High	82.1 (79.8-84.3)	44.0 (41.1-47.0)	Mali-Segou	Annual	Control	2
					EPHP	*Not yet reached*
High	47.6 (44.8-50.5)	11.5 (9.7-13.4)	Mali-Bamako/ Koulikoro	Annual/ Biennial	Control	1
					EPHP	*Not yet reached*

2.3.2 *Schistosoma haematobium*

All programmes had a baseline *S. haematobium* prevalence of heavy-intensity infection above 5%, except for Malawi and Yemen and, by the second treatment round, all except for Niger were below this threshold, meeting the control of morbidity criteria (Figures 2.7 and 2.8 and Table 2.4). The prevalence of heavy-intensity infection in Niger fell following a single treatment round, from 21.3% [95% CI: 19.4-23.3] to 5.4% [95% CI: 4.6-6.3], only just missing the control of morbidity target.

Although three country programmes reached <1% heavy-intensity infection prevalence aggregated across sentinel sites (Figure 2.7), none of the programmes in the study reached this threshold in every sentinel site for *S. haematobium*, and thus did not meet the EPHP requirement (Figure 2.8).

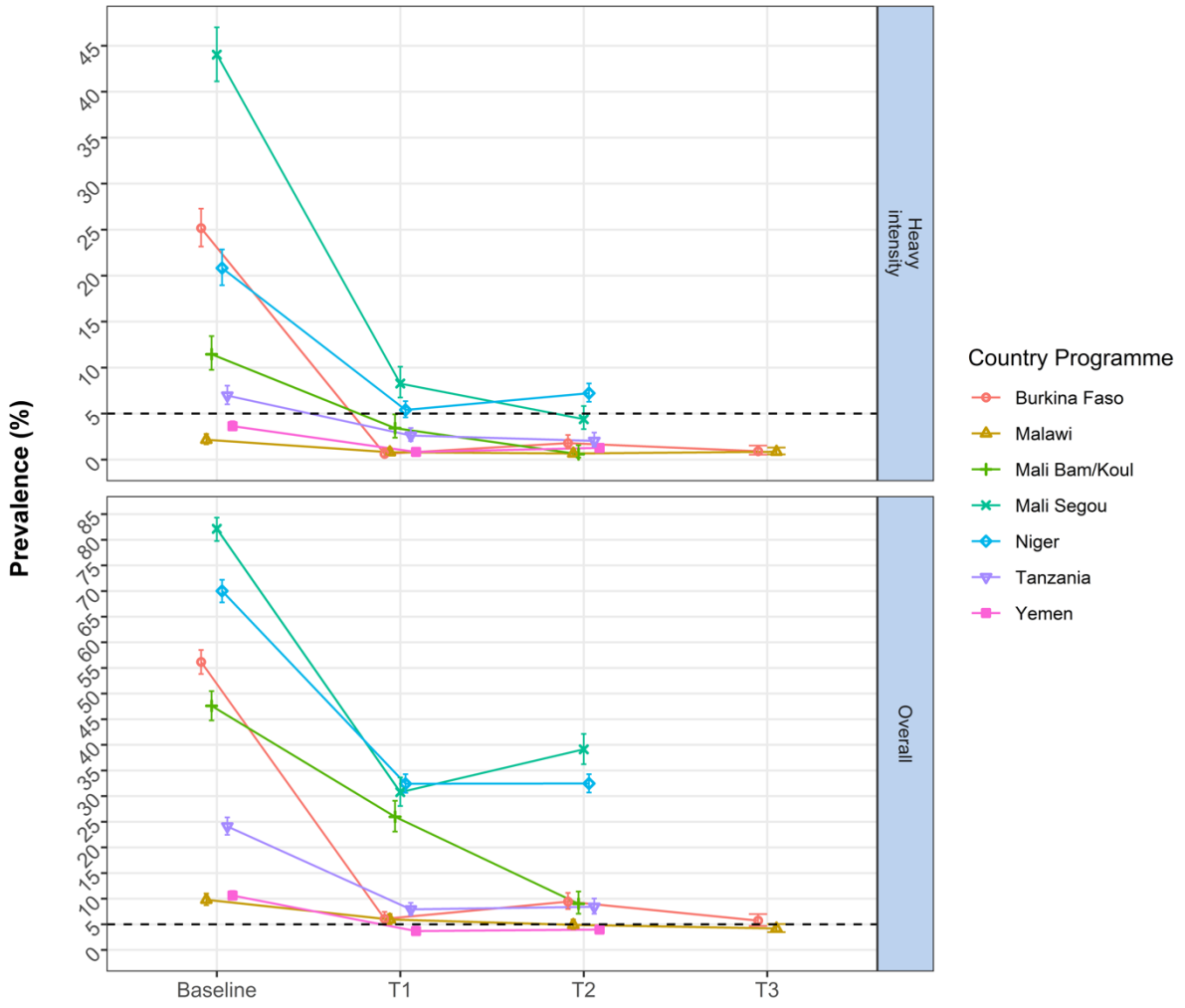

Figure 2.7. Temporal changes in prevalence of *Schistosoma haematobium* infection in school-aged children (SAC) aggregated across sentinel sites of each country. The dashed lines show the 5% and 1% cut-offs for prevalence of heavy-intensity infection (control of morbidity and EPHP targets, respectively). Top panel shows the prevalence of heavy-intensity infection. Bottom panel shows the overall prevalence of infection respectively. The error bars show the 95% confidence intervals, accounting for clustering of the data at the level of the sentinel sites.

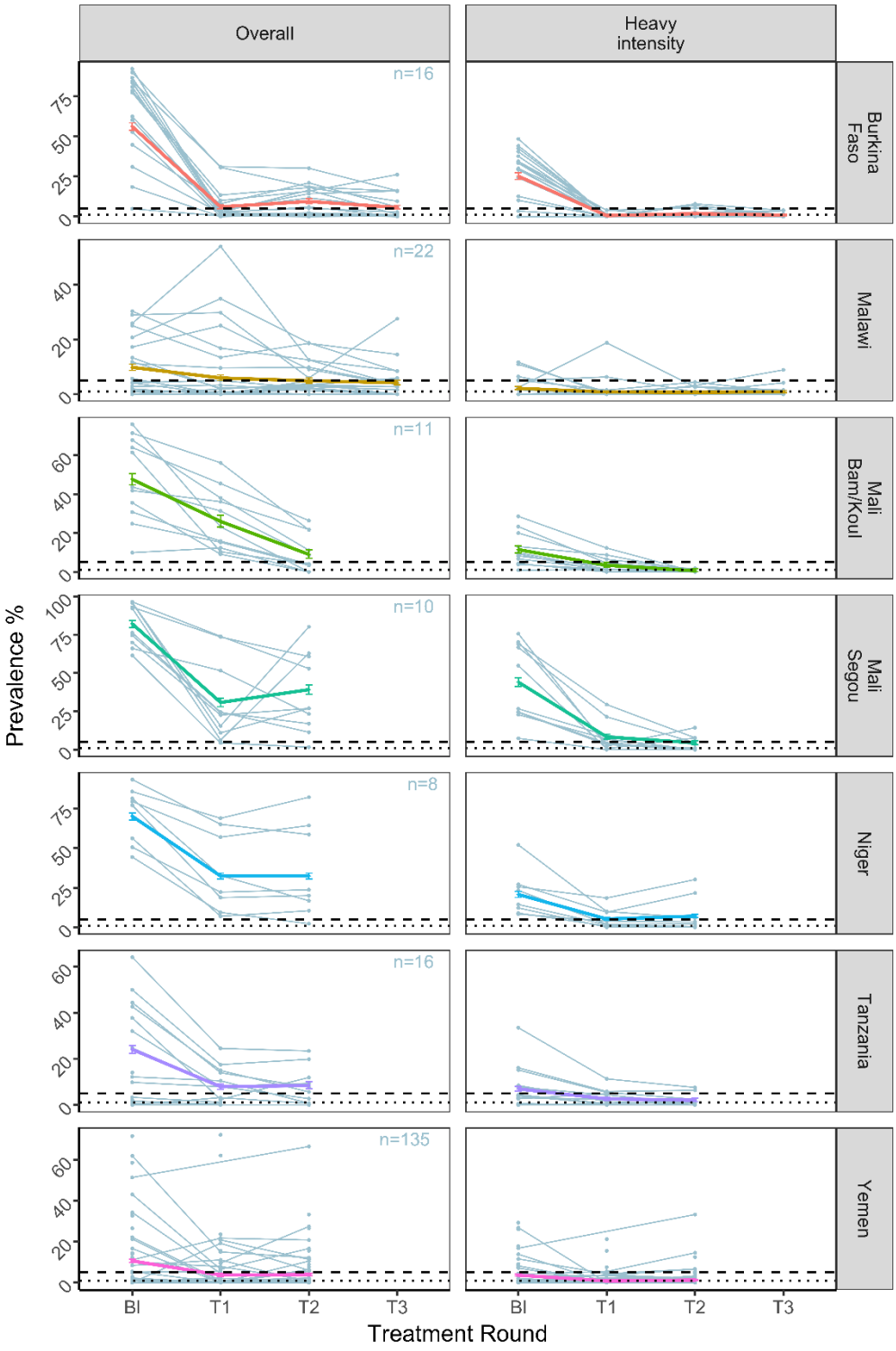

Figure 2.8. Temporal changes in prevalence of *Schistosoma haematobium* infection in school-aged children (SAC) by sentinel site for each country (light blue lines) and aggregated across sentinel sites from each country (coloured lines), where n= number of sentinel sites. The black dashed lines show the 5% cut-offs for prevalence of heavy-intensity infection indicating control of morbidity (for mean prevalence, coloured lines) and the black dotted lines show the 1% cut-offs for prevalence of heavy-intensity infection indicating elimination as a public health problem (EPHP, referring to the light blue lines for sentinel sites in each country). Columns represent overall prevalence and heavy intensity infection prevalence. 95% confidence intervals were calculated accounting for clustering of the data by sentinel site. Note the different y-axes scales.

2.3.3 Relationship between prevalence of infection and prevalence of heavy infection

The relationship between overall prevalence of infection (used in mapping) and prevalence of heavy-intensity infection (which requires collection of intensity data) was shown to vary over time, by *Schistosoma* species, and by treatment round (Figure 2.9). For *S. mansoni,* the relationship between prevalence of heavy-intensity (and moderate- plus heavy-intensity) infection *vs* overall infection prevalence was non-linear. A wide range of prevalence values within and between treatment rounds corresponded to <5% heavy-intensity infection (and moderate- plus heavy-intensity) infection. Similar patterns were observed for *S. haematobium.*

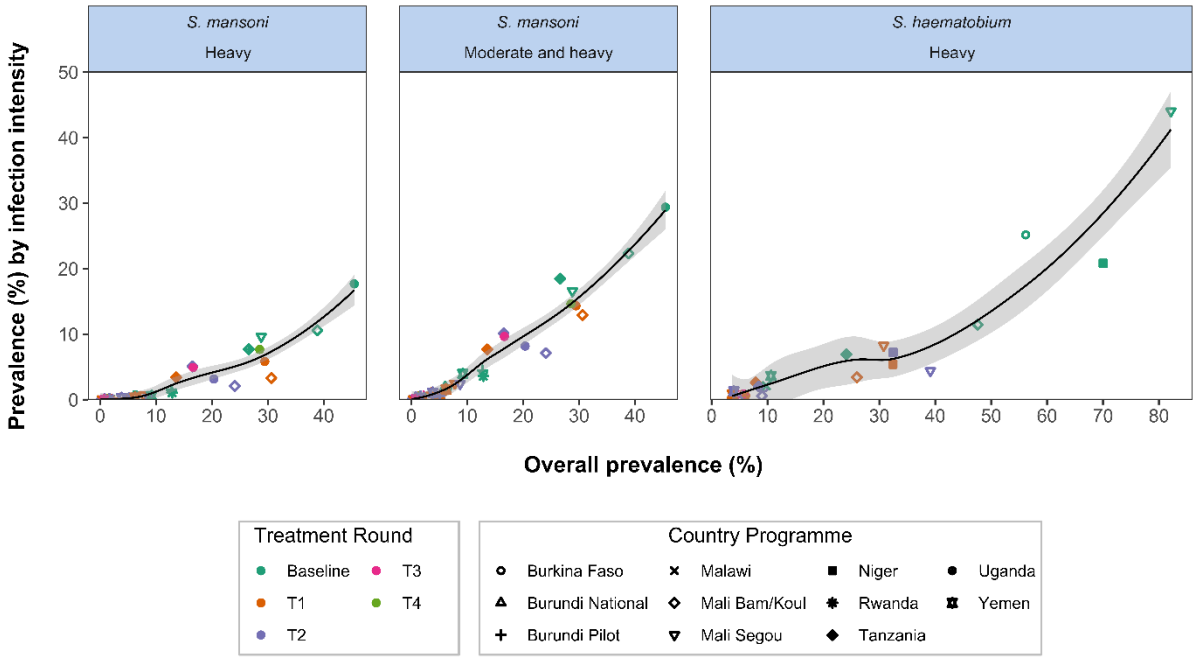

Figure 2.9. Relationship between prevalence of heavy intensity infection (and moderate and heavy intensity infection for *Schistosoma mansoni*) and overall prevalence in school-aged children (SAC) across all sentinel sites by species. Best fit (black line) and standard error (grey band) were obtained by fitting a loess smoothed line. Colours represent treatment round and shapes represent country programme.

2.4 Discussion

The WHO guidelines outline the expected number of years of treatment necessary for reaching morbidity control of schistosomiasis and EPHP (i.e. 5-10 years and 3-6 years, respectively). This study shows that where the operational goals were reached (though not necessarily sustained), they were reached much sooner than estimated by the guidelines (whether annual or biennial treatment frequency was implemented). We demonstrate here that all country programmes in this study reached the WHO thresholds for control (with the exception of the Niger programme for *S. haematobium*) in two treatments rounds or fewer. Six programmes started with a prevalence of heavy-intensity infection below 5% for *S. mansoni*, indicating that they were already at 'control' at endemic level. The subsequent goal of EPHP for *S. mansoni* was reached by five of these programmes, requiring three or fewer treatment rounds. This highlights the need for clarity in the guidelines for what approach to adopt in such cases.

The *S. haematobium* country programmes used in this study had a higher overall baseline infection prevalence than the *S. mansoni* areas and none of those programmes reached the EPHP goals within the lifetime of the study. The findings demonstrate that endemically low prevalence foci are likely to have low baseline prevalence of heavy-infection intensity (in this study 1.5% or less for *S. mansoni* and is further demonstrated in Section 2.3.3 of this Chapter through the prevalence of heavy-intensity infection and prevalence of infection relationship), which resulted in the achievement of EPHP sooner than proposed by the guidelines.

The case of Uganda illustrates that goals may be reached but are reversible, though exact reasons for this particular case are unknown at present, these could have been due to migration patterns for that year or poor treatment coverage or compliance for the control programme or changes in drug efficacy.

This is particularly relevant where programme stability is impeded (due to, for example, civil unrest, such as in Burundi, war, such as in Yemen, and/or population displacement, such as an influx of south Sudanese refugees into Uganda). Figures 2.6 and 2.8 highlight the variability between sentinel sites in each country (light blue lines), which needs to be taken into consideration when looking at country-level control of morbidity target proposed by the WHO. Additionally, the effectiveness of programme implementation may vary through time (treatment fatigue, climatic changes, changes in programme staff, migration patterns, etc.), as may potentially drug efficacy (due to resistance)[122]. It is, thus, important to define time periods over which control and elimination targets should be sustained to declare success and to be particularly vigilant to recrudescence of disease if elimination of transmission has not yet been achieved.

It is likely that *any* level of infection is relevant to morbidity [121], therefore moderate- plus heavy-intensity infections were combined to form a more realistic yet conservative morbidity metric for *S. mansoni.* The infection-intensity thresholds for each species were proposed by the WHO Expert Committee in 1987, but it is not clear why no moderate intensity group exists for *S. haematobium* nor why the egg-count intensity thresholds were defined as such (though flexibility in these thresholds had been proposed) [123]. Figures 2.5 and 2.6 show that, as expected, programmes will take much longer to reach the same goals if using prevalence of moderate- plus heavy-intensity infection metric. When considering the aims of controlling and eliminating morbidity, since control thresholds were reached relatively quickly and the relationship between infection intensity and morbidity remains highly uncertain, it would be worth considering the more ambitious metric of prevalence of moderate-plus heavy-intensity infection.

The <5% and <1% prevalence of heavy-intensity targets are the current metrics for control and elimination of schistosomiasis-related morbidity, respectively, which use the egg-count cut offs presented in Table 2.2. However, these metrics, definitions and egg-count cut offs need to be carefully and urgently addressed, particularly since potentially a single miracidium infecting a snail could result in the snail releasing thousands of cercariae, each with the potential of infecting a human host [124]. Additional analysis of available data (and the ability to collect such information routinely as part of large-scale control programmes) and further research, such as understanding the link between current infection and morbidity, are required to establish a robust evidence base for these (or updated) targets, which will be critical especially as countries aim to transition to interruption of transmission. None of the programmes in this study reached the interruption of transmission targets, which further question the feasibility of transmission by 2025 even with the current guidelines.

As expected, there was a strong positive association between the overall infection prevalence and either the prevalence of heavy-intensity infection, or the prevalence of moderate- plus heavy-intensity infection (Figure 2.9). However, two characteristics stand out from these graphs. First, there was substantial spread of the data points, such that for any given value of one variable there was a range of corresponding values of the second variable. This variation arose due to the heterogeneity of parasite loads (likely due to exposure variation) which follow a negative binomial distribution (most individuals having zero or low parasite load and a few having very high parasite load, using egg counts as a proxy for worm load), so disease/morbidity prevalence can vary substantially among settings with similar overall prevalence. Second, the size of the change in infection metric following treatment varied substantially between programmes. Further research is required to reach consensus on the

most appropriate morbidity indicator. Once it has been identified, it needs to be applied consistently across programmes and in guidelines.

Some of the limitations of the study are due to the lack of detailed information available, in particular, treatment coverage which can vary significantly in NTD treatment programmes. Other information such as migration patterns, school-enrolment, and school-attendance rates may play a role in determining reductions in infection and may, partly, explain variation between study areas. Detailed information on these metrics was not collected routinely.

Another important aspect that was not covered thus far was the fact that more than half of the programmes had sentinel sites of mixed infections (as opposed to *S. mansoni* or *S. haematobium* only). For this study, both species were analysed independently, but this does not address the issue of having a potentially higher infection prevalence and/or intensity when both are combined, or understanding any underlying interactions between the two species [125]. When the species are analysed separately, a country may reach control and EPHP for one species but not for the other, as is the case of Burkina Faso in this study. If individuals were infected with both species, could a 'low intensity' of infection with each species combine into a moderate intensity of mixed infection, and what would be the morbidity repercussions? What if individual sentinel sites or entire countries contained mixed infections and what impact will this have on determining whether a country achieves the 2020 and 2025 goals? These issues require further development and clarification in the guidelines.

The WHO guidelines also do not differentiate between *S. mansoni* and *S. haematobium* in terms of progression towards interruption of transmission (which is in fact, currently undefined). Though similar, they have differences which may impact the feasibility and required duration for a control programme to reach the 2020/2025 targets. From a biological perspective, earlier studies have shown that the number of eggs laid by a female worm, and subsequently expelled by the host, depends on the species of infecting schistosome, with female *S. mansoni* worms laying on average more eggs than *S. haematobium*, (which would imply higher levels of transmission into the environment as well as individual morbidity from *S. mansoni* infection) [126]. Another difference is that it may be considered an 'easier route' to contribute to the transmission cycle with urogenital schistosomiasis (infection with *S. haematobium*), which requires only urination in fresh water to transmit *Schistosoma* eggs into the environment as opposed to defecation (which is less frequent and with greater social barriers to doing so). These are some of the differences that would cause the two schistosome species to behave differently in terms of infection. Alongside these are potential issues of hybridisation and animal reservoirs [31] which would impact disease dynamics and which may mean the species are not equally amenable to reaching the WHO 2020 targets. However, China (endemic species *S. japonicum*) and

Brazil (*S. mansoni*) have shown great progress towards achieving interruption of transmission, particularly in China which has the added challenge of having the animal reservoir due to the ability of *S. japonicum* to have multiple primary host species including humans. This highlights the impact of development and strong health systems along with a 'one health' approach, all of which are still lagging in the majority of the SSA setting.

The current WHO guidelines are based on Kato-Katz for *S. mansoni* diagnosis, and urine filtration and haematuria for *S. haematobium* diagnosis. As infection intensity levels decrease, it will become increasingly difficult to diagnose infection accurately. One clear priority is the identification of alternative affordable diagnostic techniques that can be implemented on a large scale to provide the data required for M&E – this will need to take into account the cost-effectiveness of moving from current tools, the relationship of intensity of infection between the former and new tools (and their relevance to the WHO guidelines) and practicality for use in the field [127–130]. The low sensitivity of Kato-Katz is likely to miss light infections and thus yield underestimates of prevalence and intensity (not to mention issues concerning the variation in egg output within a stool and between days, and the reluctance of people to provide stool samples). The point-of-care (POC) urine circulating cathodic antigen (CCA) test is a promising tool already in use in some areas, although it introduces challenges for determining heavy-intensity infections (as it provides only a semi-quantitative measure of intensity for *S. mansoni*)[131,132]. Urine filtration for *S. haematobium*, though a more sensitive tool than Kato-Katz for *S. mansoni*, is also limited particularly since egg output varies in the urine throughout the day (and urine volumes provided can often be low due to dehydration). The WHO guidelines for CCA are currently under development and will be available in the near future, though these will be for *S. mansoni* only (as CCA does not detect *S. haematobium*).

For the criterion for EPHP, the requirement is that *every* sentinel site needs to have <1% prevalence of heavy-intensity infection. Yet for the control of morbidity target, there is an exception which allows the country to progress to the next stage if a single site is at ≥5% heavy-intensity infection prevalence - which would be regarded as its own implementation unit allowing the rest of the country to progress to EPHP (referenced in the guidelines as a small footnote)[99]. However, there is no such exception for the EPHP in the guidelines. This could mean that a single sentinel site not reaching these aims could hold the rest of the country back from declaring EPHP and receiving an enhanced treatment strategy (as was the case for Mali-Segou, in which all sentinel sites but one reached EPHP by the second treatment round). A possible intermediate marker could be the percentage of sentinel sites reaching below <1% heavy-intensity infection, prior to <1% in <u>all</u> sentinel sites. This brings us to the topic of 'hot-spots', which currently does not have a widely-agreed definition but is essentially a catch-

all term to describe epidemiological heterogeneity in focal infectious diseases [133]. More specifically, 'hot-spots' are usually isolated areas of persistent infection despite regular treatment at high coverage, often with unknown causal mechanism [134,135]. To help achieve the 2020/2025 targets we emphasise that these hot-spot areas should be addressed separately as areas of persistent infection (not necessarily high infection) that are strictly isolated and require a more tailored local intervention approach.

The WHO guidelines focus on infection levels and treatment in SAC. It remains incompletely understood how infection patterns in SAC relate to infection in the wider community, particularly following multiple rounds of SAC treatment, where there is a high potential of a reservoir of heavily infected pre-school aged children (PSAC) and adults. In other words, is reaching the control and EPHP targets in SAC enough to be confident that the same has been achieved in adults and PSAC and has control or elimination of morbidity really been achieved? This has been the focus of recent modelling and cost-effectiveness studies [114,136–138], which state that elimination is unlikely without the treatment of non-treated populations, particularly the adult community, with further empirical studies required to address these questions.

Conclusion

The key messages of this chapter are that programmes reach the first goal of morbidity control with very few treatment rounds, and the 'one-size-fits-all' approach currently adopted is not appropriate for all programmes (though attractive in terms of international guidelines), as results differ between starting endemicity levels and species of schistosome. Further work is required to investigate the impact of mixed infections and strategies to manage these and hotspot areas, as well as the use and applicability of the 'prevalence of moderate- plus heavy-intensity infection' metric and the proportion of sentinel sites reaching EPHP. In addition, if programmes are to follow the timelines proposed to transition to the next goal towards interruption of transmission, then this may take many countries beyond the fast-approaching target of 2020 and 2025. Moreover, some programmes were already at <5% heavy-intensity infection prevalence at baseline. Should programmes in these situations aim immediately for EPHP or continue with the WHO guidelines and treat as per control aims for 5-10 years? What do reaching these thresholds earlier mean for programmes, in terms of the potential to adjust PC (to twice a year for example) or include complementary interventions (such as WASH, snail control etc.) to reach the goals sooner? We hope that the results of this chapter will open a dialogue for further discussion.

This chapter presents the most extensive and relevant data available to test the guidelines. In conclusion, most of the schistosomiasis programmes evaluated here reached operational thresholds for morbidity control in two treatment rounds or fewer, considerably sooner than proposed in the WHO guidelines (which state 5-10 years to reach control and 3-6 years to reach EPHP) before progression to the subsequent stage of transmission interruption. Very few countries have programmes that have been running for the suggested periods – indeed for many programmes, the indicated number of years would take them well beyond the 2020 milestone for control alone. This chapter highlighted the need for more specific guidelines for countries starting with different endemicity levels and schistosome species, as a universal approach is not appropriate. The programmes in this study showed mixed results. For the control of morbidity, the target was reached in all programmes for both schistosome species with the exception of one programme. This supports the feasibility of the relevant WHO 2020 goal as it is currently defined. For EPHP, while it is true that five datasets did reach the EPHP target, it is also true that these all had very low infection prevalence at baseline (1.5% prevalence of heavy-intensity infection or lower), and no datasets with either moderate or high baseline endemicity reached the EPHP target within the relatively short period of follow-up. Additional work is required to validate the feasibility and utility of the EPHP target.

CHAPTER 3. DEVELOPMENT AND EVALUATION OF A MARKOV MODEL TO PREDICT CHANGES IN SCHISTOSOMIASIS PREVALENCE IN RESPONSE TO PRAZIQUANTEL TREATMENT

*This chapter is adapted from the following published paper: Arminder Deol, Joanne P Webster, Martin Walker, Maria-Gloria Basáñez, T Déirdre Hollingsworth, Fiona M Fleming, Antonio Montresor, and Michael D French. Development and evaluation of a Markov model to predict changes in schistosomiasis prevalence in response to praziquantel treatment: a case study of Schistosoma mansoni in Uganda and Mali. Parasit. Vectors **9,** 543 (2016). Appendix 3.*

This chapter presents the development and refinement of a Markov model to capture changes in the prevalence of infection intensity categories for *Schistosoma mansoni* over multiple rounds of MDA with PZQ. The model was parameterized using two-year (two consecutive time points) longitudinal data from Uganda and Mali. The model was then used to make longer-term projections (5 years+) and to compare the outputs with different variations of the datasets. The results show that this is a promising M&E tool for programmes by allowing short-term projections of prevalence under interventions.

3.1 Introduction

As the multi-country study described in Chapter 2 showed, many large-scale schistosomiasis control programmes have been running for several years, and have achieved their primary target of controlling schistosomiasis-related morbidity (i.e. reducing prevalence of heavy-intensity infection to <5% across sentinel sites), whether from intestinal schistosomiasis (caused predominantly by *Schistosoma mansoni*) or from urogenital schistosomiasis (caused predominantly by *S. haematobium*)[99,139].

As part of the Monitoring and Evaluation (M&E) component that runs alongside the treatment campaigns, the Schistosomiasis Control Initiative (SCI) has collected rich longitudinal datasets from numerous countries to demonstrate the impact of treatment on prevalence, intensity and morbidity associated with schistosomiasis. Preventive chemotherapy (PC) by mass drug administration (MDA) with praziquantel (PZQ) has been demonstrated to be, in general, highly effective in reducing both the prevalence and intensity of schistosome infection. This is shown in the datasets introduced and analysed in Chapter 2 [140–142]. The development of a user-friendly, quantitative, tool that uses these impact measurements to inform programme managers as to whether their programme is on

target to meet their goals would be valuable in assisting programme design and evaluation, and in providing an early warning of potential transmission 'hotspots' or poor programme performance.

A Markov statistical model had been developed to capture soil-transmitted helminth (STH) infection dynamics under PC (with benzimidazoles), by Montresor and colleagues in 2013. This was extended in 2016 to other datasets which focussed on the robustness of the model (work in which the candidate was directly involved, and which was published in *PLoS Negl Trop Dis* in 2016)[143,144]. The authors demonstrated that the model successfully predicted changes in the prevalence of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (*Ancylostoma duodenale* and *Necator americanus*) through five rounds of PC. The model used data collected in Vietnam at baseline and after one round of treatment to parameterize the Markov Transition Probability (MTP) matrix; the essential ingredient of such Markov models. The predictive capability of the model was successfully validated against STH data from 26 control programmes in 16 countries [144].

Here, for the first time, the discrete-time Markov model approach was extended, in which both time and infection states (intensity groups) were defined and used to describe a *S. mansoni* control programme. The model was tested under contrasting control programme scenarios, using the extensive datasets from SCI-supported programmes in Uganda and Mali as described in Chapter 2. This methodology would aid programmes from donor relations and advocacy (through model projections using its estimates) to as an additional planning and monitoring tool of programme performance (by measuring the effectiveness of a program against its goals of reducing infection through comparison between observed vs predicted prevalence).

The specific aims in this chapter were to: i) develop a discrete-time Markov model for schistosomiasis using data on the intensity and prevalence of *S. mansoni* infection during mass treatment with PZQ; ii) introduce measurements of precision around predictions in the form of 95% PIs; iii) evaluate the performance of the model by estimating changes in the overall infection prevalence and the prevalence in infection intensity categories over time; iv) qualitatively compare the predictive capabilities of the model parameterized using data from different settings within the same country (Uganda) and from a different country (Mali), to test the transferability of the predictions to different regions; v) test the robustness of the model's predictive capabilities when parameterized using data from non-baseline years; and vi) investigate the usefulness of different data types (longitudinal and cross-sectional data) to test the model predictions.

3.2 Material and methods

Data

Raw data were initially formatted by the candidate and used from the Uganda historical programme [140,145–147] to parameterize (using longitudinal data) and evaluate (using both longitudinal and cross-sectional data) the model in different scenarios, simulated through various data subsets (Table 3.1). To further evaluate the model, using independent data (i.e. not used for model parameterization), historical data from the Mali programme were formatted and used. The data were collected as part of a treatment campaign in Uganda for SAC from 2003 to 2006 (the baseline overall Kato-Katz prevalence was 43.0% for *Schistosoma mansoni*) and in Mali from 2004 to 2007 (the baseline overall Kato-Katz prevalence was 26.5% for *S. mansoni*)[145,146].

To develop and parameterize the Markov model, longitudinal data were required from the data subsets due to the methodology discussed below. Participant unique identifiers, sentinel site and sex between different years of the programme were all matched, excluding individuals who were not followed between baseline and year 1. This was used for model parameterization. The model was also tested against both longitudinal data as well as cross-sectional data. For the cross-sectional data testing, all individuals were used. The model was evaluated through two methods: 1. using different datasets to parameterize the model, and 2. testing the capacity of each model to predict different datasets.

The data used to validate and test the model and its variations were primarily from SAC. This is because the aim of the model was to show overall projections of the programme, since most schistosomiasis interventions focus on this age group, who tend to harbour the highest burden of infection as measured by egg counts (Chapter 1)[34,47,112,148–151].

Table 3.1. Data used to parameterise and evaluate the Markov Model and its variations.

Dataset	Data type	Description	Sample size (*n*)	Baseline prevalence (%)
1	Uganda longitudinal baseline to year 3	Full longitudinal data set	747	43.0
2	Uganda longitudinal baseline to year 3	4 Ugandan districts out of 7	400	46.5
3	Uganda cross-sectional baseline to year 3	Varying sample size per year, full programme data	Baseline: 4222 Year 1: 3973 Year 2: 4192 Year 3: 3373	45.2
4	Mali longitudinal baseline to year 2	Full longitudinal data set	897	26.5

Model outline

The model was developed for *S. mansoni,* with the proportion of individuals in each of the four WHO-recommended infection classes defined by estimates of eggs per gram (epg) of faeces (not infected, 0 epg; infected at light intensity, 1-99 epg; infected at moderate intensity, 100-399 epg; infected at high intensity, ≥400 epg [36]) and referred to as "condition states" (CS), calculated from pre-treatment baseline data [100]. Subsequently, an individual's probability of transition (if any) to other CS prior to the next round of treatment (year 1) was calculated using the observed change in the proportion of followed-up individuals in each category (from baseline to year 1). These observed changes were used to parameterize a matrix of Markov Transition Probabilities (MTP), formed from a set of 16 transition probabilities (TPs), as illustrated in Figure 3.1. The model was initialised using observed baseline starting values. Then, through a series of Markov processes defined by the MTP matrix (see Equations 3.1-3.4 in the following section), projections were made on the proportion of infected individuals by intensity class following subsequent rounds of MDA.

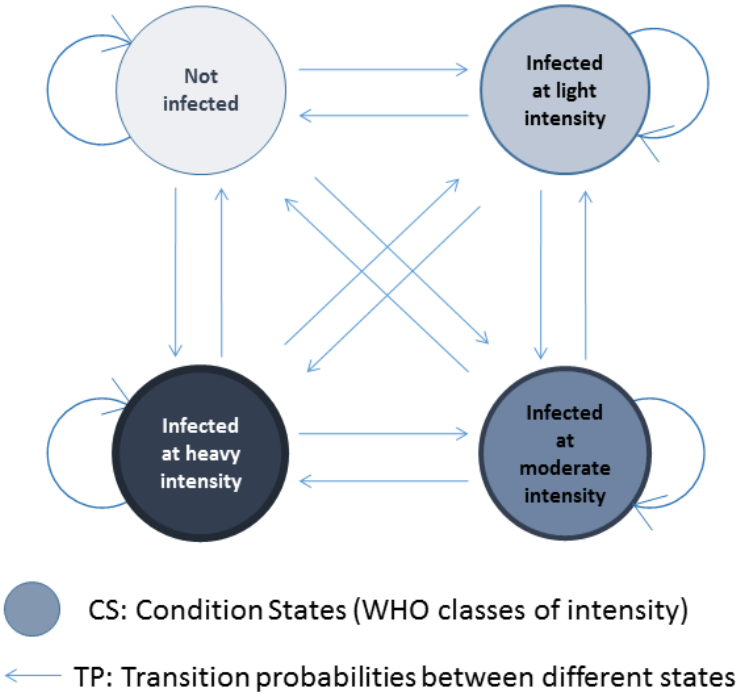

Figure 3.1. Transition diagram illustrating a Markov transition probability (MTP) matrix parameterized using data on the prevalence and intensity of *Schistosoma mansoni* infections collected during mass drug administration in Uganda [143].

Markov model formulae, model parameters

The following expression describes the transition probabilities between two time points (t and t_{t+1}):

$$P_{ij} = P\left(CS_{t+1} = s_j \,\middle|\, CS_t = s_i\right) \tag{3.1}$$

where P_{ij} is defined as the probability of moving from state i to state j after one follow-up round (which is one year for this study) and assumed to be time-homogeneous and dependent only on CS_t (Eqn. 3.1), where CS_t is the conditional state at time point t.

The probability distribution of the initial state is represented by an n x m matrix (i.e. the TP matrix P), where n represents the discrete conditional states, i.e. not infected, light-, moderate-, and heavy-intensity infection (Eqn. 3.2).

$$P = \begin{bmatrix} P_{11} & P_{12} \cdots P_{1m} \\ P_{21} & P_{22} \cdots P_{2m} \\ \vdots & \vdots \quad \ddots \quad \vdots \\ P_{n1} & P_{n2} \cdots P_{nm} \end{bmatrix}$$

(3.2)

Where for all *i*:

$$\sum_{j=1}^{S} P_{ij} = 1$$

and

$$P_{ij} \geq 0$$

(3.3)

The probability of moving from one conditional state to another can then be calculated using Eqn. 3.4., i.e. the number of individuals *observed* moving from state *i* to state *j* (e.g. heavy- to moderate-intensity).

$$P_{ij} = \frac{\#\left\{CS(\tau_t^n) = i, CS(\tau_{t+1}^n) = j, \tau_t^n - \tau_{t+1}^n = I, n \in [1, N]\right\}}{\#\left\{CS(\tau_t^n) = i, n \in [1, N]\right\}}$$

(3.4)

Table 3.2. Table of parameters used in the model.

Symbol	Definition	Description
$\boldsymbol{P_{ij}}$	Transition probability	Probability of moving from state *i* to state *j* after one follow-up round
CS	Conditional state	*CS* is used to describe the state space (i.e. intensity class)
$\boldsymbol{\tau_t^n}$	Time	Observed time of sample *n*
N	Total sample	Total sample size
n	Number of samples n	Number of samples from total sample population *N*
#	Number of common samples	Number of samples that satisfy the subsequent formula

Model development

In the first instance, focus was on *S. mansoni* data collected from Uganda between the inception of the programme in 2003 and for the first three annual follow-up rounds after baseline. As part of the national control programme, data were collected as egg counts (expressed as the arithmetic mean epg) from a cohort of 125 children (aged 6-13 years) per school, from 37 schools across the country, over a time span of four years.

For the calculation of the TPs from the Uganda dataset, longitudinal data between baseline and year 1 were used (i.e. only data from those individuals who could be identified at each time point, 1,258 individuals). To quantify uncertainty around the model projections (expanding on the previously published version of the model applied to STH [143,144]), 95% prediction intervals (95% PIs) associated with each TP were calculated through bootstrap resampling (with replacement) for 10,000 iterations, using the R package 'boot' version 1.3-9 [152–155]. Bootstrapping is a powerful technique which, amongst other things, enables a data set to estimate uncertainty using no more information than that available in the dataset (i.e. without making any assumptions of the underlying distribution), by randomly resampling from the original dataset (and replacing the sample so each data point can be sampled again) until the full same sample size is reached as the original. This represents one bootstrap iteration. The 95% PIs were calculated in the following steps: 1) a new 'dataset' was generated through bootstrapping allowing for the calculation of a new MTP matrix (set of 16 TPs); 2) the model was run (using these TPs) to calculate the reduction in prevalence over time; 3) steps 1) and 2) were repeated 10,000 times; 4) for each time point, the predicted mean prevalence was calculated; and 5) from the range of predicted prevalence levels generated, the 95% PIs were constructed using the 2.5% and 97.5% percentiles. Initially, for the observed data, the full cohort of individuals who were followed up from baseline to year 3 of the intervention (in Uganda) was included (757 individuals). Since some of the individuals in this dataset were also used for the calculation of the TPs (as would be the case in practice when using these models), it was expected that the predicted prevalence at year 1 would follow the observed values from the full dataset 1 (Table 4.2) very closely.

To test the transferability of the model using independent data, the TPs, calculated using baseline and year 1 data from the full Uganda dataset, were also used to test model predictions against longitudinal data from Mali. Conversely, to further test the robustness of the model, longitudinal baseline and year 1 data from Mali were also used to parameterize a separate model and tested against observed longitudinal data from Uganda (i.e. a cross-validation approach). This tested the flexibility of the model to different starting baseline prevalence levels (for Mali the baseline overall prevalence of *S. mansoni* infection was 26.5%, whereas for Uganda the overall prevalence was 43.0%).

Datasets used and models developed

The data were collected as part of a treatment campaign in Uganda for school-aged children (SAC) from 2003 to 2006 and in Mali from 2004 to 2007 (Figure 3.2). SCI data from Uganda were selected as the primary dataset to parameterize and validate the model because: (a) Uganda was the first SCI-supported country to commence large-scale control of schistosomiasis in 2003 and thus has the most extensive longitudinal datasets (including pre-intervention baseline); (b) *S. haematobium* infections are highly localised to specific regions within Uganda, with prevalence mostly below 1%, and hence the potentially confounding impact of *S. haematobium* infection on the transition probabilities can be assumed to be minimal[156], and (c) despite the upsurge in prevalence (treatment round 4) and intensity (treatment round 3) as seen in Chapter 2 (Figure 2.5), Uganda has been very successful in implementing control[140], making this country a good candidate to move towards elimination of schistosomiasis as a public health problem. The extensive Ugandan dataset also enabled the model to be tested against data obtained from districts with contrasting disease endemicities. Three districts were selected based on their geographic spread and the distribution of infection intensities: Moyo (only low intensity infections); Busia (only low and moderate intensity infections); Masindi (only moderate and high intensity infections). There were no districts with only moderate or only high infection intensities. The remaining districts on which the model was tested contained a mixed composition of intensities. See Figure 3.2 and Table 3.5 for further details on the districts. The dataset and its different subsets that were used to test the predictive capabilities of the models are listed in Table 3.3. Table 3.4 shows other MTP matrices that were developed by the same method described in the previous sub-section, *Model development*.

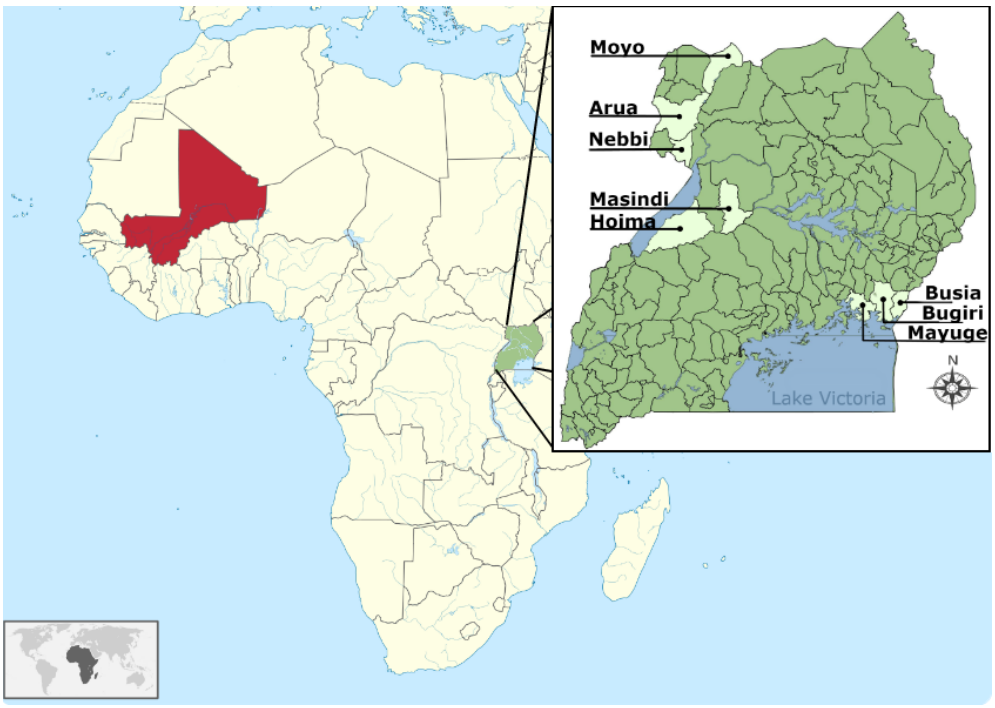

Figure 3.2. Map of Africa showing Mali (red) and Uganda (green). Inset: Uganda by district in study sample.

