



QUANTIFYING THE INVISIBLE

Modelling the epidemiology of intestinal
parasitic worm infections for better control

Veronica Malizia

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Quantifying the invisible

Modelling the epidemiology of intestinal parasitic
worm infections for better control

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Quantifying the invisible

Modelling the epidemiology of intestinal parasitic
worm infections for better control

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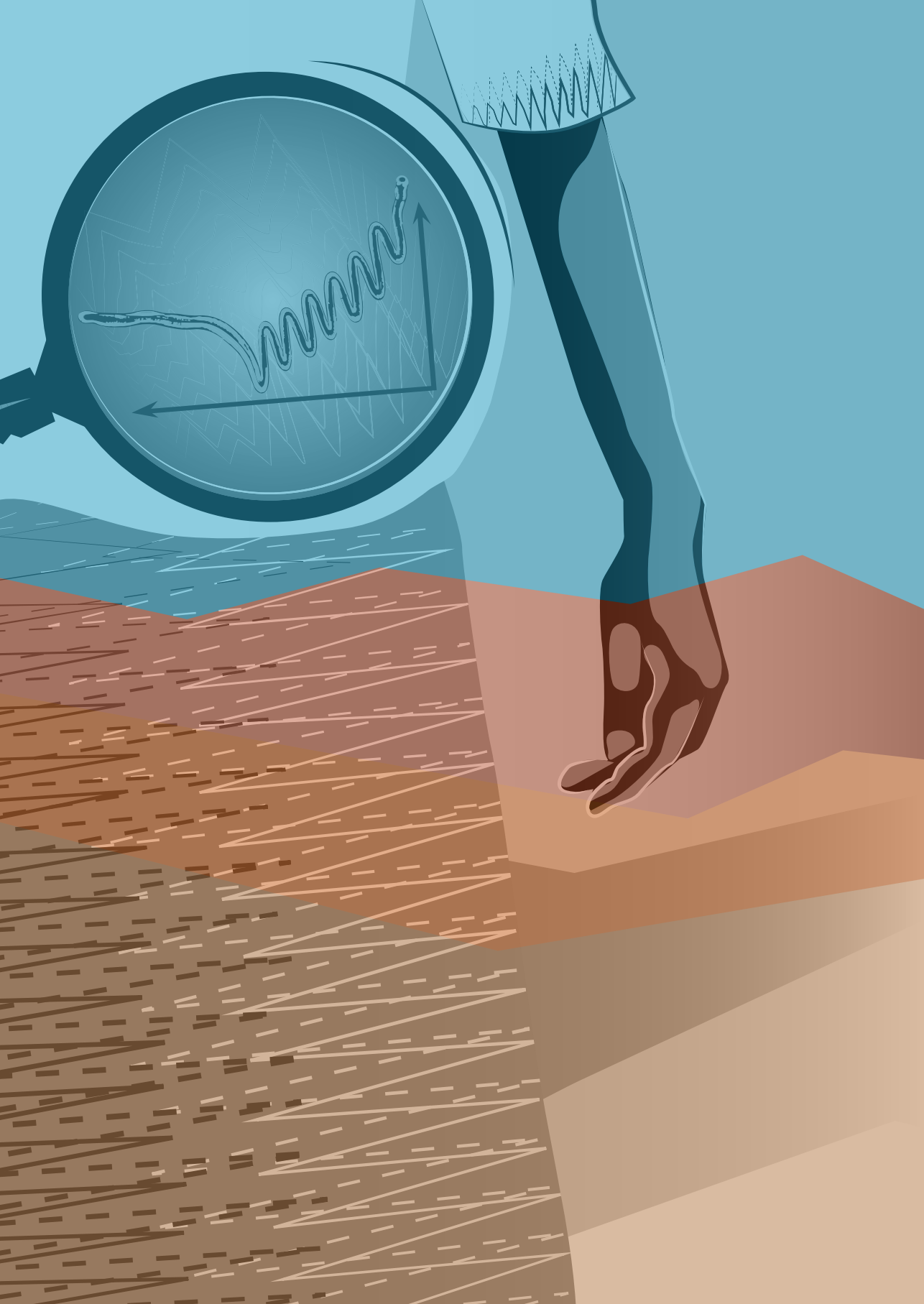
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Chapter 1 General introduction

The World Health Organization (WHO) classifies as Neglected Tropical Diseases (NTDs) a group of 21 diseases that affect populations in tropical and subtropical regions, especially in areas with poor healthcare settings and hygiene regulations [1, 2]. NTDs cause debilitating morbidity and social and economic burden. Among the NTDs, intestinal parasitic worm (helminths) infections cause millions of people to suffer from related morbidities, especially children [3]. Two important examples are soil-transmitted helminths [4] and *Schistosoma mansoni* [5]. In this chapter, I give a brief introduction to the epidemiology, morbidity, diagnosis and control of these parasites (**Section 1.1** and **Section 1.2**). Next, I elaborate on the role of mathematical models and methods to bridge the gaps in the study of intestinal parasites (**Section 1.3**) and to inform control decisions (**Section 1.4**). Finally, I present the main objectives (**Section 1.5**) and the outline of this thesis (**Section 1.6**).

1.1. Soil-transmitted helminths

Life cycle and epidemiology

Three main species of parasitic nematodes fall in the group of soil-transmitted helminths (STH): hookworms (*Necator americanus* and *Ancylostoma duodenale*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*). STH are a major public health concern, affecting over 1.5 billion individuals predominantly in low- and middle-income countries, with the highest prevalence reported from sub-Saharan Africa, South America and Asia [6]. These infections are transmitted through soil contaminated with STH eggs excreted through human faeces, leading to a cycle of reinfection and persistent transmission. The full life cycle of STH is shown in **Figure 1.1** [7]. Human hosts are infected via skin penetration of larvae (hookworm), e.g. by walking barefoot, or via ingestion of eggs (*A. lumbricoides* and *T. trichiura*), e.g. by children swallowing contaminated soil or due to consumption of raw food. Within the human host, the eggs or hookworm larvae migrate through the lungs and establish in the intestine, where they mature into adult worms. Here, the female worms can become inseminated by adult male worms, undergoing sexual reproduction [6]. The eggs of *A. lumbricoides* and *T. trichiura* remain viable in the soil for several months [7], while hookworm eggs hatch in the soil and release infective larvae that can survive in the environment for several weeks. The distribution of STH in the human population is observed to be highly overdispersed [8, 9]. This means that a small number of individuals carry a disproportionately high number of parasites, while most individuals

have few or none. Inseminated female worms produce thousands of eggs each day [10, 11]. The lifespan of adult worms within the human host differs by STH species, with an average of 3 years for hookworm [8, 12], and 1 year for *A. lumbricoides* [10, 12] and *T. trichiura* [8, 12, 13].

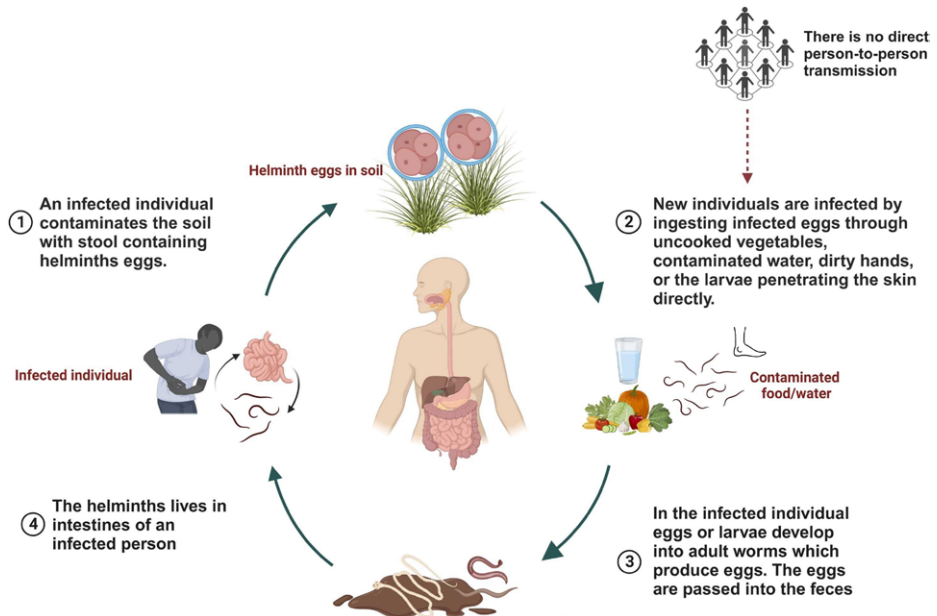


Figure 1.1. Life cycle of soil-transmitted helminths. Adapted from figure published in [14].