Table 3.3. Data and subset description (data type) used for testing model/matrices, and baseline infection prevalence and infection-intensity category prevalence (for *Schistosoma mansoni*), in Uganda and Mali.

				Observed Baseline Prevalence by Intensity Group (%)			
Dataset	**Data type**	**Description**	**Sample size (*n*)**	**Overall prevalence**	**Low intensity**	**Moderate intensity**	**High intensity**
1	Uganda longitudinal baseline to year 3	Full longitudinal data set	747	43.0	16.6	11.4	15.0
2	Uganda longitudinal baseline to year 3	4 Ugandan districts out of 7*	400	46.5	15.5	12.3	18.8
3	Uganda cross-sectional baseline to year 3	Varying sample size per year, full programme data	Baseline: 4,222 Year 1: 3,973 Year 2: 4,192 Year 3: 3,373	45.2	16.0	11.7	17.6
4	Mali longitudinal baseline to year 2	Full longitudinal data set	897	26.5	12.5	7.1	6.9

* These districts were selected for their wide range of infection intensities and NOT used for the development of matrix C (see Table 3.4).

Table 3.4. Markov transition probability (MTP) matrices developed from Uganda data (and its various subsets) and Mali.

MTP matrix	Country	Number of districts	Time points used to develop matrix	Sample size (*n*)
A	Uganda	7	Baseline and year 1	1,245
B	Uganda	7	Year 1 and year 2	1,260
C	Uganda	3	Baseline and year 1	540
D	Mali	-	Baseline and year 1	1,092

Table 3.5. Uganda data subset information for Uganda dataset 2 and matrix C. *Mayuge, Bugiri, Hoima and Nebbi were used to test the predictive capacity of the model.

District	Sample size (all years followed)	Sample size followed from baseline- year 1 (matrix C)*	Intensity groups present in each district
Moyo	142	217	Low
Mayuge	85	-	Low/High
Masindi	69	128	Med/High
Bugiri	110	-	Low/High
Busia	142	204	Low/Med
Hoima	99	-	Low/Med/High
Nebbi	110	-	Low/Med/High
Total	**757**	**549**	**-**

In summary, four matrices (A-D) were developed: A–C from Uganda and D from Mali. These were tested on four datasets (1-4, Table 3.3):

- Dataset 1 comprises the full longitudinal cohort data from Uganda;
- Dataset 2 comprises a subset of dataset 1 using districts not used to parameterize matrix C (as an independent matrix from a subset of the country data;
- Dataset 3 comprises cross-sectional data across all years from Uganda, and;
- Dataset 4 comprises data from Mali, which acted as a completely independent dataset.

Matrix A was an 'ideal' scenario where longitudinal baseline and year 1 data from a large programme were available to parameterize the model and develop the TPs. The TPs were assumed to be fixed throughout the years. In practice, since changes between intensity groups are likely to be more dramatic after the first treatment in a treatment-naïve area, matrix B was developed using TPs from post-baseline treatment, between year 1 and year 2. The use of matrix C predictions on dataset 2 is an illustration of a scenario where an 'independent' matrix might be used, calculated from a smaller dataset, to estimate changes on a 'separate' smaller dataset (dataset 2) that is not used to develop

the TPs. Matrix D illustrates a case where longitudinal data from another country are used to develop the TPs (Mali) to predict changes in prevalence in a separate country (Uganda).

In the following sections a distinction is made between 'estimation' (the estimated TP values), 'prediction' (the model outputs), 95% prediction intervals (95% PIs, constructed as described above), and 95% confidence intervals (95% CIs) around the data (calculated as binomial proportion confidence intervals). As a conservative approach to the qualitative model assessment, the focus is on the ability of the models to capture the observed point prevalence values within the 95% PIs whilst also highlighting whether the 95% PIs of the model encompass the 95% CIs of the observed data.

Matrix and dataset combinations

Matrix A, datasets 1, 2, 3, 4

Matrix A was calculated using all 1,245 individuals that were followed from baseline to year 1 in the Uganda dataset. Dataset 1 contains 747 of these individuals who were followed for a further three years (lower numbers due to follow-up loss). Therefore, it is expected that Matrix A provides the most accurate predictions on dataset 1. In addition, to test how the model performed with smaller sample sizes, less complete data, and other data types, selected districts (dataset 2) and cross-sectional data (dataset 3) were used. To test how the model performed using matrix A on a completely independent dataset, longitudinal data from Mali (baseline to year 2; dataset 4) were used.

Matrix B, datasets 1, 2, 3

It is important to understand how the model and its outputs differ between two different time points within the same settings, since the model explicitly assumes that the TPs remain constant. In addition, this would be a way of 'updating' the TPs as they become available to the model users. To explore this, instead of using the baseline and year 1 data to calculate the TPs for the matrix, data derived from follow-up years 1 and 2 were used from the full Uganda dataset (matrix B). The outputs from these TPs were compared to the observed values from datasets 1–3.

Matrix C, datasets 1, 2, 3

A comparison was made between model outputs using smaller sample sizes for situations in which fewer data are available to parameterize the TPs. This was achieved by selecting district-level subsets of the data for calculating TPs. The predictions were also tested against dataset 1 (longitudinal Uganda dataset) to represent a case where limited data would be used for the development of the TPs to project the expected impact of a much larger programme. In addition, to test the least favourable

data scenario, in which there are very high levels of follow-up loss, the model was also used to estimate changes in the proportions infected according to cross-sectional data, i.e. small sample size for TP development and poor follow-up to test the model (dataset 3).

Matrix D, dataset 1

Transition probabilities developed from the Mali baseline and year 1 data (Matrix D) were used to predict the longitudinal Ugandan dataset (dataset 1). This was performed by way of testing model performance when a dataset other than the Ugandan data are used for calculation of the TPs. This addresses issues on the generalizability of the MTP approach among endemic settings.

3.3 Results

We focused on the ability of the models to capture the observed point prevalence values (and accompanying uncertainty) within the 95% PIs. Where the upper or lower bounds of the 95% CIs overlapped with the model predictions (or their 95% PIs) only, the model was deemed to capture the estimates within the bounds of their associated uncertainty, but not the point prevalence.

1. Predictions made on dataset 1 (Uganda full dataset)

Table 3.6 shows all the predictions that were made for dataset 1. The symbol ɤ next to the values highlights predictions that were closest to the observed point prevalence values and the values in bold highlight predictions where the observed point prevalence estimates fell outside the 95% PIs; in most cases however, the model predictions were consistent with the uncertainty around the estimated values (10 cases out of 13 shown in bold).

All of the predictions from each matrix captured the observed point prevalence values within their PIs for the prevalence of low-intensity infection in each year with the exception of matrix D (the Mali dataset) - year 1 and marginally for year 2 - and for the prevalence of high-intensity infection with the exception of matrix C (Uganda data subset) in year 3, although in both cases the 95% PIs and the 95% CIs overlapped. When using the TPs derived from matrix A (the full Ugandan dataset) to predict forward the reduction in *overall* infection prevalence as well as in the prevalence of all infection intensity groups, the outputs matched the observed data within the 95% PIs for all time points with the exception of the moderate intensity group and the overall prevalence for year 2 (Figure 3.3 and Table 3.6), which indicated that the observed prevalence of each infection intensity group was below

the lower bound of the prediction intervals of the estimated prevalence. However, in both instances, the model captured the 95% CIs of the observed values.

As with matrix A, matrices B (Appendix 2, Figure A1a) and D (Figure 3.4) also 'highlighted' year 2 for both prevalence of moderate infection intensity and overall prevalence as a year in which observed values fell below 95% PIs (with matrix B capturing the upper 95% CI around the data, as with matrix A). Matrix C, however, did not highlight any of the same time points identified by the other matrices but instead highlighted different years in the moderate intensity, high intensity and overall prevalence groups as time points in which observed point prevalence levels were higher than predicted by the model (Appendix 2, Figure A1b).

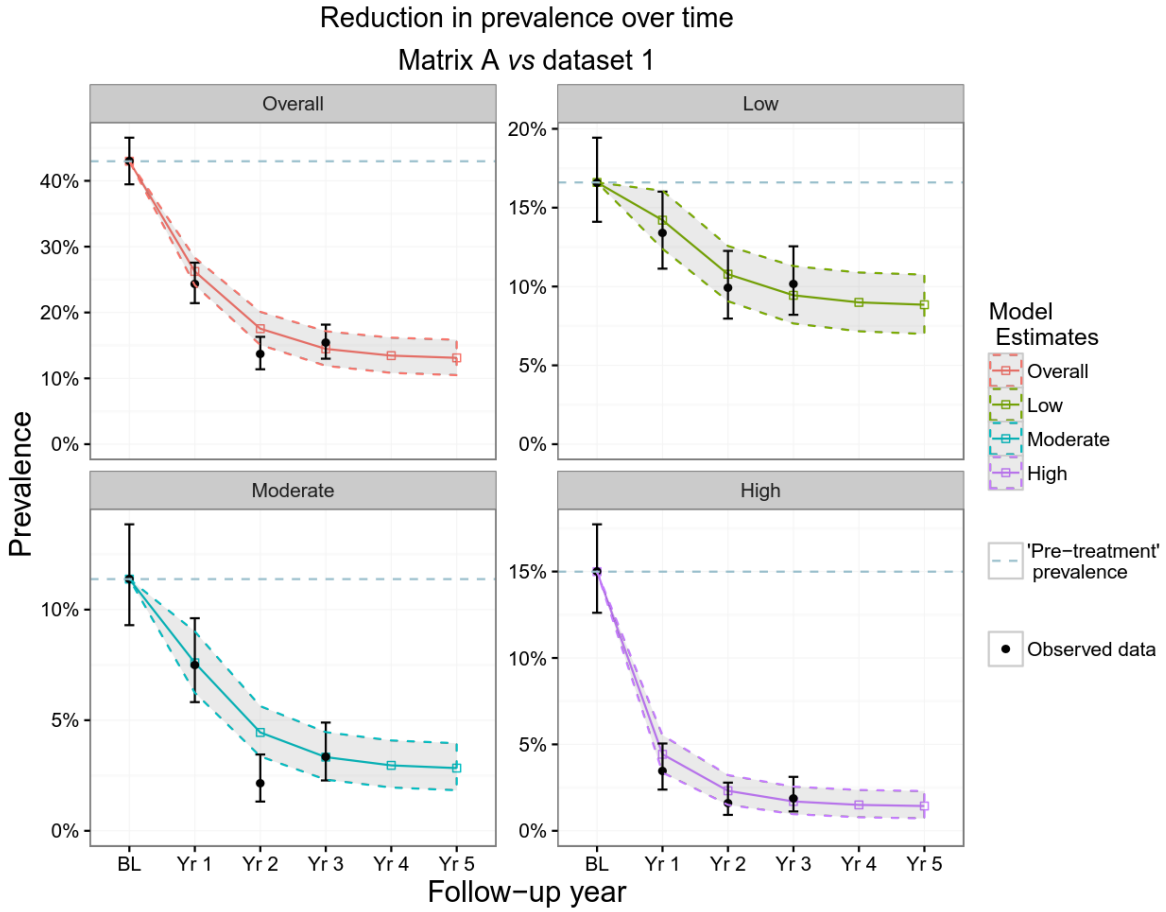

Figure 3.3. Matrix A predictions alongside dataset 1 observations. Matrix A was composed of transition probabilities calculated from Uganda baseline and dataset 1, representing the full longitudinal Ugandan observations. These four plots show the predicted reduction in prevalence by Matrix A (coloured outline with bands representing 95% PIs) vs observed (black points with vertical lines representing 95% CIs) in Uganda by overall prevalence group and by prevalence of intensity group. The dashed horizontal lines represent the pre-intervention prevalence values.

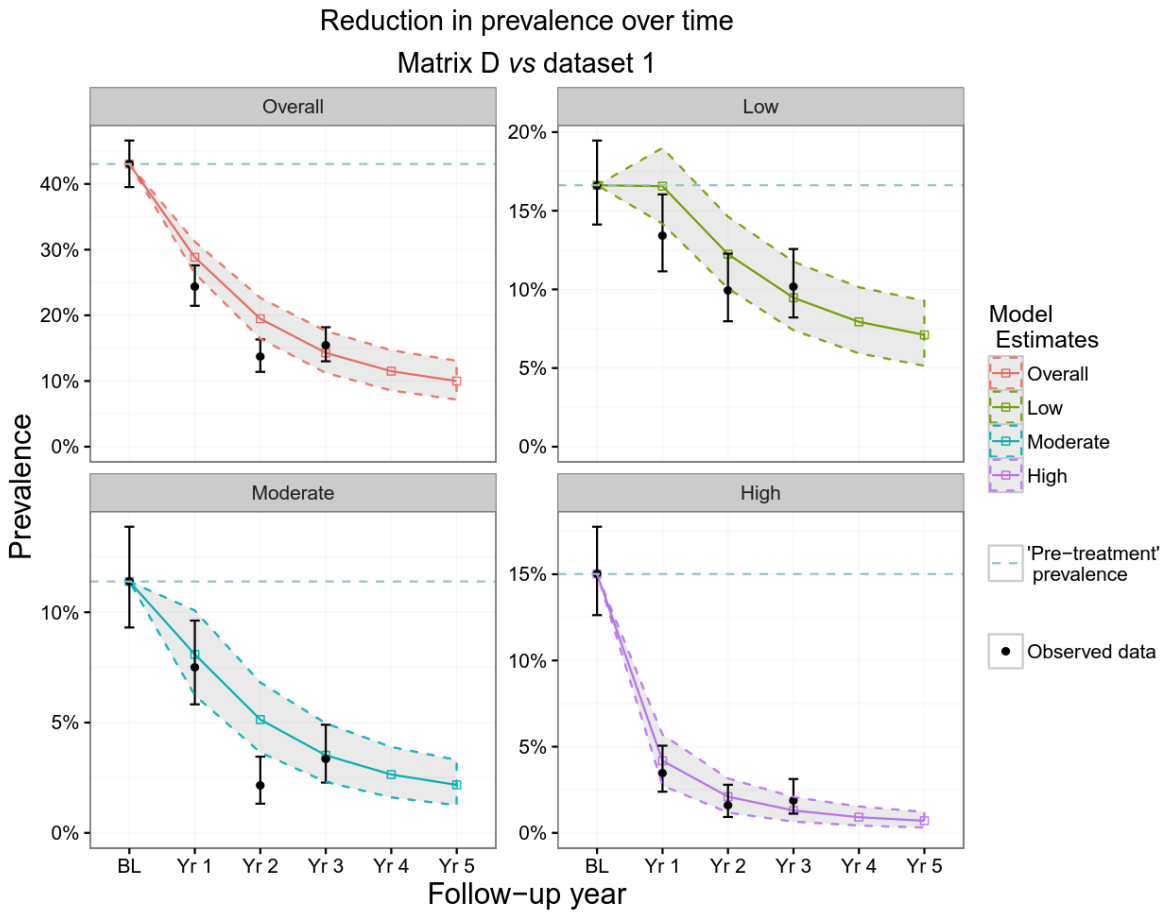

Figure 3.4 Matrix D predictions and dataset 1 observations. Matrix D was composed of transition probabilities calculated from Mali baseline and year 1 data and dataset 1 represents the full longitudinal Ugandan observations. These four plots show the predicted reduction in prevalence by Matrix D (coloured outline with bands representing 95% PIs) vs observed (black points with vertical lines representing 95% CIs) in Uganda by overall prevalence group and by intensity group. The dashed horizontal lines represent the pre-intervention prevalence values.

Table 3.6. Predicted mean prevalence by matrices A-D for dataset 1 (full longitudinal Ugandan observations).

	Low intensity (predicted mean prevalence and 95% CI)			Moderate intensity (predicted mean prevalence and 95% CI)			High intensity (predicted mean prevalence and 95% CI)			Overall prevalence (predicted mean prevalence and 95% CI)		
Matrix	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
Observed prevalence dataset 1	*0.134 (0.111-0.160)*	*0.099 (0.080-0.123)*	*0.102 (0.082-0.126)*	*0.075 (0.058-0.096)*	*0.021 (0.013-0.035)*	*0.033 (0.023-0.049)*	*0.035 (0.024-0.051)*	*0.016 (0.009-0.028)*	*0.020 (0.011-0.031)*	*0.244 (0.214-0.276)*	*0.137 (0.114-0.163)*	*0.154 (0.130-0.182)*
Matrix A Full dataset	0.142 (0.123-0.161)	0.108 (0.091-0.126)	0.095ɣ (0.077-0.113)	0.075ɣ (0.062-0.090)	**0.044 (0.033-0.056)**	0.033ɣ (0.023-0.045)	0.044 (0.033-0.055)	0.023 (0.015-0.032)	0.017ɣ (0.010-0.026)	0.261 (0.240-0.282)	**0.175 (0.151-0.200)**	0.144ɣ (0.119-0.171)
Matrix B Uganda year 1 to year 2	0.135ɣ (0.112-0.158)	0.105 (0.086-0.126)	0.090 (0.072-0.109)	0.069 (0.051-0.090)	**0.039 (0.028-0.051)**	0.028 (0.019-0.038)	0.048 (0.031-0.066)	0.024 (0.015-0.036)	0.016 (0.009-0.024)	0.252ɣ (0.225-0.278)	**0.168 (0.141-0.197)**	0.133 (0.108-0.160)
Matrix C 3 selected districts	0.152 (0.122-0.183)	0.096ɣ (0.071-0.122)	0.082 (0.057-0.108)	**0.045 (0.027-0.065)**	0.016ɣ (0.008-0.027)	**0.009 (0.003-0.017)**	0.027 (0.013-0.043)	0.011ɣ (0.003-0.021)	**0.008 (0.001-0.018)**	0.223 (0.193-0.255)	0.123ɣ (0.093-0.156)	**0.099 (0.069-0.132)**
Matrix D Mali full dataset	**0.165 (0.141-0.190)**	**0.122 (0.100-0.146)**	0.095ɣ (0.073-0.117)	0.081 (0.062-0.101)	**0.051 (0.037-0.068)**	0.035 (0.023-0.049)	0.042ɣ (0.028-0.057)	0.021ɣ (0.012-0.032)	0.031 (0.007-0.021)	**0.288 (0.264-0.312)**	**0.195 (0.164-0.226)**	0.143 (0.113-0.175)

Bold = observed values fell outside of the predicted boundaries; ɣ = closest predictions to observed values

2. Predictions made on dataset 2 (data from selected districts)

Table 3.7 shows the predictions that were made for dataset 2 (see also Appendix 2, Figure A2). All three matrices in this group indicated the same time point for the prevalence of low-intensity infection category (year 3) and the overall prevalence group (year 1 and year 3) as performing below the expected values, i.e. higher observed point prevalence values than predicted (although matrix A also identified year 2 for better programme performance than expected, for overall infection prevalence). The same pattern in predicted vs. observed prevalence from dataset 1 by all matrices was observed for the prevalence of moderate-intensity infection group for all time points, except for year 3 for matrix B, which mirrored matrix C estimates. Matrices A and B performed similarly as in dataset 1 for the high intensity group (i.e. all observations at each time point were within the prediction intervals of the model predictions) but matrix C indicated that the observed prevalence values from years 1 and 2 were marginally higher than expected. Matrix A predictions were consistent with the uncertainty associated with the point estimates in all 12 observed values of dataset 2; matrix B was consistent with 10 out of 12 and matrix C was consistent with 9 out 12.

Table 3.7. Predicted mean prevalence by matrices A-C for dataset 2 (selected Ugandan districts).

	Low intensity (predicted mean prevalence and 95% CI)			Moderate intensity (predicted mean prevalence and 95% CI)			High intensity (predicted mean prevalence and 95% CI)			Overall prevalence (predicted mean prevalence and 95% CI)		
Matrix	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
Observed prevalence dataset 2	*0.158 (0.125-0.196)*	*0.105 (0.079-0.139)*	*0.143 (0.112-0.180)*	*0.100 (0.074-0.133)*	*0.020 (0.010-0.030)*	*0.045 (0.029-0.070)*	*0.055 (0.037-0.082)*	*0.030 (0.017-0.052)*	*0.018 (0.009-0.036)*	*0.313 (0.269-0.360)*	*0.155 (0.123-0.194)*	*0.205 (0.168-0.247)*
Matrix A Full dataset	0.152ɣ (0.133-0.172)	0.112 (0.095-0.130)	**0.096 (0.078-0.115)**	0.085ɣ (0.070-0.101)	**0.048 (0.036-0.060)**	0.034ɣ (0.024-0.046)	0.051 (0.039-0.063)	0.025 (0.017-0.035)	0.018ɣ (0.010-0.026)	**0.289 (0.268-0.311)**	**0.185 (0.161-0.211)**	**0.148 (0.123-0.175)**
Matrix B Uganda year 1 to year 2	0.140 (0.115-0.166)	0.109ɣ (0.089-0.129)	**0.092 (0.074-0.111)**	0.078 (0.055-0.102)	**0.042 (0.030-0.055)**	**0.029 (0.020-0.039)**	0.055ɣ (0.035-0.077)	0.027ɣ (0.016-0.040)	0.017 (0.009-0.026)	**0.272 (0.242-0.302)**	0.178ɣ (0.149-0.208)	**0.137 (0.111-0.165)**
Matrix C 3 selected districts	0.166 (0.132-0.199)	0.099 (0.075-0.124)	**0.082 (0.057-0.108)**	**0.052 (0.031-0.075)**	0.018ɣ (0.009-0.029)	**0.010 (0.003-0.018)**	**0.031 (0.014-0.051)**	**0.012 (0.003-0.023)**	0.008 (0.001-0.018)	**0.249 (0.216-0.282)**	0.129 (0.098-0.162)	**0.100 (0.070-0.132)**

Bold = observed values fell outside of the predicted boundaries; ɣ = closest predictions to observed values

3. Predictions made on dataset 3 (cross-sectional data)

Table 3.8 shows the predictions that were made for dataset 3 (cross-sectional observed data). Figure 3.5 shows the output obtained from using the matrix A model on dataset 3 and Appendix, Figure A3 shows the plots corresponding to applying matrices B and C on dataset 3.

All data points in the low-intensity prevalence group were estimated accurately by each matrix, where both the observed point prevalence values as well as their 95% CIs were consistent with the model. As with dataset 1, matrices A and B produced similar outputs, with the observed data points and their 95% CIs predicted by the models, except for year 3, in moderate intensity, high intensity and overall prevalence groups. For matrix C, other than the low infection intensity group, the observed prevalence levels in all the other infection intensity groups in all years were greater than the predicted range.

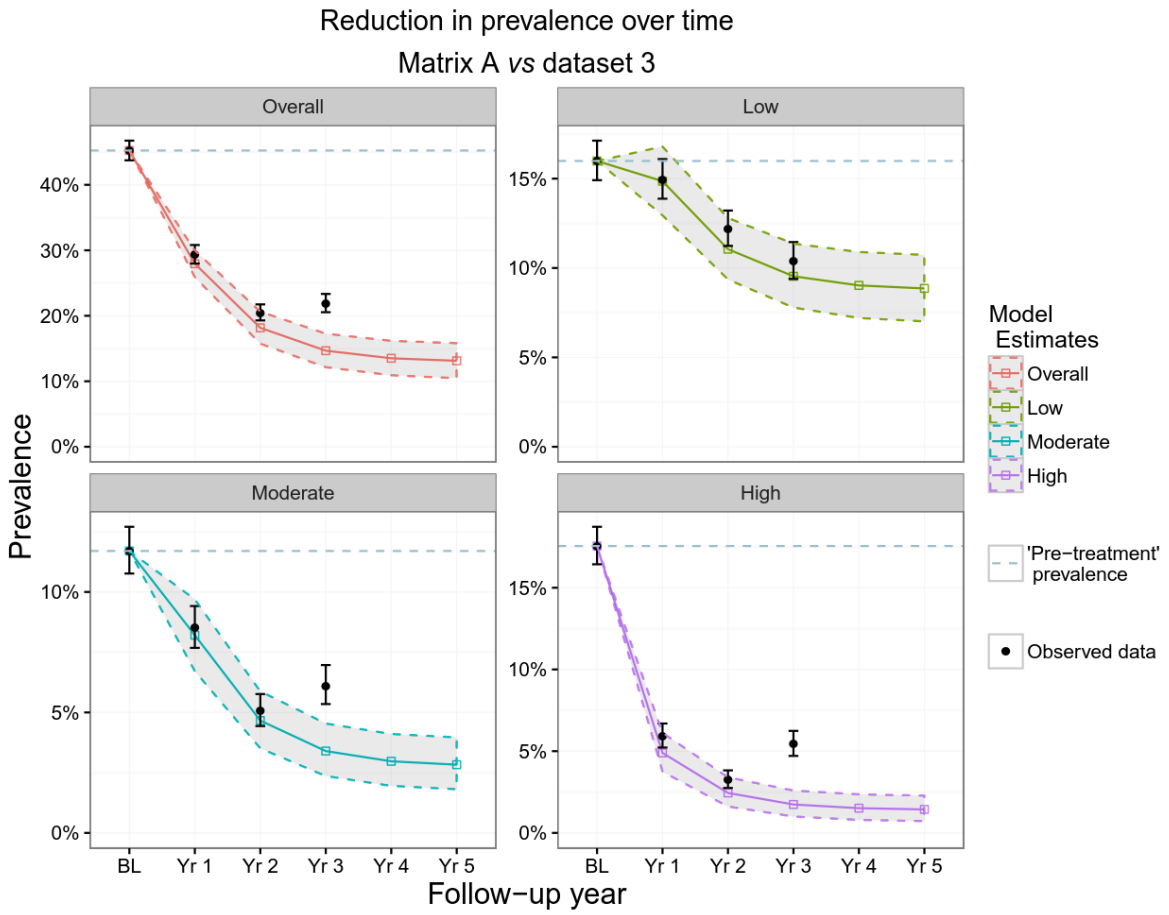

Figure 3.5. Matrix A (full Ugandan baseline and year 1 transition probabilities) predictions and dataset 3. Dataset 3 represents cross-sectional Uganda observations. These four plots show the predicted reduction in prevalence by Matrix A (coloured outline with bands representing 95% PIs) vs cross-sectional observed (black points with vertical lines representing 95% CIs) in Uganda by overall prevalence group and by intensity group. The dashed horizontal line represents the pre-MDA prevalence.

Table 3.8 Predicted mean prevalence by matrices A-C for dataset 3 (cross-sectional Ugandan data).

	Low intensity (predicted mean prevalence and 95% CI)			**Moderate intensity (predicted mean prevalence and 95% CI)**			**High intensity (predicted mean prevalence and 95% CI)**			**Overall prevalence (predicted mean prevalence and 95% CI)**		
Matrix	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
Observed prevalence dataset 3	*0.150 (0.139-0.161)*	*0.122 (0.112-0.132)*	*0.104 (0.094-0.115)*	*0.085 (0.077-0.094)*	*0.051 (0.044-0.053)*	*0.061 (0.053-0.070)*	*0.059 (0.052-0.070)*	*0.032 (0.028-0.038)*	*0.054 (0.048-0.062)*	*0.294 (0.280-0.308)*	*0.205 (0.193-0.218)*	*0.219 (0.205-0.233)*
Matrix A Full dataset	0.149ɣ (0.130-0.168)	0.111ɣ (0.093-0.128)	0.095ɣ (0.078-0.114)	0.082ɣ (0.068-0.097)	0.047ɣ (0.035-0.059)	**0.034 (0.024-0.045)**	0.049 (0.037-0.061)	0.024 (0.016-0.034)	**0.017 (0.010-0.026)**	0.280ɣ (0.259-0.301)	0.182ɣ (0.157-0.207)	**0.147 (0.121-0.173)**
Matrix B Uganda year 1 to year 2	0138 (0.114-0.163)	0.108 (0.088-0.128)	0.091 (0.073-0.110)	0.075 (0.053-0.098)	0.041 (0.029-0.054)	**0.028 (0.019-0.039)**	0.052ɣ (0.033-0.073)	0.026ɣ (0.016-0.039)	**0.017 (0.009-0.025)**	0.265 (0.235-0.295)	0.174 (0.146-0.205)	**0.136 (0.110-0.163)**
Matrix C 3 selected districts	0.160 (0.128-0.193)	0.098 (0.074-0.123)	0.082 (0.057-0.108)	**0.050 (0.029-0.072)**	**0.017 (0.008-0.029)**	**0.009 (0.003-0.018)**	**0.030 (0.014-0.049)**	**0.011 (0.003-0.022)**	**0.008 (0.001-0.018)**	**0.240 (0.208-0.273)**	**0.127 (0.096-0.159)**	**0.100 (0.070-0.131)**

Bold = observed values fell outside of the predicted boundaries; ɣ = closest predictions to observed values

4. Predictions made on dataset 4 (Mali full dataset)

Figure 3.6 and Table 3.9 show the model outputs when Ugandan TPs were used to estimate changes in the longitudinal data from Mali. The results show that the model predictions match the changes in prevalence closely, with only year 2 observations from the low and high infection intensity groups falling outside of the prediction intervals, yet consistent with the uncertainty associated with the point estimates. The low intensity year 2 prediction shows an increase in prevalence, but inspection of the high intensity group shows that this may be due to individuals moving from the higher infection intensity groups to the low intensity and the non-infected group. Appendix 2, Figure A4 also shows the output obtained when applying Matrix D to dataset 4, where all data points were consistent with the model except for year 2 in the low intensity group. In all years however, the results of matrix D were consistent with the 95% CIs of all observed data points.

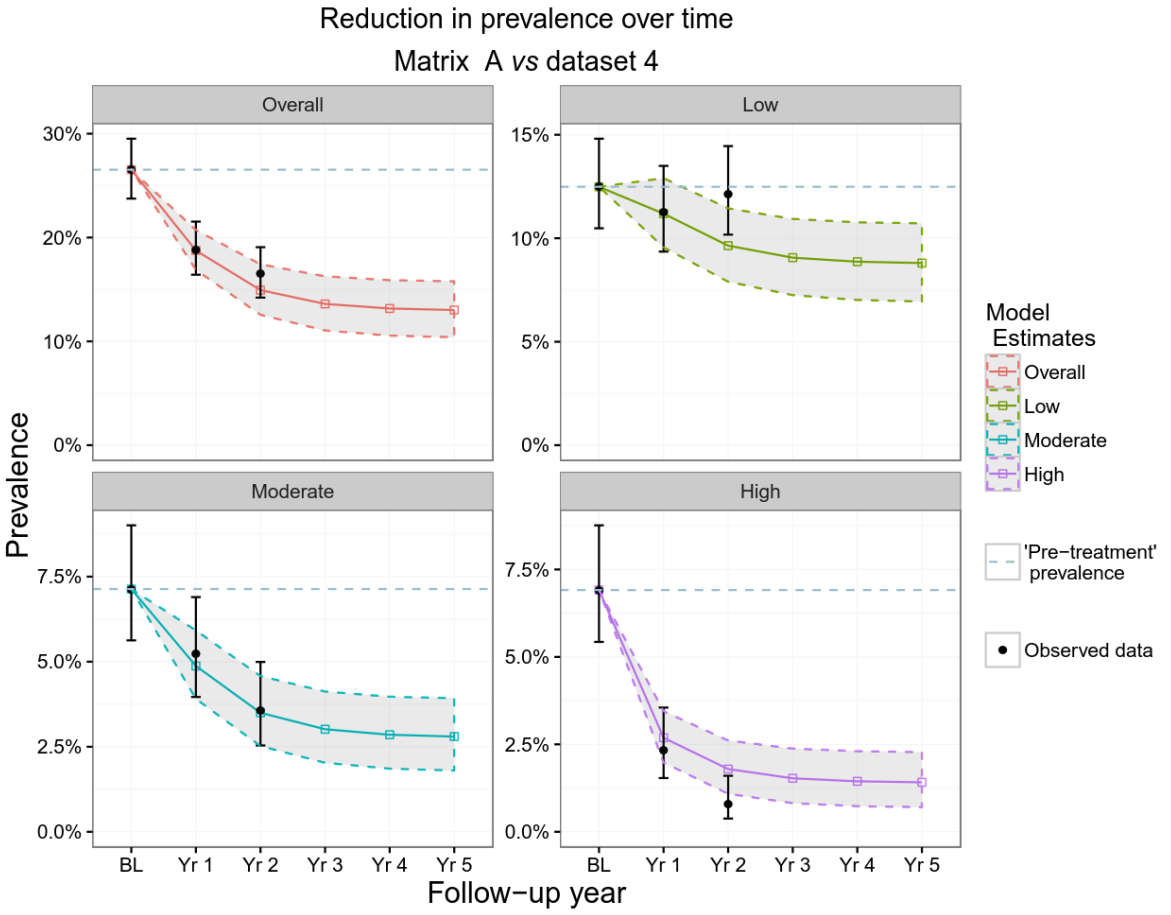

Figure 3.6. Matrix A (Uganda baseline and year 1 transition probabilities) predictions and dataset 4. Dataset 4 represents full longitudinal Mali observations. These four plots show the predicted reduction in prevalence by Matrix A (coloured outline with bands representing 95% PIs) vs observed (black points with vertical lines representing 95% CIs) in Mali by overall prevalence group and by intensity group. The dashed horizontal line represents the pre-MDA prevalence.

Table 3.9 Predicted mean prevalence by matrix A for dataset 4 (longitudinal Mali data).

	Low intensity (predicted mean prevalence and 95% CI)		Moderate intensity (predicted mean prevalence and 95% CI)		High intensity (predicted mean prevalence and 95% CI)		Overall prevalence (predicted mean prevalence and 95% CI)	
Matrix	**Year 1**	**Year 2**	**Year 1**	**Year 2**	**Year 1**	**Year 2**	**Year 1**	**Year 2**
Observed prevalence dataset 4	*0.113 (0.094-0.135)*	*0.122 (0.102-0.145)*	*0.052 (0.040-0.069)*	*0.036 (0.025-0.050)*	*0.023 (0.015-0.036)*	*0.008 (0.004-0.016)*	*0.188 (0.164-0.215)*	*0.165 (0.142-0.191)*
Matrix A Full dataset	0.112 (0.095 - 0.129)	**0.096 (0.079 - 0.115**)	0.049 (0.039 - 0.059)	0.035 (0.025 - 0.046)	0.027 (0.020 - 0.035)	**0.018 (0.011 - 0.027)**	0.188 (0.169 - 0.207)	0.149 (0.126 - 0.174)

Bold = observed values fell outside of the predicted boundaries; ϒ = closest predictions to observed values

3.4 Discussion

The primary aim of this work was to develop a quantitative tool to help programme managers to monitor and evaluate the progress of their schistosomiasis interventions and determine whether they are meeting their targets. For this, a Markov model was developed, parameterized and validated by the candidate using an extensive longitudinal dataset of *S. mansoni* infection in Ugandan children treated yearly with PZQ. Additionally, to test the robustness of the model predictions in a completely different setting, model predictions were compared against data from comparable school-aged children from the national control programme in Mali. The focus was on the ability of the models to capture the observed point prevalence estimates. It is anticipated that programme managers will be able to use their own baseline and year 1 data to predict changes in infection prevalence in subsequent years of the same programme, as this is the scenario where the model performed best.

This work demonstrates that the Markov modelling approach is useful when making (relatively short-term) predictions on infection trends with large datasets from which a subset has been used to parameterize the model (as seen by matrix A vs dataset 1 and matrix D vs dataset 4). Smaller datasets from programmatic settings will likely produce less accurate results in practice due to sampling effect and transient factors (for example influx of groups of fishermen or a longer rainy season than usual), having a larger impact on the prevalence outcomes. Further studies would be required to determine if smaller datasets from a research setting (rather than programmatic setting) can be used to make predictions.

Additionally, the model performs adequately when using independent data from another country for parameterization and when predicting cross-sectional data. These results are particularly noteworthy since the majority of sentinel site survey data tend to be cross-sectional in design given the logistical

and financial advantages of this approach to sampling. Matrices A (baseline and year 1 Uganda full dataset used to parameterise the model) and B (year 1 and year 2 used to parameterise the model) performed similarly. It is important to test the performance of the model using data from a different country as this is one scenario for which a programme manager may use this model. For this reason, data from Mali (dataset 4) were used to both separately test the model with Ugandan TPs (matrix A) and parameterize the model (baseline and year 1 data for matrix D). Both models were able to predict a large majority of data points within the estimated 95% PIs, in both cases. Conversely, matrix C (using data from selected districts in Uganda) performed least well. However, it is not possible to determine how the trends would continue without further data; therefore, this study is limited to the data that were available at the time of analysis.

In its current form, the model is a useful tool for programme managers, provided they have the data available for parameterisation of the model (ideally with respect to the local setting for optimal predictions), and is particularly useful for the interpretation of data from low and high infection intensity areas where all of the models performed best. This is ideal for programmes preparing to move from control of morbidity to interruption of transmission and elimination of infection (more feasible in low infection intensity areas) or to elimination of schistosomiasis as a public health problem (more severe in high infection intensity areas). The use of data from Mali for parameterization to predict changes in Uganda and vice versa (Figures 3.4 and 3.5) illustrated that the model could be considered useful for predicting prevalence changes in countries where the same data were not used for parameterizing the model. Additional analyses using data from other countries would be useful to test this further.

These models are aimed to be a tool to aid programmatic decisions and stimulate further investigation when needed rather than be used as a precise prediction of likely impact. Therefore, it is hoped that this heuristic technique may be useful for programme managers as a quick and simple means of assessing the progress of programmes. However, as seen by the results concerning dataset 4 (Mali longitudinal cohort), it is important to interpret the data for all four infection intensity groups together, since an observed increase in the low infection intensity group compared to model outputs, may likely be linked to a corresponding decrease in the proportion of the heavier infection intensity groups. The precise change in infection patterns following treatment will depend on a multitude of factors related to programmatic design and performance. These will include therapeutic coverage and treatment adherence, which in turn will be related to other programmatic variables, such as the performance of the drug distribution teams, the accuracy of census data (for calculating coverage),

and the effectiveness of social mobilization techniques, among others. Identifying the respective impact of each of these factors is beyond the scope of the work presented in this chapter.

Limitations

Despite its advantages, the limitations of the Markov approach must be understood if it is to constitute a useful programmatic tool. The model employed in this study is referred to as a time-homogenous Markov process[157], which assumes that the TPs remain constant through time. It is also assumed that they are invariant with respect to setting (endemicity, geographic location etc.) and host age group. This may not hold for long-term projections as interventions (in this case MDA) are likely to have an impact on the transmission environment. For these reasons, such models may indicate 'abnormalities' in the observed datasets because of inevitable or expected changes over time; therefore, the usefulness of the approach resides in its value as an additional tool for monitoring and evaluation and short-term projection rather than a definitive tool for longer-term projections and strategic design of interventions. The data used to validate and test the models are primarily from SAC, since most schistosomiasis interventions focus on this age group [34,47,112,148–151]. Therefore, the models do not consider the broader impact of MDA on the entire community via the indirect (herd) effects on transmission that result from reducing the force of infection, which is where mechanistic transmission models can play an important role as they are able to incorporate these finer important parameters [77,138,140,158]. Moreover, the method also implies that the same intervention is used each year using the same treatment schedule, not accounting for complementary interventions that may be implemented, such as those relating to sanitation or education, increase in public awareness that may accompany the progression of a control programme, or changes in the frequency and/or coverage of MDA. The model is based on a closed system and, therefore, assumes no population migration or extraneous introduction of new infections. This is an important limitation for mobile communities that may comprise so-called super-spreading individuals (such as fishermen or bicycle washers for example) who contribute disproportionately to community-wide transmission and who may be more likely to miss treatment. However, this is also a general limitation of most helminth mechanistic transmission models, which rarely consider the spatial aspects of transmission.

Further work and conclusion

With these limitations in mind, this work demonstrates that using constant TPs from the same dataset or from different datasets provides a satisfactory prediction of data on the overall prevalence of infection and the prevalence of high-, moderate- and light-intensity infections for up to three follow-up years. This method could also be extended to *S. haematobium*, adapting the model to the different

WHO intensity classes for this species (defined as 1-50 eggs/10ml of urine as light intensity and >50 eggs/10ml of urine as heavy intensity, with no moderate intensity group)[36,99] as well as to *S. japonicum* and *S. mekongi*. In the case of *S. japonicum*, the transmission dynamics among multiple definitive hosts would potentially pose less of a problem to this modelling approach when compared to other models that do not take into account the zoonotic reservoir, as the TPs calculated from the initial data would implicitly include all of the transmission-related processes occurring between the two time points [159–161]. This work could also be expanded further by comparing different TPs estimated from other datasets. In addition, the models could be adapted to make longer-term predictions (since the present work is focussed on short-term changes of 1-3 years post-baseline due to the stationary TP limitation), using datasets spanning longer periods and incorporating MDA coverage information. These extensions could, in principle, be captured using multiple TPs based on existing data of varying treatment coverage, or the possibility of having dynamic TPs that change with time or are simply updated as new data become available (developing new TPs from the more recent followed cohort). The use of year 1 to year 2 TPs in this work illustrated the potential for updating TPs as the programme progresses to estimate changes in subsequent years. This would overcome the constraints imposed by using baseline and year 1 data only, for projecting over long-running programmes.

The results from this study show that this is not only a promising instrument for programmes in their early years of implementation as a complementary M&E and advocacy tool, but also a useful quantitative approach for making short-term projections of prevalence trends under interventions.

CHAPTER 4. WHAT IMPACT HAS OVER A DECADE OF TREATMENT HAD ON AGE-INFECTION PROFILES FOR SCHISTOSOMIASIS IN UGANDA? A DESCRIPTIVE STUDY

An adapted version of this chapter has been submitted for publication, entitled, "What impact has over a decade of preventive chemotherapy had on age-infection profiles for schistosomiasis? A case study in Uganda."