Morbidity

STH-related morbidity is associated with the number of worms harboured [6]. Individuals with mild or light infections (few worms) typically experience no or mild symptoms. However, more severe infections can lead to various symptoms, including diarrhoea and abdominal pain, growth impairment, and debilitating conditions such as malnutrition and anaemia, due to malabsorption and nutrient loss, which can exacerbate susceptibility to other infections [4, 12]. The severity and nature of morbidities vary according to the species, intensity of infection, and individual factors of the host. Anaemia is the primary morbidity associated with hookworm infection. Different from both other STH species, hookworms are equipped with hooked teeth that they use to attach to the mucosa of the human small intestine to feed on blood. This blood uptake, along with the additional loss from wounds left by detaching worms, reduces the host's haemoglobin and iron levels. As a result, the nutritional iron reserves and intake can become insufficient to meet the body's needs [15].

Although in hookworm-endemic regions anaemia is often also associated with other infections (e.g. malaria) or low iron intake, hookworm infection has been shown to significantly contribute to the global burden of anaemia in many countries [16, 17].

While severe cases show evident symptoms, many STH infections result in subtle morbidity that can be challenging to detect and measure but still significantly impact health and quality of life, especially for children, whose health is mostly affected by the disease [18, 19]. The WHO identifies other vulnerable categories, such as women of reproductive age (including pregnant and breastfeeding women) due to the effects of iron-deficiency anaemia during pregnancy; and adults in certain high-risk occupations that might be exposed to higher levels of STH [6].

Diagnosis

Clinical diagnosis of STH infections is based on identification of eggs in the human faeces [4]. A traditional diagnostic technique is the Kato-Katz (KK) method, consisting of the examination of stool smears to count parasite's eggs [20]. The WHO categorises infections with light, moderate, and heavy intensity, based on the number of eggs per gram of stool (EPG) detected in a stool sample with the KK test. For *A. lumbricoides*, light is 1-4999 EPG, moderate is 5000-49999 EPG, and heavy is $\geq 50,000$ EPG. For *T. trichiura*, light is 1-999 EPG, moderate is 1000-9999 EPG, and heavy is $\geq 10,000$ EPG. For hookworm, light is 1-1999 EPG, moderate is 2000-3999 EPG, and heavy is ≥ 4000 EPG [21].

Although KK is the standard in detecting STH infections, offering a simple, cost-effective, and field-applicable approach, it is subject to several limitations. In fact, it results in high variation in egg counts due to the used sampling scheme, i.e. the combination of the number of stool samples collected per person (days) and the number of slides prepared per sample. The quantity of stool on a single sample is standardised to 41.7 mg. The number of excreted eggs is highly variable between repeated slides based on the same stool sample, where eggs do not distribute homogeneously, and between multiple stool samples [22, 23]. In addition, the egg shedding pattern is not homogeneous throughout the day. These variations lead to an overall low sensitivity of the KK test, especially for light infections. When no eggs are detected, the individual's infection intensity is recorded as zero. The collection of multiple stool samples on different days demands more resources, but it can increase

the likelihood of detecting the eggs and thus prevalence, although it does not affect the population-level estimates of mean intensity of infection [23-25]. Several WHO indicators for decision-making in STH are defined in terms of prevalence of infection or heavy infection. One single stool sample is the gold standard. However, there is no clear recommendation for the number of slides per sample. Research is crucial to assess how different diagnostic sampling schemes affect the sensitivity of prevalence measurements, which are used as indicators to guide policy decisions.

The limitations of KK have prompted the development of more advanced diagnostic tools. Techniques such as quantitative polymerase chain reaction (qPCR) and other molecular assays have emerged, offering greater sensitivity by detecting parasite DNA [26]. Additionally, advancements in immunoassays provide alternative diagnostic approaches by detecting parasite antigens or host antibodies [27]. The inclusion of serological diagnosis in guidelines for guiding STH prevention and control programmes is limited [27]. The integration of innovative techniques alongside efficient use of traditional methods enhances diagnostic accuracy, supporting more effective monitoring and control of STH. However, challenges remain, particularly in resource-limited settings, where the adoption of newer technologies is constrained by cost and technical facilities.

Control programmes

The history of control programmes for STH dates back to the early 20th century, driven by the recognition of the significant public health impact of these parasitic infections, historically neglected. The Rockefeller Sanitary Commission, established in 1909 in the United States, was one of the earliest large-scale public health initiatives aimed at controlling hookworm disease, which was endemic in the southern US states [28, 29]. This programme combined mass pharmaceutical treatment, education on hygiene practices and improved sanitation, marking the beginning of organized STH control efforts.

Following the success of the Rockefeller campaign, similar programmes were initiated in other regions of the world, particularly in areas with high prevalence of STH. In the mid-20th century, the WHO began to recognize the global burden of STH, especially in tropical and subtropical regions. However, it was not until the late 1990s and early 2000s that STH control ranked high on the public health agenda.

In 2001, the WHO set a target to treat at least 75% of school-aged children (SAC) in endemic areas by 2010 through mass drug administration (MDA) [6]. This initiative was part of a broader effort to combat NTDs, with STH being one of the main targets. Pharmaceutical companies began donating large quantities of anthelmintic drugs like albendazole and mebendazole, which facilitated the scale-up of MDA programmes across many low- and middle-income countries. The drugs are aimed to reduce worm burdens within the human host and thereby development of morbidity, as well as transmission in the population. These programmes often targeted SAC due to their higher risk of infection and the ease of administering treatments in school settings. The success of these initiatives has been significant, with millions of treatments administered annually, leading to substantial reductions in STH prevalence and related morbidities in many regions. In 2021, more than 500 million children in endemic regions received anthelmintic treatment, covering 62% of children at risk. Between 2010 and 2019, the annual Disease-Adjusted Life Years (DALYs) lost due to STH decreased by over 50% as a result of large expansion of MDA efforts in endemic areas [6].

Over time, the integration of STH control with other public health initiatives, such as nutrition programmes and WASH (Water, Sanitation, and Hygiene) interventions, has been prioritised to further enhance the effectiveness of control efforts [20]. These initiatives focus on providing access to clean water, promoting handwashing with soap, and ensuring the proper disposal of human excreta to disrupt the lifecycle of STH. The inclusion of health education in these programmes, raising awareness on the disease or promoting the use of shoes and accessibility to latrines, has also been crucial in promoting sustainable changes in hygiene practices and reducing reinfection rates.

The WHO key control targets for STH control by 2030 [20, 21] are as follows:

1. **Morbidity Elimination:** The primary goal is to achieve and maintain the elimination of STH as a public health problem (EPHP). This target is defined as reducing the prevalence of moderate-to-heavy intensity (M&HI) infections, used as a morbidity indicator, to less than 2% among at-risk populations, particularly preschool-aged and school-aged children.
2. **Treatment Coverage:** Sustain effective mass drug administration (MDA) to ensure that at least 75% of preschool-aged and school-aged children in endemic areas receive regular deworming treatment. This target also

includes expanding treatment to women of reproductive age and other at-risk groups in certain settings.

3. **Integrating Control Efforts:** Enhance the integration of STH control with WASH campaigns and behavioural interventions to reduce impact on health and sustain goals beyond 2030.

However, challenges remain, particularly in achieving and sustaining high coverage in MDA programmes and ensuring the long-term sustainability of control efforts. Moreover, the WHO indicator for STH morbidity is the prevalence of moderate-to-heavy intensity (M&HI) of infection. Considering anaemia as the major morbidity caused by STH, especially for hookworm, the worm burden associated with anaemia is influenced by multiple factors, including host nutritional status and concurrent parasitic infections. It is crucial to account for the common underlying prevalence of anaemia to appropriately assess the definition of the WHO morbidity target (M&HI prevalence < 2% in SAC) to guide policy decisions. Nevertheless, the history of STH control programmes demonstrates the effectiveness of large-scale public health interventions.

1.2. Schistosomiasis

Life cycle and epidemiology

Schistosomiasis is caused by parasitic worms of the *Schistosoma* species and is one of the most persistent NTDs, affecting over 200 million people in tropical and subtropical areas, predominantly in sub-Saharan Africa [30]. Schistosomiasis is prevalent in communities affected by poverty, especially those without access to clean water sources and adequate sanitation. The primary species that infect humans are *S. haematobium* (which causes urogenital schistosomiasis) and *S. mansoni* (which causes intestinal schistosomiasis). The life cycle of *Schistosoma* is complex, involving freshwater snails acting as intermediate hosts (**Figure 1.2**) [5]. Both species differ for the anatomical location where the worms settle in the human host. Humans become infected when they come in contact with water bodies containing cercariae, the free-living larval stage released by infected snails. Upon skin penetration, the larvae enter the human bloodstream and migrate to the liver of the human host to mature. Mature worms then pair and migrate to the venous systems of the intestines (*S. mansoni*) or the bladder (*S. haematobium*). Monogamous in its nature, *Schistosoma* worms live as

a pair in the human host once mated, with the female worm, thinner and longer, living in the so-called gynaecophoric canal of the male. Female worms produce hundreds of eggs per day, which are either excreted in urine or faeces of the human host, thus continuing the cycle if they reach water sources and hatch close to where specific snail species are present. The persistence of this life cycle is facilitated by frequent human contact with contaminated water, often due to agricultural activities, bathing, or general lack of access to clean water sources. As for STH, distribution of *Schistosoma* parasites in the human population is highly overdispersed [9], with a small number of individuals carrying a disproportionately high number of parasites, while most individuals have few or none.