Additionally, a subset of the data generated for this chapter was used in a book publication: Advances in Parasitology Volume 94, Pages 1-430 (2016) "Mathematical Models for Neglected Tropical Diseases Essential Tools for Control and Elimination, Part B", Edited by Maria Gloria Basáñez and Roy M. Anderson [162]. *The book chapter (Chapter 4) is entitled: "Studies of the Transmission Dynamics, Mathematical Model Development and the Control of Schistosome Parasites by Mass Drug Administration in Human Communities."*

4.1 Introduction

Morbidity is traditionally hypothesized to be directly related to the intensity of schistosomiasis infection [163]. Parasite eggs, as counted in an individual's stool or urine, are used as an indirect measurement of infection intensity (worm burden) during routine monitoring and evaluation (M&E) programmes. However, the relationships between excreted eggs and worm burden and between excreted eggs and morbidity are poorly understood [164,165]. Nonetheless, the primary aim of a control programme is to reduce and prevent morbidity from schistosomiasis, through repeated preventive chemotherapy (PC) in school-aged children (SAC) and other high-risk groups to reduce worm burden, using praziquantel (PZQ)[22,23], since the most heavily infected individuals tend to experience the highest morbidity (see Chapter 1, Section 1.2.1 for a comparison of WHO's egg count-intensity thresholds for each schistosome species)[36,98].

The current WHO targets for schistosomiasis (Chapter 1, Figure 1.7) are to achieve:

- Control of morbidity (defined as <5% prevalence of 'heavy' infection averaged across all sentinel sites) in all endemic areas by 2020; and
- Elimination as a public health problem (<1% prevalence of heavy infection in all sentinel sites) by 2025; and
- Elimination of transmission (incidence of infection reduced to zero) expected in many regions by 2025 [99].

School-aged children, whether or not attending school, often harbour the highest prevalence and intensity of schistosome infections. This typically decreases with age, possibly due to a combination of factors such as decrease in exposure, the onset of puberty (i.e. impact of host hormonal changes on parasite metabolism, skin thickness on cercariae penetration) and the slow emergence of acquired immunity [22,29,34,46,49,50,99,150,166]. The aim of this chapter is to describe the change in shape of the full age-infection pattern at different population stratifications in response to multiple rounds of treatment.

With 2020 and 2025 on the horizon, there is an increasing need for researchers, governments, and the global health community to help drive schistosomiasis programmes towards success. With this in mind, there is a need for high-quality M&E of control programmes and research-based evidence of progress made using current WHO treatment strategies (Chapter 1, Figure 1.7). One method for gathering empirical evidence is through the collection of age-infection (prevalence and intensity) profiles. Age-infection profiles in parasitology can provide a picture of temporal patterns of infection across all age groups during an intervention. Additionally, they can be used to calibrate and validate mathematical models of transmission [46,167]. However, very few studies to date have collected infection information from a large sample across all host age groups to understand the impact of control programmes (Chapter 1, section 1.2.1)[140,165,168], due predominantly to the costly, time consuming and logistically challenging nature of the task. Moreover, it has been assumed that parasitological data from SAC provide a proxy for infection in the wider community (e.g. low prevalence and intensity levels in SAC indicates low prevalence and intensity levels in the rest of the community). Though this assumption targets the most at-risk individuals in a community with often limited resources available to the programmes, it provides only a restricted perspective of the true picture as patterns in high risk adults and pre-school-aged children (PSAC) may differ due to the high heterogeneity of infection.

This chapter aimed to collect detailed parasitological data in Uganda across all age groups, to produce accurate age-infection across three years of MDA (2014-2016), after more than a decade of treatment with PZQ through the control programme [35]. Ten sites were selected, stratified by their endemic prevalence (following WHO prevalence categorisation [Chapter 1, Figure 1.7], determined from baseline mapping results, Chapter 1, Section 1.5) and history of PZQ treatment. The outcomes of this analysis will help to understand how the patterns of infection have changed over the course of PC years and provide policy makers with a snapshot of the journey towards the 2020 goals.

4.2 Methods

For Research Objective 3, SCI and WHO sample collection protocols (Figure 4.1) were used to carry out the fieldwork in Uganda, where the candidate trained and supervised 10 teams annually for 3 years. The parasitological survey was carried out in ten sites each year, over a period of 3 years. It was important to move between teams, contributing to the sample collection as well as to ensuring quality and consistency between teams, addressing any concerns or obstacles that the teams experienced. In addition, a quality control staff member travelled between teams, re-examining 10% of the slides for quality control (where slides would be re-read from the day if there was a large discrepancy between quality-controller readings and technical readings). In the second year, the candidate supervised a volunteer (Elizabeth Hollenberg) who recruited a local team of volunteers and conducted a social survey in one of the sites (publication in progress but not part of this PhD). The aim was to understand behavioural patterns, duration of residence at site and general schistosomiasis understanding in the same individuals from the parasitological survey. Additional data (not included in this PhD) on soil-transmitted helminthiases (STH) were also collected using the same samples and diagnostic tool (Kato Katz) for the parasitological survey.

4.2.1 Fieldwork preparation

Fieldwork preparation was a lengthy process requiring the input of various departments and teams at SCI, Imperial College London, and the Uganda MoH. Ethical approval was received during protocol development from Imperial College London and the Uganda MoH. A detailed budget was drawn up for the activities (Appendix 1) and a contract between SCI and the MoH was developed and signed. Uganda was chosen as the survey country because it has the longest running programme at SCI, with detailed treatment history and baseline mapping results [140,145–147]. Additionally, the MoH Vector Control Division staff are highly skilled at fieldwork and have access to additional technical staff from Makerere University.

Parasitological forms were developed for the field technicians and consent forms were developed for the participants, which contained information about the study and why their samples were needed (Appendix 1). For SAC, the consent forms were signed by the school head-teacher if sampled at school, or by the parent/guardian if the child was sampled outside of the school, and each child also provided verbal consent. All adults signed their own forms, and for pre-school aged children (PSAC) parents/guardians signed the forms, allowing the collection and use of their stool sample and

information in the study. The survey was designed to take place approximately one month prior to the mass drug administration (MDA) round and infected individuals were informed of their infection status and advised to seek treatment during the MDA campaign.

The equipment was procured as per budget (developed by the candidate, using standard costs from SCI's routine surveys); funds were transferred from SCI to the MoH and the district health officers (DHOs) were all contacted to help prepare the teams for the specific sites. For the parasitological survey, the SCI forms used in routine impact surveys were modified (to incorporate additional questions on occupation or school class, whether the participants had taken part in the survey the previous year, whether they were attending school, and whether they had taken treatment the previous year) and used for this survey.

Sample selection plan and characteristics

A sample size of 750 individuals per site was chosen to provide representation across all age groups, with a total of 7,500 individuals sampled each year of the survey (Table 2.1). The 6-9-year age group was also the age group targeted by the national control programme's impact survey, so it was initially planned that the same children in this age group be used as part of the survey (hence the sample size of 125 individuals). In practice, this was not logistically feasible as the teams for this survey would also be required for the impact survey, so it was not possible for the two activities to take place at the same time. The standard SCI method of sampling individuals from the same age group (calculating sampling intervals and selecting the individual in line corresponding to the sampling interval, and then selecting the next individual from there at the sampling interval and so on, until the required sample size is reached) was not used. An attempt was made to recruit the entire population of these age groups at the sites, as the sites were relatively small, thus this was a form of convenience sampling (which can introduce sampling bias as well as risk the sample not bring representative of the target population). Where there were insufficient individuals in an age group from one site, further participants were sought in neighbouring areas close to the same water-sites, provided they fulfilled the same endemic group requirements and fell within the same treatment schedule.

Table 4.1 Age categories and number of individuals targeted (per survey site)

Age category (years)	0-3	4-5	6-9	10-12	13-15	16-19	20-29	30-39	40-49	≥50	TOTAL
Sample (per site)	50	50	125	75	75	75	75	75	75	75	**750**
Total in survey (per year)	500	500	1250	750	750	750	750	750	750	750	**7500**

4.2.2 Fieldwork methods

Ten field teams were assembled, each consisting of the following:

- 3 senior microscopists from the MoH (one acting as team leader)
- 1 junior microscopist/field assistant/sample collector and processor (to contribute to in-country capacity building, from Makerere University)
- 1 sample collector and processor
- 1 district health officer (DHO, local to each survey site)
- 1 experienced field driver

The equipment was procured and distributed to the ten teams. Training was conducted by the candidate, over two days in the first year, and over one day in the second and third years (as only a refresher was required). In the first year, the candidate accompanied one team over the whole duration of the survey (~6 weeks), whilst staying in phone communication with the other teams, to deal with any unforeseen and systematic challenges and assist the teams. Challenges encountered included not being able to obtain sufficient numbers of young adolescent males as they were working in the lakes and farms. This was mitigated by sending members of the team further away from the centre of the site to recruit them. In years two and three, it was essential to move between teams to ensure consistency between them. Table 4.2 shows the sites of the survey by village level, sub-country level and district level, by WHO prevalence category of schistosomiasis (determined at baseline mapping, see Chapter 1, section 1.4.2 and Figure 1.7) and Figure 4.2 shows the geographic location of the sites.

The ten sites consisted of three “high endemic” sites (which had received more than five rounds of treatment of SAC and high-risk adults) and seven “low endemic” sites as defined by the WHO at the time of the mapping stage [36]. The low endemic sites were further grouped into “low, treated” (having received more than five treatment rounds in SAC, becoming low endemic through these rounds of treatment) and “low, untreated” (sites untreated prior to the 2014 survey, after which they received annual treatment of SAC).

Preparation night before:

- Cut black bin bag into pieces (for stool samples)
- Cut cellophane into pieces (to be used as cover slip for slides) and place into jar.
- Prepare and pour methylene blue glycerol solution into jar containing cellophane strips, leave overnight.

1. Label slide with IDs (write on pieces of masking tape). 2. Using a spatula take small amount of faeces from the fresh sample and place on the sieve.	
3. Scrape the flat-sided spatula across the lower surface of the sieve to collect the sieved faeces. 4. Add faeces from spatula so that hole of template on slide is completely filled.	
5. Remove template carefully so that sample of faeces is left on slide. 6. Cover faeces with pre-soaked cellophane strip.	 
7. Invert the microscope slide and firmly press the faecal sample against the cellophane strip on a smooth hard surface (such as on a newspaper on the table). 8. Carefully remove the slide by gently sliding it sideways to avoid separating the cellophane strip.	

Figure 4.1 The Kato-Katz procedure as per World Health Organization guidelines [169].

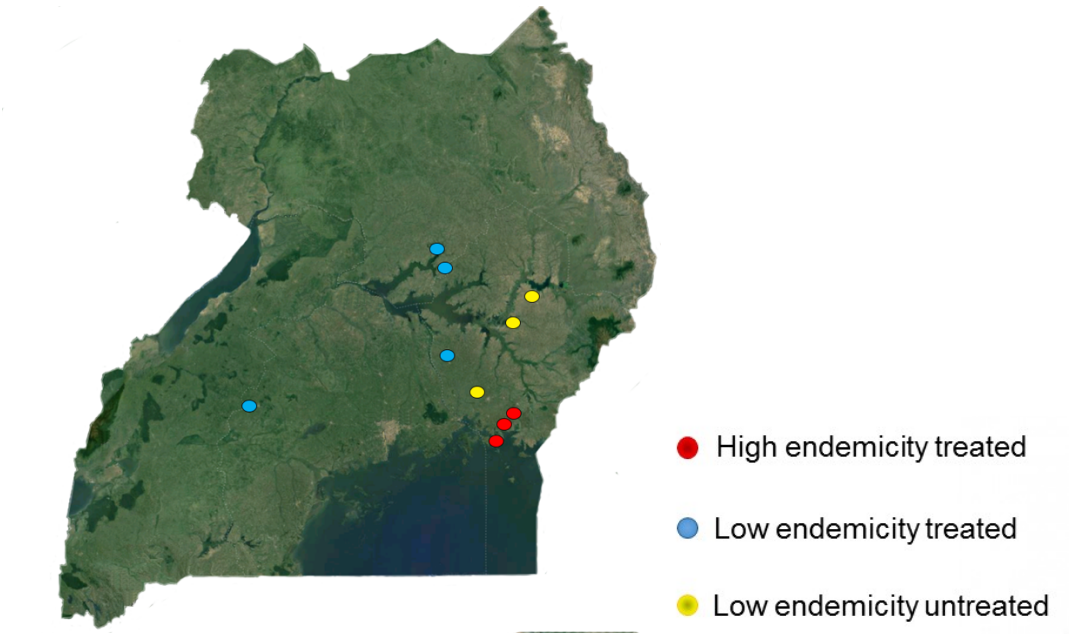

Figure 4.2. Geographical locations for the ten Ugandan survey sites categorised by schistosomiasis baseline mapping endemicity level and treatment group.

Table 4.2. WHO endemic group by district, survey site (sub-county) and school where the survey was based.

WHO endemic group	District	Survey site (sub-county)	Survey base (school)
Low endemicity Treated >5 times (4 sub-counties)	Mubende	Kasambya$^{\phi}$	Muyinayina p/s
	Dokolo	Kangai$^{\phi}$	Adeknino
		Agwata$^{\phi}$	Abwola
	Kamuli	Balawoli$^{\phi}$	Nabitalo
Low endemicity Untreated (3 sub-counties)	Kumi	Ongino$^{\phi}$	Akide P/S
	Pallisa	Agule$^{\phi}$	Bukaade P/S
	Luuka	Bukanga$^{\phi}$	Odusai P/S
High endemicity Treated >5 times (3 sub-counties)	Bugiri	Bulidha$^{\nabla}$	Wakawaka P/S
	Mayuge	Kigandalo$^{\nabla}$	Musubi Church of God P/S
		Wairasa$^{\nabla}$	St. Jude Musoli

$^{\phi}$ These sites received biennial treatment for school-aged children (SAC). $^{\nabla}$ These sites received treatment annually in SAC and high-risk adults.

Community Sensitisation

Two days prior to the survey, teams visited the site and spoke to the village heads and head teachers with the assistance of the DHO. Either the same day, or the next day, a meeting was held for the community, where the survey process and consent forms were explained by the team together with

the village heads. The village heads, head teacher and DHO were vital to help encourage recruitment of participants for the study.

Kato-Katz

For the Kato-Katz method of detection of schistosome and STH eggs, the standard WHO operating procedure was used [169]. All of the equipment was washed and reused including the spatulas and 41.7mg templates, except for the cellophane (placed on top of the slide samples) and the polythene stool bag (a black bin bag cut up into squares, which was used for the stool sample, tied with a piece of grass). A washable metal sieve was used for the stool sample. Slides were prepared and examined within 30-45 mins at peak delivery collection, under 5 mins at quieter times. Figure 2.2 shows the step-by-step process the teams carried out for the survey. All biological materials were then disposed of by being burned at the end of the day.

Parasitological indicators, data collection and entry

Stool samples from between 7,485 to 7,493 individuals were collected across ten sentinel sites, varying in treatment history and underlying endemicity level and collected from approximately the same number of females and males. Egg counts for *S. mansoni* and STH infection were obtained from double Kato-Katz thick smears - with each individual providing two stool samples over two consecutive days and each stool providing two slides which was read by two independent field microscopists [44,45]. The evenings were used to consolidate the double slide readings from each microscopist onto one data sheet and prepare for the next day's sample collection. Individuals were requested to return to the temporary lab set up at the school to be informed of their infection status. If they were infected, the teams informed them of the date of the oncoming MDA and advised them to seek treatment, and the list of infected individuals was also provided to the local health clinic and District Health Officer (DHO). For the untreated sites (where MDA was not to take place), the teams took along a supply of praziquantel (PZQ) to treat infected individuals – though infection was very low in these areas. The data were then double-entered into purpose-built MS Excel databases by two independent data-entry clerks at the Vector Control Division of the MoH in Kampala, overseen by the senior data manager. For the analysis by the candidate, only those individuals that provided all stool samples were included in the study (as otherwise, individuals with only one sample would provide less accurate results due to the diagnostic insensitivity).

4.2.3 Data analysis

For each parasite species, the raw faecal egg counts recorded per slide were converted to eggs per gram of faeces (epg) by multiplying by 24 as per standard protocol [44,170].

Intensity of parasite infection

The mean egg count per person, and per age-group, was calculated using the mean egg count across the four slides obtained for each parasite species. The 95% confidence intervals (95% CIs) were calculated through bootstrap resampling for 10,000 iterations.

Prevalence of parasite infection

The prevalence of each parasite infection for each age category was calculated as a percentage by dividing the total number of infected by the total examined and multiplying by 100. The 95% CIs for the prevalence values were also calculated via 10,000 bootstrap iterations.

The statistical software R version 3.5.0 was used for all analyses [171]. The bootstraps were conducted using the R package 'boot' version 1.3–20 [152–155].

4.3 Results

In each year of the study, there were approximately equal numbers of males to females (with slightly more females than males), in the study (Figure 4.3). The following age groups were sampled (years): 0-3, 4-5, 6-9, 10-12, 13-15, 16-19, 20-29, 30-39, 40-49 and ≥50. Table 4.3. shows the age distribution and the number of samples collected over the study period.

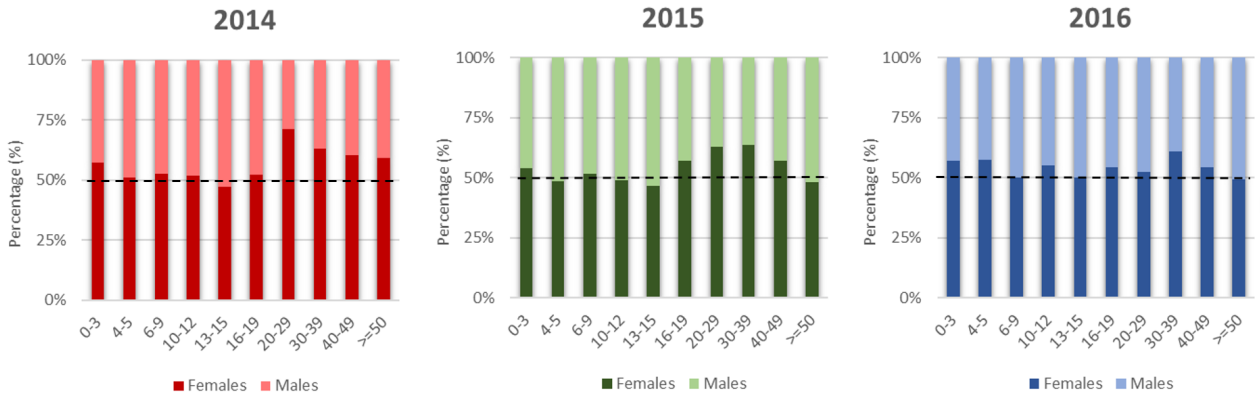

Figure 4.3. Percentage (%) of females and males in each survey year by age group (years).

Table 4.3. Age categories and distribution of individuals examined in each year of the survey (2014-2016, all sites combined). Children aged 6-9 were purposively oversampled as this is the age group targeted for impact surveys.

Age category (years)	Number of individuals in each age group		
	2014	2015	2016
0-3	498	495	494
4-5	506	504	498
6-9	1254	1247	1257
10-12	747	750	750
13-15	746	749	751
16-19	747	749	748
20-29	748	749	750
30-39	745	750	750
40-49	748	750	737
>=50	751	750	750
Total	**7490**	**7493**	**7485**

Between 2014 and 2015, the overall survey level (all study sites combined) prevalence and intensity remained relatively stable, although in 2016 both metrics showed a reduction (significantly for prevalence at 16.9% [95% CI: 16.08-17.78] and non-significantly for intensity at 86.71epg [95% CI: 77.93-95.46], Figure 4.4.).

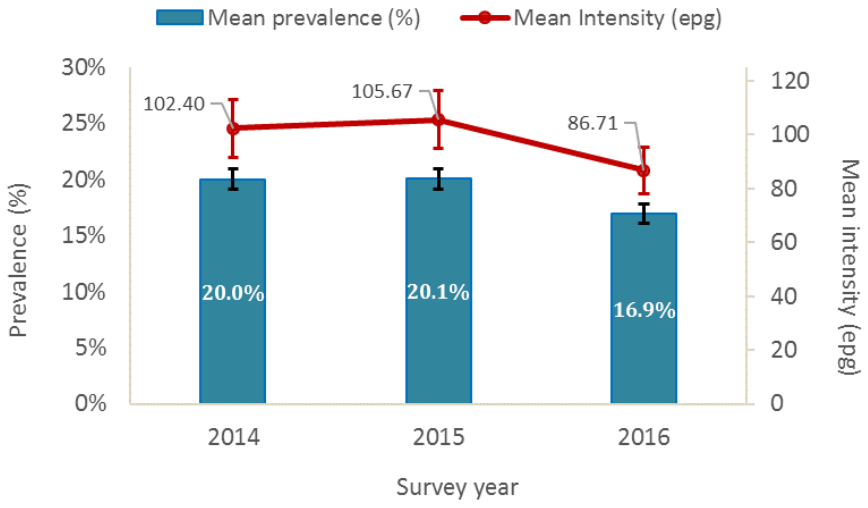

Figure 4.4. Prevalence (blue bars) and mean intensity (measured as eggs per gram of faeces, red solid line) by survey year of all sites combined (error bars represent 95% confidence intervals).

4.3.1 Prevalence of infection

The age-prevalence profiles for *S. mansoni* showed the classic convex patterns as shown by historical studies in literature [47,168] (Chapter 1, section 1.2.1), that is, an increase in prevalence from PSAC to peak in the SAC population, and declining in adulthood.

4.3.1.1 Prevalence vs age by survey year (all sites combined)

The age-prevalence profiles from the 2014 and 2015 surveys were statistically similar, with the exception of the 10-12 year olds where the prevalence was 27.44% [95% CI: 25.60-29.20] in 2014 and 31.47% [95% CI: 29.57-33.38] in 2015 and in the 16-19-year age group where the prevalence was 25.97% [95% CI: 23.69-28.28] in 2014 and in 2015 was 20.96% [95% CI: 18.77-23.14] (Figure 4.5, Table 4.4). In 2016, the prevalence in all age groups showed a reduction (signficantly from 2014 and 2015 in age groups 6-9 and 10-12) except for the ≥50 age group. Prevalence peaked in the 13-15 year age group at 29.09% [95% CI: 26.99-31.17] in 2014, 10-12 year age group in 2015 at 31.47% [95% CI: 29.57-33.38] and, as in 2014, peaked in the 13-15 age group at a prevalence of 25.57% [95% CI: 23.62-27.52] in 2016. Prevalence in the PSAC group peaked at 18.85% [95% CI: 16.02-21.64] in the 4-5-year age group, in 2015.

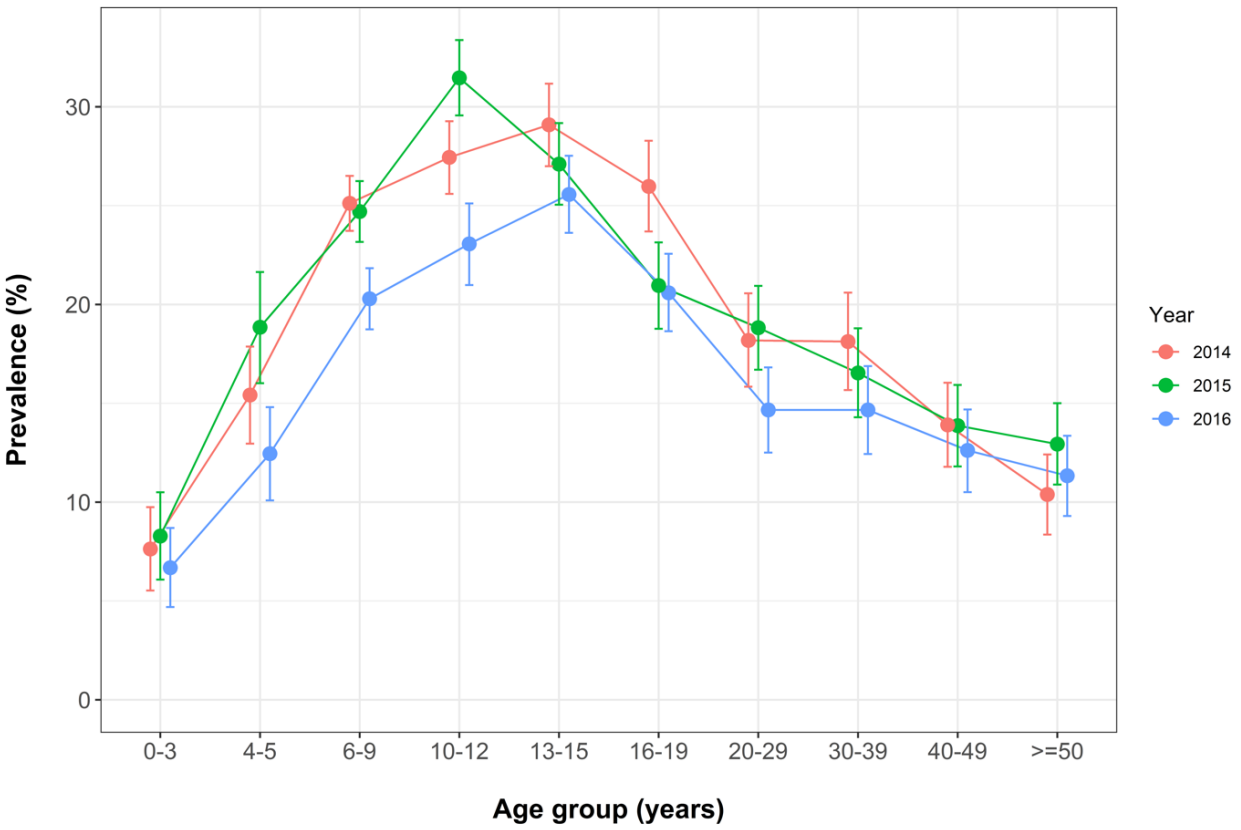

Figure 4.5. Age-prevalence profile by survey year (all ten survey sites and treatment histories combined). Error bars represent 95% confidence intervals.

Table 4.4. Table of prevalence by age category and survey year (all sites and treatment histories combined). Grey highlight represents peak prevalence value and values in the square brackets represent 95% confidence intervals.

Age Category (years)	Prevalence (%)		
	2014	2015	2016
0-3	7.63 [5.53-9.74]	8.28 [6.08-10.50]	6.68 [4.65-8.70]
4-5	15.42 [12.95-17.87]	18.85 [16.02-21.64]	12.45 [10.07-14.84]
6-9	25.13 [23.72-26.51]	24.70 [23.17-26.24]	20.29 [18.76-21.82]
10-12	27.44 [25.60-29.20]	31.47 [29.57-33.38]	23.07 [20.97-25.11]
13-15	29.09 [26.99-31.17]	27.10 [25.05-29.18]	25.57 [23.62-27.52]
16-19	25.97 [23.69-28.28]	20.96 [18.77-23.14]	20.59 [18.60-22.60]
20-29	18.18 [15.84-20.57]	18.83 [16.70-20.94]	14.67 [12.50-16.82]
30-39	18.12 [15.67-20.60]	16.53 [14.29-18.80]	14.67 [12.41-16.91]
40-49	13.90 [11.78-16.04]	13.87 [11.80-15.93]	12.62 [10.52-14.68]
>=50	10.39 [8.36-12.41]	12.93 [10.89-15.01]	11.33 [9.31-13.36]

4.3.1.2 Prevalence by WHO endemic group/treatment history

Here we assess age-prevalence curves with sites categorized by WHO endemic site and treatment history (Table 4.5 and Figure 4.6). In 10-12 year olds, the peak prevalence reached over 80% in 2014 and 2015 in the "high" prevalence group (82.74% [95% CI: 77.91-87.63] and 83.56% [95% CI: 78.76-88.37], respectively, Figure 4.6 top panel). Treatment in previously untreated areas (Figure 4.6, bottom panel) appeared to have a greater impact than continued treatment in low endemic areas (Figure 5.4 middle panel) as shown by the reduction in prevalence by almost 10 percentage points in 2015 and 2016 from 2014 (from a peak of 13.90% [95% CI: 9.99-17.82] in 16-19-year olds in 2014 down to a peak of 3.29% [95% CI: 0.53-6.08] in 4-5-year olds in 2015 and 4.00% [95% CI: 1.49-6.49] in both 30-39- and 40-49-year age groups in 2016). In the low endemic, treated sites, there was a significant increase in prevalence from 2.68% [95% CI: 0.83-4.53] in 2014 to 15.33% [95% CI: 12.27-18.42] in 2015 in the 10-12-year age group, subsequently decreasing significantly to 4.65% [95% CI: 2.36-6.93] in 2016. Prevalence in PSAC peaked in 2015 in the high endemic group, at 25.17% [95% CI: 18.17-32.14] in 0-3-year olds and at 50.33% [95% CI: 42.37-58.24] in 4-5-year olds. In both low endemic categories, the prevalence in both PSAC age-groups was below 10%.

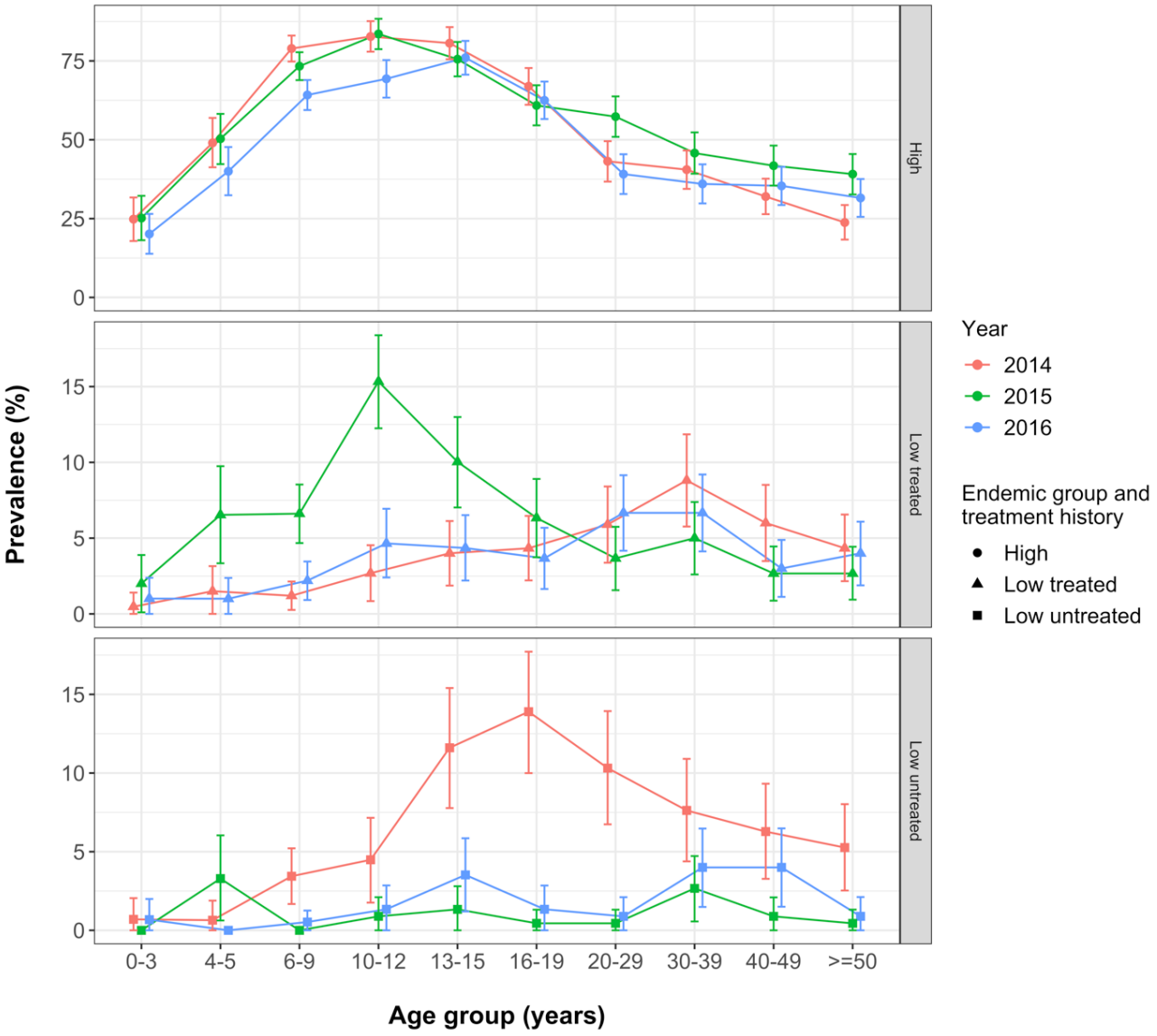

Figure 4.6. Age-prevalence profiles by WHO endemicity level and treatment history of site and by survey year. Note the y-axis scale for the high endemic group where the youngest pre-school aged children in the survey had 20% or higher prevalence of infection (error bars represent 95% confidence intervals). Note different y-axes scales.

Table 4.5. Prevalence in each age category by WHO endemicity level of site and survey year. Grey highlights represent peak prevalence values and values in the square brackets represent 95% confidence intervals.

Age Category (years)	Prevalence (%)								
	High endemic group			Low endemic, treated			Low endemic, untreated		
	2014	2015	2016	2014	2015	2016	2014	2015	2016
0-3	24.83 [17.96-31.65]	25.17 [18.17-32.14]	20.13 [13.83-26.44]	0.48 [0.00-1.40]	2.00 [0.11-3.88]	1.01 [0.00-2.40]	0.70 [0.00-2.04]	0.00 [0.00-0.00]	0.68 [0.00-2.00]
4-5	49.01 [41.20-56.94]	50.33 [42.37-58.24]	40.00 [32.25-47.69]	1.50 [0.00-3.17]	6.53 [3.33-9.76]	1.00 [0.00-2.36]	0.65 [0.00-1.90]	3.29 [0.53-6.08]	0.00 [0.00-0.00]
6-9	78.93 [74.86-83.03]	73.33 [68.93-77.71]	64.19 [59.40-68.96]	1.20 [0.25-2.14]	6.61 [4.64-8.58]	2.20 [0.94-3.44]	3.44 [1.66-5.21]	0.00 [0.00-0.00]	0.53 [0.00-1.25]
10-12	82.74 [77.91-87.63]	83.56 [78.76-88.37]	69.33 [63.34-75.33]	2.68 [0.83-4.53]	15.33 [12.27-18.42]	4.65 [2.36-6.93]	4.48 [1.74-7.16]	0.89 [0.00-2.12]	1.34 [0.00-2.84]
13-15	80.63 [75.46-85.79]	75.56 [70.08-81.09]	76.00 [70.59-81.47]	4.00 [1.92-6.12]	10.03 [7.13-13.02]	4.35 [2.18-6.52]	11.61 [7.74-15.42]	1.33 [0.00-2.82]	3.52 [1.20-5.84]
16-19	66.96 [61.17-72.81]	60.8 [54.47-67.20]	62.50 [56.68-68.27]	4.33 [2.19-6.50]	6.33 [3.70-8.94]	3.67 [1.64-5.69]	13.90 [9.99-17.82]	0.45 [0.00-1.32]	1.34 [0.00-2.82]
20-29	43.18 [36.78-49.53]	57.33 [50.83-63.75]	39.11 [32.84-45.27]	5.90 [3.37-8.41]	3.67 [1.58-5.76]	6.67 [4.16-9.23]	10.31 [6.70-13.99]	0.45 [0.00-1.32]	0.89 [0.00-2.11]
30-39	40.53 [34.47-46.66]	45.78 [39.27-52.32]	36.00 [29.76-42.17]	8.81 [5.76-11.88]	5.00 [2.60-7.40]	6.67 [4.12-9.20]	7.62 [4.31-10.94]	2.67 [0.60-4.75]	4.00 [1.49-6.49]
40-49	32.00 [26.37-37.65]	41.78 [35.45-48.08]	35.38 [29.27-41.39]	6.00 [3.48-8.47]	2.67 [0.88-4.47]	3.00 [1.13-4.86]	6.28 [3.21-9.33]	0.89 [0.00-2.09]	4.00 [1.49-6.50]
>=50	23.77 [18.33-29.20]	39.11 [32.73-45.46]	31.56 [25.46-37.60]	4.33 [2.12-6.55]	2.67 [0.90-4.44]	4.00 [1.89-6.13]	5.26 [2.45-8.01]	0.44 [0.00-1.32]	0.89 [0.00-2.09]

4.3.1.3 Prevalence at site level

Disaggregation into survey site level (i.e. sub-county) highlighted the variation between sites (Figure 5.5) which explains the patterns observed in Figure 5.4. For the low endemic, untreated group, one of the sites, Bukanga, had a peak prevalence of 38.7% in 2014 in 16-19-year olds whereas the remaining two sites peaked at only around 4% (4.1% Agule and 3.9% Ongino), which meant the peak in the last panel of Figure 4.6 was heavily driven by Bukanga. This peak was reduced to <5% in 2015 and 2016, likely through the first round of PC 2014 (post-survey). For the low endemic, treated group, Balawoli drove the peak observed in the middle panel of Figure 4.6, at 56.0% in 10-12-year olds in 2015 (reducing to 13.2% in 2016). The remaining sites remained at low prevalence levels (peaking at 8.0% prevalence for Kasambya in 2014).

For the high endemic group, prevalence was still high (over 80% prevalence in Wairasa in all years) despite multiple rounds of historical and on-going treatment. There was also considerable fluctuation of prevalence in the adult groups (>20 years), particularly at Bulidha, highlighting that year-to-year variation can be substantial in these age groups.

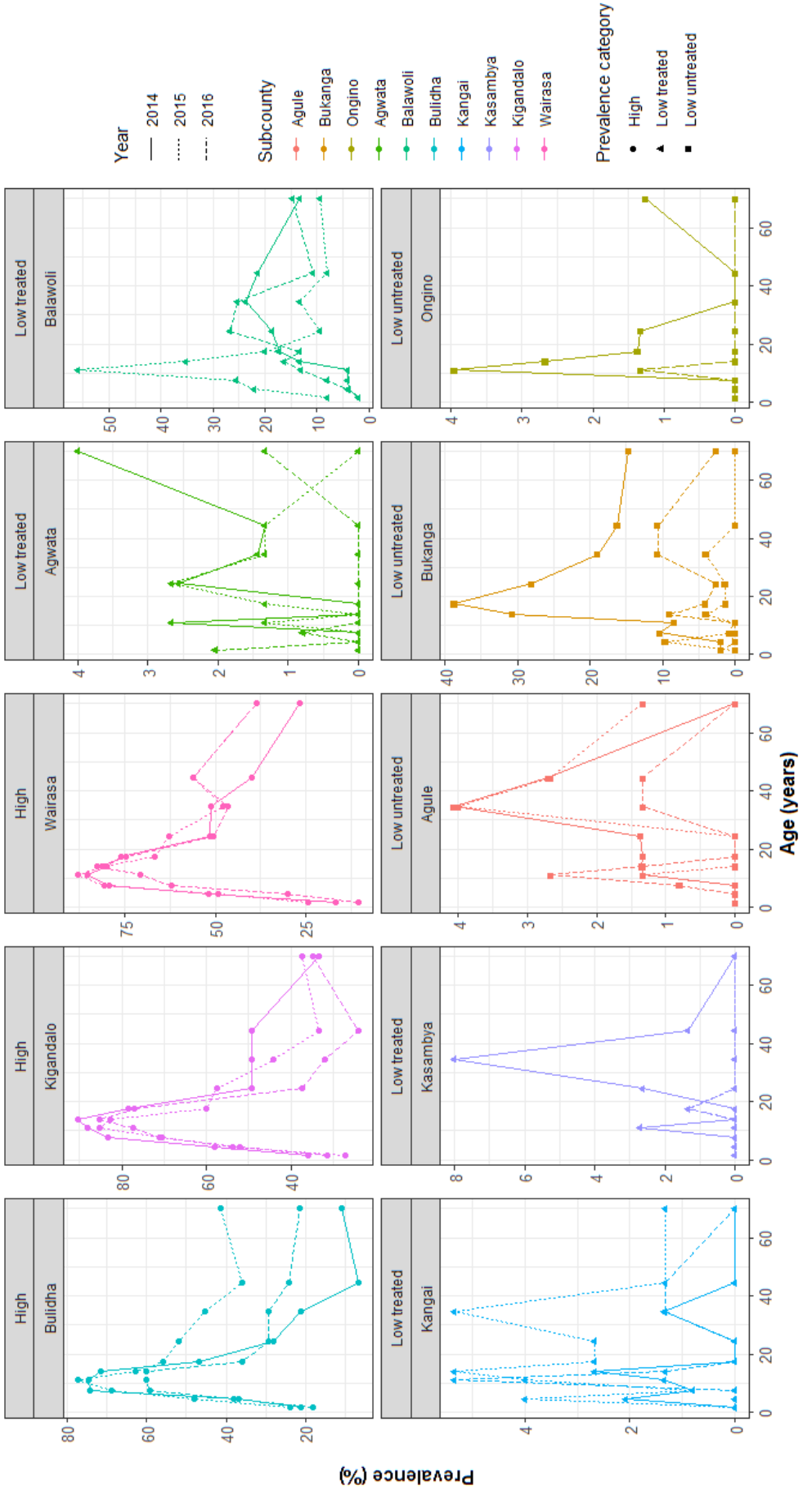

Figure 4.7. Age-prevalence profiles of *S. mansoni* by sub-county (site), survey year, WHO endemicity level and treatment history of site.

4.3.2 Intensity of infection

The age-intensity profile (Figure 4.8) across all sites illustrates the classic convex pattern [47], peaking in similar ages to the age-prevalence profiles, but showing a more chronologically consistent reduction following treatment.

4.3.2.1 Overall intensity vs age by survey year (all ten sites)

Mean infection intensity peaked in the 10-12-year age group in 2014 and in the 13-15-year age group in 2015 and 2016 (218.51 epg [95% CI: 168.73-268.77] and 170.50 epg [95% CI: 135.15-205.87], respectively). The mean egg count was 250.80 epg [95% CI: 203.10-298.15] in 2014 which reduced to 208.25 epg [95% CI: 167.55-249.40] in 2015 and further down to 134.42 epg [95% CI: 102.99-165.96] in 2016 (Figure 4.8 and Table 4.6). Infection intensity fell within the target treatment SAC group (6-15 years) each year. In the 20-29 age group and older, infection intensity remained below 100 epg (i.e. light-intensity infection). The mean epg in both PSAC age-groups was below 100 epg.