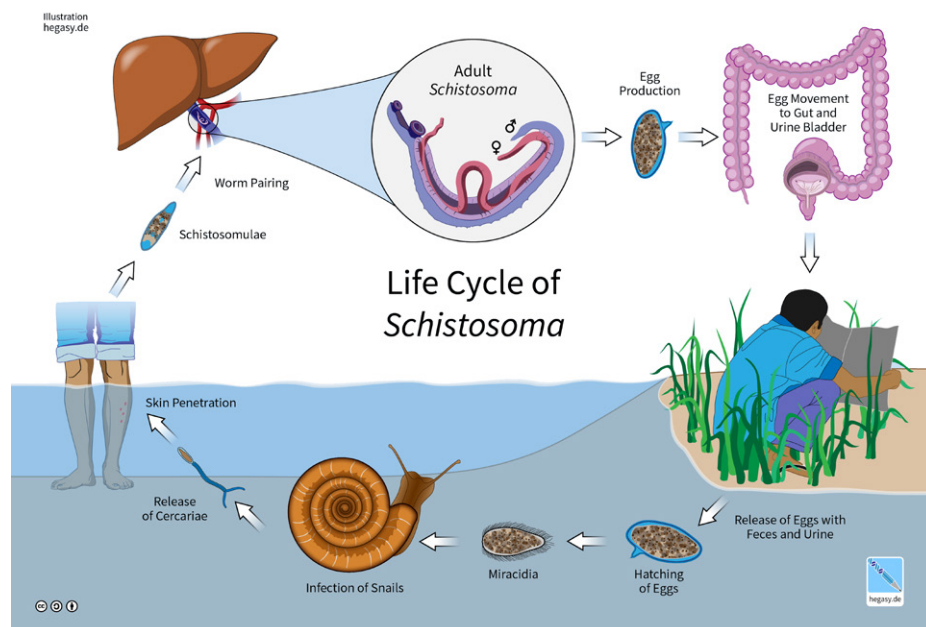


Figure 1.2. Life cycle of *Schistosoma*. The example egg depicted refers to *S. mansoni*. Illustration downloaded and adapted from www.hegasy.de

Morbidity

The morbidities associated with schistosomiasis are diverse, primarily resulting from the body's immune response to schistosome eggs trapped in tissues. Chronic infection can lead to severe morbidity depending on the *Schistosoma* species involved. In urogenital schistosomiasis, caused by *S. haematobium*, the deposition of eggs in the bladder and reproductive organs

leads to haematuria (blood in urine), bladder fibrosis, and an increased risk of bladder cancer. Women with urogenital schistosomiasis are also at higher risk of infertility and complications during pregnancy. In intestinal schistosomiasis, caused by *S. mansoni*, the eggs are trapped in the intestinal wall causing chronic inflammation and blood loss due to tissue damage. Part of the eggs can be transported by the blood stream, eventually reaching the liver. This can result in periportal fibrosis, portal hypertension and in severe cases life-threatening complications. Above all, the subtle and chronic morbidity caused by schistosomiasis contributes to malnutrition, stunted growth in children, cognitive impairment, and reduced work capacity, perpetuating a cycle of poverty and disease in endemic communities [5, 30]. Although some conditions are associated with heavy intensity of infection as for the case of other helminths, some morbidities, especially related to *S. mansoni* can occur at all levels of infection and may not always correlate with infection intensity [31].

Diagnosis

As for STH, the traditional method of diagnosis is the microscopic examination of human excreta to detect schistosome eggs. For *S. haematobium*, urine filtration and microscopy are commonly used. For *S. mansoni*, the KK technique is usually employed to detect eggs in stool samples. The WHO categorises *S. mansoni* infections with light (1-99 EPG), moderate (100-399 EPG), and high (≥ 400 EPG) intensity, based on the number of EPG detected via the KK test [21]. To overcome the limitations regarding the low sensitivity of the test already discussed for STH, particularly in light infections, more advanced diagnostic techniques such as qPCR offer greater accuracy by detecting parasite DNA in various biological samples [32, 33]. Newer diagnostic assays that detect worm antigens, specifically, circulating cathodic antigen (CCA) and circulating anodic antigen (CAA), in urine samples have shown higher sensitivity. The Point-of-Care Circulating Cathodic Antigen (POC-CCA) test is a rapid diagnostic tool designed to detect the presence of CCA in urine, which are released by adult *S. mansoni* worms. The test to detect CAA instead, is valid for all major human *Schistosoma* species, and has proven highly sensitive, as it can detect very low levels of CAA, even in cases of light infections. However, the test is not yet widely available as a routine field diagnostic due to high cost and advanced laboratory requirements [34]. Conversely, POC-CCA provides results within approximately 20 minutes and is especially valuable in field settings due to its ease of use and rapid turnaround time. These tools (as well as repeated urine/stool samples) have revealed that it is not uncommon that individuals harbour adult schistosome worms without excreting detectable eggs, a condition

termed “egg-negative/worm-positive schistosomiasis”. The discovery of a substantial population with undetected infections challenges existing public health policies and strategies aimed at schistosomiasis elimination [35]. The development of rapid diagnostic tests that combine accuracy with ease of use in resource-limited settings, as well as reassessment of guidelines to incorporate these more sensitive diagnostic tools, remains a priority for improving schistosomiasis control.

Additionally, environmental DNA-based xenomonitoring is a recently employed surveillance strategy that involves detecting *Schistosoma* spp. DNA in water bodies rather than directly in human populations. This method can give indication on water contamination with cercariae and thus infected snails. It provides valuable insights into the transmission dynamics of the disease, especially in low endemic settings, and aids in monitoring control programmes and effectively allocate resources [36, 37]. However, these advanced techniques require more resources, which limits their widespread use in endemic regions.

Control programmes

The implementation of schistosomiasis control programmes has grown significantly over the past century. The development of praziquantel in the 1970s, a highly effective and safe drug acting by killing adult worms, revolutionised schistosomiasis control [38]. It was first used for individual treatment (due to its relatively high cost), but since donations by pharmaceutical companies started in the early 2000s, MDA with praziquantel has become the primary measure for schistosomiasis control, significantly reducing morbidity and transmission in many endemic areas [39]. The WHO launched global initiatives to expand access to praziquantel, aiming to treat at least 75% of SAC in endemic areas by 2020. Although this target was not fully met given the persistent nature of schistosomiasis, substantial progress has been made with 105 millions of people treated in 2019. However, many control programmes for neglected tropical diseases, including schistosomiasis, were interrupted in 2020, to comply with the global regulations for the containment of the COVID-19 pandemic [40]. In 2021, 29.9% of individuals in need of treatment for schistosomiasis were reached globally, with 43.3% of SAC requiring preventive chemotherapy receiving treatment. This represents a 38% decline compared to 2019 [30]. Although schistosomiasis programmes have since restarted, there is no clear evidence whether coverage and progress have fully returned to the prepandemic trajectory. Modelling predictions

should help evaluating whether and to which extent COVID-related gaps will delay 2030 control targets.

In addition to MDA, integrated control strategies have been prioritised in most recent WHO guidelines [41], as essential for sustainable schistosomiasis control. These strategies include improving access to clean water, sanitation, and hygiene (WASH) to reduce human contact with contaminated water, snail control through molluscicides and biological agents, and health education to raise awareness and promote behavioural changes.

The WHO key control targets for schistosomiasis control by 2030 [1, 21, 41] are as follows:

1. **Morbidity elimination:** achieving and sustaining elimination of schistosomiasis as a public health problem (EPHP) in all 78 endemic countries, defined as reducing the prevalence of heavy infections to less than 1%.
2. **Interruption of transmission:** eliminating infections in humans from at least 25 endemic countries, defined as registering zero incidence of autochthonous cases in humans for at least 5 consecutive years.
3. **Treatment coverage:** reaching at least 75% of the target risk group as a minimal coverage target for endemic countries.

Despite the challenges and the difficulty to handle persistent hotspots of infection, defined as geographic areas where the prevalence and/or intensity of infection do not decrease meaningfully after at least 2 years of effective mass drug administration (MDA) [21, 42], the history of schistosomiasis control demonstrates that with sustained effort it is possible to significantly reduce the burden of this debilitating disease.

1.3. Bridging the gaps: mathematical modelling of intestinal parasitic worm transmission dynamics

Statistical and mathematical models have been historically employed to fill the gaps in the understanding of STH and schistosomiasis biology and transmission dynamics. With increased understanding of the parasite dynamics, rigorous transmission models can be developed to reproduce the complicated transmission cycle and predict the impact of interventions. Modelling results have been incorporated in the recent WHO guidelines

for schistosomiasis control [41] to evaluate the level of scientific evidence supporting each recommendation. In general, mathematical models are increasingly recognised as important tools to inform policy regarding the control of schistosomiasis and STH.

A matter of intensity

The intensity of infection in STH and schistosomiasis is a critical determinant of disease severity and transmission. Unlike diseases such as malaria or respiratory diseases, where infection is usually considered as a binary variable (infected vs. not infected), helminth infections are better understood through the intensity of infection, i.e. the number of worms individuals harbour, which is commonly an invisible variable. Intensity of infection is at most indirectly observed through the eggs contained in the excreta. This intensity is a key factor to investigate both the clinical outcomes, as morbidity is associated with (a history of) heavy intensity, and the potential for transmission.

Statistical and mathematical models have been crucial to unravel the relationship between observed egg counts and harboured number of worms. The initial models by Anderson and May [3, 8, 43, 44] already described a framework where the average number of worms influences the level of egg shedding and the force of infection in a human population. Statistical models can help to analyse how parasites are distributed and produce eggs across a population. Deterministic transmission models have been developed to describe the mean worm burden within humans over time. In both approaches, the worm burden is usually modelled as a latent variable assuming a certain heterogeneity between individuals. The highly aggregated nature of parasites within the human population can be well described by a Negative Binomial distribution, which is parametrised through its mean and an aggregation parameter k [8, 9, 44-47]. The skewed distribution reflects the fact that some individuals are more likely to harbour high numbers of parasites, while others are uninfected or lightly infected. The aggregation parameter represents the overdispersion around the mean (i.e. the degree of clustering): smaller k values indicate lower aggregation (more overdispersion), while larger k values approach a Poisson distribution, where variance equals the mean (i.e. no overdispersion). This aggregation is key to reproduce and understand heterogeneity in human exposure to infection.

As a third important modelling approach, agent-based models (ABMs) or individual-based models have been developed to study the infection dynamics

of parasites in humans by simulating the heterogeneous characteristics of individual "agents" within a population [48-53]. Each agent represents a human host and is assigned unique attributes such as age, exposure risk, access to treatment, and other individual factors. The model tracks these agents over time, allowing to account for individual heterogeneities, and stochastic events to emerge naturally. In ABMs the worm burden is explicitly tracked for each individual. The heterogeneity in intensity is incorporated through the process of worm acquisition. More precisely, each human host is assumed to acquire new worms according to a Poisson process with a given rate parameter. This rate parameter is multiplied by an individual factor assumed to follow a Gamma distribution with mean 1.0 and shape and rate (or 1/scale) equal to k , which can be interpreted as the aforementioned aggregation parameter. The process of worm acquisition is then a Poisson-Gamma mixture, namely a Negative Binomial distribution with aggregation parameter k .

All three model types make it possible to gain insights into the worm distribution within human hosts using observed available data indirectly measuring infection in humans, i.e. excreted eggs. Statistical and mathematical models further often use the Negative Binomial distribution to simulate the results of different schemes of KK diagnostic tests for *S. mansoni*. In this case, the aggregation parameter captures the high variability in repeated egg counts per person and has been used to quantify different sources of variation, such as between- and within-sample variability [47].

Modelling transmission

Deterministic and stochastic mathematical transmission models, including ABMs, typically aim to reproduce transmission of helminths in the host population. Transmission of helminths in humans is modelled by focusing on the interaction between human agents and a contaminated environment (i.e. the soil for STH and water bodies with snails for schistosomiasis), which serves as a reservoir for infection [53-55]. A schematic representation of the agent-based framework for modelling the transmission of STH and *S. mansoni* is displayed in **Figure 1.3**.

The interactions between human agents and the environment are often modelled using age-specific functions that represent both human exposure and contribution to the environmental reservoir of infection. Here, the behavioural dynamics to capture, in the context of low- or middle-income settings, are diverse: age-patterns are primarily considered to peak during

specific life stages, typically childhood, when contact with contaminated soil or water bodies is highest. However, additional variability can be observed due to other factors such as sex (women might be more exposed to water bodies because of daily activities related to household management, usually accompanied by their young infants), occupation (e.g. fishermen), or regional-specific settings [56], urban versus rural settings, socioeconomic conditions, e.g., walking barefoot, which facilitates infection with hookworms through skin penetration. Human agents excrete helminth eggs into the environment through their faeces (for STH and *S. mansoni*), often through inadequate sanitation that leads to the practice of open defecation, contributing to soil or water contamination. Age and behavioural patterns also influence the human contribution to the contaminated environment. Transmission models are important tools for understanding how different assumptions about human behavioural patterns of exposure and contribution to infection shape the transmission dynamics [57].

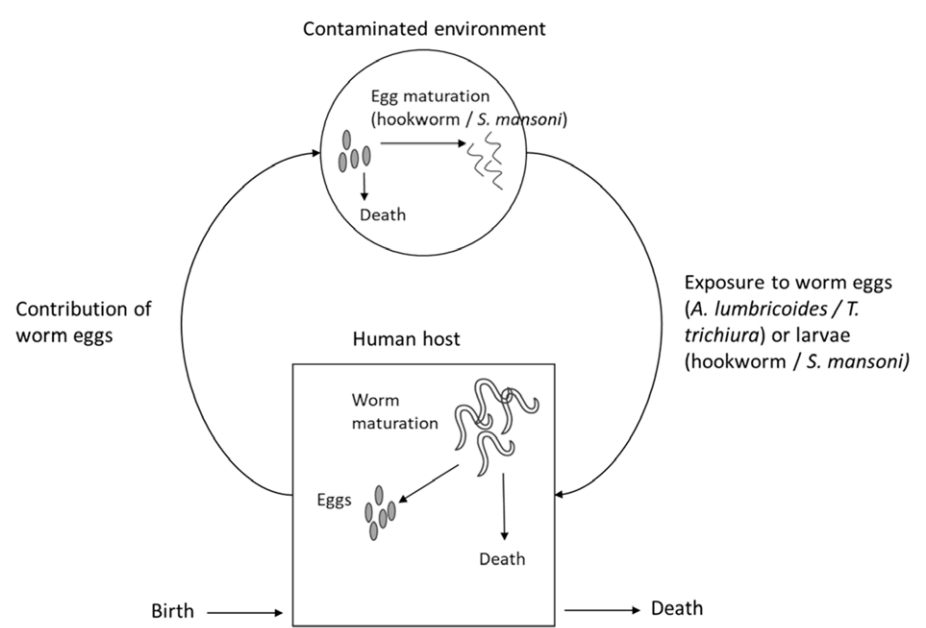


Figure 1.3. Schematic representation of an agent-based modelling framework for the transmission of soil-transmitted helminths (STH) and *S. mansoni*. The model captures the interactions between the human hosts and the contaminated soil (STH) or water (*S. mansoni*) environment. The within host life history of worms is simulated. Figure adapted from [54]. Worm icons made by Pixel perfect from www.flaticon.com

The dynamics within the environmental reservoir of infection are usually based on a deterministic flow, to capture the processes of survival, maturation, and presence of infective stages (e.g., eggs or larvae) in the environment. Within ABM frameworks for STH transmission, eggs are added to the reservoir at each time step, and a fixed proportion of the infective material from the previous time step is carried over, basically leading to an exponential survival of infective particles [58, 59]. For schistosomiasis, the infective dynamics in water are characterised by the presence of the snail intermediate host. The snails host the parasite's asexual reproduction phase acting as a second (in addition to egg production within the human host) amplifying factor for transmission. However, they can at the same time restrict transmission due to the depletion of susceptible snails, castration of infected snails, and increased snail mortality following infection [60-62]. The challenges in collecting data on snails [63] makes most of these dynamics invisible, i.e. almost unobservable for quantification. Field studies on snail populations and their infection status are relatively sparse, and shedding dynamics are usually only elucidated in laboratory studies, revealing a commonly low prevalence of infected snails [64-66]. Although key parameters related to snail-parasite-environment interactions are still poorly understood, modelling efforts have shown the importance of explicitly incorporating snail infection dynamics [67]. Modelling studies only focussing on the snail population have demonstrated how ecological and environmental factors, such as rainfall seasons, aquatic vegetation, and predators influence snail abundance and cercarial production [68], further driven by intraspecific competition for resources [69, 70]. Some deterministic transmission models of schistosomiasis have incorporated explicit infection dynamics among snail populations as a deterministic compartmental model interacting with the human population and the environment [71, 72]. One study elucidated the importance of snail age structure for the transmission on humans and related predictions for control strategies [67].