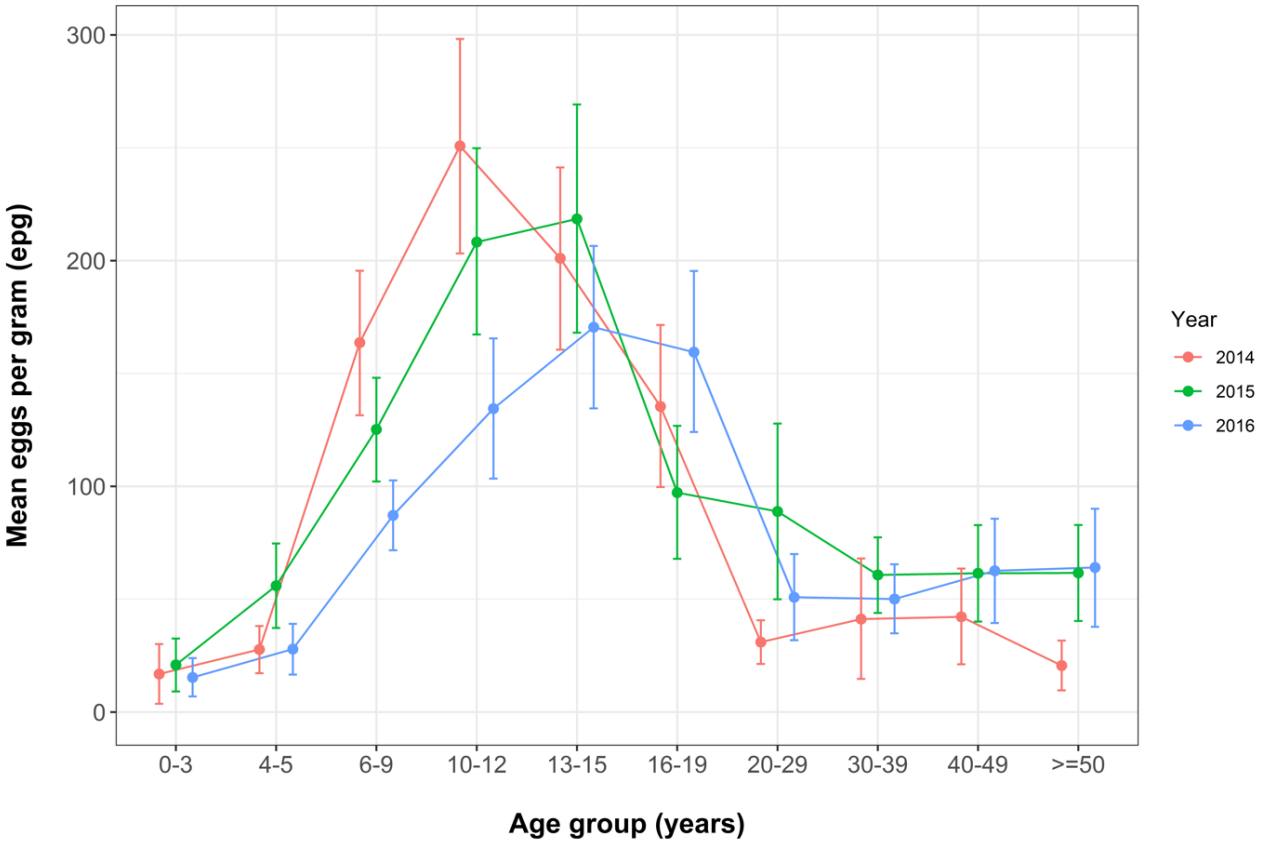

Figure 4.8. Mean age-intensity profile of *S. mansoni* across all ten survey sites in Uganda between years 2015-2016 (error bars represent 95% confidence intervals).

Table 4.6. Table of mean intensity of infection by age category and survey year. Grey highlight represents peak mean intensity value and values in the square brackets represent 95% confidence intervals.

	Mean intensity (epg)		
Age Category (years)	**2014**	**2015**	**2016**
0-3	16.86 [3.52-30.08]	20.90 [9.34-32.37]	15.30 [6.76-23.89]
4-5	27.71 [17.20-38.10]	55.97 [36.89-74.90]	27.92 [16.77-39.19]
6-9	163.64 [131.89-195.81	125.23 [102.15-147.96]	87.11 [71.57-102.67]
10-12	250.80 [203.10-298.15]	208.25 [167.55-249.40]	134.42 [102.99-165.96]
13-15	201.03 [160.48-241.97]	218.51 [168.73-268.77]	170.50 [135.15-205.87]
16-19	135.38 [100.14-171.51]	97.22 [67.47-127.24]	159.48 [124.23-194.90]
20-29	30.99 [21.15-40.80]	88.84 [50.01-128.67]	50.88 [31.81-69.79]
30-39	41.20 [13.98-67.81]	60.72 [44.12-77.41]	50.09 [34.64-65.52]
40-49	42.20 [20.73-63.42]	61.50 [40.27-82.90]	62.60 [39.60-85.81]
>=50	20.60 [9.81-31.56]	61.64 [39.99-83.17]	64.08 [38.01-90.37]

4.3.2.2 Intensity by WHO endemic group/treatment history

When disaggregating by WHO endemicity level and treatment history site, it can be observed that the infection intensity patterns in the high-endemic sites follow the convex shape more closely than those in the low-endemic-treated site (Figure 4.9). This is likely due to stochastic effects and the overdispersed distribution, whereby infection is skewed by a few individuals. The mean number of epg in high-endemic sites peaked at 823.14 epg [95% CI: 667.84-979.79] in 2014 in the 10-12-year age group and was ≥ 400 epg between the age groups of 6-9 to 16-19 years inclusive, indicative of heavy intensity infection. The peak intensity in 2015 in the low-endemic treated group closely resembles the prevalence trends in the same year in all age-groups (Figure 4.6), peaking in the 10-12 year age group at 67.16 epg [95% CI: 26.27-108.14], whereas in the low endemic untreated group, a less consistent profile of intensity is evident in 2014 (and peaked in 16-19-year olds in this year at 22.01 epg [95% CI: 2.13-42.05]). However, for both low-endemic groups (treated and untreated), the mean intensity of infection was maintained below 100 epg, indicating an average low-intensity infection. For the PSAC, in the high endemic group the mean intensity of infection peaked in 4-5-year olds, at 153 epg [95% CI: 100.77-205.66] and remained below 100 epg in all other years and endemic groups, in both PSAC age categories.

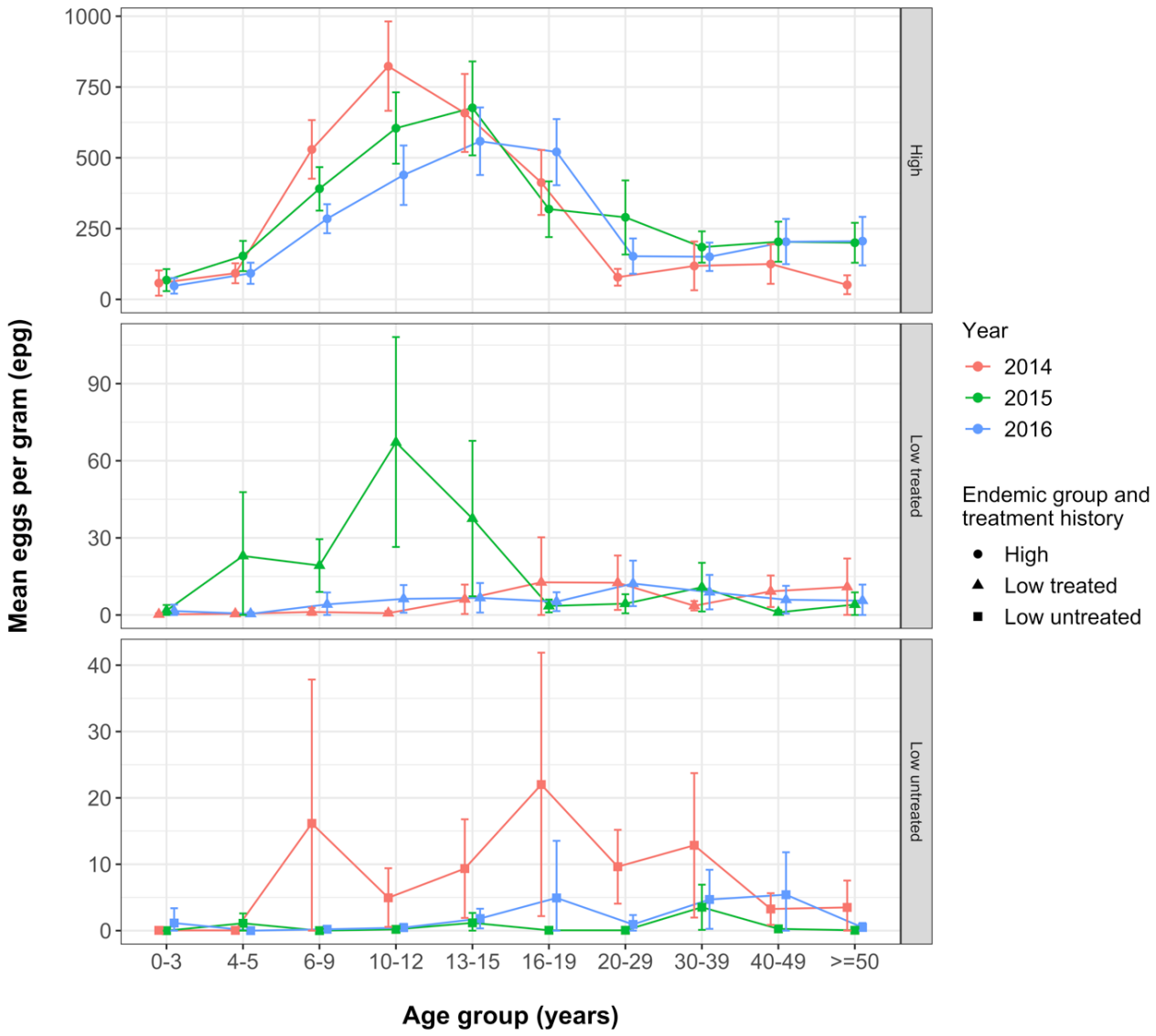

Figure 4.9. Mean Age-intensity profiles of *S. mansoni* by WHO endemicity level and treatment history of site and by survey year (error bars represent 95% confidence intervals).

Table 4.7. Mean intensity of infection in each age category by WHO endemicity level and treatment history of site and survey year. Grey highlights represent peak mean intensity values and values in the square brackets represent 95% confidence intervals.

	Mean intensity (epg)								
Age Category (years)	High prevalence group			Low prevalence treated			Low prevalence untreated		
	2014	2015	2016	2014	2015	2016	2014	2015	2016
0-3	57.52 [13.41-102.77]	68.04 [29.38-106.58]	47.56 [19.31-75.69]	0.23 [0.00-0.67]	1.71 [0.00-3.86]	1.55 [0.00-4.04]	0.04 [0.00-0.12]	0.00 [0.00-0.00]	1.14 [0.00-3.36]
4-5	92.23 [57.37-126.92]	153.39 [100.77-205.66]	92.08 [54.76-129.14]	0.45 0.00-0.98]	22.97 [0.00-47.83]	0.45 [0.00-1.14]	0.04 [0.00-0.11]	1.11 [0.00-2.59]	0.00 [0.00-0.00]
6-9	529.34 [424.71-634.04]	390.82 [314.91-467.30]	284.75 [233.70-336.64]	1.19 [0.00-2.75]	19.25 [9.07-29.25]	4.13 [0.00-8.71]	16.16 [0.00-38.23]	0.00 [0.00-0.00]	0.21 [0.00-0.53]
10-12	823.14 [667.84-979.79]	604.44 [479.99-727.83]	439.23 [333.96-544.59]	0.72 [0.00-1.51]	67.16 [26.27-108.14]	6.28 [0.97-11.65]	4.95 [0.47-9.47]	0.19 [0.00-0.50]	0.46 [0.00-1.03]
13-15	657.81 [522.36-795.27]	676.37 [514.27-839.68]	558.40 [438.44-678.94]	6.14 [0.44-11.91]	37.51 [6.91-67.68]	6.66 [0.76-12.53]	9.35 [1.69-16.86]	1.17 [0.00-2.68]	1.82 [0.37-3.28]
16-19	412.51 [296.79-528.98]	318.91 [218.92-417.83]	520.71 [403.76-638.94]	12.72 [0.00-30.31]	3.50 [0.99-6.01]	5.16 [1.54-8.81]	22.01 [2.13-42.05]	0.05 [0.00-0.16]	4.93 [0.00-13.59]
20-29	78.19 [48.40-107.88]	289.81 [160.76-420.37]	152.35 [89.88-214.83]	12.55 [2.01-23.02]	4.40 [0.68-8.09]	12.24 [3.52-20.97]	9.63 [4.03-15.20]	0.05 [0.00-0.16]	0.93 [0.00-2.35]
30-39	117.94 [31.22-205.08]	184.48 [130.38-239.16]	150.40 [100.83-200.64]	3.58 [1.71-5.40]	10.80 [1.31-20.28]	8.90 [2.09-15.56]	12.86 [1.78-23.79]	3.53 [0.16-6.98]	4.69 [0.25-9.14]
40-49	124.80 [54.44-195.11]	203.38 [133.35-273.24]	203.46 [122.28-284.14]	9.20 [3.15-15.32]	1.02 [0.16-1.87]	5.94 [0.57-11.32]	3.26 [0.91-5.65]	0.27 [0.00-0.66]	5.41 [0.00-11.81]
>=50	51.09 [17.80-84.84]	200.01 [128.13-271.27]	205.68 [120.41-292.28]	10.92 [0.00-21.99]	4.06 [0.00-8.75]	5.58 [0.00-11.85]	3.50 [0.00-7.59]	0.05 [0.00-0.16]	0.48 [0.00-1.15]

4.3.2.3 Intensity of infection at site level

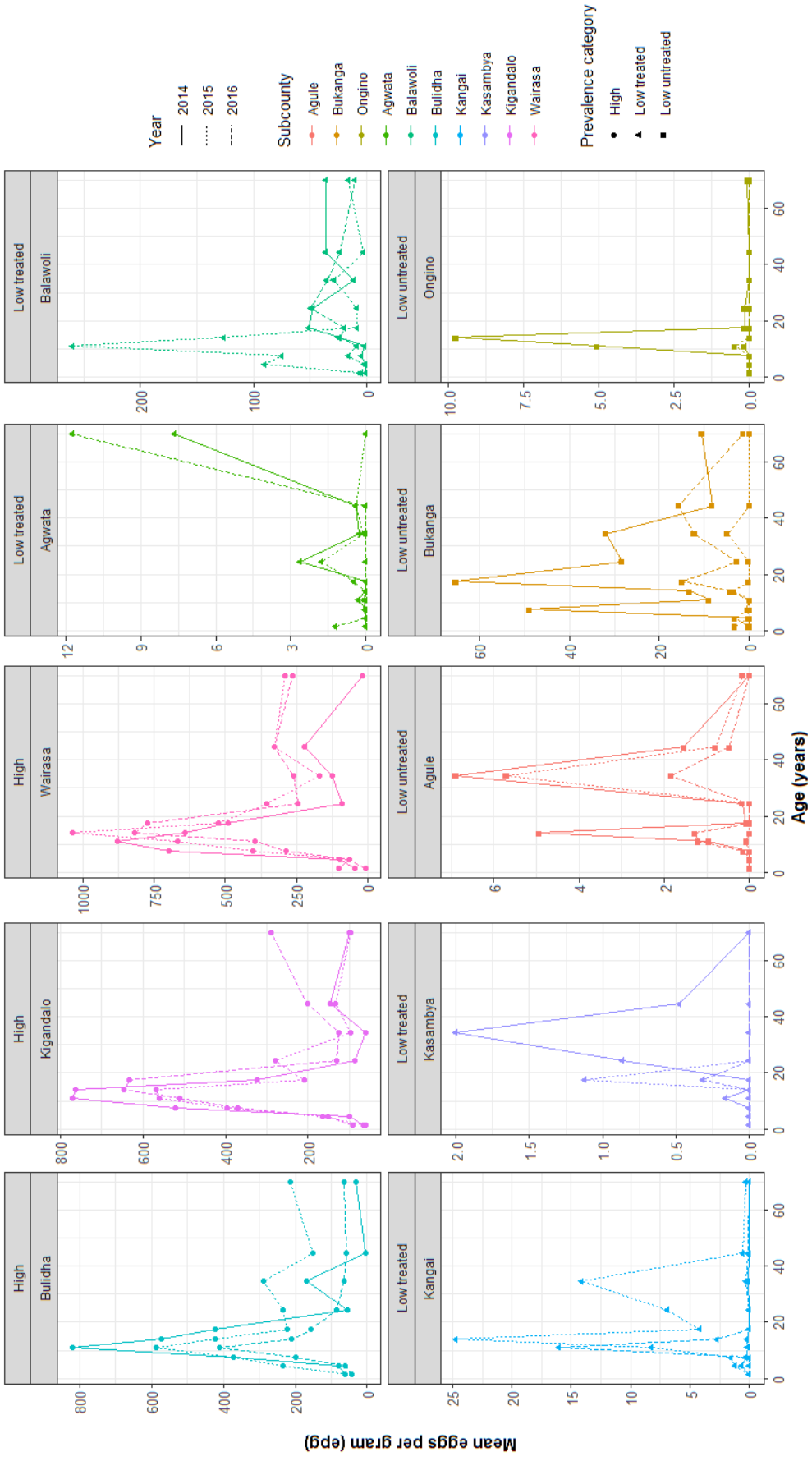

Figure 4.10. Age-intensity profiles by sub-county (site), survey year and WHO endemicity level and treatment history of site.

At the sub-county level, Bukanga (a low endemic, untreated site) showed a peak prevalence of almost 40% (Figure 4.10) in the 16-19-year age group in 2014, but which corresponded to a peak mean intensity of 65.2 epg, indicating that while prevalence was high, infections were mainly of light intensity. Conversely, Balawoli, a low endemic treated site, showed a peak prevalence of 56.0% in 10-12-year olds in 2015 and peak intensity in the same year and age group of 260.3 epg. The infection intensity levels in this age group in 2014 and 2016 showed low infection intensities (<10 epg) at this site. For the high endemic treated sites, all demonstrated heavy-intensity infection peaks (>=400 epg) in age groups 10-14, 13-15 and 16-19 years. Infection intensity in adult age groups all remained lower than 400 epg (i.e. not heavy-intensity infections).

4.3.3 Prevalence of heavy-intensity infection and the WHO goals of morbidity control

The WHO considers that "control of morbidity" has been attained if heavy-intensity infections fall below 5%, averaged across all sentinel sites in the country. According to this criterion, the study sites putatively attained control of morbidity in 2014 (mean prevalence of heavy-intensity infection 4.1%) and 2016 (4.5%), with 2015 marginally missing the target (5.0%) when all sites were combined (data not shown). However, when disaggregating by WHO endemic category, the hypothetical control target was not achieved in the high endemic group sites (Figure 4.11, black dotted line marking the 5% threshold), which had above 13% (13.22% [95% CI: 11.83-14.61]) prevalence of heavy-intensity infection in all years. When analysing by age group (all sites combined), the prevalence of heavy-intensity infection peaked in 2014 in age groups 10-12 years at 11.78% [95% CI: 9.87-13.68] (Figure 4.12), in 2015, in the same age group at 10.13% [95% CI: 8.22-12.04], and in 2016 in the 13-15-year age group at 8.92% [95%CI: 7.20-10.67]. The prevalence of heavy-intensity infection in both PSAC age groups remained below 5% in all survey years. Moderate-intensity and heavy-intensity infections were combined here to provide a more conservative metric of morbidity (rather than heavy intensity infections alone). Not surprisingly, the same age groups demonstrated the peak prevalence of moderate- plus heavy-intensity infection as with heavy-infection intensity only, and this metric was above 15% peak prevalence in all survey years in these age groups (Figure 4.12, purple line).

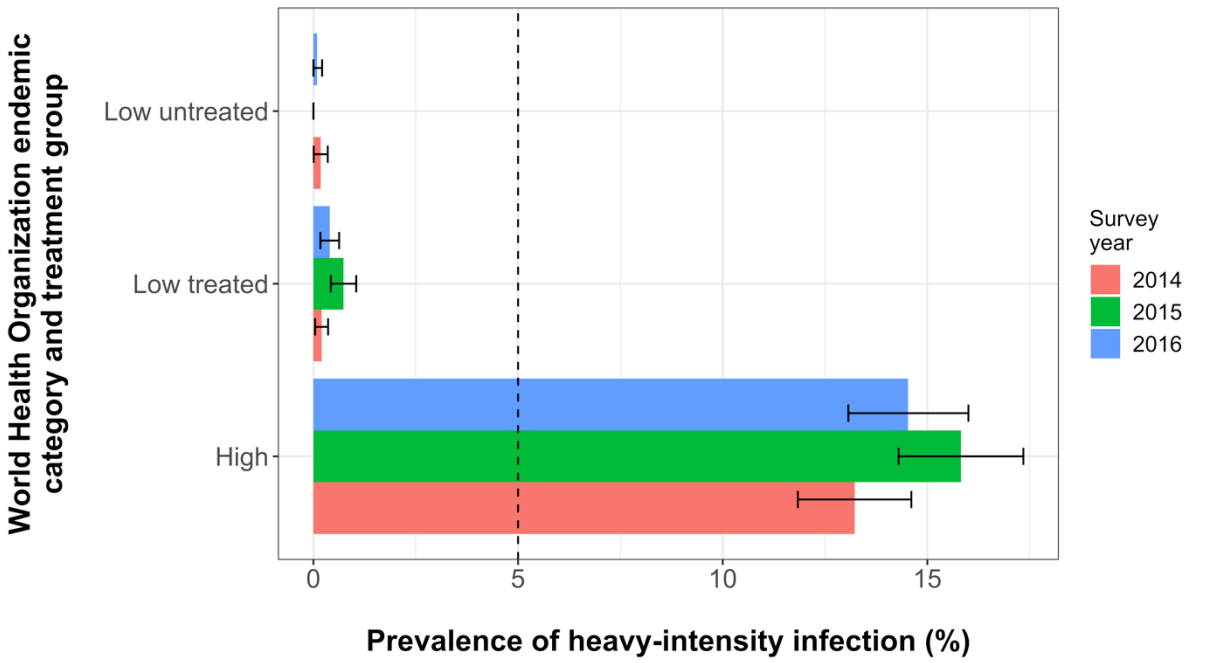

Figure 4.11. Prevalence of heavy-intensity infection by WHO endemic group and survey year (error bars represent 95% confidence intervals).

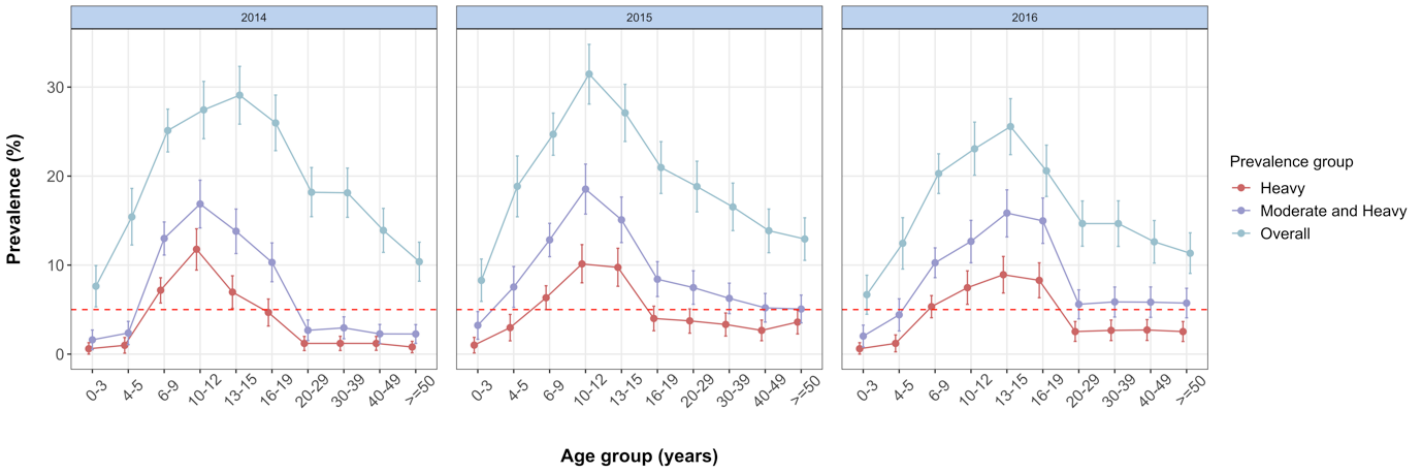

Figure 4.12. Prevalence by infection intensity group (overall prevalence, prevalence of heavy-intensity infection and prevalence of moderate-plus heavy-intensity infection) by age category and survey year (error bars represent 95% confidence intervals).

The control of morbidity target is based on country-level estimates. However, the results in this survey showed a high level of variability between sites. Therefore, further analyses were conducted to investigate the prevalence of heavy-intensity infection at different scales by age-group. At the endemic group level, it was shown, as expected, that the high endemic group had the highest level of

heavy-intensity infection and drove the observed shape in Figure 4.12 (Figure 4.13), peaking in the SAC group. The low endemic groups both had heavy-infection intensities below 5%, consistent with Figure 4.11. At the individual site level, interesting trends were observed. Firstly, one low endemic treated site, Balawoli, had two age groups (4-5 and 10-12-year olds) that exceeded 5% in heavy-intensity infections, both in 2015 (Figure 4.14). Secondly, the high endemic sites showed different trends: Bulidha demonstrated the expected reduction in prevalence of heavy-intensity infection between study years in the SAC population but showed an increase in 2015 in ages above 20 years. Lastly, both Kigandalo and Wairasa showed a peak prevalence that shifted upwards in age category by year, with Kigandalo also increasing in peak prevalence value each year by 2016.

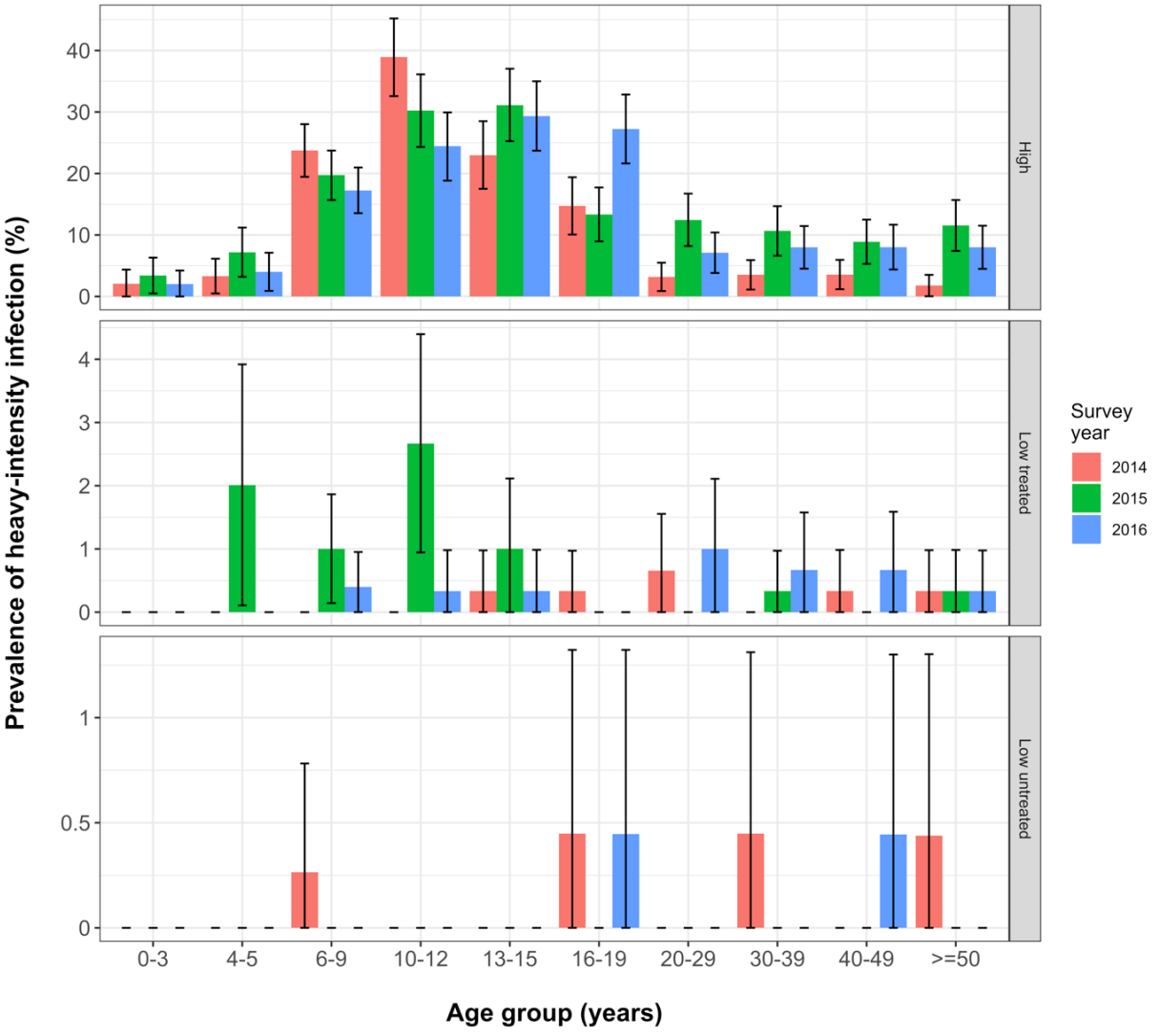

Figure 4.13. Prevalence of heavy-intensity infection vs age category by survey year, WHO endemicity level and treatment history of site. Note the different scales of the y-axis (error bars represent 95% confidence intervals).

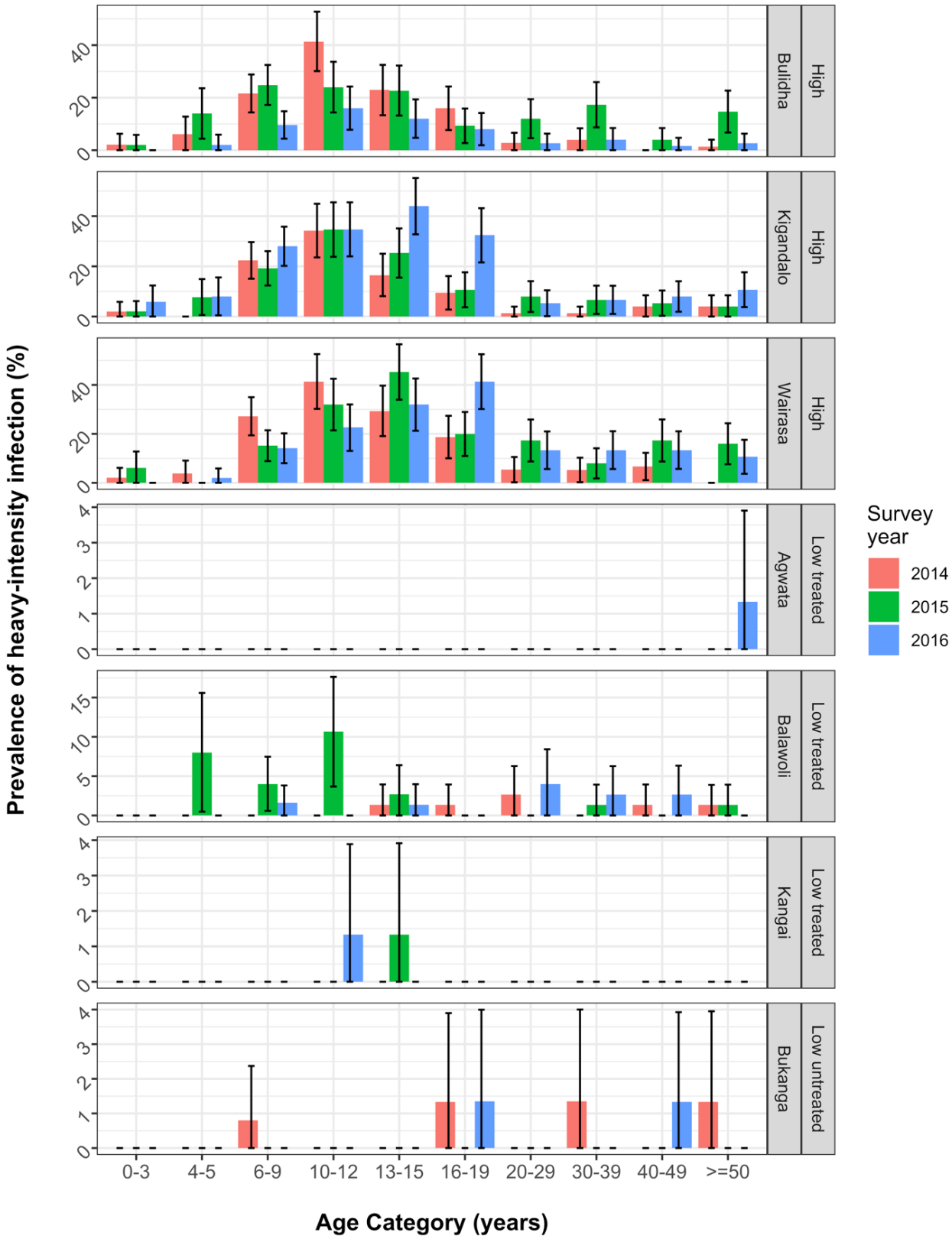

Figure 4.14. Prevalence of heavy-intensity infection vs age category, by sub-county (site, with the exception of Agule, Ongino and Kasambya as they did not have heavy intensity infections), survey year and WHO endemicity level and treatment history of site (error bars represent 95% confidence intervals).

4.3.4 Distribution of infection in each age group

Mean intensities are often used to provide an overall metric of infection within a community or group. However, infection typically follows an overdispersed distribution approximated by the negative binomial distribution (NBD) or a zero-inflated negative binomial distribution (ZINBD). Due to this overdispersion, mean egg counts alone can be misleading. The high variance in this dataset has been captured in Figures 4.15-4.16. The high endemic group was used to illustrate this, in which distribution of infection is heavily skewed with most individuals having zero or low egg counts and a few harbouring high infections (Figure 4.15).

Outliers can have a disproportionate impact on the mean epg, which is particularly a problem in light-intensity infection areas where a few heavily infected individuals could impact the mean intensity levels. This has been illustrated in Figure 4.16 which shows infected individuals only. The prevalence of heavy-intensity infections may therefore be a more accurate metric for measuring infection and possible related morbidity, though this is heavily reliant on the egg-count thresholds being a good representation of morbidity.

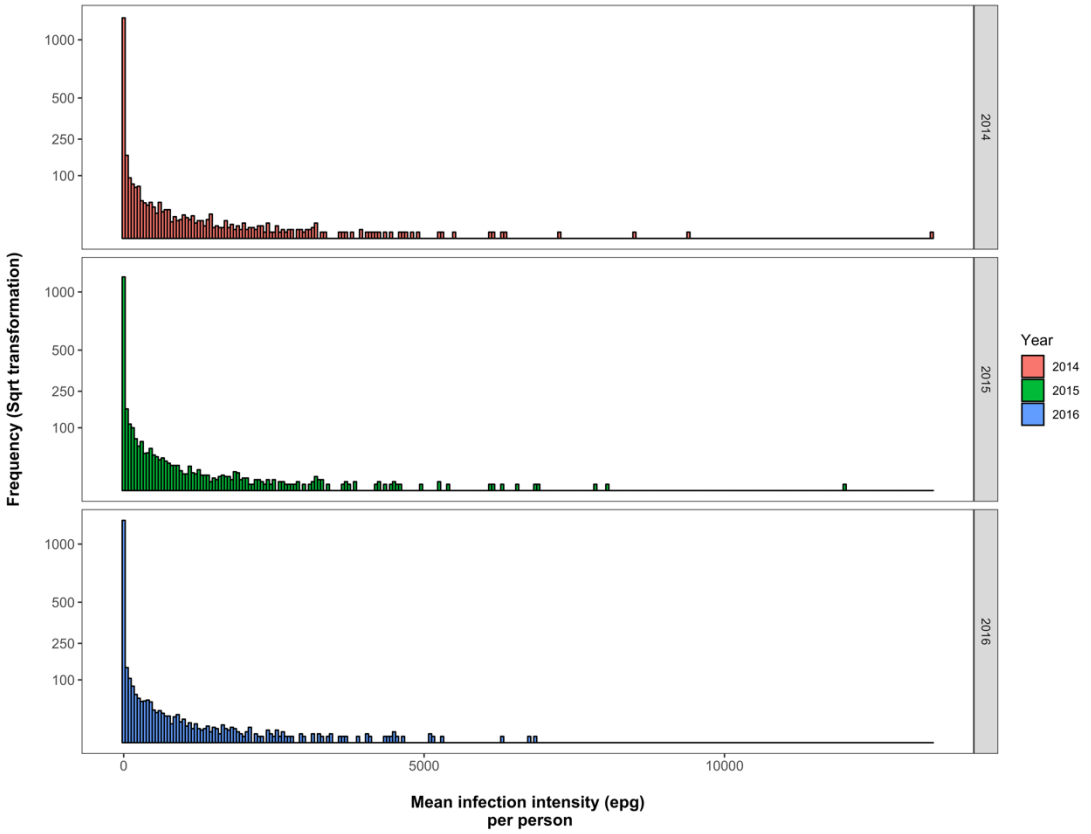

Figure 4.15. Distribution of infection amongst individuals in the survey population (histogram of mean egg counts per person), by survey year in the high endemic treated group.

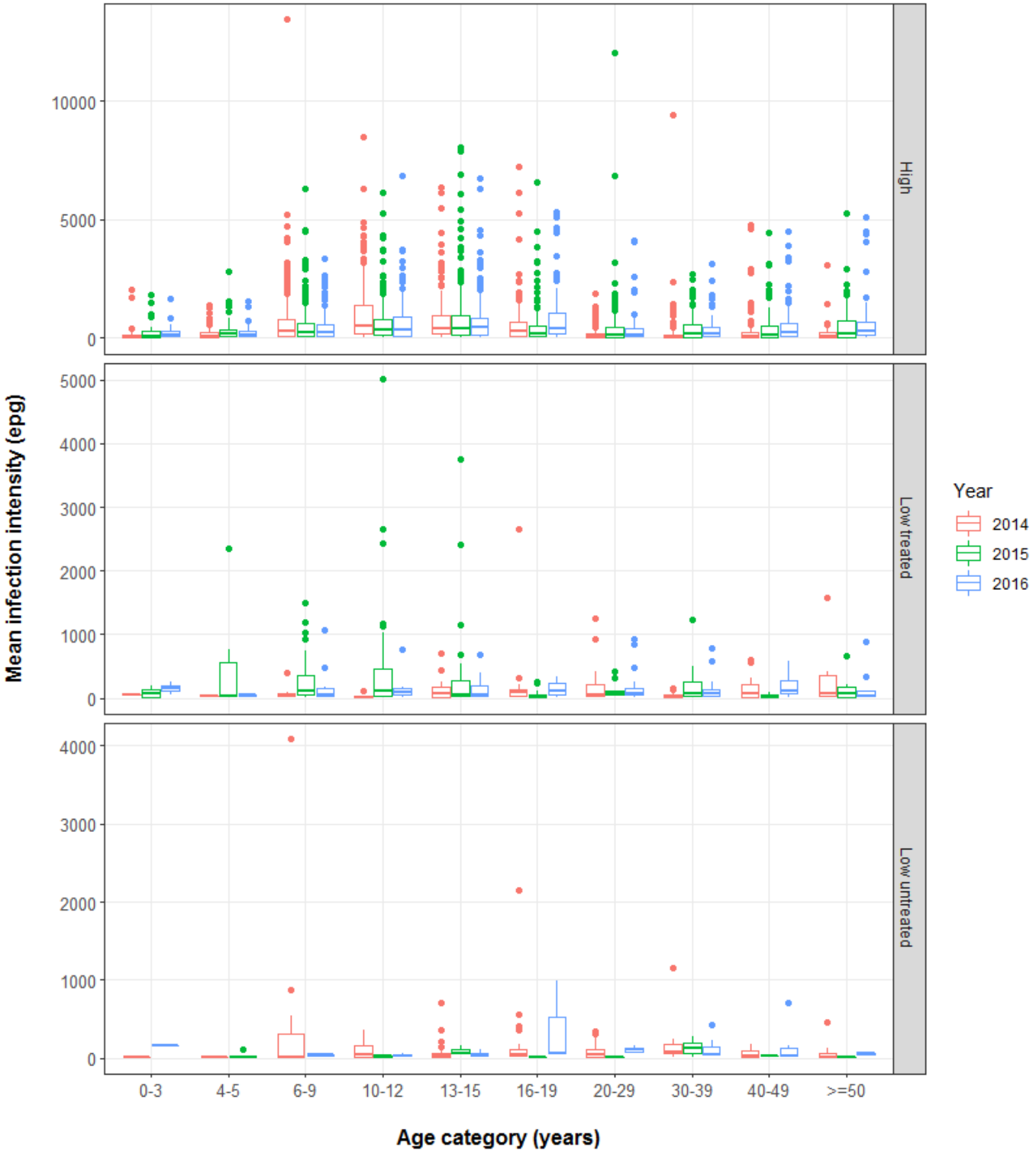

Figure 4.16. Boxplot (with interquartile ranges) of mean infection intensity (EPG) in infected individuals (dots) vs age group, by WHO endemicity level and treatment history of site and survey year.