Regulating mechanisms of transmission

Transmission dynamics of infectious diseases are largely determined by mechanisms that limit transmission when infection levels become high, especially for parasitic worm infections, where individual worm burdens can potentially be very high. It is crucial for transmission models to include appropriate regulating mechanisms. For instance, density dependent fecundity within the human host, i.e. the egg output per female worm diminishes with increasing worm burden, has been demonstrated experimentally for STH by relating individual egg counts to worm counts, after expulsion through

deworming treatment [3, 43]. Density dependent fecundity in STH is further influenced by the overdispersion of parasites among hosts. When parasites are highly overdispersed, density-dependent effects become more pronounced. This means that the relationship between the average worm burden and its contribution to transmission is non-linear, with strong regulation occurring when parasites are clustered within certain hosts [73]. Modelling results have shown that density-dependence mechanisms influence the observed prevalence, a key epidemiological variable employed for control and monitoring and evaluation programmes [74, 75]. For instance, reducing infection intensity through treatment usually does not proportionally decrease transmission due to density-dependent factors [57]. While density-dependence in worm fecundity is an established concept in models of STH, the role and magnitude of density-dependent fecundity for *Schistosoma* is more debated. Schistosomes have been considered to exhibit density-dependent fecundity [3, 43], just like STH, but the evidence is less consistent. Scientific evidence supporting this assumption for schistosomiasis has traditionally relied on historical human autopsy data [76, 77], the relevance of which has been challenged [46]. Recent molecular analyses using sibship reconstruction [78] have provided some evidence of density dependence in egg production for *S. haematobium*, but the findings were inconclusive for *S. mansoni*. Clearly, regulating mechanisms at other stages of the transmission cycle of *Schistosoma* need to be considered.

Regulation can also be assumed based on the ecology of the snail population. Snail infection dynamics can regulate transmission primarily through the depletion of susceptible snails and excess mortality of snails upon infection. For example, a logistic population growth well describes a population growth pattern in which the growth rate decreases as the population size approaches the carrying capacity of the environment. This is a good representation of intraspecific competition for resources. A limited population growth is likely to eventually favour the depletion of susceptible snails.

Furthermore, immunity mechanisms can potentially regulate transmission at the human level. Immunity generated in humans by schistosomiasis and STH involves complex immune responses that develop over time, typically following repeated intensive exposure to the parasites. Both types of infections elicit a range of immune reactions, and the mechanisms and outcomes of immunity vary due to differences in parasite biology. In STH infections, immunity may involve the production of antibodies specific to the

parasite's surface antigens, as well as a cell-mediated immune response [79]. Immunological and molecular studies have investigated the mechanisms of the immune response. For example, an increased mucus production in the gut helps to physically eliminate the parasites. The immune system may also limit the egg output and parasite survival [79-81]. Immunity generated by STH infections in humans has not been explicitly included in modelling studies. The current understanding of immunity to STH is primarily derived from rodent models, which do not fully replicate the natural infection process in humans [82, 83]. For schistosomiasis, host-acquired immunity protecting from reinfections has been proposed based on antibody detection studies [84-86] and its mechanism alongside the transmission dynamics was investigated with some deterministic age-structured models [87-89]. However, a clear and comprehensive understanding of the mechanisms of acquired immunity (e.g., triggers, development rate) and its potential role in regulating transmission is still poor. It is important to bridge the gap between modellers and immuno-epidemiologists to derive empirically grounded immunity parameters [90].

Overall, mathematical models used to inform policy have given limited attention to host-acquired immunity and to explicitly representing the dynamics of the intermediate host. A deeper understanding is needed of how the interplay of regulating mechanisms operating at the worm, human, and snail level contributes to observed epidemiological patterns, and how these mechanisms influence estimates of intervention impact.

1.4. Modelling intestinal parasitic infections for policy

Statistical and mathematical models constitute a significant potential for guiding policy decisions on helminth control across multiple levels. First, models have been globally employed to evaluate the appropriateness of WHO control indicators, providing insights into whether current targets and thresholds are adequate for reducing disease burden [31, 91]. Second, modelling results have supported the design of tailored monitoring and evaluation strategies by simulating the predictive performance of various sampling designs for the evaluation of the control target [92], helping to prioritise resources in endemic regions. Third, transmission models have proved crucial to test the effectiveness of control scenarios and explicitly predict the impact of control strategies even before their implementation.

For instance, intervention programmes, such as MDA for different target populations or through different administration schemes, possibly combined with other interventions such as WASH, can be directly modelled to assess the feasibility to reach the WHO control targets on achieving control and/or elimination.

For STH, modelling results have suggested that in areas of low and medium endemicity, current MDA programmes, targeting 75% of SAC and women of childbearing age, are effective to achieve WHO control targets. However, in high endemic regions more frequent treatment with high coverage, combined with interventions that reduce environmental contamination, would be necessary for effective control [54, 93]. The recent inclusion of women of reproductive age during adolescence and pregnancy in the WHO 2030 Roadmap has also been supported by modelling results, which showed that annual deworming treatment of adolescent girls can reduce the prevalence of M&HI infections in this age group by up to 60% [94]. Numerical simulations have also supported the integration of health education and sanitation with campaigns of MDA [95]. While WASH interventions may have limited observable short-term impact during ongoing MDA programmes, they are crucial for sustaining long-term control and achieving elimination of STH infections after MDA cessation [93, 96].

Also in the fight against schistosomiasis, WASH has been identified crucial, given its persistence despite a long history of deworming programmes [42, 97]. Modelling predictions have regularly demonstrated that MDA alone, even with high coverage, will not allow achieving schistosomiasis elimination, highlighting the necessity for integrated control measures [98, 99]. Insights from quantitative studies and mathematical modelling on the proposed WHO 2030 goal for schistosomiasis [100] have suggested that in low to moderate prevalence settings, the current guidelines that only focus on treating SAC may suffice to achieve elimination as a public health problem (EHPH). However, in high-prevalence areas, achieving EPHP is much less likely, unless both SAC and adults are treated, and perhaps even pre-school-aged children. These insights have also highlighted challenges such as individuals who are never treated (e.g. children not enrolled in school programmes) and the potential for disease resurgence, which could impede progress towards EPHP.

Specifically, stochastic ABMs have proven ideal for testing interventions targeted at specific age groups and population categories. For instance, individuals never treated can be explicitly modelled [101]. ABMs allow the

computation of the probabilities to elimination (proportion of stochastic runs that meet the target), which support and quantify feasibility to reach WHO control targets. The computation of probability to elimination cannot be performed with a deterministic model. More on opportunities and challenges of deterministic and stochastic transmission models is elaborated in the General discussion (**Chapter 7**).

Mathematical models rely heavily on biological knowledge to inform the underlying assumptions, as well as prioritising research and data needs, for example through laboratory studies (for data about the natural history of the disease) or direct observations (e.g. for data about human behaviour). On the one hand, even when not calibrated on empirical epidemiological data, models can still provide valuable insights into the impact of biological assumptions [57] or the expected time to elimination for different control and endemicity scenarios. On the other hand, models that are fitted to detailed epidemiological data are tailored to reproduce region-specific settings, leading to accurate predictions only for this setting. Well calibrated models can refine control strategies based on real-world data, helping to optimise disease control in particular settings. By aligning model outputs with observed data (e.g. intensity patterns, prevalence pre- and post-control), models better reflect the complex realities of transmission dynamics, environmental influences and human behaviour. This process enhances the reliability of predictions for intervention planning and highlights gaps in knowledge and data. For example, if a model fails to accurately simulate prevalence in a specific setting, it signals that the model lacks a mechanism to properly explain the data, urging targeted data collection in this setting. In general, for schistosomiasis, better data on snail population and water exposure is needed, while for STH, more data on soil contamination and sanitation coverage would enhance model accuracy and intervention targeting. These data gaps underscore the importance of strengthening data collection efforts for reproducible and more precise model predictions [102]. Model calibration is not always straightforward, especially for complex models as ABMs with strong computational demands. There is growing attention on developing and comparing efficient calibration methods to optimise parameter search strategies [103, 104].

Mathematical modelling serves as a valuable tool to inform helminth control strategies and to ensure the efficient use of resources to achieve sustainable public health goals [105].

1.5. Aims of this thesis

This thesis advances the modelling of the transmission cycle of intestinal parasitic infections (soil-transmitted helminths and *S. mansoni*) that affect human populations, with the goal of supporting more effective control strategies to reduce infection burden. It provides models and tools that can help informing policy at multiple levels of the decision-making process. The focus of the thesis is on:

1. Assessing the appropriateness of the WHO indicator threshold for defining the STH morbidity targets (**Chapters 2 and 3**).
2. Estimating the effectiveness of various MDA strategies and feasibility to reach the WHO 2030 targets for STH in the exceptional situation of COVID-19-related interruption of deployment of control programmes (**Chapter 4**).
3. Revisiting the modelling assumptions of regulating mechanisms of *S. mansoni* to assess their impact on control targets (**Chapter 5**).
4. Assessing parameter uncertainty and data needs through model calibration (**Chapter 6**).

1.6. Outline of the thesis

In **Chapter 2** the suitability of the WHO threshold for morbidity control (M&H prevalence in children < 2%) to reflect morbidity attributable to hookworms is assessed. The focus is on anaemia as the primary morbidity associated to hookworm infections, using a hierarchical statistical model to simulate individual haemoglobin levels, incorporating the effects of hookworm burden while accounting for other potential causes of low haemoglobin. This results in estimates of the prevalence of anaemia attributable to hookworm in relation to prevalence of infection, across various endemicity scenarios and diagnostic sampling schemes.

Although the WHO prevalence indicators for STH are commonly defined via Kato-Katz diagnostics, the prevalence is found to depend on the sampling scheme, due to high variation between and within stool samples. The impact of different sampling schemes on WHO indicators for STH control targets is further expanded in **Chapter 3** using data from diverse epidemiological settings, under the constraint of a fixed budget.

In **Chapter 4** an existing stochastic agent-based model (ABM) is used to simulate the impact of missing one or more rounds of MDA against STH, in response to an abrupt interruption of all control activities in endemic countries, due to the COVID-19 pandemic. The impact of this disruption on the progress towards the WHO 2030 target for STH is investigated, as well as to which extent the effects can be mitigated by additional strategies, such as more frequent treatment or targeting the whole community.

The impact of different MDA intervention strategies is further studied for schistosomiasis in **Chapter 5**, in relation to varying modelling assumptions. Here, the newly developed SchiSTOP model is presented: a stochastic ABM for *S. mansoni* transmission in an age-structured human population. SchiSTOP is used to explore the interplay of different assumptions on the mechanisms regulating transmission. For each modelling assumption, the ability of the model to explain observed epidemiological patterns for *S. mansoni* is assessed.

Chapter 6 addresses the task of efficiently calibrating SchiSTOP using history matching with emulation, a methodology that employs surrogate models (emulators) to explore parameter space, while limiting the computational demands of complex models. The model is calibrated to field data of infection intensity and prevalence, first using data from SAC, and then incorporating data about the entire population. The aim is to investigate what types and richness of data are most informative for improving parameter estimation and therefore accuracy of model predictions.

Finally, **Chapter 7** provides an overarching view on the core scientific findings and their practical consequences. The chapter further discusses broader considerations in mathematical modelling for policy support, including current challenges and future directions, concluding with final remarks.

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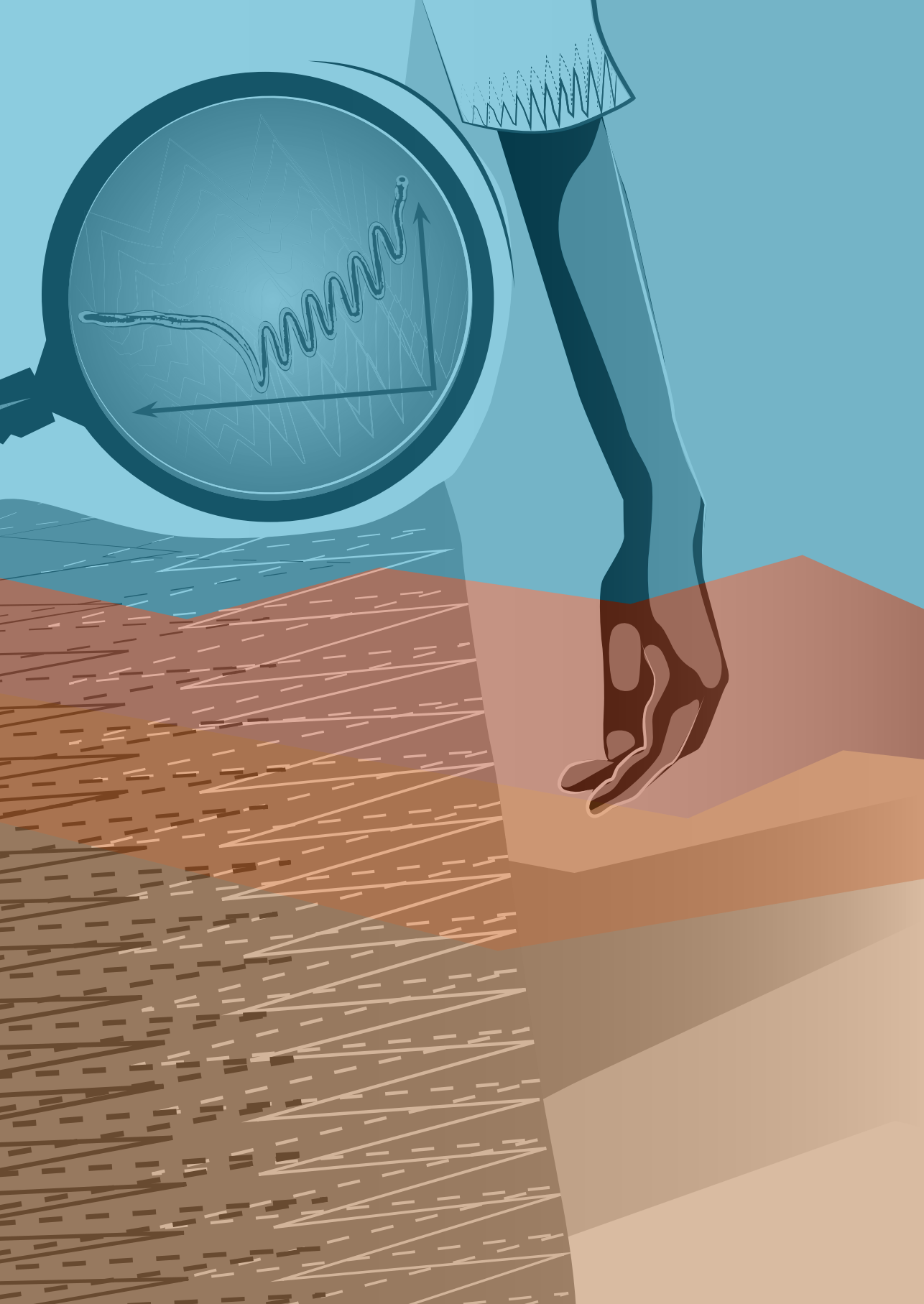
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Chapter 2 Appropriateness of the current parasitological control target for hookworm morbidity: a statistical analysis of individual-level data

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Abstract

Background

Soil-transmitted helminths affect almost 2 billion people globally. Hookworm species contribute to most of the related morbidity. Hookworms mainly cause anaemia, due to blood loss at the site of the attachment of the adult worms to the human intestinal mucosa. The World Health Organization (WHO) aims to eliminate hookworm morbidity by 2030 through achieving a prevalence of moderate and heavy intensity (M&HI) infections below 2%. In this paper, we aim to assess the suitability of this threshold to reflect hookworm-attributable morbidity.

Methodology/Principal Findings

We developed a hierarchical statistical model to simulate individual haemoglobin concentrations in association with hookworm burdens, accounting for low haemoglobin values attributable to other causes. The model was fitted to individual-level data within a Bayesian framework. Then, we generated different endemicity settings corresponding to infection prevalence ranging from 10% to 90% (0% to 55% M&HI prevalence), using 1, 2 or 4 Kato-Katz slides. For each scenario, we estimated the prevalence of anaemia due to hookworm. Our results showed that on average, haemoglobin falls below the WHO threshold for anaemia when intensities are above 2000 eggs per gram of faeces. For the different simulated scenarios, the estimated prevalence of anaemia attributable to hookworm ranges from 0% to 30% (95%-PI: 24% - 36%) being mainly associated to the prevalence of M&HI infections. Simulations show that a 2% prevalence of M&HI infections in adults corresponds to a prevalence of hookworm-attributable anaemia lower than 1%.

Conclusions/Significance

Our results support the use of the current WHO thresholds of 2% prevalence of M&HI as a proxy for hookworm morbidity. A single Kato-Katz slide may be sufficient to assess the achievement of the morbidity target. Further studies are needed to elucidate haemoglobin dynamics pre- and post- control, ideally using longitudinal data in adults and children.

Author summary

Soil-transmitted helminths affect almost 2 billion people globally. About 65% of the related morbidity is attributable to hookworm infection, especially anaemia, which is caused by adult worms attaching to the intestinal mucosa

of the human host to feed on blood. The World Health Organization (WHO) defines the target for the elimination of morbidity as reaching moderate-to-heavy intensity infections prevalence $< 2\%$. In this paper, we aim to assess the suitability of the current WHO threshold to reflect hookworm-attributable anaemia. To this end, we developed a statistical model to simulate individual haemoglobin concentrations in association with hookworm burdens in adults, accounting for low haemoglobin values attributable to other causes, such as malnutrition and malaria. We used model outcomes to estimate the prevalence of hookworm-attributable anaemia in different endemicity scenarios. Our predictions suggested that anaemia is mainly associated to moderate-to-heavy intensity infection and that the 2% threshold corresponds to a prevalence of hookworm-attributable anaemia $< 1\%$. These results support the use of the current WHO threshold as a proxy for hookworm morbidity. Our predictions represent a first step towards better quantifying the prevalence of anaemia due to hookworm infection.

2.1. Introduction

Soil-transmitted helminths (STH) are estimated to affect almost 2 billion people globally [1], with the vast majority living in developing countries. Transmitted through contaminated soil, STH are responsible for considerable morbidity. About 65% of the overall estimated STH morbidity is attributable to hookworm infection, which is commonly caused by the helminth parasites *Necator americanus* and *Ancylostoma duodenale* [2]. The most common condition associated with hookworm infection is anaemia resulting from adult hookworms attaching to the mucosa of the small intestine in the human host to feed on blood. The uptake of blood and the extra loss due to wounds left by detaching worms reduce haemoglobin (Hb) and iron levels of the host, until the nutritional iron reserves and intake are not sufficient anymore [3]. Hookworm infection has been shown to significantly contribute to the global burden of anaemia in many countries [4].