4.4 Discussion

As 2020 and 2025 fast approach for the WHO control and elimination as a public health problem (EPHP) targets, it is important to understand the finer scale infection patterns that are likely to be missed when analysing aggregated datasets at higher administrative levels (such as national level), especially since programmatic data generally do not contain PSAC and adult data. Generally, SAC have been the focus of studies and control programmes, due to the typical age-related infection patterns highlighting that this population group experiences the highest burden of schistosomiasis (and that it is logistically easier to deliver treatment to schools). However, if EPHP is to be reached and demonstrated, then it is vital that the patterns of infection in PSAC and adult age groups are also understood. This study aimed to increase our understanding of the prevalence and intensity patterns amongst different age groups from areas of varying endemicities and schistosomiasis treatment histories, in response to the long-running programme in Uganda. To our knowledge, this is the largest data collection study to date involving all age groups, using thorough field methods with experienced teams, assessing programmatic impact.

The age-related infection and prevalence patterns revealed key information when analysed at different levels of aggregation. For instance, the overall prevalence and intensity (across all sites) were very similar between 2014 and 2015 (Figures 4.4 and 4.5). But sub-analysis at age-group, WHO endemicity level and treatment history, site and individual level revealed underlying heterogeneities that would not otherwise have been evident. Treatment in previously untreated areas was shown to be highly effective during the survey years in reducing prevalence compared to the other two treated groups (Figure 4.6), highlighting the importance of understanding treatment history when predicting impact of treatment. In the high endemic sites, there was high year-to-year variation in prevalence in adults (Figure 4.7). This could be due to lower treatment coverage in adults and/or a different population of adults in the samples each year, which may explain why these adult age groups also experience an increase in heavy-intensity infections from 2014 (Figures 4.13 and 4.14). Pre-school aged children are not currently included in routine PC; results showed that in the high endemic group, prevalence ranged from 20.13% [95% CI: 13.83-26.44] (in 2016) to 25.17% [95% CI: 18.17-32.14] (in 2015) in the 0-3-year olds and 40.00% [95% CI: 32.25-47.69] (in 2016) to 50.33% [95% CI: 42.37-58.24] (2015) in 4-5-year olds (Figure 4.6 and Table 4.5). Corresponding infection intensities were in the low prevalence category (i.e. <100 epg), with the exception of the 4-5-year olds in 2015 in the high endemic group which was 'moderate intensity' at 153.39 epg [95% CI: 100.77-205.66]. However, when assessing the proportion of individuals infected with heavy-intensity infections in these age-groups (Figure 4.13), particularly by individual survey site (Figure 4.14), Kigandalo in the high endemic

group showed an increasing prevalence of heavy-intensity infections, and, in the low endemic treated site of Balawoli, the 4-5-year PSAC age group showed prevalence of heavy-intensity infection of over 5% in 2016 (with no heavy-intensity infection in 2014 or 2015 in PSACs). These results highlight the urgent need to treat PSAC as part of the routine programmes to avert morbidity from these infections in these age-groups and to reduce overall transmission in the community, particularly since there are likely to be heavily infected PSAC in high endemic areas (see top panel of Figure 4.16). Though safe, programmes have been reluctant to provide the standard PZQ tablets to PSACs, which have a bitter taste and pose a choking hazard [172,173]. With the more appealing paediatric formulation of PZQ on the horizon [174], it is hoped that routine PC in this vulnerable population will be soon implemented along with the SAC group, particularly since previous studies have already highlighted the importance of treating this age-group [175,176].

In summary, the age-prevalence and age-intensity plots demonstrated the classic convex patterns, peaking in 10-12 and 13-15-year olds (i.e. SAC, who are routinely targeted in control programmes for treatment)[47,177]. This pattern was less pronounced in low endemic areas except for the low endemic untreated group in 2014, which peaked in the 16-19 age group for both prevalence and mean infection intensity. These sites had not previously received treatment, so pre-treatment equilibrium exhibited the expected age-infection curves. However, the intensity of infections was low in all age-groups, so the age-intensity curves were less pronounced for the same year and endemic group. In 2015, the low endemic treated group showed a sharp increase in the 6-15-year olds (i.e. SAC), peaking in the 10-12-year age group for both prevalence and mean intensities of infection. At the level of the individual survey site, the low endemic site Balawoli was where the sharp increase between years was taking place. This is a significant finding as it shows that this site, which is defined as a 'low endemic site' (and receives treatment accordingly, see Chapter 1, Figure 1.7 and Table 4.2 for treatment strategy) experienced a peak mean intensity of 260.5 epg (in the 10-12 year age group), i.e. a mean *moderate* intensity in this age group, and a peak mean prevalence of 56%, i.e. *high* prevalence in this age group. This highlights the need for precision mapping that would reveal these details and for subcounty/community specific treatment strategies. The trend in Balawoli is further highlighted in Figure 4.14 which shows that in 2015 two age groups, 4-5 and 10-12-year olds, had a prevalence of above 5% heavy-intensity infections (over 7% and 10%, respectively). Further investigation would be required to determine the cause, where possible reasons include (but are not exclusive to):

- An influx of new students joining the school from infected regions (as this was a repeated cross-sectional study);

- children who were from the site but who had not taken part in the survey during 2014 and 2016;
- seasonal fluctuations in transmission patterns (e.g. via higher rainfall) and/or snail populations
- community factors such as market days (sellers and their children coming into the area and taking part in the survey);
- infrastructure factors, such as water pumps which were found to be broken during some years and not others (causing people to use the lake water more than usual).

The findings in section 4.3.3 illustrate why using an aggregated country-level metric is not appropriate to determine whether control of morbidity has been reached. Using these survey sites as an example, the prevalence of heavy-intensity infection was 5% or less each year. Yet at the WHO endemicity group level, the high endemic group had heavy-intensity infections of over 13% in all survey years (Figure 4.11). At the age-group level, it was shown that the SAC group were the most heavily infected with a prevalence of heavy-intensity infection >5% (Figure 4.12). By age and WHO endemic group, it was shown that those age groups with heavy-intensity infection >5% were all in the high endemic group, yet at the survey site level, it was shown that Balawoli (a low endemic, treated site) also had age groups with heavy-intensity infection >5% as already mentioned. New WHO guidelines are currently under development, so these findings come at a key time and need to be taken into consideration if we are to accurately understand our progress in controlling morbidity, especially when there is such a large variation in infection intensity between individuals (Figures 4.15 and 4.16). The results show that the low endemic sites need to be reassessed since previously untreated areas may now require (more) treatment and that treatment in high endemic sites is not sufficient to eliminate transmission. Overall, treatment was effective in reducing intensity of infection (as shown by the overall reduction in intensity in SAC in Figure 4.8). In the low endemic untreated sites, treatment had a positive impact, which may be due to the low underlying transmission or lack of treatment fatigue in the community. The results also highlight that MDA alone will unlikely be enough to control or eliminate morbidity in some of these foci areas and will require complementary interventions such as Water, Sanitation and Hygiene (WASH) control, snail control and behaviour change through health education in addition to treatment of adults and PSAC. Programmes also need to consider migratory habits of populations in order to tailor control strategies. Persistently high year-to-year infection prevalence and intensity in the high endemic group, despite over a decade of treatment could be due to a number of factors, including high levels of transmission, poor coverage levels, community resistance to treatment, transitory populations (where the same population may not be receiving treatment each year), or reduced susceptibility of the parasite. Results were presented to Ministry of Health (MoH) staff at the time of findings to address these concerns and the

MoH is now in the process of carrying out an alternative 'zonal reassessment'. The method involves creating 5km treatment zones from the water bodies rather than by district to try and capture pockets of higher infection within low prevalence districts.

Coverage in control programmes can range vastly and have likely never reached 100% of the target population due to the inherent challenges faced by programmes (such as non-attending school children, systematic non-compliance to treatment, hard-to-reach areas, ineffective sensitisation, or low community awareness of the programme, etc.). In Uganda for instance, the validated treatment coverage (from a coverage survey conducted by the SCI) in 2014 ranged from 7.7% - 86.4% at the district level (reported coverage in the country MDA report ranged from 31%-98% at the district level), which may explain some of the high prevalence estimates observed in this study. With high coverage, MDA may be sufficient to control morbidity in SAC, or even eliminate schistosomiasis as a public health problem provided that adults are also treated. But attaining high treatment coverage (WHO recommends a target of at least 75% coverage in SAC) is challenging. In addition, the WHO recommends implementing complementary interventions in addition to the MDA, in order to interrupt transmission and eventually eliminate transmission of schistosomiasis.

Section 4.3.4 (distribution of infection amongst hosts) could be expanded further by fitting different distributions using regression models (i.e. the negative binomial distribution and compare with zero-inflated negative binomial model), and also comparing the aggregation parameter k (the 'shape' parameter of the negative binomial distribution) with age group and year as suggested by Basáñez et al. [165]. Parasite aggregation can be the result of multiple factors, such as individual-specific infection rates and susceptibility – individual-level characteristics that are not homogenous in the population. The type and extent of aggregation is important to understand as it also highlights the possible level of morbidity in a host population (or 'host fitness'), the extent of heterogeneity in the population and highlights individuals who are likely to be 'super-spreaders'. Investigating the change in distribution following treatment (particularly if using longitudinal data and comparing in low-prevalence untreated 2014 as a baseline with 2015 and 2016 from the same sites) would further show the impact of PZQ on infection amongst individuals.

Limitations

The limitations of this study include some of the following factors. The generalisability of the results of this study is limited to these study regions of Uganda due to the high spatial heterogeneity in infection, and the different infection profiles present around Lake Albert compared to Lake Victoria which were not taken into account. Additionally, the survey was not powered to make inferences at

any administrative level (such as district or sub-county). The WHO endemic groups may also differ widely in finer characteristics between countries due to the profile of their transmission environment (e.g. underlying transmission dynamics, population structure, geographical characteristics, behavioural characteristics), so results may not be applicable to other countries. In addition, as this study was carried out in collaboration with the control programme and MoH staff, PSAC and adults who were found to be infected in the study were informed of their status, as well as the District Health Officer (DHO) and asked to seek treatment at the next MDA (the study was scheduled approximately one month prior to the MDA for this reason), and under medical supervision for PSAC at the local health centre, where a supply of PZQ was available. The survey did not record or follow up with the DHO whether any individuals had sought treatment and, as it was a cross-sectional survey, the impact of treatment on these individuals could not be assessed. The advantages of using a cross-sectional format, however, are that it is not impacted by an ageing cohort, which would give misleading results in understanding impact of treatment [165]. The diagnostic tool used in this study was Kato-Katz, which is insensitive to detecting eggs in low-prevalence settings (especially due to the high day-to-day egg output variation), and is likely to have missed positive infections in individuals in the two low prevalence groups. This could be mitigated by preparing more than two slides per sample, and more samples per person for the Kato-Katz, or alternatively, using CCA to detect positive infections in these areas (which will not provide age-intensity profiles due to its semi-quantitative output).

Further studies and conclusions

The rich data collected in this study provides opportunities for further studies. Soil-transmitted helminth (STH) data were also collected at the time (not included in this thesis), so further work could be conducted in age-infection profiles for STH infections and levels of polyparasitism in the same individuals, comparing against those with single-species parasite infection. Another further analysis could be to convert the cross-sectional data to longitudinal data and to compare with the cross-sectional analysis already conducted in this chapter. Longitudinal data analysis would look at the impact of treatment on the treated population rather than the standard impact of treatment on the wider community. Results from cross-sectional data are reliant on the characteristics of the non-treated population (e.g. economic migrants that might be heavily infected, such as fishermen).

The fieldwork in this thesis was based on Uganda, a predominantly *S. mansoni*-endemic country with a relatively long and well-established control programme. To investigate age-related infection patterns in other endemic regions, it is important to collect data in a range of settings as the results from the data in this thesis alone may not be applicable to these areas. For future studies, the fieldwork could be extended to countries with *S. haematobium* infection and both *S. mansoni* and *S.*

haematobium, which have relatively recently instigated control programmes, areas with no previous history of treatment and/or in different regions of SSA. One of the countries that meets these criteria is Liberia, which has experienced a recent history of civil unrest and even more recently, the deadly Ebola outbreak, setting many disease programmes back by several years. Unlike Uganda, Liberia represents a scenario on the other end of the spectrum with only sporadic and partial geographical coverage for treatment for schistosomiasis. This would enable a comparison to be drawn between the two countries from testing the robustness of the outputs to differences in the environment, to testing the feasibility of the fieldwork protocol described in this chapter being used across settings.

The 2012 World Health Assembly resolution 65.21 on elimination of schistosomiasis indicates that MDA with PZQ is not a standalone solution and highlights the requirement for an integrated approach for elimination [82]. This study provides further evidence that for such a focal disease as schistosomiasis, not only are tailored treatment and intervention strategies required but so is treatment to the wider community that includes PSAC and adults and detailed M&E at the site level to identify high endemic areas.

CHAPTER 5. GENERAL DISCUSSION

This PhD aimed to provide empirical evidence (through data collected by the candidate as part of this PhD and elsewhere) to aid policy development that will help control and eliminate schistosomiasis as a public health problem in sub-Saharan Africa (SSA). The study began with a global level overview with *Research Objective 1: To determine where we are now in sub-Saharan Africa (SSA) and Yemen in terms of schistosomiasis transmission, and understand how historical data can inform WHO guidelines* (Chapters 1 and 2). This was followed by a country-level study with *Research Objective 2: Design, develop and evaluate a tool to aid schistosomiasis programmes for programme managers and policy makers* (Chapter 3) through the development of a Markov model to project the likely impact of a national-level control programme. The PhD concluded with a finer-grain analysis of *Research Objective 3: To understand age-related epidemiology at multiple scales of heterogeneity, treatment history and WHO endemicity level of sites, using data collected as part of PhD* (Chapter 4), using Uganda as a case-study and analysing patterns of infection at varying levels of aggregation. Throughout the PhD, factors have been identified that impact the epidemiology of schistosomiasis and subsequently the aims of its control and elimination as a public health problem (EPHP). This PhD has highlighted and synthesized possible emergent factors that cannot be understood by the study of the micro- or macro-epidemiology in isolation but require a more holistic approach (Figure 5.1).

When the WHO treatment guidelines for PZQ were developed (Chapter 1, Section 1.5.1), there was an urgent need of direction for new programmes, and since observational studies were scarce, guidelines were developed based on expert opinion [80–82]. These guidelines have played a useful role in assisting countries to implement programmes to reduce prevalence and intensity of infection and have enabled several countries to achieve the goal of morbidity control. Some countries have been able to use these as a guide for achieving EPHP (Chapter 2). However, some of the gaps in the guidelines may affect the feasibility of programmes reaching the 2020 and 2025 targets. With 2020 goals of control of morbidity and 2025 goals of EPHP fast approaching, the public health community has an opportunity to gather new information and utilize the current evidence available to provide a more tailored strategy to achieve these goals and to potentially transition to a more ambitious target of the interruption of transmission. The findings of this PhD have direct implications on control, EPHP, and interruption of transmission and the validation or reformulation of the WHO guidelines.

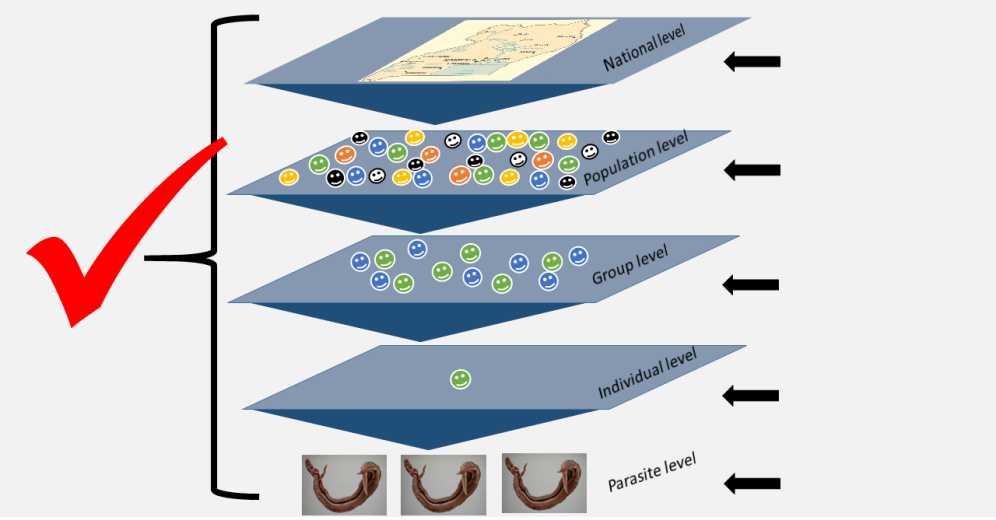

Figure 5.1 Illustration of the narrative of this thesis and the approach to informing policy using a holistic perspective. Each layer represents an understanding of schistosomiasis at different levels, from the individual host to the national level, which when taken together can provide a fuller picture than if studied in isolation.

5.1 Summary findings for each Research Objective

For Research Objective 1, Chapter 2 was developed to address the global status of countries with schistosomiasis control programmes. This thesis presents the first multi-country study using programmatic data (from 11 control programmes in SSA and Yemen) to track a range of progress metrics by *Schistosoma* species and baseline endemicities (Chapter 2). Whilst a one-size-fits all approach to treatment (and other interventions) guidelines was a useful original starting point, this should now be updated using available empirical data, including the outputs of Chapter 2. Chapter 2 highlights that many endemic countries have already attained 'control of morbidity' under its current definition, particularly those for which the starting endemicity was low, with control being achieved in two treatment rounds or fewer. This means that countries of low initial endemicity could potentially start with the aim of EPHP, skipping the 'control' strategy entirely, which leads to the question of whether separate targets for 'control' and EPHP are necessary. Countries with endemically low prevalence foci (Burkina Faso, Burundi National, Burundi Pilot, Malawi and Rwanda) reached EPHP within three treatment rounds. This is not only typical of schistosomiasis. Other NTDs such as onchocerciasis (river blindness, caused by the *Onchocerca volvulus* worm transmitted through the bite of a blackfly), for example, has shown to be eliminated in countries with low initial endemicity levels, such as Colombia and foci in Guatemala [178] and trachoma (caused by *Chlamydia trachomatis* bacterium transmitted via contact with infected eye and nose discharge and spread by flies) was

shown to require 10 treatment rounds to reach 5% rates in areas where initial prevalence was greater than 50% (i.e. high baseline endemicity) [179]. Baseline endemicity thus plays an important role, with countries starting at low prevalence likely to reach the goals of control and EPHP sooner than the guidelines suggest. These were the same countries where prevalence of heavy-intensity infection was lower than 5% (i.e. indicating 'controlled' morbidity). Whilst some countries have been implementing schistosomiasis control programmes for many years and are at the reassessment phase to determine what future strategy to follow, some countries have only recently started treatment and may not meet the 2020 and 2025 goals if following the recommended timelines. The outputs from Chapter 2 show that updated WHO guidance should be tailored to starting endemicity levels and schistosome species. With such variation of prevalence in each country, it is difficult to justify the use of aggregated country-level figures for prevalence of heavy infection to define the control target for such a focal epidemiology. Moreover, morbidity targets need to be updated with appropriate morbidity markers, diagnostic tools and population scale. With the international deadlines approaching, these findings are timely for programme managers and policy makers.

To address Research Objective 2, Chapter 3 was devoted to developing and evaluating a Markov model, a highly user-friendly tool for programme managers and policy makers. The Markov model is a (relatively) simple but useful framework which was shown to predict accurately the reductions in prevalence reached in two countries, for different schistosome species, and in several different epidemiological scenarios. The model can be used for advocacy, M&E, and to inform policy (though more complex mechanistic models also have an important role to play here) [180,181]. The availability of user-friendly tools such as the Markov model could greatly improve the monitoring and performance of helminth PC programmes [143,144]. The model itself uses programmatic data to predict (short-term) subsequent changes in prevalence in follow-up years and can be adapted for use in different settings and at different starting times. These findings come at a key moment in the field of NTD modelling, given the impetus for programme managers and policy makers to bridge the gap between models and end-users. In fact, the WHO has shown an interest in its use (the candidate's collaboration with the WHO also resulted in a second-author publication for a Markov model for soil-transmitted helminths [144]). The next steps for this model are to create a mechanism by which the transition probabilities can be updated as more data become available. At present, further development of the model is being conducted by the candidate for online web use (free access) using RShiny (Figure 5.2) with the aim of aiding its wider use.

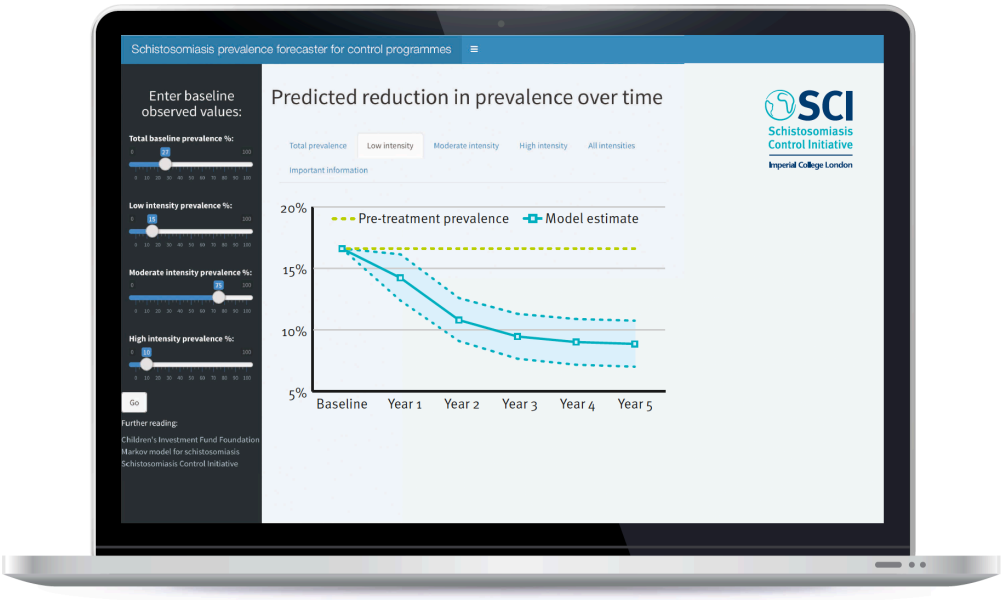

Figure 5.2 Current design of the user-interface for the Markov Model app. RShiny is being used to develop a web tool which will enable users to access and use the model freely by entering their data in the sliders on the left (outputs shown on the right, by infection intensity group). This is still currently under development, but a beta version has been created (shown here).

For Research Objective 3, Chapter 4 was used to design the necessary surveys for the data collection which was used for the analysis, describing the organisation and leading by the candidate of an annual large epidemiological fieldwork survey in Uganda which spanned three years, overseeing 70 members of the national MoH and local staff. The candidate also trained and supervised ten teams on diagnostic tools, parasitological methods, and data analysis using Excel and R. The experience shed considerable light on some of the challenges faced during fieldwork and some of the unique characteristics of the sites which would not have been appreciated without being first-hand involved in the fieldwork (such as proximity of the sites to water sources, the observation of broken water pumps, the poor maintenance of WASH facilities in some sites, market towns indicating mobile populations, etc.). This survey enabled the generation of the extensive and detailed datasets used for the rest of the chapter. Overall, treatment has had a positive impact in most areas, particularly in low endemic sites evidenced by sustained reductions in prevalence and intensity of infection. However, some areas were less impacted by treatment than expected. However, and as expected given the strongly nonlinear relationship that exists between infection prevalence and intensity, particularly at high intensity levels (Chapter 2 Section 2.3.3, Appendix 3, [165]), treatment effected stronger reductions in infection intensity than in prevalence.

School-aged children (SAC) are the main target populations for treatment programmes but it is vital to include adults and PSAC if morbidity is to be effectively reduced in the population and eventually, sustained EPHP is to be reached. The WHO guidelines (and consequently, the majority of treatment programmes and resulting M&E data that have been collected) largely recommend treatment of SAC. Irrespective of whether infection indicators in SAC provide reliable information about the intensity of transmission in other population groups in the community, results showed heavy-intensity infections were present in PSAC (who are consistently missed during PC campaigns) and adults, and are an indication of the potential existence of a substantial reservoir of (possibly heavily) infected PSAC and adults in other areas. Reaching control and EPHP in SAC may, therefore, not translate into these goals also being achieved in the remaining (mostly untreated) age groups. Cost-effectiveness studies have shown that including PSAC and adults in treatment programmes is beneficial in the long-run, and modelling suggests that inclusion of these groups may be necessary to reach the control and EPHP targets and essential for interrupting transmission, though WHO has only recently included the PSAC group in the revised treatment guidelines and the drugs are not donated for general adult treatment [136–138,182]. Further empirical studies are required to address these questions, but the target group would need to be widened if the 2020/2025 goals are to be truly achieved (rather than just by WHO definition of what morbidity elimination means). It is important to reach mobile populations, which may have explained some of the persistent high prevalence levels (over 80% in 10-12-year olds in 2014 and 2015) observed in the high endemic sites in Chapter 4. This would require information on these characteristics being collected at the site level for a tailored treatment strategy. An example of the impact of mobile populations is best exemplified by the recent Corsica outbreak – where there was fortunately a swift and effective response, containing the outbreak and tracing its source (down to the original migrant route from where the infection stemmed) [183].

Additionally, the outputs of Chapter 4 highlighted the importance of obtaining fine-grain data, particularly in those cases in which interpretations differed through analyses of different population levels of the same data. Mathematical models will need to take into account these finer details through the use, for instance, of precision-mapped data if they are to produce more locally accurate predictions. Without these, informing policy would remain rather a general endeavour, which could have adverse implications for communities located in sites being classed as 'low endemic' when in fact they are 'high endemic', resulting in making incorrect treatment decisions. This problem is not only specific to schistosomiasis; in onchocerciasis large areas classified as hypo-endemic and hence not under ivermectin treatment, have shown to mask pockets of high endemicity [184]. Not only does this lack of micro-epidemiological understanding risk the application of incorrect treatment schedules, but also it risks the re-introduction of infection to well-controlled areas or areas considered of lower

endemicity. Likewise, using cross-sectional data alone can be potentially misleading without an understanding of the history of the individuals examined, for example, whether they have migrated from outside, uncontrolled or less well-controlled areas, or whether they were part of the treated population.

5.2 Avenues for further research

The datasets and methods generated in this PhD could be used to investigate further the questions identified here. Understanding biological and social determinants of infection will advance current understanding of non-responsive areas/hotspots and why some areas may not be reaching their targets. Exploring alternative intensity cut-offs for egg counts, markers of morbidity and diagnostic tools will be vital to ensure that the targets for schistosomiasis (whether control or EPHP) are truly met, since the targets are heavily dependent on intensity definition and diagnostic sensitivity [185]. Following on from there, understanding the relationship between infection intensity and morbidity will be important if 'true' control and elimination of morbidity is to be achieved, as there may still be considerable morbidity in the population despite having reached the targets of control and EPHP as currently defined by the WHO. Geographical and temporal model projections could be used to direct resources as well as for advocacy. These will now be discussed in further detail.

Determinants of infection susceptibility

Individual-based data were used for Chapters 2 and 4. An understanding of infection patterns could be further developed through analysing the distribution of infection amongst individuals in a population, by year, treatment history, species, starting endemicity and country – varying by population groups such as PSAC, women of child-bearing age, mobile populations and adults. Data on occupation, school attendance and length of time lived at the sites were also collected as described in Chapter 5 so these could be used to understand the different disease prevalence and intensities amongst occupation groups (where certain occupations such as fishing are associated with high prevalence and intensities of infection [186]), attending vs non-attending school children (where non-attending school children may experience higher levels of infection [187]), and the dynamics of infection in short-term vs long-term residents (as long-term residents would likely benefit from consistent PC programmes and be more receptive to behaviour changes to avert infection). This would increase understanding of which groups consistently harbour the most infections and contribute most to transmission and which groups respond least to treatment.

Diagnostic tools and egg-count thresholds for morbidity

One of the major limitations for parasitological surveys is the lack of field-ready accurate diagnostic tools. The Kato-Katz (KK) method for *S. mansoni* is known to lack sensitivity, particularly in low endemic areas or in those in which prevalence has decreased as a result of interventions, but there are other uncertainties surrounding this technique. The functional relationship between egg output and worm burden within the host remains poorly understood (there have been very few expulsion studies and only a handful of post-mortem studies [63]) and the relationship between intensity and morbidity is also poorly understood, yet the egg output is used as an indirect measure of infection intensity and infection intensity is used as an indication of morbidity (through heavy-intensity infections) [188]. There is a high variation in egg output between stool samples from the same individual and even within the same stool sample [56,189,190]. There is also uncertainty as to the proportion of eggs that remain trapped in the host, and it is these which cause the immunopathological response that leads to granuloma formation and subsequent morbidity. A further challenge is being able to accurately identify and enumerate the species eggs under field conditions. The point-of-care circulating cathodic antigen (POC-CCA) test is a promising tool already in use in many areas [53]. It has an increased sensitivity for detecting *S. mansoni* infection than Kato-Katz and is urine based so has logistical and compliance advantages. However, it introduces challenges for determining heavy-intensity infections (as it provides only a semi-quantitative measure of intensity for *S. mansoni*) [131,132]. Urine filtration for *S. haematobium*, though more sensitive in comparison to KK, is limited by the diurnal variation in egg output in the urine. The up-converting phosphor-lateral flow circulating anodic antigen (UCP-LF CAA) test is a more sensitive and specific tool designed to diagnose *S. haematobium* infection but is not yet field-ready as it costly and currently requires centrifuging and pipetting for diagnosis (although work on making this field-ready is underway) [55,191]. The new diagnostic tools need to be able to provide the data required, or the guidelines need to be adapted to these tools. Many studies have compared CCA to KK, showing that the prevalence is between 1.5- to 6-fold higher for *S. mansoni* infection when using the former and that the relationship is non-linearly related below 50% prevalence (though results are comparable when prevalence is above 50%) [131]. This has major implications on the control and elimination targets for country programmes and international targets, as some areas may be further from the goals than originally thought (and the goals may need to change). The WHO guidelines for CCA are currently under development and will be available in the near future. However, Kato-Katz is also the primary diagnostic tool for soil-transmitted helminth (STH) infections (*Ascaris lumbricoides, Trichuris trichiura* and hookworm) since there is no direct equivalent POC-CCA for STHs, so programmes may not be able

to stop using KK in the near future (though quantitative polymerase chain reaction, qPCR, has shown to be accurate and sensitive, but is not a POC test and is costly [62]).

The data in this thesis could be used to further investigate the relationships between prevalence, intensity and egg-count thresholds, by conducting a sensitivity analysis to understand how changes in threshold definition result in variations in the proportion infected with these categories. For example, for *S. mansoni*, rather than 0-99 epg representing "low infection intensity", starting with 0-49 epg representing low intensity infection, 50-199 epg representing moderate infection and 200+ representing heavy infection, could have implications for the categorisation of endemic areas into infection-intensity groups and for measuring country progress towards the 2020/2025 goals. An important question is whether the current categories of infection are truly useful and appropriate or whether should they change to be aligned more closely with the probability of developing morbidity, and hence with the goals of control and EPHP. An associated question is whether, if the current categories were not to be changed, separate definitions should be applied for control of morbidity and EPHP. These questions need to be urgently addressed if the KK diagnostic tool will continue being used in M&E surveys for *S. mansoni* and if CCA outputs will be compared with KK outputs for the determination of infection intensity. Comparing the outputs of Chapters 2, 3 and 4 with alternative diagnostic tools such as CCA, CAA and PCR would provide a valuable opportunity to investigate some of these questions.

True relationship between infection intensity and morbidity

Any level of infection (including low intensity) could potentially give rise to morbidity [121]. The infection-intensity thresholds (*S. mansoni*: light, moderate and heavy intensity corresponding to 1-99 epg, 100-399 epg and 400+ epg, respectively, and *S. haematobium*: light and heavy intensity only, corresponding to 1-50 eggs/10 ml and above 50 eggs/10 ml, respectively [36]) were proposed by the WHO Expert Committee in 1987, but it is not clear why no moderate intensity group exists for *S. haematobium* nor why heavy intensity infection is defined as 50 eggs/10ml for *S. haematobium* and for *S. mansoni* it is defined as ≥ 400 epg (though flexibility in these thresholds had been proposed) [123]. If a lower egg count is indeed causing an unacceptable amount of morbidity (which then gives rise to the question of what is acceptable?), this means that the metrics being used to define 'control' and 'elimination as a public health problem' may be incorrect. Moreover, when aiming for elimination of infection, a single infected human, even with light infection, has the potential to re-introduce the disease back into the population (due to an asexual multiplicative development stage in the intermediate, snail host), further highlighting the need to address light intensity infections if interruption of transmission is to be achieved [124]. The type of morbidity and threshold intensities

vary for the two main species of *Schistosoma* affecting humans. For example, for female (and male) genital schistosomiasis (caused by *S. haematobium*) and its sequelae (including, but not exclusive to, associated pain and increased susceptibility to HIV, HPV), intensity may not need to be 'heavy', so a country with a prevalence of <5% heavy-infection intensity across sentinel sites may consider morbidity 'controlled', when in fact a large proportion of the population is still experiencing significant morbidity [192,193]. Another complicated factor is that individuals may no longer be infected (or not excreting schistosome eggs) yet still experience morbidity from earlier chronic infection such as irreversible organ damage [194].

Ultrasound studies may elucidate the level of morbidity through detecting pathological changes (such as periportal fibrosis, portal hypertension and intestinal wall thickening) in infected individuals of any infection intensities [195,196]. This could mean that although a country may have reached EPHP as per the current definition, the true morbidity caused by non-heavy infection intensities may still be considerable. The use of 'moderate plus heavy intensity infection' as the morbidity indicator, as well as the recognition of an intermediate intensity group for *S. haematobium* could help to mitigate this whilst new morbidity thresholds are being investigated. However, this does not address morbidity associated with past experience of infection sequelae (for which clinical management will be required), and as mentioned earlier, nor does it address other long-lasting and stigmatising consequences, such as infertility, genital schistosomiasis and the interactions of the latter with HIV and HPV [197,198]. Other NTDs, such as trachoma and lymphatic filariasis (LF) for example, have taken a dual approach of 1) MDA (with diethylcarbamazine (DEC), albendazole or ivermectin for LF and azithromycin for trachoma) to reduce infection and prevent the development of future morbidity, and 2) Morbidity Management and Disability Prevention (MMDP) to treat current morbidity. For MMDP, examples include daily washing of affected limbs to prevent secondary infection (LF), hydrocele surgery (LF) and eye surgery for *trachomatous trichiasis* (where otherwise infection would cause scarring of the eye resulting in the eye lashes turning in, scratching the surface of the cornea leading to eventual blindness) [199,200]. Further studies are required to redefine the relationship between egg output and morbidity since currently, "heavy" intensity as defined above, is taken as the universal metric of infection-associated morbidity, used to define the control and EPHP targets. Moreover, the first two morbidity targets are based largely on data from SAC since it is that school-aged children harbour the highest prevalence and intensities of infection. If the objective is to reach morbidity control or elimination by 2020 or 2025, respectively, then the peak schistosomiasis-associated mortality age range of 30-49 years is being missed in surveys (Figure 5.3), and even in treatment programmes themselves, which is particularly important [201].

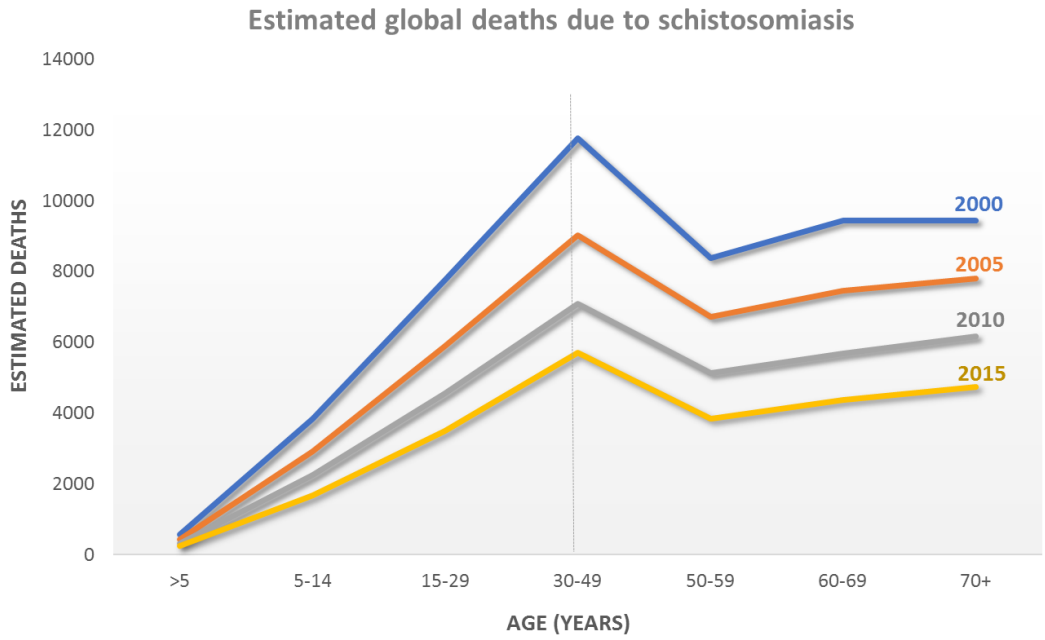

Figure 5.3. Estimated deaths due to schistosomiasis globally by age group by year. Plotted using reported data from [201].

Geographical and spatio-temporal model projections

The Markov model developed here (Chapter 4 and reference [202]) could be easily adapted to include data from CCA and from adjusted infection intensity thresholds. The development and use of powerful tools will be essential as programmes move closer towards attaining the global goals, using appropriate targets with tailored treatment and intervention approaches. To aid countries and policy makers further, predictive maps could be developed from Markov model projections, varying by administrative level and by population groups where data are available. This would help to provide a macro- to micro-level visual illustration of changes in infection under intervention and could be piloted using the data presented in this thesis. If a method for updating transition probabilities can be developed, increasing the accuracy and time-range of outputs, these maps could be a powerful M&E and advocacy tools for countries and policy makers.

Chapters 2 and 4 can also be expanded to include STH infections. Indeed, data were also collected for STHs in Chapter 4 since the same diagnostic method is used. The candidate is currently conducting work on age-infection profiles for hookworm infection (as *A. lumbricoides* and *T. trichiura* infections

were very low, at less than 3% overall prevalence) as well as a multi-country study on STH infection, stemming from the fieldwork conducted in this thesis.

5.3 Possible pilot studies

The WHO has provided a range (in years) to reassess whether the goals of control or EPHP have been achieved, but with the push towards 2020 and 2025, there is a need to specify a time or adjust these goals. When scrutinising the definitions for control and EPHP, it is clear that morbidity is not in fact eliminated when potentially there are members of the population suffering from an undefined level of morbidity (the population in the <1% of heavy-intensity infection in each sentinel site for instance, or the PSAC/adult untreated/unmonitored group). The EPHP target may in fact be a closer definition of an 'acceptable' level of true morbidity control than the official definition of control. Three possible short-term modifications to the guidelines could be piloted:

1) Omit the 'control of morbidity' target and move straight into EPHP targets. Chapter 3 showed that the goal of reaching <5% prevalence of heavy-intensity infection is feasible in a relatively short period. Therefore, a more ambitious approach could be for new country programmes to already start adopting the EPHP strategy of intensified treatment to meet the 2025 goals. This would omit the need for reassessment between the 'control' and 'EPHP' phases with resultant cost savings and would prevent countries from having to change an established strategy. This could also apply to current programmes that are on a 'control' strategy to move directly to the intensified strategy to reach EPHP.

2) Redefining egg-count and morbidity thresholds. Redefining the egg-count thresholds for the WHO intensity (light, moderate [for *S. mansoni* only] and heavy) infection categories and then following the proposed operational thresholds of <5% across / <1% prevalence of heavy-intensity infections within each sentinel site for control and elimination of morbidity, respectively. Morbidity studies will need to be conducted to determine the relationship between egg output and disease; morbidity thresholds will also need to be defined (from mild to severe), including any parasite density-dependence effects on the worm population.

3) Should the aim be interruption of transmission at all? A more controversial approach is to maintain EPHP, without changing the (currently undefined) strategy to reach interruption of transmission, at least towards selected high-risk groups - who would continue to receive intensified PC and benefit from additional interventions. By maintaining low (or zero) morbidity in the population this way, other

essential sectors, such as health system strengthening, water and sanitation infrastructure etc., in the country would gradually 'catch up' in development (provided there is government/political stability). This could eventually lead to the elimination of transmission, especially if complementary and effective interventions have been integrated (i.e. snail control, behaviour change and implementation of water, sanitation and hygiene (WASH) measures). Countries currently aiming for interruption of transmission have typically seen a significant improvement in socio-economic development. The benefits of this strategy compared to, say, a downscaling treatment approach is that the latter drastically reduces treatment numbers. This could result in potentially devastating recrudescence of infection, especially in a susceptible population that may by then have a reduced levels of acquired protective immunity to infection and be vulnerable to a higher level of morbidity from the same intensity levels (aggressive morbidity) [34].

5.4 Conclusions

The aim of this PhD was to generate evidence from the field level up to the global level in order to inform and influence policy. Chapter 2 highlighted that many countries have reached control targets much earlier than anticipated, calling for a re-evaluation of the current operational thresholds for morbidity control and EPHP; Chapter 3 provided a tool for programme managers and policy makers to assess year-to-year progress of individual countries and finally, Chapter 4 described the approaches to generate a detailed dataset for analysis and modelling and used the data generated/collected, to show that achieving control of morbidity at one scale may be dangerously misleading due to the high heterogeneity assessed at finer scales.

As we approach the 2020 goal of the control of morbidity and the 2025 goal of elimination of schistosomiasis as a public health problem, it is vital for the public health and research community to come together and produce effective guidelines and policy to ensure that countries reach these goals, help alleviate the burden of this debilitating disease and unlock the potential of millions of individuals.

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1. Appendix for Chapter 3

Figure A1. Results from applying transition probability (TP) matrices B and C on dataset 1 (full longitudinal Uganda data set).

Figure A1a Matrix B (using year 1 and year 2 Ugandan data for TPs) and dataset 1

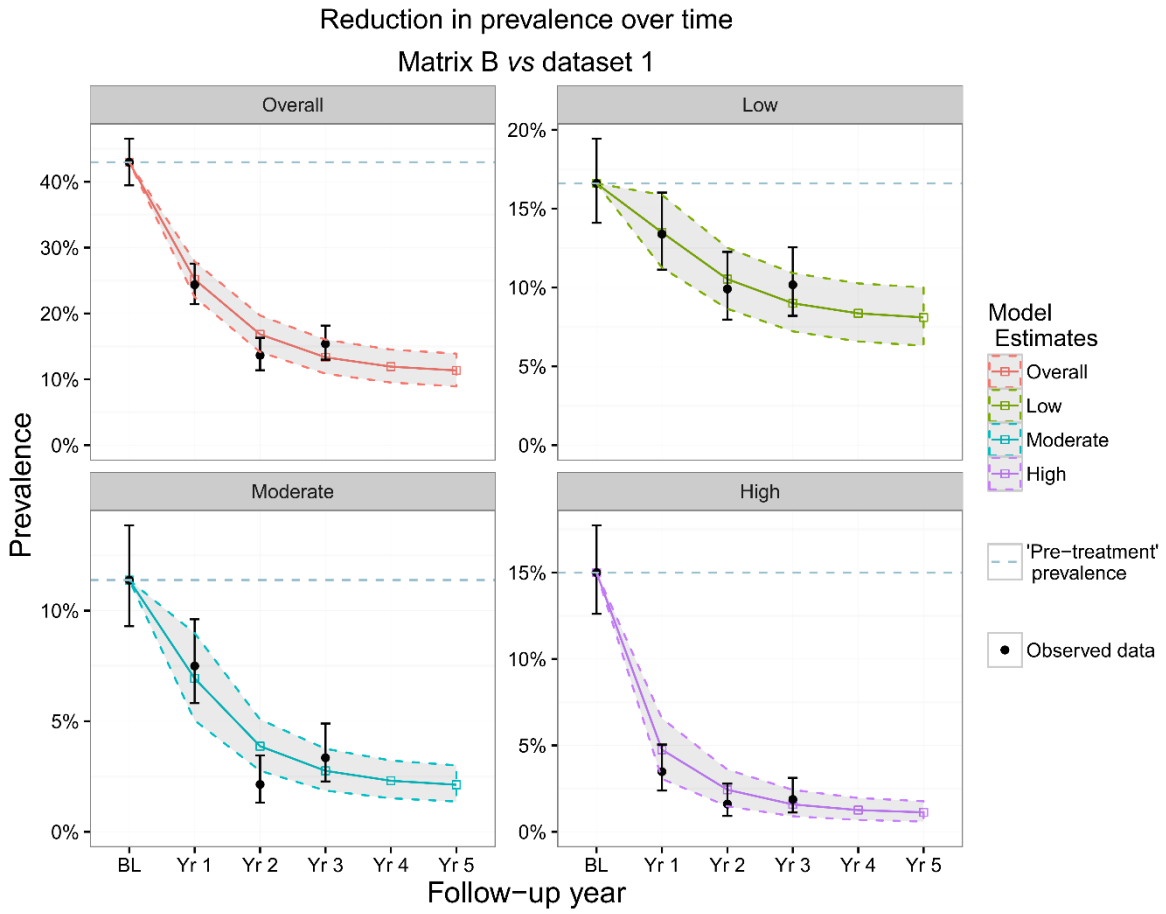


Figure A1b Matrix C (selected Ugandan districts for TPs) and dataset 1

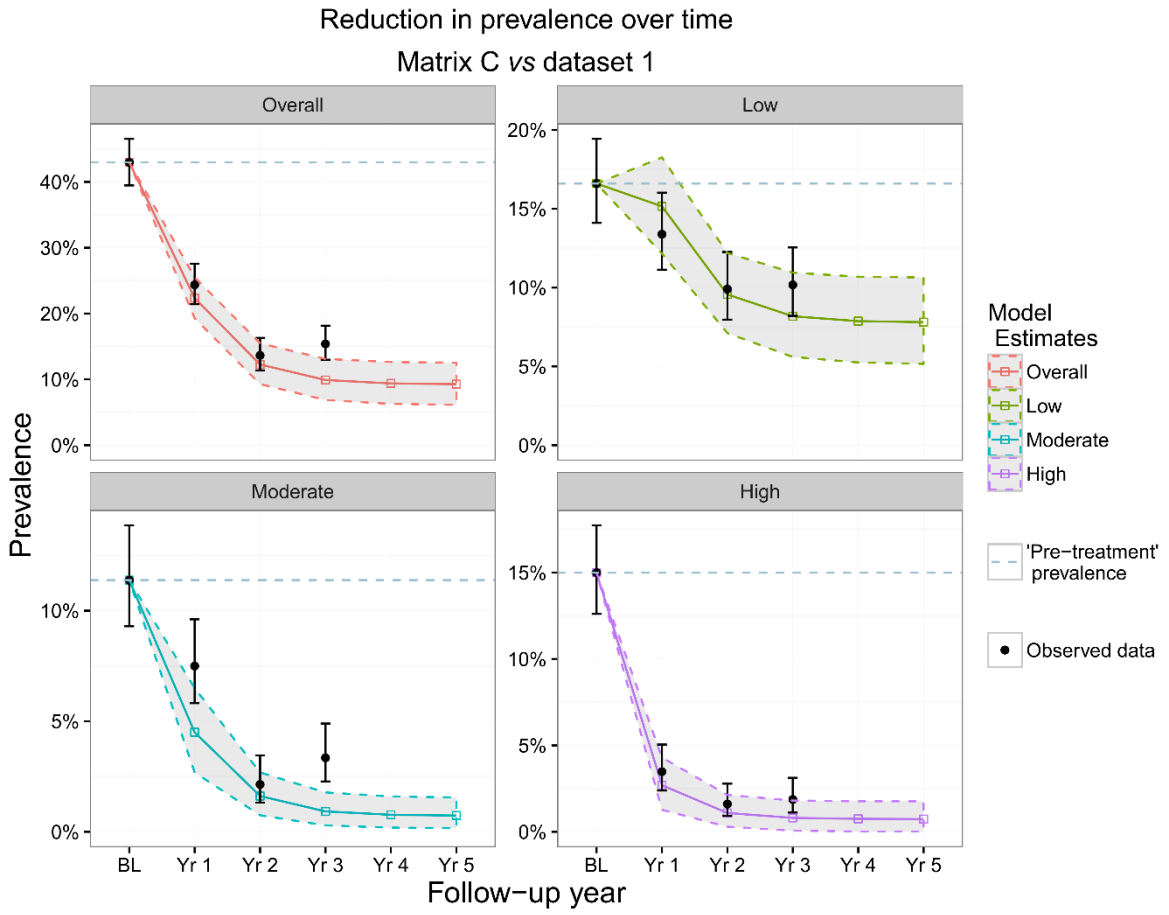


Figure A2. Results from applying TP matrices A-C on dataset 2 (selected Ugandan districts)

Figure A2a Matrix A (full Ugandan data for TPs) and dataset 2

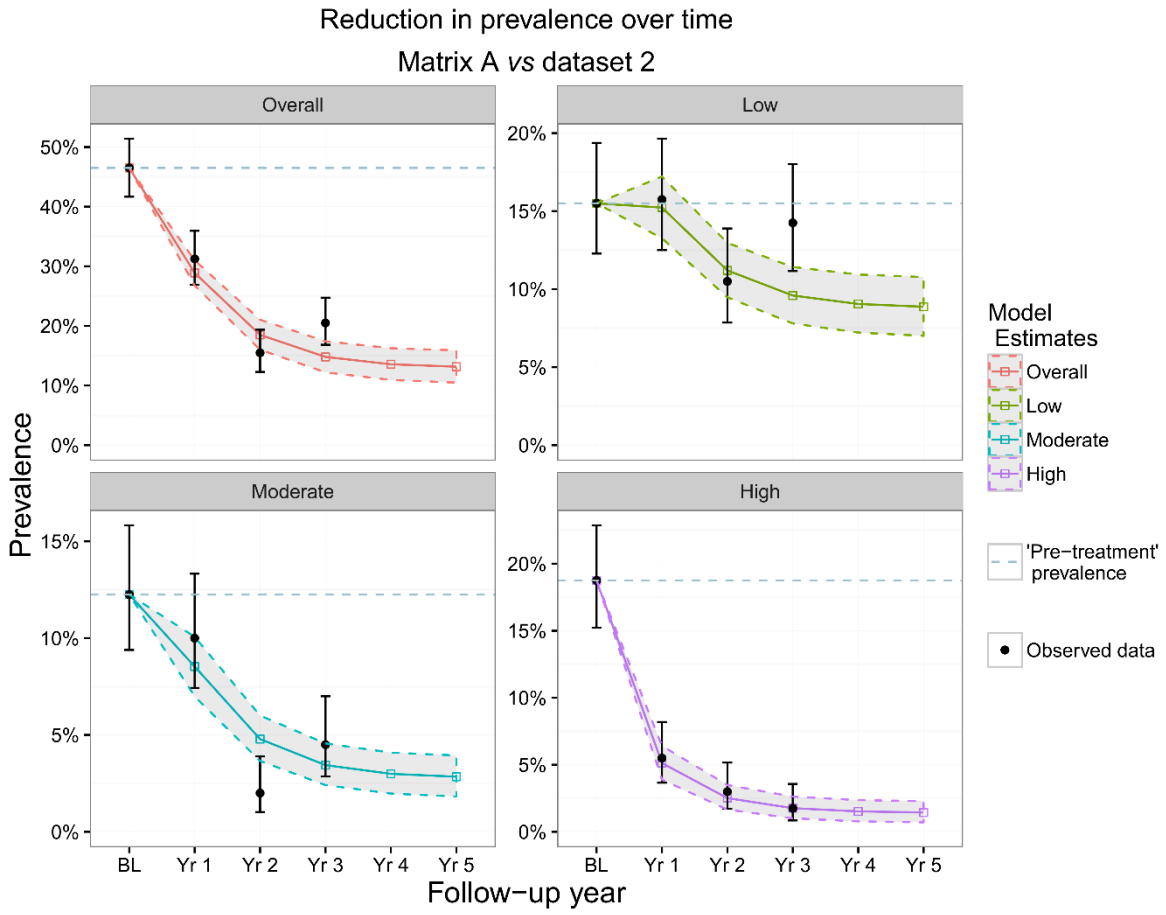


Figure A2b Matrix B and dataset 2

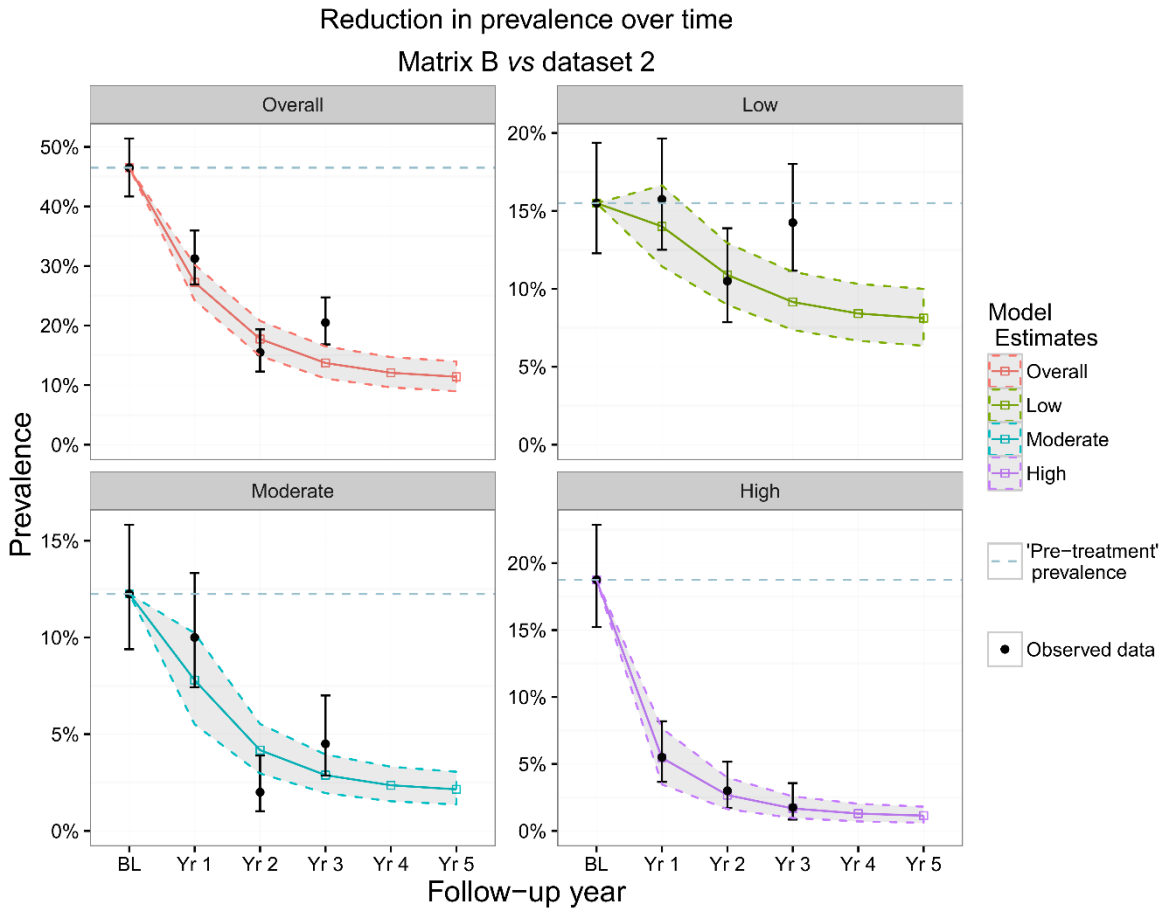


Figure A2c Matrix C and dataset 2

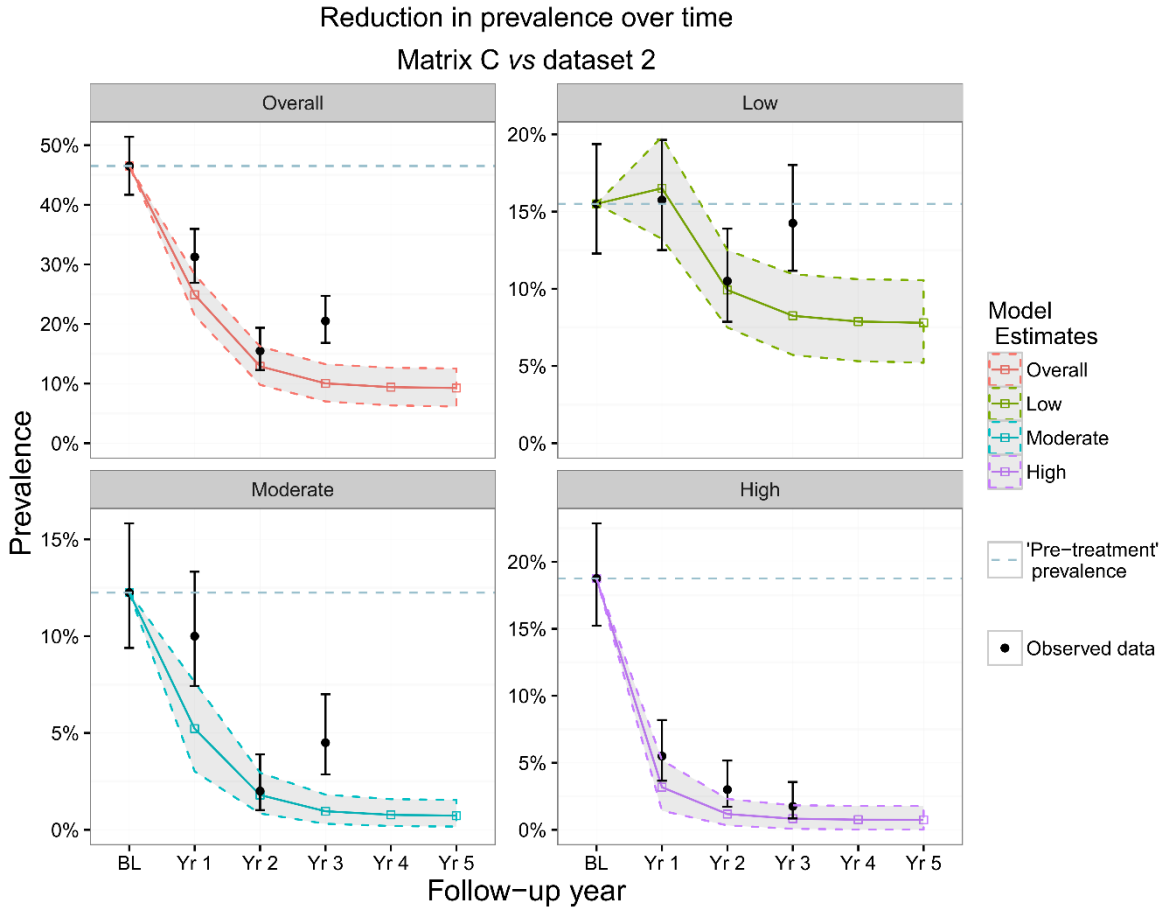


Figure A3. Results from applying TP matrices B and C on dataset 3 (cross-sectional Ugandan dataset)

Figure A3a Matrix B and dataset 3

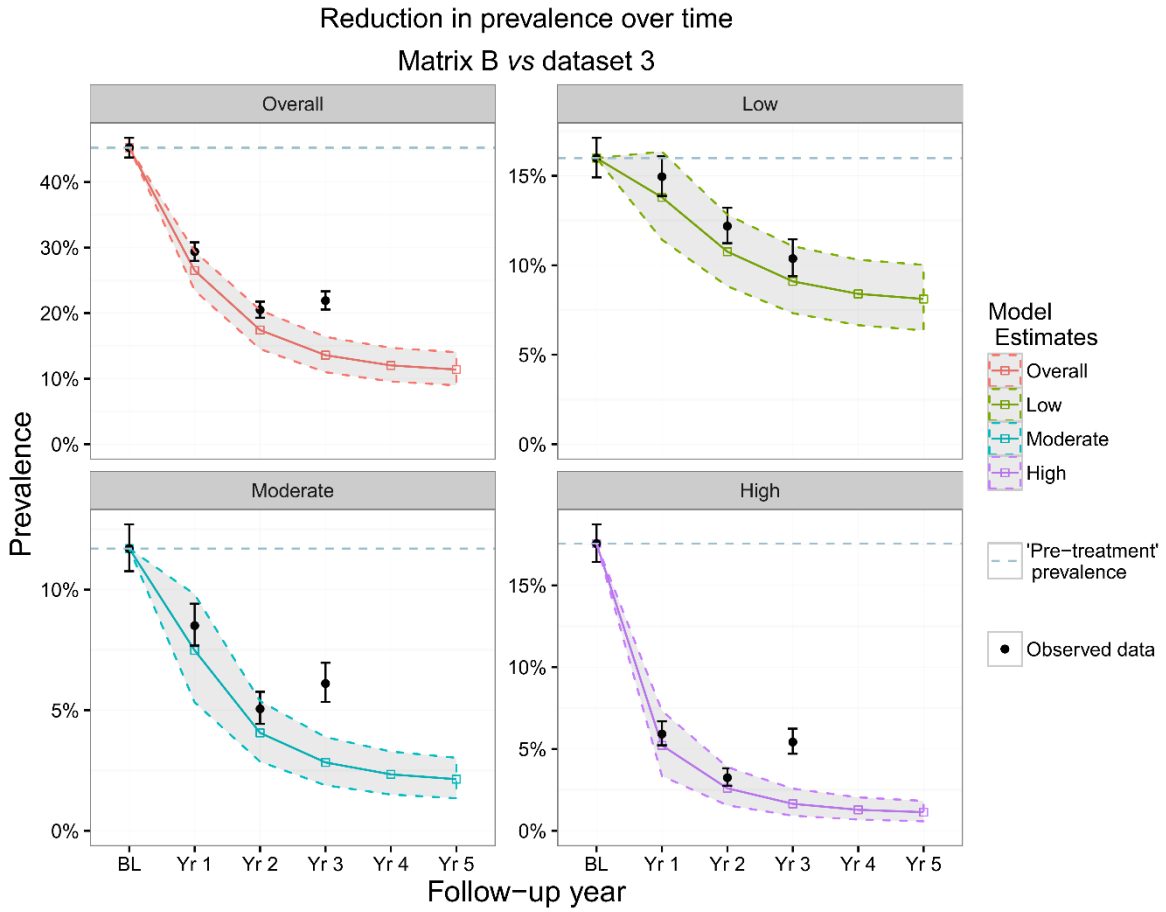


Figure A3b Matrix C and dataset 3

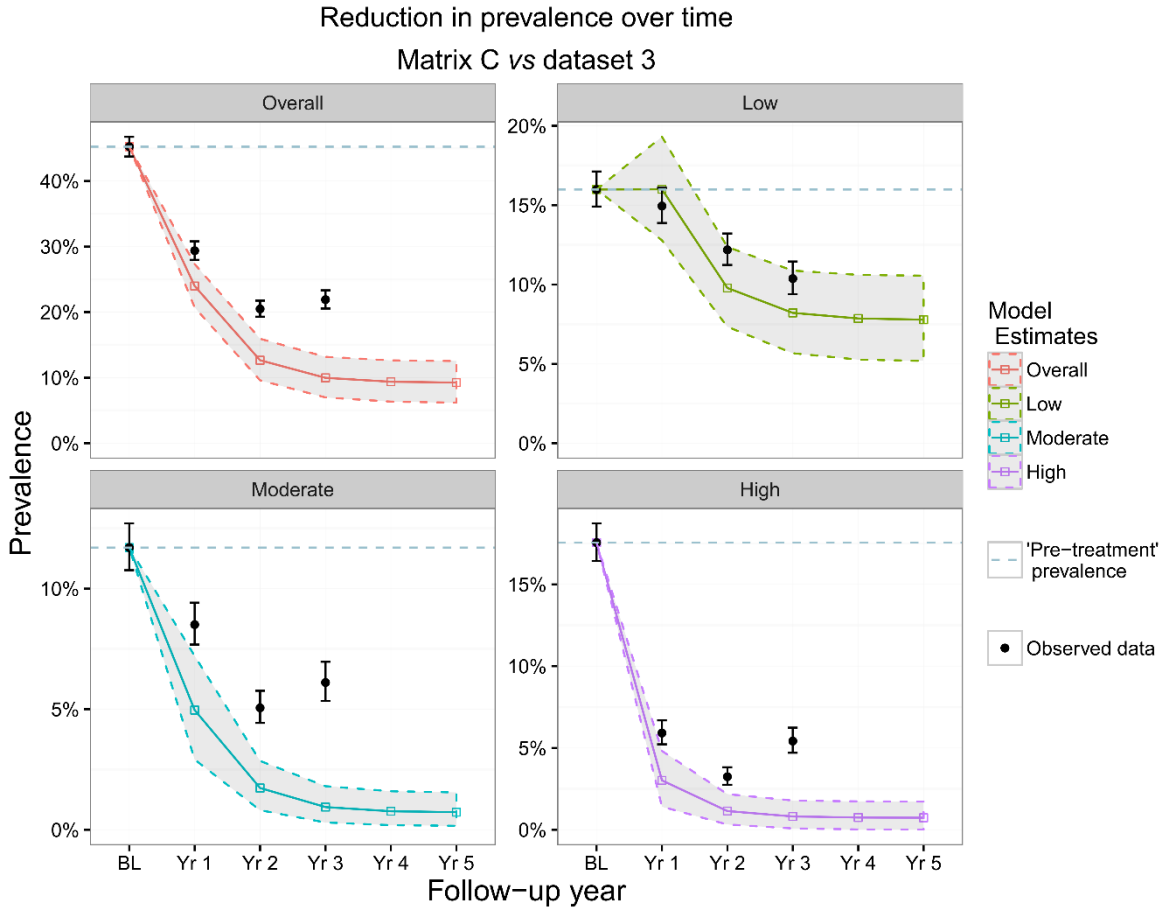
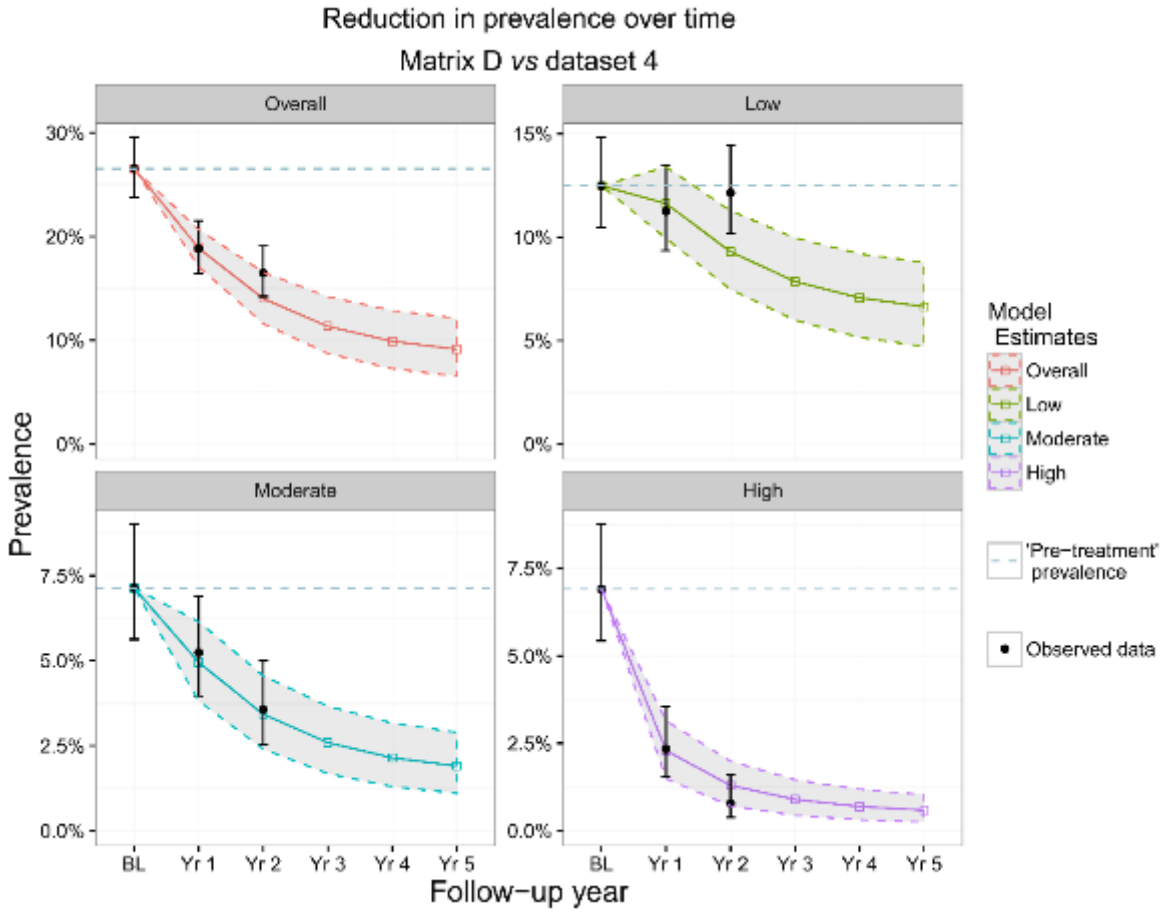


Figure A4. Results from applying TP matrix D (baseline and year 1 Mali data for TPs) on dataset 4 (longitudinal Mali dataset)



2. Appendix for Chapter 4: Budget

	NAME		DUTY	DAYS	RATE	UGX	GBP (as of 31 May 2
Team members	Entomologist	Ento	Team leader	26	110,000	2,860,000	581.507
	Technician	VCO	Schisto microscopy	26	100,000	2,600,000	528.642
	Technician	VCO	Schisto microscopy	26	100,000	2,600,000	528.642
	Technician	VCO	Schisto microscopy	26	100,000	2,600,000	528.642
	Technician	AUX	Stool processing	26	75,000	1,950,000	396.482
	Driver 1	DRIVER	Driving	26	75,000	1,950,000	396.482
	DVCO		Offical guide	20	20,000	400,000	81.330
	Teacher/VHT		Community/school g	20	5,000	100,000	20.332
	Airtime				50,000	50,000	10.166
					subtotal for personnel	**15,110,000**	3072.226
Fuel/vehicles							
Return Journey (250km)						291,667	59.303
Local running for 20 days - 20 litres per day at 3500 per litre						1,400,000	284.654
					subtotal for travel	**1,691,667**	343.956
					subtotal for each team	***16,801,667***	3416.182
Total number of teams required							
5 teams for ten CIFF							
survey sites					***SUBTOTAL***	***84,008,333***	17080.910
Data entry	Data entry clerks		Entering field data i	10	50,000	500,000	101.662
					subtotal for data entry	**500,000**	101.662
Total number of data entry clerks required							
4 teams for ten CIFF							
survey sites					***SUBTOTAL***	***2,000,000***	406.648
CENTRAL SUPERVISION							
	NAME		**DUTY**	**DAYS**	**RATE**	**UGX**	GBP (as of 31 May 2
Supervision	Supervisor		Supervision	7	130,000	910,000	185.025
	Driver 1	DRIVER	Driving	7	55,000	385,000	78.280
	Airtime				50,000	50,000	10.166
					subtotal for personnel	**1,345,000**	273.471
Fuel/vehicles							
Round trip (Ave 800km)						933,333	189.769
Local running for 6 days - 20 litres per day at 3500 per litre						420,000	85.396
Vehicle Hire for 7 days						1,800,000	365.983
					subtotal for travel	**3,153,333**	641.148
					subtotal for each team	***4,498,333***	914.619
Total number of Supervision teams required							
2 teams for ten CIFF							
survey sites					***SUBTOTAL***	***4,498,333***	914.619

LAB REQUIREMENTS				
ITEMS	**QTY**	**Unit COST**	**Total cost (UGX)**	**GBP**
Slide labels	140	6,000	840,000	170.792
Fine tip markers	23	50,000	1,166,667	237.211
Newsprint	280	2,000	560,000	113.861
Pens	5	20,000	93,333	18.977
Gloves	280	19,000	5,320,000	1081.684
Omo	42	9,000	378,000	76.856
Jik	9	94,000	877,333	178.383
Insecticide	28	9,000	252,000	51.238
Climax	5	20,000	93,333	18.977
Matchbox	23	2,500	58,333	11.861
Waste bags	93	5,000	466,667	94.885
Masking tape	224	3,500	784,000	159.406
Dettol Soap	14	30,000	420,000	85.396
GPS batteries	93	7,000	653,333	132.838
Box files	47	5,000	233,333	47.442
Toilet paper	19	100,000	1,866,667	379.538
Polythene sheets	467	1,200	560,000	113.861
Lens tissue	23	15,000	350,000	71.163
Photocopying paper	93	20,000	1,866,667	379.538
Distilled water (1 Jerry can)	1	25,000	25,000	5.083
Paraffin for burning wastes(each team needs 10 Litres)	50	3,000	150,000	30.499
Glycerine (2.5litres) costs 98,000	1	98,000	98,000	19.926
Malachite green powder (50mg)	1	190,000	190,000	38.632
Photocopier ink	9	150,000	1,400,000	284.654
subtotal for lab consumables			***18,702,667***	3802.701
	Qty	Unit Price		
Vehicle Maintenance (Minor fixtures and repairs during field)			0	0.000
Vehicle Hire(5 teams* 26 days)	130	180,000	23,400,000	4757.782
Vehicle service	-	350,000	0	0.000
subtotal additional vehicle costs			***23,400,000***	4757.782

	UGX	**GBP**
TOTAL CIFF FIELDWORK BUDGET	**132,609,333**	**£26,962.660**

CIFF Uganda M&E Parasitology Form F5 (CCA/KK Schools)

ID Number ***(DD.SC.SSS.NNN)****	|___|___|.|___|___|.|___|___|___|.|___|___|___|	Interviewer Initials	|___|___|___|
***DD – district code, SC – sub-county, SSS – school code, NNN – ID number (00-999)**		**Date of survey** *(DD/MM/YYYY)*	|___|___|-|___|___|-|___|___|___|___|
Name of Village (*adults*):			

A. Individual

1. **Name:**				
2. **Sex:** *1=Male 2=Female* |___|		3. **Age** ***(years):*** |___|___|		
4. **Attending school?: Y/N** |___|	5. **Class** ***(if student):*** |_____|			
6. **Occupation:** Housewife ☐	Farmer ☐	Teacher /Professor ☐	Unemployed ☐	Other: _____

B. Kato Katz

Date *(DD-MM-YYYY)*	|___|___|-|___|___|-|___|___|___|___|	|___|___|-|___|___|-|___|___|___|___|	|___|___|-|___|___|-|___|___|___|___|			
Slide	*Day 1 Slide A*	*Day 1 Slide B*	*Day 2 Slide A*	*Day 2 Slide B*	*Day 3 Slide A*	*Day 3 Slide B*
Microscopist initials	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|
S. mansoni*	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|	|___|___|___|
Hookworm*	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|
Ascaris*	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|
Trichuris*	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|	|___|___|___|___|

*Egg count per slide i.e. do not multiply by 24; **ensure zero counts are recorded; if missing leave blank.**

Notes:

2. Appendix for Chapter 4: Participant ID forms

CIFF M&E Participant Identification Form F1

Date of Survey *(DD-MM-YYYY)*	|___|___|-|___|___|-|___|___|___|___|	Registers Initials	|___|___|___|
District Name		District Code	|___|___|
Sub-county Name		Sub-county Code	|___|___|
School Name		School Code	|___|___|___|
Name of Village/Community		Village code	|___|___|___|

Participant Identification –M&E 2016

	ID Number *(DD.SC.SSS.NNN)*[1]	Name	Class	Sex[2]	Age
1.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
2.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
3.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
4.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
5.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
6.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
7.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
8.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
9.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
10.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
11.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
12.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
13.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
14.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
15.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
16.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
17.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
18.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
19.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|
20.	|___|___|.|___|___|.|___|___|___|.|___|___|___|			|___|	|___|___|

[1] *DD – district, SC – sub-county code, SSS – school code or village code if not school aged, NNN – ID number (00-999)*
[2] M = Male, F = Female

2. Appendix for Chapter 4: School forms

CIFF 2015 M&E School/Village Form F2

Date of visit	*(DD-MM-YYYY)*	|__|__|-|__|__|-|__|__|__|__|	Reporters Initials	|__|__|__|

A. Site Details		
1. District Name		
2. District Code	*(DD)*	|__|__|
3. Sub-county Name		
4. Sub-county Code	*(SC)*	|__|__|
5. Village/Community Name		
6. Village/Community Name Code		

B. GPS (at time of…)	
1. Arrival decimal degrees **east**	|__|__|__|.|__|__|__|__|__|__|__|__|__|
2. Arrival decimal degrees **south**	|__|__|__|.|__|__|__|__|__|__|__|__|__|
3. Departure decimal degrees **east**	|__|__|__|.|__|__|__|__|__|__|__|__|__|
4. Departure decimal degrees **south**	|__|__|__|.|__|__|__|__|__|__|__|__|__|

C. School details			
1. School Name			
2. School Code	*(SSS)*		|__|__|__|
3. Name of Headmaster			
4. Contact Number of Headmaster			
5. Have pupils in your school received PZQ treatment in the last year?	*0=No 1=Yes 2=Don't know*		|__|
6. Number of staff	*Male* |__|	*Female* |__|	
7. **Lowest** Class taught	*1=One 2=Two 3=Three 4=Four 5=Five 6=Six 7=Seven 8=Nursery*		|__|
8. **Highest** Class taught	*1=One 2=Two 3=Three 4=Four 5=Five 6=Six 7=Seven*		|__|

D. Village/Community details		
9. Village/Community Name		
10. Village/Community Code	*(SSS)*	|__|__|__|
11. Name of Head		
12. Contact Number of Head		
13. Have people in this area received PZQ treatment in the last year?	*0=No 1=Yes 2=Don't know*	|__|
14. Number of individuals	*Male* |__|	*Female* |__|

E. Transmission sources		
Is there a transmission source nearby?	*0= No 1 = Yes*	|_____|
What is/are the names of the transmission source(s)		
How many kilometres /meters is the nearest transmission sources	|_____| km	|_____| m

[CIFF M&E School Form] Version 11102013 Page **1** of **1**

2. Appendix for Chapter 4: Adult/parent consent forms

ADULT/PARENT CONSENT FORM FOR COMMUNITY/PRE-SCHOOL SURVEY OF SCHISTOSOMIASIS AND INTESTINAL WORMS

Institutions: Vector Control Division (VCD), Ministry of Health, Kampala, Uganda.
Schistosomiasis Control initiative (SCI), Imperial College, London.

Investigators: Dr Edridah T.Muheki (VCD) and Ms Arminder Deol (SCI)
Tel: Kampala 41 251 927, Fax: Kampala 41 346 885

CONSENT FORM FOR INDIVIDUALS PARTICIPATING

Bilharzia (schistosomiasis), hookworms and other intestinal worms are endemic through large parts of Uganda and pose a major public health threat. The Vector Control Division (VCD) of the Ministry of Health, in collaboration with the Schistosomiasis Control Initiative, Imperial College London are extending coverage of treatment to an additional number of age groups in the community. These extra groups will provide essential information for the development of a full age-infection intensity profile (how heavily infected individuals are, by age group) to represent the current situation in Uganda so that we can better understand the infection levels in different age groups and determine the best possible treatment strategy for the following years.

With your permission, you and/or your child will be included in a community survey. You will decide whether you/your child would like to enrol in the study. The individuals taking part in this survey will be asked to provide a stool sample every day for two days. They will also be asked questions about their name, age and sex.

This information will be recorded on forms that will be kept in a locked room at the VCD laboratory in Kampala. Only staff from the VCD and SCI will have direct access to the forms. The information will be kept confidential and individuals' names will be removed during the analysis of data. The forms will be kept securely for the next 6 years and will then be burned.

All information will be treated as strictly confidential. You are free to withdraw yourself and/or your child from the study at any stage without disadvantages. All individuals found to be infected will be offered treatment against bilharzia and worms. For further information call Dr Edridah Tukahebwa on 0772443659. If you agree for yourself or your child to participate in this important study, you are requested to say the words below and endorse them with your signature or finger-print.

"The study objectives have been explained to me in a language I understand. I have been provided the opportunity to ask questions and a thorough explanation has been given to me. I now voluntarily agree for myself and/or my child to participate in this study."

VILLAGE/SCHOOL: **SCHOOL STAMP *(if applicable)*:**

ADULT/CHILD NAME: **ADULT/GUARDIAN SIGNATURE:**

Do you agree to the above study? **Yes / No** **DATE: __ / __ / ____**

CIFF Adult/Guardian Consent Form Mapping & Diagnostics. Version 10082015

2. Appendix for Chapter 4: Headteacher consent forms

HEADTEACHER CONSENT FORM SCHOOL SURVEY OF SCHISTOSOMIASIS AND INTESTINAL WORMS

Institutions: Vector Control Division (VCD), Ministry of Health, Kampala, Uganda.
Schistosomiasis Control initiative (SCI), Imperial College, London.

Investigators: Dr Edridah T.Muheki (VCD) and Ms Arminder Deol (SCI)
Tel: Kampala 41 251 927, Fax: Kampala 41 346 885

CONSENT FORM FOR INDIVIDUALS PARTICIPATING

Bilharzia (schistosomiasis), hookworms and other intestinal worms are endemic through large parts of Uganda and pose a major public health threat. The Vector Control Division (VCD) of the Ministry of Health, in collaboration with the Schistosomiasis Control Initiative, Imperial College London are extending coverage of treatment to an additional number of age groups in the schools and community. These extra groups will provide essential information for the development of a full age-infection intensity profile (how heavily infected individuals are, by age group) to represent the current situation in Uganda so that we can better understand the infection levels in different age groups and determine the best possible treatment strategy for the following years.

With your permission, we will conduct a survey at your school. Each child will also decide and verbally indicate whether they would like to enrol in the study. The table below shows the ideal maximum number of pupils per age group our survey will require. The pupils taking part in this survey will be asked to provide one stool sample every day for two days. They will also be asked questions about their name, age and sex.

Age range (yrs)	Number required
4-6	50
6-9	125
10-12	75
13-15	75
16-19	75

This information will be recorded on forms that will be kept in a locked room at the VCD laboratory in Kampala. Only staff from the VCD and SCI will have direct access to the forms. The information will be kept confidential information and individual's names will be removed during the analysis of data. The forms will be kept for the next 6 years and will then be burned. All information will be treated as strictly confidential. The children are free to withdraw from the study at any stage without disadvantages. All school-age children will be treated for bilharzia and worms shortly after whether or not they are in the study group. For further information call Dr Edridah Tukahebwa on 0772443659. If you agree to participate on behalf of your pupils in this important study, you are requested to say the words below and endorse them with your signature or finger-print.

"I have been explained the study objectives in a language I understand. I have asked questions and thorough explanation has been given to me. I now voluntarily agree to allow the pupils of my school to participate in this study."

SCHOOL: **SCHOOL STAMP:**

HEADTEACHER'S NAME: **HEADTEACHER'S SIGNATURE:**

Do you agree to the above study? Yes / No **DATE: __ / __ / ____**

CIFF Headteacher Consent Form CCA Mapping & Diagnostics. Version 10082015

2. Appendix for Chapter 4

Observed relationship between prevalence and intensity

The relationship between infection intensity and prevalence of infection in the survey was non-linear as expected[203], and consistent when comparing mean intensity with prevalence and prevalence of heavy-intensity infection with overall prevalence (Figure A5). This non-linearity was more evident for the high prevalence sites, while patterns were less consistent when investigating by prevalence group (Figure A6). The relationship between mean intensity of infection (epg) and prevalence of infection in the low prevalence groups was less pronounced (top row Figure A6 – note the y axis scale), indicating that higher prevalence does not necessarily correspond to higher intensity. When comparing the prevalence of heavy- infection against prevalence of any infection, the high prevalence group showed similar trends to mean intensity vs prevalence (bottom row, Figure A6), and indicates that the majority of the age groups have above 5% heavy-intensity infection prevalence. However, for the low prevalence groups, the plots are more informative highlighting that many of the age categories had 0% prevalence of heavy-intensity infection (particularly for the low prevalence untreated group).