The World Health Organization (WHO) categorises hookworm infections as light (≤ 1999 eggs per gram of faeces (epg)), moderate (2000 – 3999 epg) and heavy (≥ 4000 epg) [5]. The current global target set by the WHO is the elimination of hookworm as a public health problem by 2030, defined as reaching a moderate-to-heavy intensity (M&HI) prevalence $< 2\%$ in school-aged children [6]. Although anaemia is thought to be a consequence of M&HI infection, lower Hb levels in adults have been associated with all levels of infection intensity [7]. The number of adult worms in the human host that are sufficient to cause anaemia depends on several factors, such as the hookworm species causing the infection, the underlying nutritional reserves of the host, and coinfection with other parasites [8]. Clear evidence for the definition of the WHO guidelines and the use of M&HI prevalence of infection as indicator of hookworm morbidity is currently lacking.

Previous studies estimated the effect of hookworm infection intensity on blood iron reserves [3] and investigated the relationship between Hb and faecal egg counts [9]. For instance, Lwambo et al. [9] showed that Hb significantly declines for infection intensities above 2000 epg. They also predicted a non-linear relationship between prevalence of infection and prevalence of hookworm-related anaemia where the latter steeply increases with high prevalence of infection. In these studies, results are presented in terms of overall prevalence of anaemia in the population. However, in most of the settings where hookworm infection is prevalent, malnutrition and coinfection

with other endemic infectious diseases (e.g., malaria, schistosomiasis, other neglected tropical diseases) are also common. Therefore, it is important to account for an underlying prevalence of anaemia in the population due to causes other than hookworm infection.

The aim of this paper is to assess the suitability of the current WHO targets using prevalence of M&HI infection as a proxy for hookworm morbidity. To do this, we estimate the prevalence of anaemia attributable to hookworm infection as a function of hookworm prevalence (M&HI and any intensity). We do so by modelling how individual level Hb concentrations change in response to individual hookworm burden, indirectly observed through excreted egg counts. We account for anaemia attributable to other causes by assuming an Hb distribution that allows low values also in absence of worms. To extend this approach to other settings, we generate different endemicity scenarios and for each we estimate the prevalence of anaemia attributable to hookworm. We further consider the impact of different sampling schemes for diagnosis using the Kato-Katz (KK) thick smear technique on the evaluation of the morbidity target.

2.3. Methods

Ethics statement

The data employed in the present study were collected for previous publication [10]. The original study protocol was approved by the Makerere University Faculty of Medicine Research and Ethics Committee (#2008-043), the Uganda National Council of Science and Technology (#HS 476) and the London School of Hygiene and Tropical Medicine Ethics Committee (#5261) [10].

Data

We analysed individual data from a rural community in Uganda (N = 2037 individuals), consisting of Hb values and egg count measurements for hookworm and *Schistosoma mansoni* detection, collected by means of two KK slides per day per individual, for a total of two consecutive days and four slides for each parasite. Age, sex, and geographical location were also recorded. These data have been previously collected and analysed to estimate the spatial and genetic variation in intensity of hookworm infection [10]. The original study protocol was approved by the Makerere University Faculty of Medicine Research and Ethics Committee (#2008-043), the Uganda National Council

of Science and Technology (#HS 476) and the London School of Hygiene and Tropical Medicine Ethics Committee (#5261) [10]. Hb concentrations and egg counts for hookworm were available for 1840 individuals. The WHO provides the definition of anaemia based on age- and sex-specific thresholds [11]: women and men > 15 years old are defined anaemic if their Hb concentration is below 120 and 130 g/L, respectively. Due to high age/sex-variation in anaemia thresholds for children and the assumption that exposure to hookworm infection stabilises in adult age [12], we focused our analysis on the adult population (≥ 20 years, both sexes). In ten individuals, extremely high egg counts were recorded (up to a maximum of 35,000 epg). We hypothesised that these few individuals were infected with the hookworm species *A. duodenale* and therefore excluded them (individuals with a mean egg count > 10,000 epg) from the analysis, due to higher range of daily egg production [8] and contribution to anaemia for *A. duodenale* [13]. The final population is composed of N=695 adults with a 52% prevalence of any intensity of hookworm infection, 4% prevalence of M&HI of infection and 41% prevalence of overall anaemia. The process of data selection is summarised in **Figure2.1**.

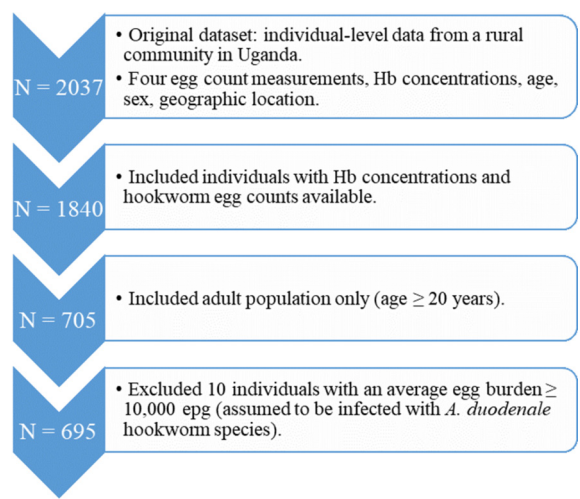


Figure 2.1. Flowchart describing the process of data selection for the statistical analysis.

Model

The association between Hb values and egg counts was studied by means of a hierarchical statistical model defined at individual level, with a latent variable representing the unobserved worm burdens in each human host. The distribution of worm burdens in a population is known to be highly over-

dispersed, with most people harbouring no or a small number of worms and only few highly infected individuals. The parasitological part of the hierarchical model is described as follows:

$$w_i | \rho, \delta, \lambda \sim p(w_i | \rho, \delta, \lambda)$$

where w_i is a semi-continuous latent variable representing the worm burden for the i -th individual. Its probability density function is defined as:

$$p(w_i | \rho, \delta, \lambda) = \begin{cases} \rho, & w_i = 0 \\ (1 - \rho) * \text{Weibull}(w_i | \delta, \lambda), & w_i > 0 \end{cases}$$

The latent variable w_i was thus modelled from a finite mixture of a Bernoulli distribution with probability ρ (i.e., the probability of having zero worms) and a Weibull distribution with shape parameter δ and scale λ . The employment of this semi-continuous variable is meant to approximate the discrete negative binomial distribution, which has commonly been employed for describing over-dispersed worm burdens in human populations. This approximation was necessary to be able to use the Hamiltonian Monte Carlo algorithm to sample from the posterior distribution, which does not allow the use of a discrete latent variable. The latent variable w_i enabled us to discriminate between infected (if $w_i > 0$) and uninfected individuals (if $w_i = 0$). The corresponding individual egg counts are simulated in the model as follows:

$$x_{i,j} | w_i, ec_i, k_e \sim NB(ec_i, k_e)$$

The variable $x_{i,j}$ is the j^{th} egg count for the i -th individual, with $j = 1, \dots, 4$. The parameters ec_i and k_e represent the expectation and the aggregation parameter k_e of the egg count distribution. The aggregation parameter encapsulates the variability within the same stool specimen and between different stool samples. The expected individual egg burden was assumed to depend on the underlying worm load w_i according to a hyperbolic saturating function [12] describing density dependent fecundity. The function is defined as follows: $ec_i = a * fw_i / (1 + \frac{a * fw_i}{b_i})$ where $fw_i = w_i / 2$ approximates the female worm load, the parameter a is the average egg production for each female worm in absence of density dependence effects, and the b_i maximum host egg output. The latter was assumed to vary between hosts due to host suitability for infection and was assumed to follow a gamma distribution with mean β representing the population average saturation level in egg production. The values of a and the shape of the gamma distribution (which dictates the level of variation in host suitability) were set to values available from previous work (**Table 2.1**).

Table 2.1. Parameters employed in the model. The parameters can be either given in input or estimated from the model. For input parameters the corresponding value is reported, the prior distribution for the Bayesian estimation otherwise. When available, the source of the information is cited. Prior distributions are parameterised in terms of mean and standard deviation (normal) or scale (Cauchy).