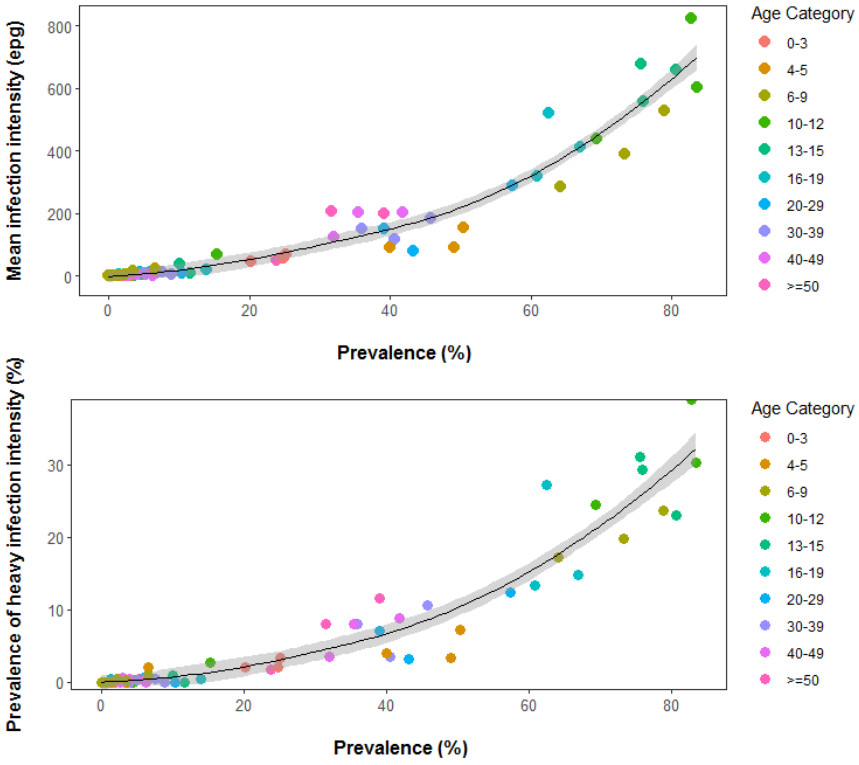


Figure A5. Relationship between mean intensity of infection and prevalence and between prevalence of heavy-intensity infection and prevalence, by age group. Best fit (black line) and standard errors (grey band) were obtained by fitting a Loess smoothed line.

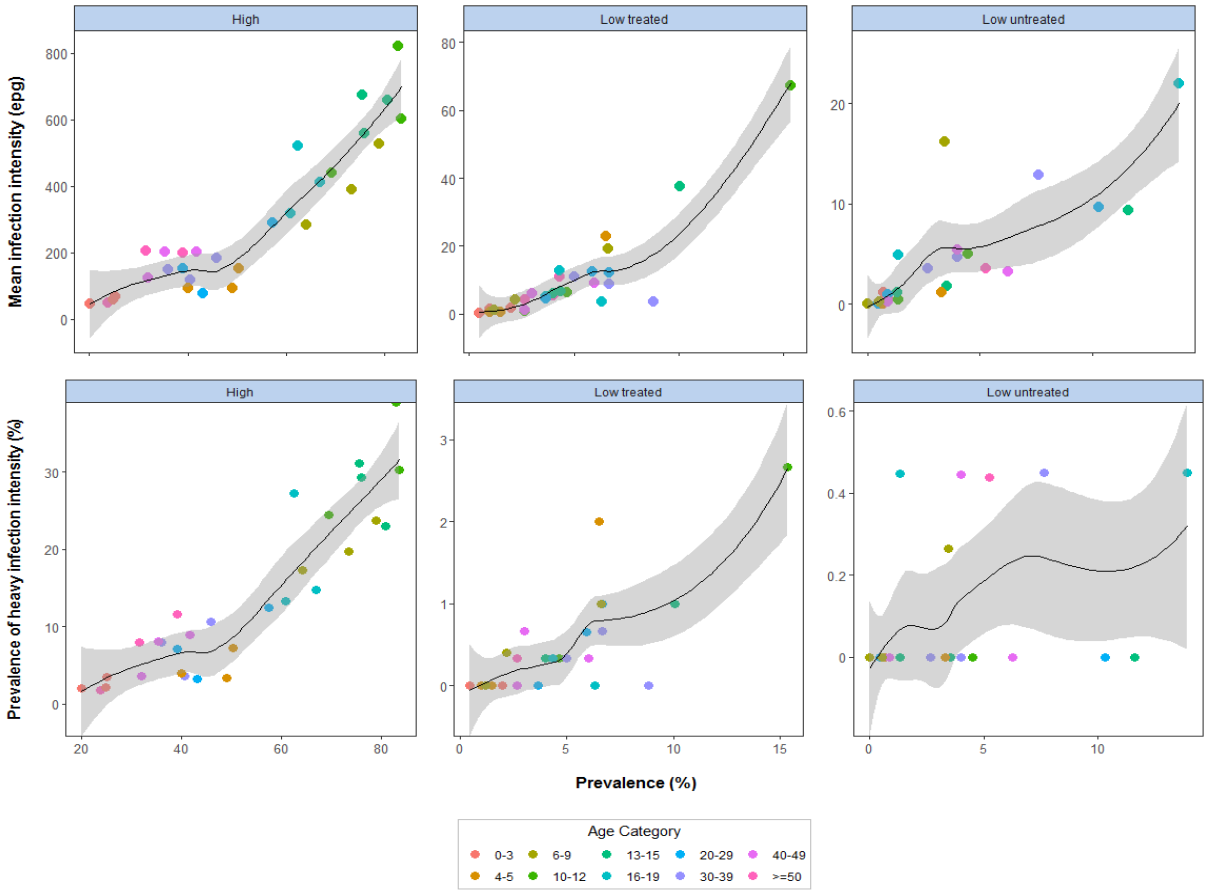


Figure A6. Relationship between mean intensity of infection vs prevalence and between prevalence of heavy-intensity infection vs prevalence, by age group and WHO prevalence group. Best fit (black line) and standard errors (grey band) were obtained by fitting a loess smoothed line.

3. Talks and achievements during PhD

The data generated, and their interpretation therein, in this PhD as well as the outputs of all three Research Objectives, have been presented at numerous conferences and meetings, including where I was invited and held a seminar to the WHO's NTD department and at the NTD Modelling Consortium technical meeting. Below is a list of meetings I attended as an invited speaker, presenting work that was part of this PhD:

Talks:

Invited Speaker:

- April 2016: Presented to modellers at the Neglected Tropical Disease Modelling Consortium Technical meeting (Warwick)
- June 2016: Held a seminar at the World Health Organization headquarters for the NTD department (Geneva)
- Sept 2016: Presented to NGO CEOs, senior staff and donors at the 7th Annual NTD NGDO Network Meeting (Washington DC)
- March 2017: Panel meeting in Uganda at the 8th AfrEA conference with senior stakeholders to discuss findings of the work done on the PhD to date (President of Uganda present).
- June 2017: Presented to the Water Infrastructure for Schistosomiasis-Endemic Regions (WISER) team (London)
- Nov 2017: Guest speaker at Imperial College London's Creative Quarter event

Others:

- Oct 2015: Gave oral presentation on the Markov model at the annual meeting of the American Society of Tropical Medicine & Hygiene (ASTMH, Philadelphia) and presented the age-intensity work as poster
- April 2015: Oral presentation at BSP (Markov model)
- September 2015: Presented a poster at European Congress on Tropical Medicine and International Health (ECTMIH, Basel) of the Markov model
- April 2016: Oral presentation on findings of Chapter 4 at British Society for Parasitology (BSP) meeting (Imperial College London)

- April 2016: Shortlisted and represented department for the 3-minute PhD thesis oral presentation competition (Imperial)
- June 2016: Results from the Markov model presented at the PhD symposium at Imperial College where I won runner up prize for oral presentation
- June 2016: Two posters at the Wellcome Trust Centre for Global Health Research Annual Meeting. One of the posters was based on the Markov model and the other was based on work of a volunteer that the candidate had supervised, based on Chapter 4 (volunteer presented, won runner up prize, Royal Geographical Society of London)
- November 2016: Attendance at Coalition for Operational Research on Neglected Tropical Diseases (COR-NTD) and ASTMH, presentation of two posters
- April 2017: Oral presentation on threshold work at BSP in Dundee
- June 2017: Oral presentation on Markov model work at the SCI open day (for donors and general public)
- June 2017: Oral presentation on threshold work to Global health students at Imperial College London
- Nov 2017: Presented two posters at ASTMH Baltimore (A-I, Thresholds)
- Nov 2017: The Wellcome Trust Centre for Global Health Research Scientific Meeting - thresholds selected for oral presenting (200 attendees)
- Nov 2017: Oral presentation at Epidemics 6, Barcelona (on Chapter 2 findings)
- April 2018: Attended Water Infrastructure for Schistosomiasis-Endemic Regions (WISER) technical meeting, Tanzania
- October 2018: Attended COR-NTD meeting (26-27 Oct), Global Schistosomiasis Alliance meeting (28 October) and ASMTH (29-1 Nov) in New Orleans.

Achievements:

- Invited to WHO for monthly technical meetings with the NTD department to discuss Markov model and further research developments to help inform guidelines.
- Supervised a volunteer who won a runner up prize for her work (work stemming from Chapter 4)
- Supervised a volunteer who went on to win the Prime Minister's Point of Light award, presented to her by former president Jimmy Carter with a personal letter from former prime minister David Cameron (work based on Chapter 2)
- Reviewed papers for key Primary journals including *Nature, Scientific Reports, PLoS NTDs*

- Mentoring two MSc students throughout their studies
- Demonstrated practical sessions for the BSc, Infectious Disease Modelling short course and MSc students
- Lectured for MSc and BSc students
- Published manuscript on the Markov model, Chapter 3
- Manuscript under consideration based on Chapter 2
- July 2017: Chaired for the PhD symposium MRC centre at Imperial College London
- Invited to WHO schistosomiasis STAG meeting during my attendance at WHO HQ

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Parasites & Vectors

RESEARCH Open Access

Development and evaluation of a Markov model to predict changes in schistosomiasis prevalence in response to praziquantel treatment: a case study of *Schistosoma mansoni* in Uganda and Mali

Arminder Deol[1*], Joanne P. Webster[1,2,3], Martin Walker[3], Maria-Gloria Basáñez[3], T. Déirdre Hollingsworth[4], Fiona M. Fleming[1], Antonio Montresor[5] and Michael D. French[1]

Abstract

Background: Understanding whether schistosomiasis control programmes are on course to control morbidity and potentially switch towards elimination interventions would benefit from user-friendly quantitative tools that facilitate analysis of progress and highlight areas not responding to treatment. This study aimed to develop and evaluate such a tool using large datasets collected during Schistosomiasis Control Initiative-supported control programmes.

Methods: A discrete-time Markov model was developed using transition probability matrices parameterized with control programme longitudinal data on *Schistosoma mansoni* obtained from Uganda and Mali. Four matrix variants (A-D) were used to compare different data types for parameterization: A-C from Uganda and D from Mali. Matrix A used data at baseline and year 1 of the control programme; B used year 1 and year 2; C used baseline and year 1 from selected districts, and D used baseline and year 1 Mali data. Model predictions were tested against 3 subsets of the Uganda dataset: dataset 1, the full 4-year longitudinal cohort; dataset 2, from districts not used to parameterize matrix C; dataset 3, cross-sectional data, and dataset 4, from Mali as an independent dataset.

Results: The model parameterized using matrices A, B and D predicted similar infection dynamics (overall and when stratified by infection intensity). Matrices A-D successfully predicted prevalence in each follow-up year for low and high intensity categories in dataset 1 followed by dataset 2. Matrices A, B and D yielded similar and close matches to dataset 1 with marginal discrepancies when comparing model outputs against datasets 2 and 3. Matrix C produced more variable results, correctly estimating fewer data points.

Conclusion: Model outputs closely matched observed values and were a useful predictor of the infection dynamics of *S. mansoni* when using longitudinal and cross-sectional data from Uganda. This also held when the model was tested with data from Mali. This was most apparent when modelling overall infection and in low and high infection intensity areas. Our results indicate the applicability of this Markov model approach as countries aim at reaching their control targets and potentially move towards the elimination of schistosomiasis.

Keywords: Schistosomiasis, Markov modelling, Transmission dynamics, Transition probabilities, Praziquantel, Prevalence, Intensity

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Background

In recent years there has been a renewed focus on the control and possible elimination of certain neglected tropical diseases (NTDs) by the global health community. One of the NTDs with the greatest human health and socio-economic burden is schistosomiasis, estimated to infect over 238 million people [1] at a global cost of 3.3–4.5 million disability-adjusted life years (DALYs). Approximately 85 % of people infected with schistosomes reside in sub-Saharan Africa (SSA), with the disease potentially causing over 200,000 deaths per year [2, 3]. National-scale control programmes are now in place in many countries, using preventive chemotherapy (PC) by mass drug administration (MDA) with praziquantel (PZQ) [4].

The pharmaceutical company Merck KGaA has donated over 290 million tablets of PZQ to the World Health Organization (WHO) and has committed up to a further 250 million tablets per year from 2016 [5]. The tablets are distributed by the Ministries of Health of endemic countries, where in some, non-governmental organizations such as the Schistosomiasis Control Initiative (SCI) provide technical support and assistance (and in some cases purchasing and supplying additional PZQ) to these programmes [6, 7]. Since its establishment in 2002, SCI has helped to provide over 140 million treatments for schistosomiasis to at-risk children and adults in SSA and the Middle East [8]. As part of the monitoring and evaluation (M&E) component that runs alongside the treatment campaigns, SCI has contributed to the collection of rich longitudinal datasets from numerous countries on the impact of treatment on prevalence, intensity and morbidity. Many schistosomiasis control programmes have been running for several years, and have achieved their primary target of controlling schistosomiasis-related morbidity (where the aim of "control" is reducing prevalence of heavy infection to < 5 % across sentinel sites at 75 % national coverage [9]), whether from intestinal schistosomiasis (caused predominantly by *Schistosoma mansoni*) or from urogenital schistosomiasis (caused predominantly by *S. haematobium*) [10]. With this in mind, the WHO, alongside its global partners, has set the agenda for the next stage of control. The London Declaration on NTDs in January 2012 endorsed the ambitious targets set by the WHO for the control and elimination of many NTDs, including schistosomiasis, with the elimination 'as a public health problem' from most WHO regions and by selected African countries by 2020 (i.e. reducing prevalence of heavy infection < 1 % in all sentinel sites) [9, 11, 12]. In some local settings, interruption of transmission is also anticipated, thereby accelerating elimination of the disease [12].

The impact of a control programme is often measured by changes in the prevalence and/or the intensity of infection. Preventive chemotherapy by MDA with PZQ has been demonstrated to be, in general, highly effective in reducing both the prevalence and intensity of schistosome infection [13–15]. The development of a user--friendly quantitative tool that uses these impact measurements to inform programme managers as to whether their programme is on target to meet their goals would be invaluable in assisting with programme design and evaluation and in providing an early warning of potential transmission 'hotspots' or poor programme performance.

A Markov statistical model was developed to capture soil-transmitted helminth (STH) infection dynamics through rounds of MDA (with benzimidazoles), by Montresor and colleagues in 2013 [16, 17]. The authors demonstrated that their model successfully predicted changes in the prevalence of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (consisting of the two species that infect humans: *Ancylostoma duodenale* and *Necator americanus*) through five rounds of MDA using data collected at baseline and after one round of treatment in Vietnam to parameterize the Markov Transition Probability (MTP) matrix; the essential ingredient of such Markov models. The predictive capability of the model was also successfully validated against STH data from 26 control programmes in 16 countries [17].

The main appeal of the Markov approach resides in its simplicity [18], whereby the underlying transmission dynamics are not modelled explicitly but are captured empirically using a purely statistical approach based on estimated transition probabilities (TP). The model can be used to track progress and to identify deviations from expected programme performance where observed values fall outside of predicted uncertainty intervals (e.g. 95 % prediction intervals, PIs).

Here, for the first time, we extend the discrete-time Markov model approach, in which both time and infection states (intensity groups) are defined, and apply it to *S. mansoni*, a causative agent of intestinal schistosomiasis across Africa, South America, and the Yemen. We test the model under contrasting control programme scenarios, using unique and extensive datasets from SCI-supported programmes in Uganda and Mali.

Our specific aims in this study were to: (i) develop and test a discrete-time Markov model for schistosomiasis using data on the intensity and prevalence of *S. mansoni* infection during mass treatment with PZQ; (ii) introduce measurements of precision around predictions in the form of 95 % PIs; (iii) estimate changes in the overall infection prevalence and the prevalence in infection intensity categories over time; (iv) qualitatively compare the predictive capabilities of the model parameterized using MTP matrices estimated from different settings within the same country (Uganda) and from a different

country (Mali), to test the transferability of the TPs to different regions; (v) test the robustness of the model's predictive capabilities using data from non-baseline years to estimate the MTP matrices; and (vi) elucidate the ability of different data types (longitudinal and cross-sectional data) to qualitatively test the predictions of each matrix.

Methods

Model development

The development of a Markov model for STH infection has been explained fully elsewhere [16]. Briefly, in relation to *S. mansoni,* the proportion of individuals in each of the 4 WHO-recommended infection classes defined by estimates of eggs per gram (epg) of faeces (not infected, 0 epg; infected at light intensity, 1–99 epg; infected at moderate intensity, 100–399 epg; infected at high intensity, ≥ 400 epg [19]) and referred to as "conditional states" (CS), is calculated from pre-treatment baseline data [20]. Subsequently, an individual's probability of transition (if any) to other CS prior to the next round of treatment (year 1) is calculated using the observed change in the proportion of followed individuals in each category (from baseline to year 1). These observed changes are used to parameterize a MTP matrix, formed from a set of 16 transition probabilities (TPs), as illustrated in Fig. 1. The model is initialised using observed baseline starting values. Then, through a series of Markov processes defined by the MTP matrix (see Additional file 1: Text S1 and Table S1), projections are made on the proportion of infected individuals by intensity class through rounds of MDA.

In the first instance, we focused on *S. mansoni* data collected from Uganda between the inception of the programme in 2003 and for the first 3 annual follow-up rounds after baseline. For further details of the control programme in Uganda see [21, 22]. As part of the national control programme, data were collected as egg counts (expressed as the arithmetic mean epg) from a cohort of 125 children (aged 6–13) per school, from 37 schools across the country, over a time span of 4 years.

For the calculation of the TPs from the full Uganda dataset, longitudinal data between baseline and year 1 were used (i.e. only data from those individuals who could be identified at each of those time points, namely 1,258 individuals). To quantify uncertainty around the model projections (expanding on the previously published version of the model applied to STH [15, 16]), 95 % prediction intervals (95 % PIs) associated with each TP were calculated through bootstrap resampling (with replacement) for 10,000 iterations, using the R package 'boot' version 1.3–9 [23–26]. The 95 % PIs were calculated in the following steps: 1) a new 'dataset' was generated through bootstrapping allowing for the calculation of a new MTP matrix (set of 16 TPs); 2) the model was run (using these TPs) to calculate the reduction in

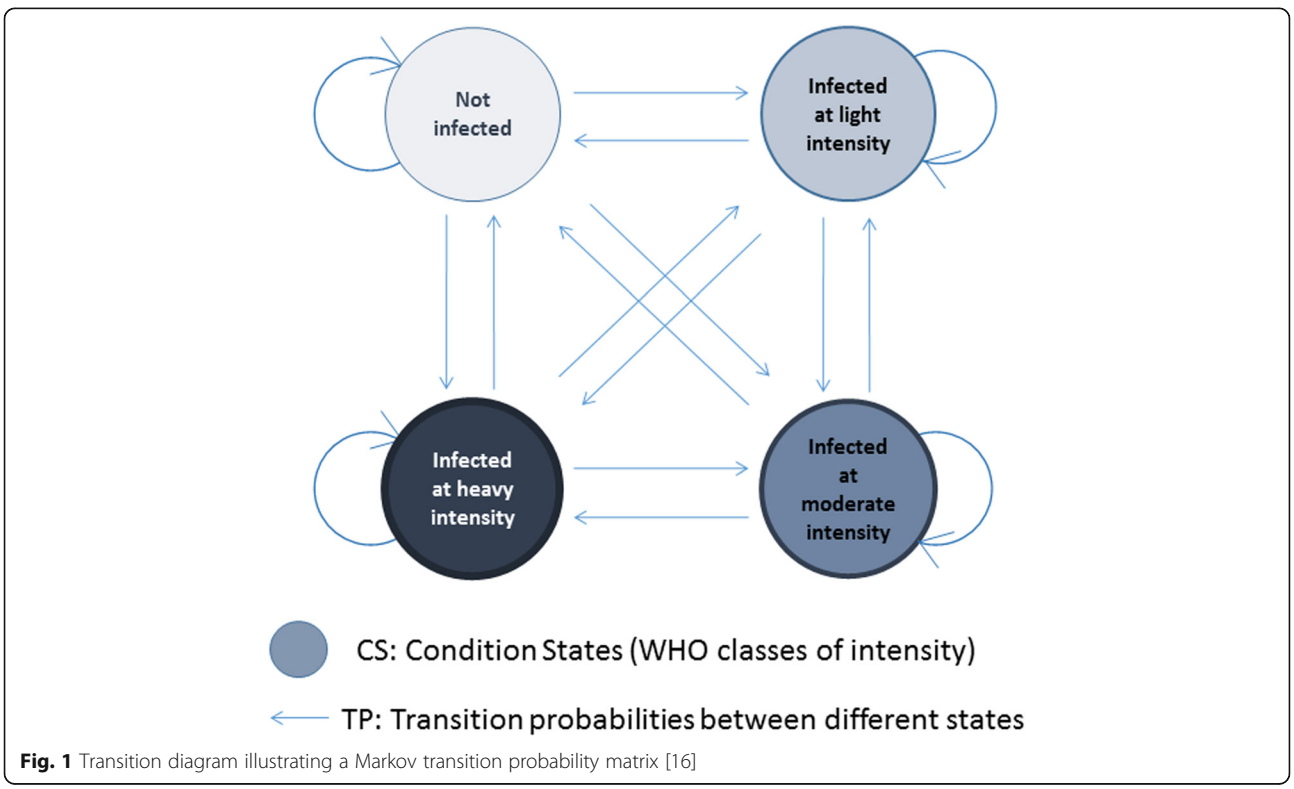

Fig. 1 Transition diagram illustrating a Markov transition probability matrix [16]

prevalence over time; 3) steps 1) and 2) were repeated 10,000 times; 4) for each time point, the predicted mean prevalence was calculated; and 5) from the range of predicted prevalence levels generated, the 95 % PIs were constructed using the 2.5 % and 97.5 % percentiles. Initially, for the observed data, the full cohort of individuals who were followed up from baseline to year 3 of the intervention was included (757 individuals). Since some of the individuals in this dataset were also used for the calculation of the TPs (as would be the case in practice when using these models), it was expected that the predicted prevalence at year 1 would follow the observed values from the full dataset 1 (Table 1) very closely. In order to test the transferability of the model using independent data, the TPs calculated from the full Uganda dataset were also used to test model predictions against longitudinal data from Mali. Conversely, to further test the robustness of the model, longitudinal baseline and year 1 data from Mali was also used to parameterize a separate model and tested against observed Uganda longitudinal data. These additionally tested the flexibility of the model to different starting baseline prevalence levels (for Mali the baseline overall prevalence was 26.5 % for *S. mansoni* infection whilst for Uganda the overall prevalence was 43.0 %).

Datasets used and models developed

The data were collected as part of a treatment campaign in Uganda for school-aged children (SAC) from 2003 to 2006 and in Mali from 2004 to 2007 (Fig. 2). We selected SCI data from Uganda as our primary dataset to parameterize and validate our model because: (i) Uganda was the first 'SCI country' to commence large-scale control of schistosomiasis in 2003, and thus has the most extensive longitudinal datasets (including pre-intervention baseline); (ii) *S. haematobium* infections are highly localised to specific regions within Uganda, with prevalence mostly below 1 %, and hence the potentially confounding impact of *S. haematobium* infection on the transition probabilities can be assumed to be minimal [27]; and (iii) Uganda has been very successful in implementing control [13], making this country an ideal candidate to move towards elimination of schistosomiasis as a public health problem. The extensive Ugandan dataset also enabled the model to be tested against data obtained from contrasting districts and disease endemicities. Three districts were selected based on their geographic spread and the distribution of infection intensities: Moyo (only low intensity infections); Busia (only low and moderate intensity infections); Masindi (only moderate and high intensity infections). There were no districts with only moderate or only high infection intensities. The remaining districts on which the model was tested (i.e. dataset 2) contained a varied composition of intensities (and were *not* used for the development of matrix C) (see Fig. 2 and Additional file 1: Table S2 for further details on the districts). The dataset and its different subsets that were used to test the predictive capabilities of the models are listed in Table 1. Table 2 shows other MTP matrices that were developed by the same method described in the previous sub-section, *Model development*.

In summary, 4 matrix variants (A-D) were used to compare different data types for parameterization: A-C from Uganda and D from Mali. These were tested on 4 datasets (1–4): dataset 1 refers to the full longitudinal cohort data from Uganda; dataset 2 to a subset of dataset 1 using districts not used to parameterize matrix C; dataset 3 to cross-sectional data from Uganda, and dataset 4 comprises data from Mali, which acted as a completely independent dataset. Matrix A was an 'ideal' scenario where longitudinal baseline and year 1 data from a large programme were available to parameterize the model and develop the TPs. The TPs were assumed to be fixed throughout the years. In practice, since changes between intensity groups are likely to be more dramatic after the first treatment in a treatment-naïve area, matrix B was developed using TPs from post-

Table 1 Data used for testing model/matrices

Observed baseline prevalence (%)							
Dataset	Data type	Description	Sample size (*n*)	Overall prevalence	Low intensity	Moderate intensity	High intensity
1	Uganda longitudinal baseline to year 3	Full longitudinal data set	747	43.0	16.6	11.4	15.0
2	Uganda longitudinal baseline to year 3	4[a] Ugandan districts out of 7	400	46.5	15.5	12.3	18.8
3	Uganda cross-sectional baseline to year 3	Varying sample size per year, full programme data	Baseline: 4,222; Year 1: 3,973; Year 2: 4,192; Year 3: 3,373	45.2	16.0	11.7	17.6
4	Mali longitudinal baseline to year 2	Full longitudinal data set	897	26.5	12.5	7.1	6.9

[a]These districts were selected for their wide range of infection intensities and NOT used to the development of matrix C

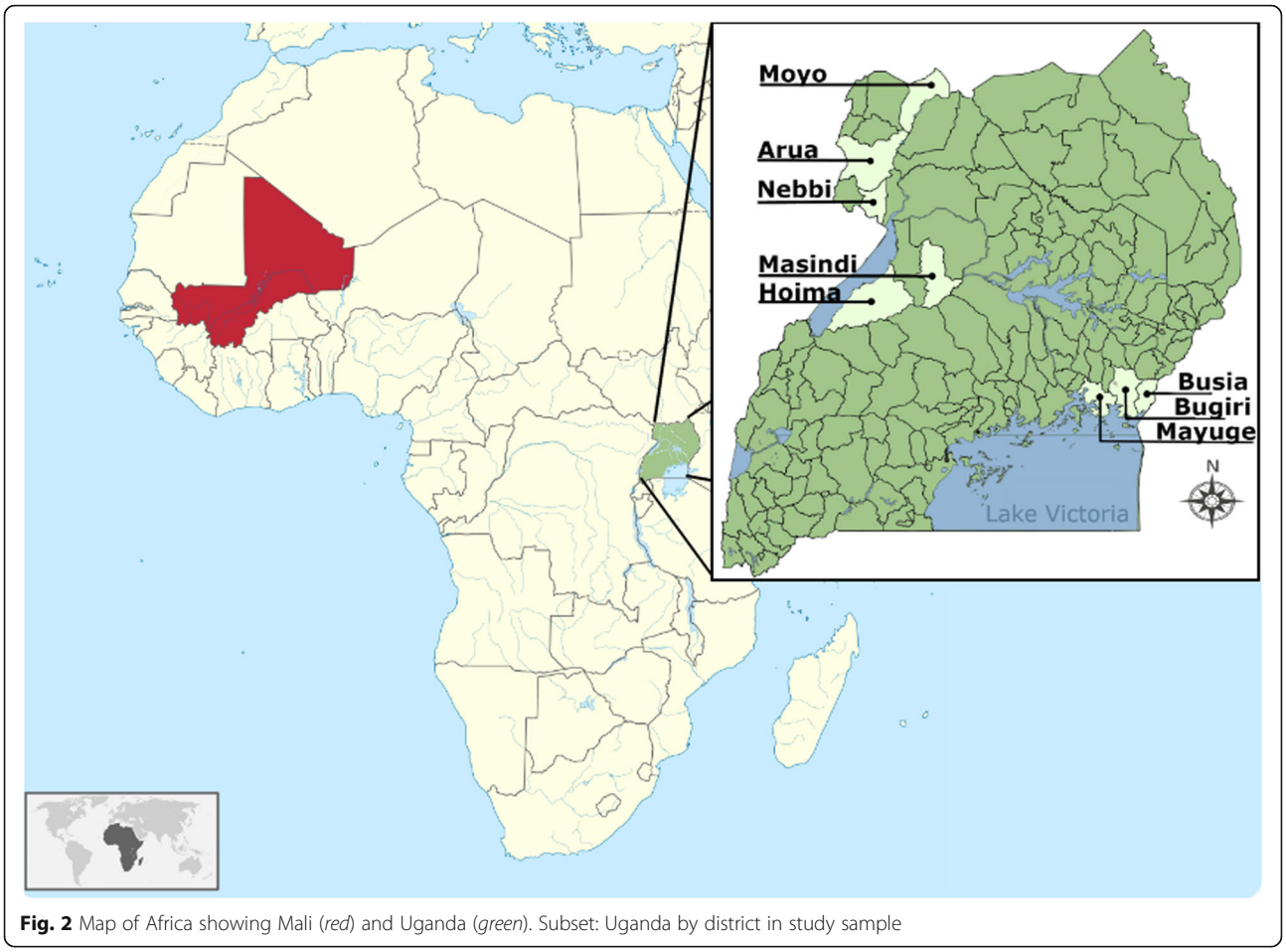

Fig. 2 Map of Africa showing Mali (*red*) and Uganda (*green*). Subset: Uganda by district in study sample

baseline treatment, between year 1 and year 2. The use of matrix C predictions on dataset 2 is an illustration of a scenario where an 'independent' matrix might be used, calculated from a smaller dataset, to estimate changes on a 'separate' smaller dataset (dataset 2) that is not used to develop the TPs. Matrix D illustrates a case where longitudinal data from another country are used to develop the TPs (Mali) in order to predict changes in prevalence in a separate country (Uganda). In the following sections we distinguish between 'estimation' (the estimated TP values), 'prediction' (the model outputs), 95 % prediction intervals (95 % PIs, constructed as described above) and 95 % confidence intervals (95 % CIs) around the data (calculated as binomial proportion confidence intervals). As a conservative approach to the qualitative model assessment, we focus on the ability of the models to capture the observed point prevalence values within the 95 % PIs whilst also highlighting whether the 95 % PIs of the model capture the 95 % CIs of the observed data.

Table 2 Markov transition probability (MTP) matrices developed

MTP matrix	Country	Number of districts	Time points used to develop matrix	Sample size (n)
A	Uganda	7	Baseline and year 1	1,245
B	Uganda	7	Year 1 and year 2	1,260
C	Uganda	3	Baseline and year 1	540
D	Mali	-	Baseline and year 1	1,092

Matrix and dataset combinations

Matrix A, datasets 1, 2, 3, 4

Matrix A was calculated using all 1,245 individuals that were followed from baseline to year one in the Uganda dataset. Dataset 1 contains 747 of these individuals who were followed for a further 3 years (lower numbers due to loss of follow-up). Therefore, we expected Matrix A to provide the most accurate predictions, on dataset 1. In addition, to test how the model performed with smaller sample sizes, less complete data, and other data types, selected districts (dataset 2) and cross-sectional data (dataset 3) were used. To test how well the model performed using matrix A on a completely independent dataset, longitudinal data from Mali (baseline to year 2; dataset 4) were used.

Matrix B, datasets 1, 2, 3

It is important to understand how the model and its outputs differ between 2 different time points within the same settings, since the model explicitly assumes that the TPs remain constant between each time point. To explore this, instead of using the baseline and year 1 data to calculate the TPs for the matrix, data derived from follow-up years 1 and 2 were used from the full Uganda dataset (matrix B). The outputs from these TPs were compared to the observed values from datasets 1–3.

Matrix C, datasets 1, 2, 3

A comparison was made between model outputs using smaller sample sizes for situations in which fewer data are available to parameterize TPs. This was achieved by selecting district-level subsets of the data for calculating TPs. The predictions were also tested against dataset 1 (longitudinal Uganda dataset) to represent a case where limited data would be used for the development of the TPs to project the expected impact of a much larger programme. In addition, to test the least favourable data scenario where there is very high loss to follow-up, the model was also used to estimate changes in the proportions infected according to cross-sectional data, i.e. small sample size for TP development and poor follow-up to test the model (dataset 3).

Matrix D, dataset 1

Transition probabilities developed from the Mali baseline and year 1 data (Matrix D) were used to predict the longitudinal Ugandan dataset (dataset 1). This was performed by way of testing model performance when a dataset other than the Ugandan data are used for calculation of the TPs. This addresses issues on the generalizability of the MTP approach among endemic settings.

Results

We focus on the ability of the models to capture the observed point prevalence values (and accompanying uncertainty) within the 95 % PIs. Where the upper or lower bounds of the 95 % CIs around the observed values overlapped with the model predictions (or their 95 % PIs) only, the model was able to capture the uncertainty in the data but not the point prevalence.

Predictions made on dataset 1

Table 3 shows all the predictions that were made for dataset 1. The symbol next to the values highlights predictions that were closest to the observed point prevalence values and the values in bold highlight predictions where observed point prevalence values fell outside the 95 % PIs; in most cases however, the model still captured some of the uncertainty around the observed values (10 cases out of 13 shown in bold).

All of the predictions from each matrix captured the observed point prevalence values within their PIs for the low infection intensity prevalence category in each year with the exception of matrix D (year 1 and marginally for year 2) and for the prevalence of high intensity infections with the exception of matrix C (year 3), although in both cases the 95 % PIs and the 95 % CIs overlapped. When using the TPs derived from matrix A (the full Ugandan dataset) to predict forward the reduction in *overall* infection prevalence as well as in prevalence for all infection intensity groups, the outputs matched the observed data within the 95 % PIs for all time points with the exception of the moderate intensity group and the overall prevalence for year 2 (Fig. 3 and Table 3), which indicated that the observed prevalence for each infection intensity group was below the lower bound of the prediction intervals of the estimated prevalence. However, in both instances, the model captured the 95 % CIs of the observed values.

As with matrix A, matrices B (Additional file 1: Figure S1a) and D (Fig. 4) also 'highlighted' year 2 for both prevalence of moderate infection intensity and overall prevalence as a year in which observed values fell below 95 % PIs (with matrix B capturing the upper 95 % CI around the data, as with matrix A). Matrix C, however, did not highlight any of the same time points identified by the other matrices but instead, highlighted different years in the moderate intensity, high intensity and overall prevalence groups as time points in which observed point prevalence levels were higher than predicted by the model (Additional file 1: Figure S1b).

Predictions made on dataset 2

Table 4 shows the predictions that were made for dataset 2 (see also Additional File 1: Figure S2). All 3 matrices in this group indicated the same time point for the low infection intensity group (year 3) and the overall prevalence group (year 1 and year 3) as performing below the expected values, i.e. higher observed point prevalence values than predicted (although matrix A also identified year 2 for better programme performance than expected, for overall infection prevalence). The same pattern in predicted *vs* observed prevalence from dataset 1 by all matrices was observed in the moderate infection intensity group for all time points, with the exception of year 3 for matrix B, which mirrored matrix C estimates. Matrices A and B performed similarly as in dataset 1 for the high intensity group (i.e. all observations at each time point were within the prediction intervals of the model predictions) but matrix C indicated that the observed prevalence values from years 1 and 2 were marginally higher than expected. Matrix A was able to

Table 3 Predicted mean prevalence by matrices A-D for dataset 1 (full Uganda cohort baseline year 0 – year 3)

	Low intensity (predicted mean prevalence and 95 % CI)			Moderate intensity (predicted mean prevalence and 95 % CI)			High intensity (predicted mean prevalence and 95 % CI)			Overall prevalence (predicted mean prevalence and 95 % CI)		
Matrix	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Observed prevalence dataset 1	0.134 (0.111–0.160)	0.099 (0.080–0.123)	0.102 (0.082–0.126)	0.075 (0.058–0.096)	0.021 (0.013–0.035)	0.033 (0.023–0.049)	0.035 (0.024–0.051)	0.016 (0.009–0.028)	0.020 (0.011–0.031)	0.244 (0.214–0.276)	0.137 (0.114–0.163)	0.154 (0.130–0.182)
Matrix A Full dataset	0.142 (0.123–0.161)	0.108 (0.091–0.126)	0.095[a] (0.077–0.113)	0.075[a] (0.062–0.090)	**0.044 (0.033–0.056)**	0.033[a] (0.023–0.045)	0.044 (0.033–0.055)	0.023 (0.015–0.032)	0.017[a] (0.010–0.026)	0.261 (0.240–0.282)	**0.175 (0.151–0.200)**	0.144[a] (0.119–0.171)
Matrix B Uganda year 1 to year 2	0.135[a] (0.112–0.158)	0.105 (0.086–0.126)	0.090 (0.072–0.109)	0.069 (0.051–0.090)	**0.039 (0.028–0.051)**	0.028 (0.019–0.038)	0.048 (0.031–0.066)	0.024 (0.015–0.036)	0.016 (0.009–0.024)	0.252[a] (0.225–0.278)	**0.168 (0.141–0.197)**	0.133 (0.108–0.160)
Matrix C 3 selected districts	0.152 (0.122–0.183)	0.096[a] (0.071–0.122)	0.082 (0.057–0.108)	**0.045 (0.027–0.065)**	0.016[a] (0.008–0.027)	**0.009 (0.003–0.017)**	0.027 (0.013–0.043)	0.011[a] (0.003–0.021)	**0.008 (0.001–0.018)**	0.223 (0.193–0.255)	0.123[a] (0.093–0.156)	**0.099 (0.069–0.132)**
Matrix D Mali full dataset	**0.165 (0.141–0.190)**	**0.122 (0.100–0.146)**	0.095[a] (0.073– 0.117)	0.081 (0.062–0.101)	**0.051 (0.037–0.068)**	0.035 (0.023–0.049)	0.042[a] (0.028–0.057)	0.021[a] (0.012–0.032)	0.031 (0.007–0.021)	**0.288 (0.264–0.312)**	**0.195 (0.164–0.226)**	0.143 (0.113–0.175)

Bold = observed point prevalence values fell outside of the predicted boundaries
[a]Closest predictions to observed values

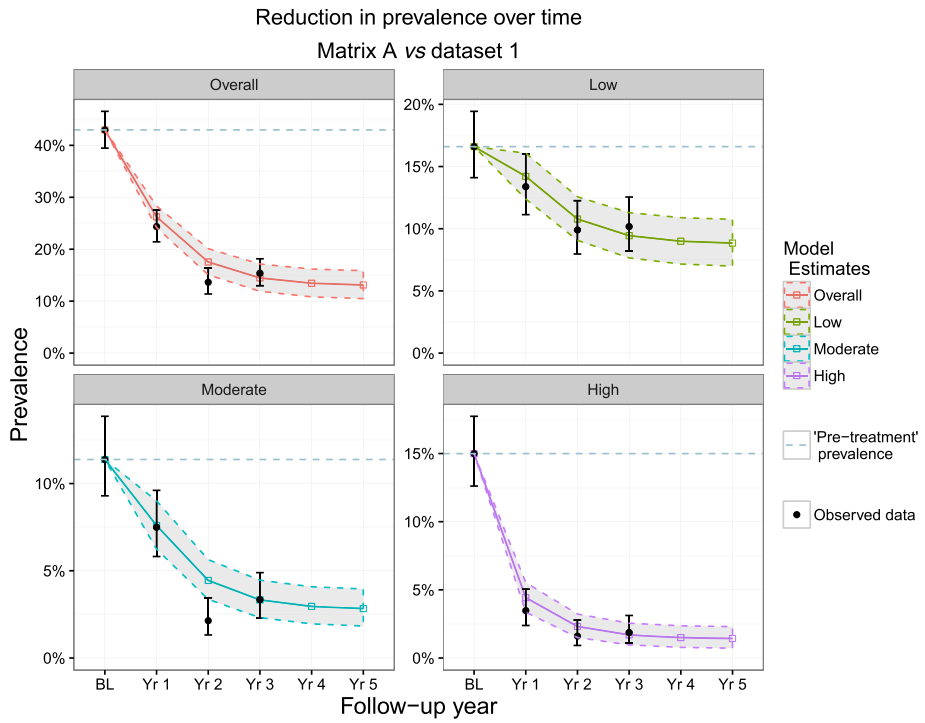

Fig. 3 Matrix A predictions and dataset 1 observations. Matrix A was composed of transition probabilities derived from Uganda baseline and year 1 data and dataset 1 represents the full longitudinal Ugandan observations. These 4 plots show the predicted reduction in prevalence by Matrix A (bands) *vs* observed (black points) in Uganda by overall prevalence group and by intensity group. The dotted line represents the pre-MDA prevalence

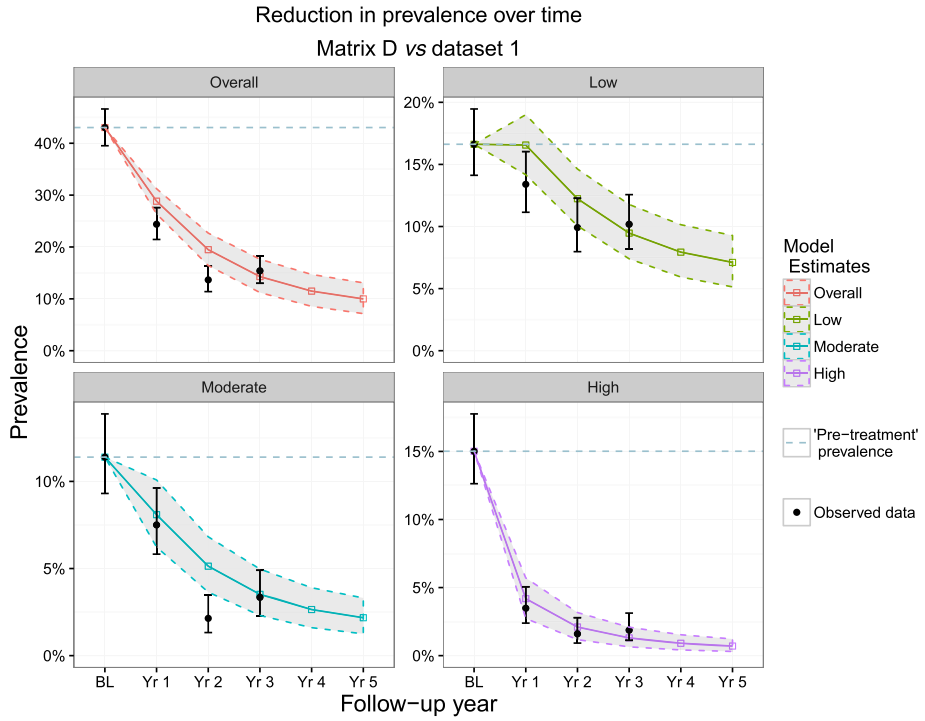

Fig. 4 Matrix D predictions and dataset 1 observations. Matrix D was composed of transition probabilities derived from Mali baseline and year 1 data and dataset 1 represents the full longitudinal Ugandan observations. These 4 plots show the predicted reduction in prevalence by Matrix D (bands) *vs* observed (black points) in Uganda by overall prevalence group and by intensity group. The dotted line represents the pre-MDA prevalence

Table 4 Predicted mean prevalence by matrices A-C for dataset 2 (selected Ugandan districts)

	Low intensity (predicted mean prevalence and 95 % CI)			Moderate intensity (predicted mean prevalence and 95 % CI)			High intensity (predicted mean prevalence and 95 % CI)			Overall prevalence (predicted mean prevalence and 95 % CI)		
Matrix	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Observed prevalence dataset 2	0.158 (0.125–0.196)	0.105 (0.079–0.139)	0.143 (0.112–0.180)	0.100 (0.074–0.133)	0.020 (0.010–0.030)	0.045 (0.029–0.070)	0.055 (0.037–0.082)	0.030 (0.017–0.052)	0.018 (0.009–0.036)	0.313 (0.269–0.360)	0.155 (0.123–0.194)	0.205 (0.168–0.247)
Matrix A Full dataset	0.152[a] (0.133–0.172)	0.112 (0.095–0.130)	**0.096 (0.078–0.115)**	0.085[a] (0.070–0.101)	**0.048 (0.036–0.060)**	0.034[a] (0.024–0.046)	0.051 (0.039–0.063)	0.025 (0.017–0.035)	0.018[a] (0.010–0.026)	**0.289 (0.268–0.311)**	**0.185 (0.161–0.211)**	**0.148 (0.123–0.175)**
Matrix B Uganda year 1 to year 2	0.140 (0.115–0.166)	0.109[a] (0.089–0.129)	**0.092 (0.074–0.111)**	0.078 (0.055–0.102)	**0.042 (0.030–0.055)**	**0.029 (0.020–0.039)**	0.055[a] (0.035–0.077)	0.027[a] (0.016–0.040)	0.017 (0.009–0.026)	**0.272 (0.242–0.302)**	0.178[a] (0.149–0.208)	**0.137 (0.111–0.165)**
Matrix C 3 selected districts	0.166 (0.132–0.199)	0.099 (0.075–0.124)	**0.082 (0.057–0.108)**	**0.052 (0.031–0.075)**	0.018[a] (0.009–0.029)	**0.010 (0.003–0.018)**	**0.031 (0.014–0.051)**	**0.012 (0.003–0.023)**	0.008 (0.001–0.018)	**0.249 (0.216–0.282)**	0.129 (0.098–0.162)	**0.100 (0.070–0.132)**

Bold = observed point prevalence values fell outside of the predicted boundaries
[a] Closest predictions to observed values

capture the uncertainty in all 12 observed values of dataset 2, matrix B captured 10 out of 12 and matrix C captured 9 out 12.

Predictions made on dataset 3

Table 5 shows the predictions that were made for dataset 3 (cross-sectional observed data). Figure 5 shows the output obtained from using the matrix A model on dataset 3 and Additional File 1: Figure S3 shows the plots corresponding to applying matrices B and C on dataset 3.

All data points in the low intensity of infection prevalence group were estimated accurately by each matrix, where both the observed point prevalence values as well as their 95 % CIs were captured by the model. As with dataset 1, matrices A and B produced similar outputs, with the observed data points and their 95 % CIs predicted by the models, with the exception of year 3, in moderate intensity, high intensity and overall prevalence groups. For matrix C, other than the low infection intensity group, the observed prevalence levels in all of the other infection intensity groups in all years were greater than the predicted range.

Predictions made on dataset 4

Figure 6 and Table 6 show the model outputs when Ugandan TPs were used to estimate changes in the longitudinal data from Mali. The results show that the model predictions match the changes in prevalence closely, with only year 2 observations from the low and high infection intensity groups falling outside of the prediction intervals, yet capturing the uncertainty around the data. The low intensity year 2 prediction shows an increase in prevalence, but inspection of the high intensity group shows that this may be due to individuals moving from the higher infection intensity groups to the low intensity and the non-infected group. Additional File 1: Figure S4 also shows the output obtained when applying Matrix D to dataset 4, where all data points were captured by the model with the exception of year 2 in the low intensity group. In all years however, matrix D captured the 95 % CIs of all observed data points.

Discussion

The primary aim of this study was to develop a simple quantitative tool to help programme managers to monitor and evaluate the ongoing progress of their schistosomiasis disease control interventions and whether they are meeting their targets. For this, we parameterized and validated Markov models using an extensive longitudinal dataset of *S. mansoni* infection in Ugandan children treated yearly with PZQ. Additionally, in order to test the robustness of the model predictions in a completely different setting, we compared model predictions against data from comparable school-aged children from the national control programme in Mali. Our focus was on the ability of the models to capture the observed point prevalence values, as a conservative approach to model assessment. It is anticipated that programme managers will be able to use their own baseline and year 1 data to predict changes in infection prevalence in subsequent years of the same programme, as this is the scenario where the model performed best.

Our study therefore demonstrated that this Markov modelling approach is useful when making (relatively short-term) predictions on infection trends with large datasets from which a subset has been used to parameterize the model (as seen by matrix A *vs* dataset 1 and matrix D *vs* dataset 4). Additionally, it is useful when completely independent data from another country have been used to parameterize the model and when predicting cross-sectional data. These results are particularly noteworthy since the vast majority of sentinel site survey data tend to be cross-sectional in design given inherent logistical and financial advantages. Matrices A and B performed similarly (with matrix A predicting changes in prevalence correctly within the 95 % PI range at more follow-up times in each infection intensity group than any other matrix variant), showing that the models performed similarly, whether TPs developed from baseline to year 1 data (matrix A) or from year 1 to year 2 (matrix B) were used to parameterize the model. It is important to test the performance of the model on a completely different country as this is 1 scenario for which a programme manager may use this model, and for these reasons data from Mali (dataset 4) were used to both separately test the model with Ugandan TPs (matrix A) and parameterize the model (baseline and year 1 data for matrix D). The model was able to predict a large majority of data points within the estimated 95 % PIs, in both cases: matrix A predicted all but 2 data points within the 95 % PIs (but captured the 95 % CIs around the data) for Mali dataset 4, and matrix D performed similarly to matrices A and B when predicting dataset 1. Conversely, matrix C (using data from selected districts in Uganda) performed least well, with only 16 of the 36 estimates in this study capturing the observed point prevalence values within the 95 % PIs. However, it is not possible to determine how the trends would continue without further data; therefore, this study is limited to the data we had available.

We conclude that, in its current form, the model is a useful additional tool for programme managers, provided they have the data available for the parameterisation of the model to the local setting, and is particularly useful for the interpretation of data from low and high infection intensity areas where all of the models performed best. This is ideal for programmes preparing to move from control of

Table 5 Predicted mean prevalence by matrices A-C for dataset 3 (cross-sectional Ugandan data)

	Low intensity (predicted mean prevalence and 95 % CI)			Moderate intensity (predicted mean prevalence and 95 % CI)			High intensity (predicted mean prevalence and 95 % CI)			Overall prevalence (predicted mean prevalence and 95 % CI)		
Matrix	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3	Year 1	Year 2	Year 3
Observed prevalence dataset 3	0.150 (0.139–0.161)	0.122 (0.112–0.132)	0.104 (0.094–0.115)	0.085 (0.077–0.094)	0.051 (0.044–0.053)	0.061 (0.053–0.070)	0.059 (0.052–0.070)	0.032 (0.028–0.038)	0.054 (0.048–0.062)	0.294 (0.280–0.308)	0.205 (0.193–0.218)	0.219 (0.205–0.233)
Matrix A Full dataset	0.149[a] (0.130–0.168)	0.111[a] (0.093–0.128)	0.095[a] (0.078–0.114)	0.082[a] (0.068–0.097)	0.047[a] (0.035–0.059)	**0.034 (0.024–0.045)**	0.049 (0.037–0.061)	0.024 (0.016–0.034)	**0.017 (0.010–0.026)**	0.280[a] (0.259–0.301)	0.182[a] (0.157–0.207)	**0.147 (0.121–0.173)**
Matrix B Uganda year 1 to year 2	0138 (0.114–0.163)	0.108 (0.088–0.128)	0.091 (0.073–0.110)	0.075 (0.053–0.098)	0.041 (0.029–0.054)	**0.028 (0.019–0.039)**	0.052[a] (0.033–0.073)	0.026[a] (0.016–0.039)	**0.017 (0.009–0.025)**	0.265 (0.235–0.295)	0.174 (0.146–0.205)	**0.136 (0.110–0.163)**
Matrix C 3 selected districts	0.160 (0.128–0.193)	0.098 (0.074–0.123)	0.082 (0.057–0.108)	**0.050 (0.029–0.072)**	**0.017 (0.008–0.029)**	**0.009 (0.003–0.018)**	**0.030 (0.014–0.049)**	**0.011 (0.003–0.022)**	**0.008 (0.001–0.018)**	**0.240 (0.208–0.273)**	**0.127 (0.096–0.159)**	**0.100 (0.070–0.131)**

Bold = observed point prevalence values fell outside of the predicted boundaries
[a] Closest predictions to observed values

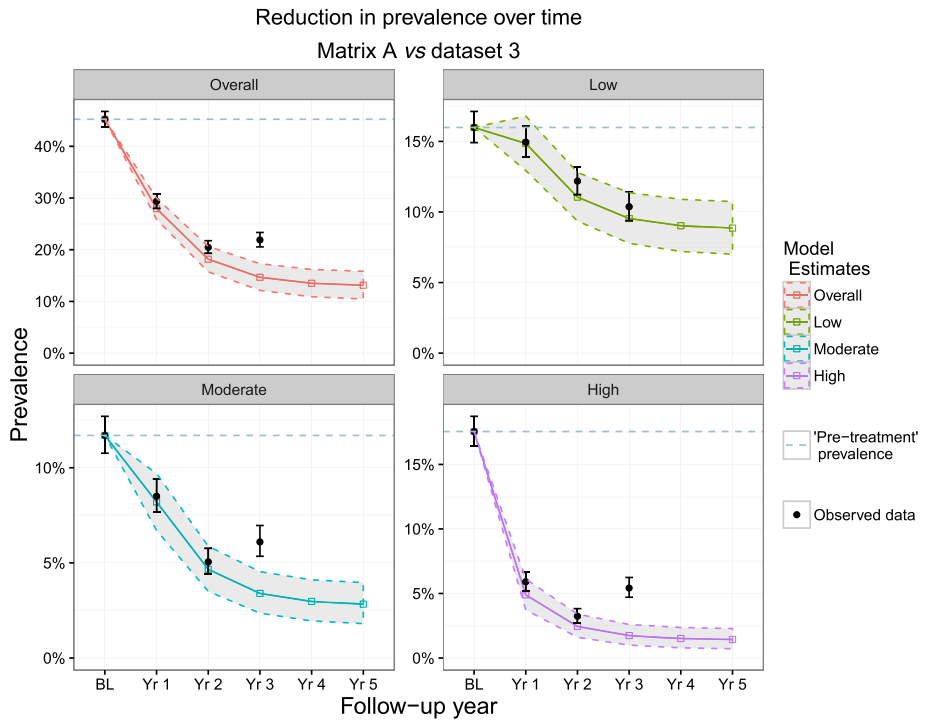

Fig. 5 Matrix A (full Ugandan baseline and year 1 transition probabilities) predictions and dataset 3. Dataset 3 represents cross-sectional Uganda observations. These 4 plots show the predicted reduction in prevalence by Matrix A (bands) *vs* cross-sectional observed (black points) in Uganda by overall prevalence group and by intensity group. The dotted line represents the pre-MDA prevalence

morbidity to interruption of transmission and elimination of infection (more feasible in low infection intensity areas) or to elimination of schistosomiasis as a public health problem (more severe in high infection intensity areas). Availability of longitudinal follow-up data is not essential, provided the sample size is large (as in this study) for cross-sectional annual data; however, longitudinal data are required to calculate the TPs. The use of data from Mali for parameterization (matrix D) illustrated that the model could, with some caution, be considered useful for predicting prevalence changes in Uganda, but more data would be required from other countries to test this further.

These models are aimed to be a tool to aid decisions and stimulate further investigation when needed rather than be used as a precise prediction of likely impact. Therefore, it is hoped that this heuristic technique may be useful for programme managers as a quick and simple means of assessing the progress of programmes. However, as seen by the results concerning dataset 4 (Mali longitudinal cohort), it is important to interpret the data for all 4 infection intensity groups together, since a large observed increase in the low infection intensity group compared to model outputs, may likely be linked to a corresponding decrease in the proportion of the heavier infection intensity groups. The precise change in infection patterns following treatment will depend on a multitude of factors related to programmatic design and performance. These will include therapeutic coverage and treatment adherence, which in turn will be related to other programmatic variables, such as the performance of the drug distribution teams, the accuracy of

Table 6 Predicted mean prevalence by matrix A for dataset 4 (longitudinal Mali data)

	Low intensity (predicted mean prevalence and 95 % CI)		Moderate intensity (predicted mean prevalence and 95 % CI)		High intensity (predicted mean prevalence and 95 % CI)		Overall prevalence (predicted mean prevalence and 95 % CI)	
Matrix	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Observed prevalence dataset 4	0.113 (0.094–0.135)	0.122 (0.102–0.145)	0.052 (0.040–0.069)	0.036 (0.025–0.050)	0.023 (0.015–0.036)	0.008 (0.004–0.016)	0.188 (0.164–0.215)	0.165 (0.142–0.191)
Matrix A Full dataset	0.112 (0.095–0.129)	**0.096 (0.079–0.115)**	0.049 (0.039–0.059)	0.035 (0.025–0.046)	0.027 (0.020–0.035)	**0.018 (0.011–0.027)**	0.188 (0.169–0.207)	0.149 (0.126–0.174)

Bold = observed point prevalence values fell outside of the predicted boundaries

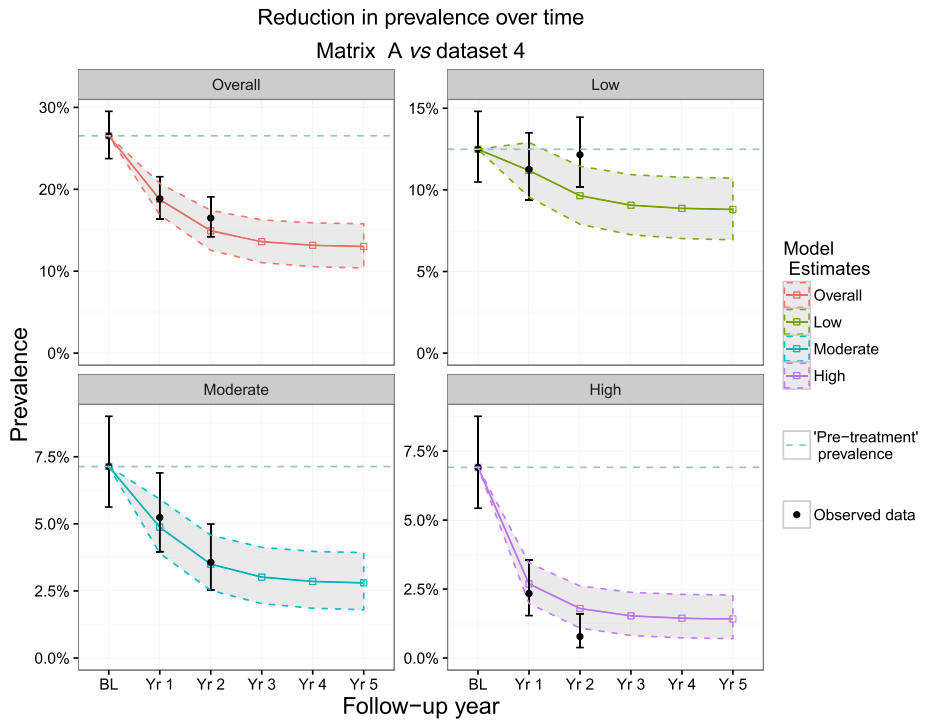

Fig. 6 Matrix A (Uganda baseline and year 1 transition probabilities) predictions and dataset 4. Dataset 4 represents full longitudinal Mali observations. These 4 plots show the predicted reduction in prevalence by Matrix A (bands) *vs* observed (black points) in Mali by overall prevalence group and by intensity group. The dotted line represents the pre-MDA prevalence

census data, and the effectiveness of social mobilization techniques, among others. Identifying the respective impact of each of these factors is beyond the scope of this paper.

Despite its advantages, the limitations of the Markov approach must be understood if it is to constitute a useful tool by programme managers. The model employed in this study is referred to as a time-homogenous Markov process [28], which assumes that the TPs remain constant through time. It is also assumed that they are invariant with respect to setting (endemicity, geographic location etc.) and host age group. This is not likely to hold for long-term projections as interventions (in this case MDA) are likely to have an impact on the transmission environment. For these reasons, such models may indicate 'abnormalities' in the observed datasets as a result of inevitable or expected changes over time, therefore the usefulness of the approach resides in its value as an additional tool for monitoring and evaluation rather than the definitive tool for this purpose. The data used to validate and test the models are primarily from school-aged children since most schistosomiasis interventions focus on this age group, who tend to harbour the highest burden of infection [29–35]. Therefore, the models do not consider the broader impact of MDA on the entire community *via* the indirect (herd) effects on transmission that result from reducing the force of infection [13]. Moreover, the method also implies that the same intervention is used each year using the same treatment schedule, not accounting for complementary interventions that may be implemented, such as those relating to sanitation or education, increase in public awareness that may accompany the progression of a control programme, or changes in the frequency and/or coverage of MDA. The model is based on a closed system and, therefore, assumes no population migration or extraneous introduction of new infections. This is an important limitation for mobile communities that may comprise so-called super-spreading individuals (such as fishermen or bicycle washers) who contribute disproportionately to community-wide transmission and who may be more likely to miss treatment. However, this is also a general limitation of most helminth transmission models, which rarely consider the spatial aspects of transmission.

With these limitations in mind, this study demonstrates that using constant TPs from the same dataset or from different datasets provides a satisfactory prediction of data (and their uncertainty) on the overall prevalence and the prevalence of high, moderate and light infections for up to 3 follow-up years. This method could also be extended to *S. haematobium*, adapting the model to the different WHO intensity classes for this species (defined as 1–50 eggs/10 ml of

urine as light intensity and > 50 eggs/10 ml of urine as heavy intensity, with no moderate intensity group) [9, 19] as well as to *S. japonicum*. In this case, the transmission dynamics among multiple definitive hosts would potentially pose less of a problem to this modelling approach when compared to other models that do not take into account the zoonotic reservoir, as the TPs calculated from the initial data would include all of the transmission-related processes occurring between the 2 time points [36–38]. This study could also be expanded further by comparing different TPs obtained from other datasets. In addition, the models could be adapted to make longer-term predictions (since the present study is focussed on short-term changes of 1–3 years post-baseline due to the stationary TP limitation), using datasets spanning longer periods and incorporating MDA coverage information. These extensions could, in principle, be captured using multiple TPs based on existing data of varying treatment coverage, or the possibility of having dynamic TPs that change with time or are simply updated as new data become available (developing new TPs from the more recent followed cohort). The use of year 1 to year 2 TPs in this study illustrated the potential for updating TPs as the programme progresses to estimate changes in subsequent years. This would overcome the constraints imposed by using baseline and year 1 data only, for projecting over long running programmes.

Conclusions

We developed and refined a Markov model to capture changes in the prevalence of infection intensity categories for *S. mansoni* infection over multiple rounds of MDA with PZQ. We parameterized our model using 2-year (2 consecutive time points) longitudinal data from Uganda and from Mali, using it to make longer-term projections against different variations of the datasets. The results from this study show that this is not only a promising instrument for programmes in their early years of implementation as a complementary M&E tool, but also a useful quantitative approach for making short-term projections of prevalence trends under interventions. With the ambitious WHO 2020 goals on the horizon, there is a need to look beyond maintaining control of schistosomiasis and shift focus to eliminating this debilitating disease. The global research community needs to develop practical tools to help programmes to achieve these goals. The Markov model has already produced encouraging results with existing programmatic data. With the push towards the elimination of schistosomiasis as a public health problem by 2020, these findings come at a key time in the field of NTD modelling for programme managers and policy makers.

Additional file

Additional file 1: Markov model equations, model parameters and additional tables and figures. **Text S1**. Markov model formulae. **Table S1**. Definition of parameters for the Markov Model. **Table S2**. Uganda subset information for dataset 2 and matrix C. **Figure S1**. Results from applying transition probability (TP) matrices B and C on dataset 1 (full longitudinal Uganda data set). **Figure S2**. Results from applying TP matrices A–C on dataset 2 (selected Ugandan districts). **Figure S3**. Results from applying TP matrices B and C on dataset 3 (cross-sectional Ugandan dataset). **Figure S4**. Results from applying TP matrix D (baseline and year 1 Mali data for TPs) on dataset 4 (longitudinal Mali dataset). (DOC 6719 kb)

Abbreviations

CI: Confidence interval; CS: Conditional state; DALY: Disability-adjusted life year; Epg: Eggs per gram of faeces; M&E: Monitoring and evaluation; MDA: Mass drug administration; MTP: Markov Transition Probability; NGO: Non-governmental organization; NTD: Neglected tropical disease; PC: Preventive chemotherapy; PI: Prediction interval; PI: Prediction interval; PZQ: Praziquantel; SAC: School-aged children; SCI: Schistosomiasis Control Initiative; SSA: Sub-Saharan Africa; STH: Soil-transmitted helminth; TP: Transition probability; WHO: World Health Organization

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Availability of data and material

The data used in this study are presented in Tables 1–6. Additional information can be requested from the corresponding author.

Authors' contributions

AD, AM, MDF: conceived the study; FMF contributed to data collection and team supervision in the field; AD analysed the data; JPW, MW, MGB, TDH, MDF contributed to the analyses; AD prepared the first draft of the manuscript; JPW, MW, MGB, AM, MDF contributed to write up. All the authors read and approved the final version of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The data used in this study were collected as part of the M&E processes of the schistosomiasis control programmes taking place in these endemic countries. Ethical approval for this was granted by the Imperial College Research Ethics Committee (ICREC 8.2.2, EC No. 03.36, R&D No. 03/SB/003E) and by the Ministries of Health ethical review boards in these countries.

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Developing tools to aid the elimination of parasitic worms: from field to policy

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1. Activities of control programmes

Mapping

Impact monitoring & Re-assessments

Update treatment strategy

Monitor if new strategy is working in reducing infection

2. Questions that are be asked by programme managers and policy makers

How is the control programme progressing to reduce prevalence and intensity of infection?

Do I need to investigate any factors that might affect programme performance?

A new intervention was introduced into the area, how has this impacted the infection prevalence and intensity?

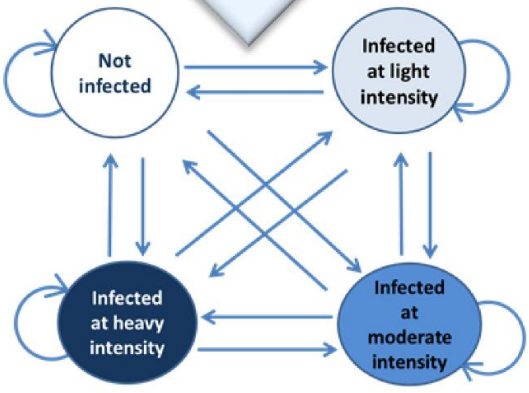
I have limited resources, if we fund a schistosomiasis control programme, how will it impact infection levels?

To help answer these questions, I developed a user-friendly model for predicting changes in infection levels

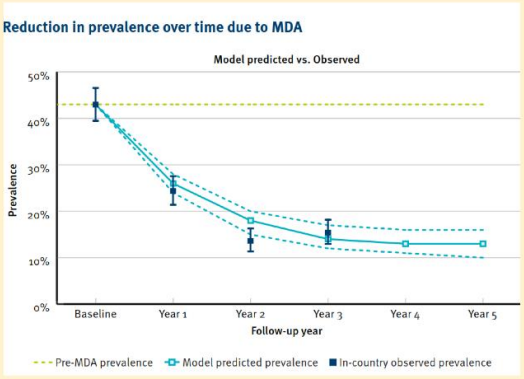
3. Model

The model was parameterised using routine data from programmes.

Infection intensity class	EPG range for *S. mansoni*
Uninfected	0
Light	1-99
Moderate	100-399
Heavy	≥400

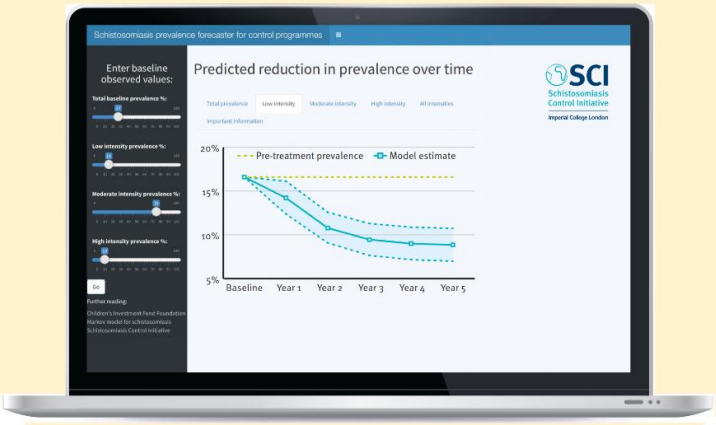


4. Model output



Outputs produced can also be specified by infection intensity group. The model is currently being developed as an open-access web tool.

5. Web-tool



LB-5452

Achieving global goals for schistosomiasis: rapidly reaching the 2020 and 2025 goals for control and elimination of morbidity

Arminder K. Deol[1,2], Fiona Fleming[1], Beatriz Calvo-Urbano[1], Martin Walker[2,3,4], Victor Bucumi[5], Issah Gnandou[6], Edridah Tukahebwa[7], Samuel Jemu[8], Upendo J. Mwingira[9], Abdulhakeem Alkohlani[10], Mahamadou Traoré[11], Wendy Harrison[1], Schistosomiasis Control Initiative[1], Maria-Gloria Basáñez[2,4], Michael D. French[12], Joanne P. Webster[4,13]

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SCI Schistosomiasis Control Initiative
Imperial College London

Introduction

- Schistosomiasis is one of the NTDs with the greatest human health and socio-economic burden
- Approx. 238 million infections, with ~ 90% are in sub-Saharan Africa

WHO Global Goals for Schistosomiasis

Controlling Morbidity <5% heavy infections across sentinel sites by 2020 (in all endemic countries)

Eliminating as a Public Health (PH) Problem <1% heavy infections in all sentinel sites by 2025 (in all endemic countries)

Eliminating Transmission by 2025 (in selected regions)

This study aimed to address the following questions:

1. After how many treatment rounds are 2020 / 2025 targets reached?
2. How are routinely-collected Monitoring and Evaluation (M&E) data best used to determine this?

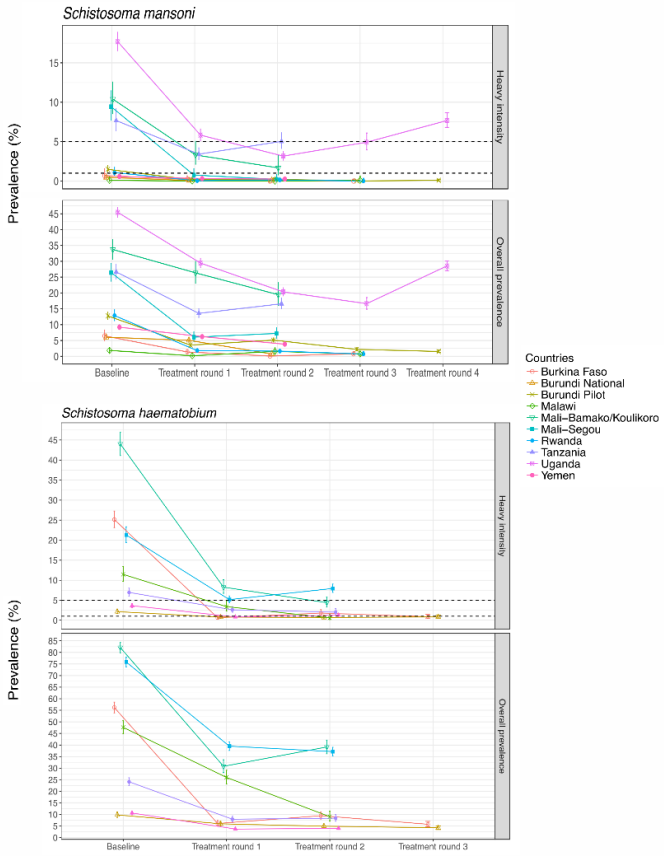
Methods

- Multi-country programmatic impact surveys, supported by the Schistosomiasis Control Initiative (SCI), were reanalysed
- We then compared WHO threshold criteria on control and elimination of morbidity (see below table) with the empirical data, to identify whether the current one-size-fits-all approach is optimal for guiding schistosomiasis strategies

Goal	Control of Morbidity	Elimination as a public health problem	Interruption of transmission
Recommended Intervention	PCT and complementary interventions where possible	Adjusted PCT and complementary interventions strongly recommended	Intensified PCT in residual areas of transmission and complementary interventions essential
Target	100% geographical and 75% national coverage **Prevalence of heavy intensity infection <5% across sentinel sites**	**Prevalence of heavy intensity infection <1% in all sentinel sites**	Reduction of incidence of infection to zero
Progression	Up to **5-10 years** from joining the group	Up to **3-6 years** from joining the group	Up to **5 years** from joining the group

Results

- Country programmes that started with a prevalence of below 5% heavy infection intensity in school-aged children for *S. mansoni* already reached the goal of control of morbidity and reached elimination as a PH problem in ≤ 3 years
- For *S. haematobium* areas, all had high starting endemicities yet all (but one) reached 'control' in ≤2years. However none reached the 'elimination as a PH problem' target
- Countries in our study reached 'control of morbidity' at earlier time points than anticipated and varied by species.
- Relationship between prevalence of heavy-intensity infection *vs* overall prevalence was non-linear. A wide range of prevalence values within and between treatment rounds corresponded to <5% heavy-intensity infection.



Conclusions

- As intensity levels decrease with the progression towards elimination, one of the major obstacles we now face is using **alternative affordable diagnostic techniques**. The current Kato-Katz technique for *S. mansoni* is not sufficient for this purpose due to its insensitivity at these levels, though the point-of-care urine antigen (CCA) test is a promising tool.
- Many countries have **now reached** the control aims, esp. for *S. mansoni,* so the question we now face is what do we do now - continue as before or proceed to the next stage?
- Some countries **start** with a prevalence of heavy infection <5%.
  - The next question is then, what treatment approach should these countries follow – the standard 'control of morbidity' or proceed directly too elimination?

Acknowledgements and partners

We'd like to thank the Ministries of Health, the National NTD Programmes, the Monitoring. Evaluation and Research team and other involved team members at the Schistosomiasis Control Initiative (SCI), as well as, the original funders of the surveys and Children's Investment Fund Foundation (CIFF) for helping to make this study possible.

LB-5112

Evolution of full age-infection profiles for schistosomiasis and soil-transmitted helminthiases following mass drug administration in Uganda: results from a three-year study

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Imperial College London; (2) Schistosomiasis Control Initiative; (3) RTI International; (4) Ministry of Health Uganda; (5) Royal Veterinary College

SCI Schistosomiasis Control Initiative
Imperial College London

Introduction

- Uganda was the first sub-Saharan African countries to implement a **national-scale** programmes, to **control** schistosomiasis-associated **morbidity** through mass drug administration
- **School-aged children (SAC) harbour the highest** prevalence and intensity of infections which then typically decrease with age.

The aims of the study were to address the following questions:

1. What do the **full age-infection profiles** show after several years of routine treatment?

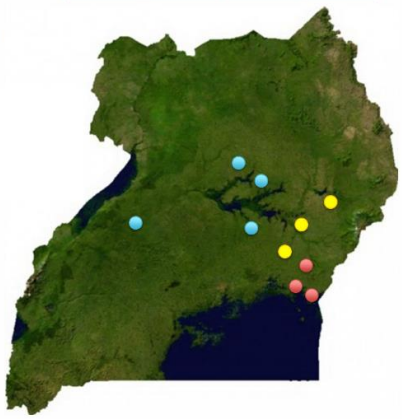
2. How do these differ between **three consecutive years of treatment?**

3. How do these differ with **endemicity and treatment history?**

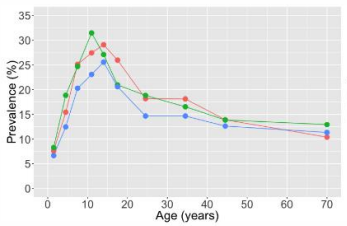
Methods

- Data were collected from 10 different sites of varying endemicities and treatment exposure from all age groups over 3 years (2014-2016).
- Eggs per gram (epg) for *S. mansoni* and Soil-transmitted helminth (STH) infection were obtained from four Kato-Katz slides per individual (2 days x 2 slides).
- 10 sites (sub-counties) were chosen, with 750 individuals per site.

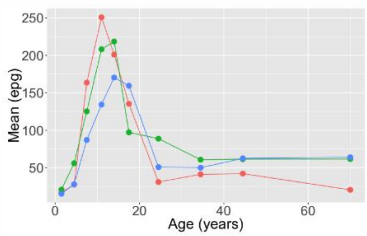
SCH WHO prevalence category	High prevalence	Low prevalence	Low prevalence
Treatment history	Treated (>5 times since 2003)	Treated (>5 times, since 2003)	Untreated (2014)
Subcounty	Bulidha Kigandalo Wairasa	Kasambya Kangai Agwata Balawoli	Ongino Agule Bukanga



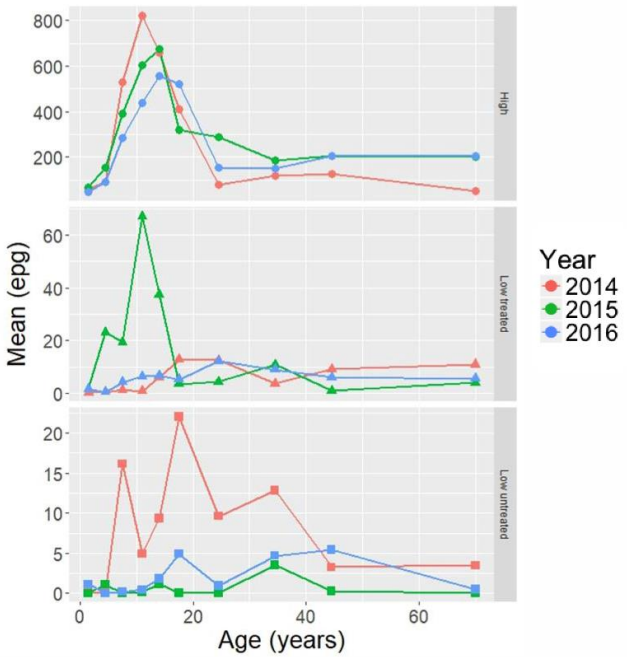
S. mansoni prevalence vs age



S. mansoni intensity vs age



S. mansoni intensity vs age
By sentinel site prevalence category and survey year



Results

- Overall prevalence and mean intensity did not show much reduction.
- High prevalence areas showed peak decrease but still very high (2016, > 75% in 10-15 year olds – dip seen in end of SAC range)
- Low prevalence peaks can be misleading – when analysing at individual level, results showed that a smaller number of individuals were heavily infected as expected, but not reflected in the standard age-intensity profiles, analysed at age-group level.
- Areas classed as 'low' prevalence were found to have 'high' prevalence in SAC in our survey.
- STHs were very low in the study areas.

Conclusions

- Where transmission is **high**, annual MDA was shown to be **insufficient** to making a significant impact on prevalence levels in SAC
- In **high** transmission areas, mean intensity of infection in SAC remained as "heavy" (400 epg or above)
- Where transmission is low, **those heavily infected could have a disproportionate impact** on the mean intensity of infection → approach?
- **WHO strategies need to be supplemented**
- Aiming for elimination will need **strengthened MDA** – high sustained coverage, ↑ frequency of treatment - and **additional interventions**

Acknowledgements and partners

First and foremost we would like to thank staff at the Vector Control Division of the MoH Uganda that collected the data and all individuals who agreed to take part in this study. This study was funded by an operational research grant from the Children's Investment Fund Foundation (CIFF)

The Persistent Parasite: Why Do *Schistosoma mansoni* Infection Levels Remain High In The Rural Ugandan Village of Wakawaka Even After Over a Decade of Treatment?

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ASTMH 65th Annual Meeting November 13-17, 2016 Atlanta, Georgia USA #tropMed16

1780

SCI Schistosomiasis Control Initiative

Imperial College London

Introduction

Despite more than a decade of mass preventive chemotherapy, age-infection profiles of *Schistosoma mansoni* have shown that prevalence and intensity of infection in an area of Eastern Uganda are still high. With a global shift to the elimination of schistosomiasis in the 2012 World Health Assembly resolution, there is a need to identify why more than 70% prevalence and high intensities of infection are still identified in those most at-risk populations, school-aged children (SAC). The aim of this study was to identify possible non-biological contributors to this trend by interviewing individuals across all age groups in Wakawaka village, a large fishing community, in the district of Bugiri located by the shores of Lake Victoria, a known infection source.

Age group	Sample size
6-9 years	30
10-12 years	37
13-15 years	31
16-19 years	29
20-29 years	30
30-39 years	30
40-49 years	27
50+ years	34

Table 1. Age groups distribution in sample

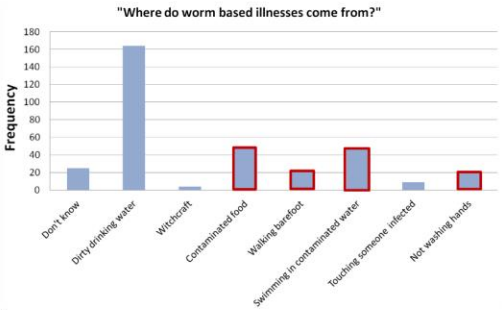

Figure 1. Where do individuals think worm infection is contracted from?

Method

The survey explored the social, behavioural and economic background of the participants, in addition to gathering information on living environments and access to healthcare. The village was selected as a site due to its high prevalence, peaking at just under 80% in school aged children (Deol et al., unpublished), remained even after multiple rounds of treatment since 2004. For children aged between 3 and 15 years an additional innovative activity was carried out which involved a colouring sheet identifying transmission routes. 248 individuals were surveyed over 11 days (table 1) and 140 SAC participated in the colouring sheet activity over 3 days. A local teacher and health worker were recruited as volunteers to help conduct the activities and received a short training prior to each.

Results

For the colouring sheet activity, only half of the colouring activity questions were marked correctly. For the survey, results revealed **82%** of the participants continue to use Lake Victoria as their primary water source for activities other than drinking (figure 1). Additionally **67%** thought that most 'worm based infections' came from drinking dirty water and only **18%** of participants correctly identified that swimming in contaminated water was a source of infection. Knowledge of soil-transmitted helminths (STHs) were similar with **98%** unable to identify walking barefoot and not washing hands as risk behaviours (figures 2 and 3) and only **30%** of the survey participants forbidding their children from defecating in the open (figure 4). Almost **14%** of the population had lived in the area for 2 years or less.

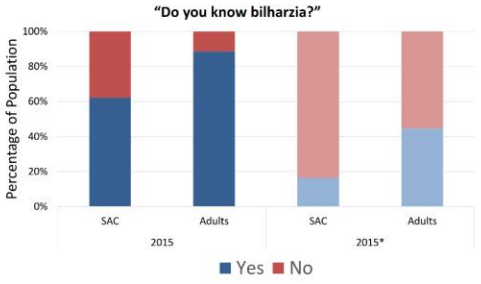

Figure 2. Can individuals correctly identify symptoms.
*Total population in each age group that correctly identified at least 1 symptom (regardless of "yes/no")

Conclusions

Results show that there is still a dearth of community level understanding of schistosomiasis and STH and their transmission routes despite numerous treatment rounds and high levels of infection. If programmes are to move from control to elimination, then we need to strengthen current strategies with improved treatment coverage and sensitisation, taking into account communities that are mobile, access to safe clean water and community awareness.

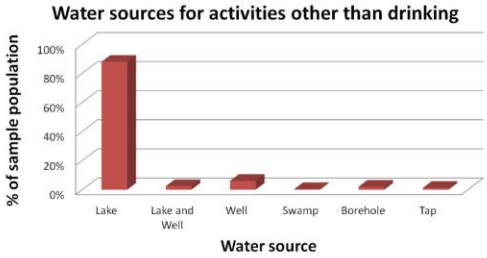

Figure 3. Sources of water for activities other than drinking.

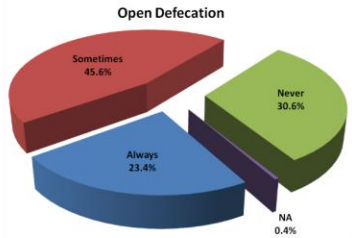

Figure 4. Open defecation by children in the household.

Acknowledgements : First and foremost we would like to thank staff at the Vector Control Division of the Ministry of Health Uganda that allowed us to work alongside them while they conducted their work and all individuals who agreed to take part in this study.