Parameter	Origin	Value	Prior	Source
Probability of having zero worms ($\epsilon \in [0, 1]$)	Estimated	-	$\rho \sim \text{Uniform}(0, 1)$	-
Shape of the Weibull distribution for worm burdens in infected individuals ($\delta > 0$)	Estimated	-	$\delta \sim \text{Normal}^+(0.5, 1)$	-
Scale of the Weibull distribution for worm burdens in infected individuals ($\lambda > 0$)	Estimated	-	$\lambda \sim \text{Cauchy}^+(2, 1)$	-
Initial slope of the egg production function (α)	Input	200 epg	-	[12]
Mean saturation level of the egg production function (β)	Input	10,000 epg	-	Pre-set
Shape and rate of the gamma distribution for individual relative susceptibility to infection	Input	50	-	[12]
Aggregation parameter for egg counts ($k_e > 0$)	Estimated	-	$k_e \sim \text{Normal}^+(0, 2)$	[12]
Logarithm of geometric mean of Hb [g/L] distribution in uninfected individuals (μ_0)	Estimated	-	$\mu_0 \sim \text{Normal}(\log(129), 0.1)$	[14, 15]
Scale parameter of Hb distribution ($\sigma > 0$)	Estimated	-	$\sigma \sim \text{Normal}^+(0, 0.5)$	[14, 15]
Steepness of the logistic decrease ($\varphi_1 > 0$)	Estimated	-	$\varphi_1 \sim \text{Normal}^+(1, 3)$	-
Location of the sigmoid ($\varphi_0 > 0$)	Estimated	-	$\varphi_0 \sim \text{Normal}^+(6, 2)$	-

* The prior distribution is left-truncated at zero.

The mean saturation level β was set to 10,000 epg to assure the model was able to catch the entire range of observed egg counts.

We further assumed that Hb concentrations (y_i) follow a LogNormal distribution with standard deviation σ representing the natural variation between individuals and a mean that depends on an individual's infection status. In absence of hookworm infection (i.e. $w_i > 0$), we assumed a mean of μ_0 . For individuals with a worm burden $w_i > 0$, we assumed the expected Hb to follow a logistic decrease on the logarithmic scale with increasing worm burden, i.e.:

$$y_i | w_i, \mu_0, \sigma, \varphi_0, \varphi_1 \sim \text{LogNormal}(\mu_0 - f(w_i), \sigma)$$

where the logistic decrease is defined as $f(w_i) = -\log(1 + e^{\varphi_1 * \log(w_i) - \varphi_0})$. Here, φ_0 represents the steepness of the decreasing function and is proportional to the x-axis intercept of the middle point of the sigmoid. The full list of employed parameters is presented in **Table 2.1**.

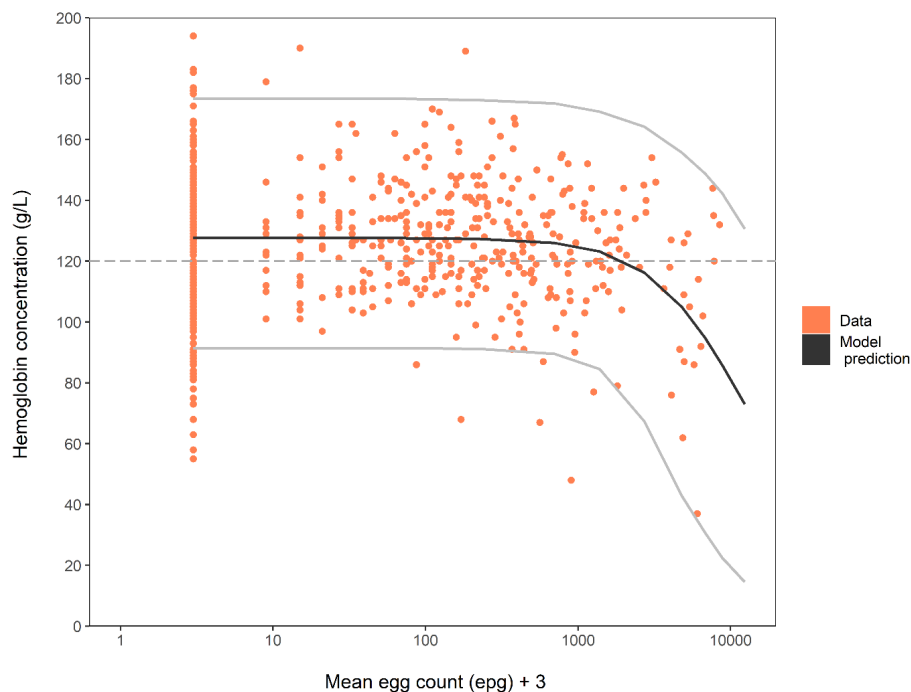


Figure 2.2. Relationship between individual haemoglobin concentrations (g/L) and mean egg count (epg). Orange bullets represent observed individual data used for model fit. The joint posterior predictive distribution of Hb and mean egg count based on 20,000 replications is displayed through the mean of the Hb predictions (y-axis) and the geometric mean of egg count predictions (x-axis) (black line). Mean egg count data are shifted of +3 epg (i.e. half of the detection limit) to display the zero counts on the logarithmic-scaled axes. The 95% Bayesian Credible Interval (light grey lines) is shown for the marginal Hb posterior predictive distribution. The WHO threshold defining anaemia used in the model is displayed as horizontal dashed line.

The model was fitted to the data within a Bayesian framework. The probability ρ of having zero worms was assigned a Uniform prior between 0 and 1. The hyper-parameters of the Weibull distribution modelling the individual worm burdens in infected individuals were assigned vague hyper-priors. Prior distributions for parameters and σ were based on information available from the literature [14, 15]. Weakly informative priors were assigned to φ_0 , φ_1 and k_e . Prior information on φ_1 and k_e is limited to mathematical constraints.

Posterior distributions of the estimated parameters and predictions were simulated in Stan [16] (code for model specification in Stan is publicly available [17]), a probabilistic programming language for statistical modelling. Stan allows the user to perform full Bayesian statistical inference using Markov Chain Monte Carlo (MCMC) sampling (based on NUTS or HMC sampling algorithm). Simulations were run and further analysed in R (version 3.6.1) [18], using the package *rstan* [19]. The algorithm was run on 4 independent Markov chains, each with 10,000 draws, for a total of 20,000 post-warmup draws (the initial 5,000 draws per chain were considered for warm-up). Convergence was assessed by visual examination of the trace plots and the convergence diagnostic methods provided by Stan. Fit evaluation was performed by means of full posterior predictive checks [20]. In this procedure, the population was replicated for each draw of the joint posterior distribution of model parameters and then compared to the original data.

Simulations

After fitting the model, the posterior distributions obtained for each of the fitted parameters were used to study the appropriateness of the current WHO parasitological target as proxy for hookworm morbidity. We simulated different endemicity scenarios characterised by a specific worm distribution in the population (i.e., a specific combination of the three parameters p , δ and λ describing the mixture distribution of worm burdens) resulting in different prevalence of hookworm infection (any intensity and M&HI) settings. The assumptions about the distributions that describe the actual egg counts, the Hb concentrations and the background risk of anaemia in the simulated populations were the same as assumed while fitting the observed data. The simulated infection prevalence ranged from 10% to 90% (any intensity) and 0% to 55% (M&HI). For each scenario, we generated a population of 1000 individuals using a random sample of 5000 draws from the posterior distribution of the parameters and we computed: i) the KK-based hookworm prevalence of any infection, ii) the KK-based prevalence of M&HI infection, iii) overall prevalence of anaemia, iv) anaemia attributable to hookworm infection. The latter is defined as the difference between the overall predicted anaemia and a baseline anaemia in the counterfactual scenario without worm infections, estimated from the model. This computation does not explore the contribution of hookworm infection to the severity of anaemia. Each of the aforementioned quantities were computed based on 3 different sampling schemes to assess the KK-based prevalence of hookworm: i) a single KK slide, which is the most common diagnostic scheme in the field, ii) duplicate slides, and iii) four repeated slides, in line with the dataset used in this study.

All analyses were performed in accordance with the Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD) criteria [21] (**2.S1 Table**). The full model specification and the code for data selection, statistical analysis and simulations are publicly available [17]. A flow diagram summarising the complete process of model specification, fitting and simulation is provided as supporting material (**2.S1 Figure**).

2.4. Results

Association between individual haemoglobin levels and egg counts

Our statistical model fitted the individual data from Uganda well, which suggests that a logistic function is a reasonable representation of the effect of increasing hookworm burden on Hb levels in adults (**Figure 2.2**).

Table 2.2. Model parameter estimates. Estimates represent posterior distributions of model parameters. For each parameter, Rhat can be used as indicator for Markov chains convergence (at convergence, Rhat=1). BCI = Bayesian credible interval, based on the central 95% percentiles of the posterior draws.

Parameter	Mean [95%-BCI]	Rhat
Probability of having zero worms ($p \in [0, 1]$)	0.38 [0.32, 0.43]	1.001
Shape of the Weibull distribution for worm burdens in infected individuals ($\delta > 0$)	0.48 [0.40, 0.55]	1.001
Scale of the Weibull distribution for worm burdens in infected individuals ($\lambda > 0$)	3.31 [2.34, 4.41]	1.001
Aggregation parameter for egg counts ($k_e > 0$)	0.66 [0.59, 0.74]	1.000
Logarithm of geometric mean of Hb [g/L] distribution in uninfected individuals (μ_0)	4.84 [4.82, 4.85]	1.000
Scale parameter of Hb distribution ($\sigma > 0$)	0.16 [0.15, 0.17]	1.000
Steepness of the logistic decrease ($\varphi_1 > 0$)	1.90 [1.33, 2.54]	1.001
Location of the sigmoid (φ_0)	9.23 [6.96, 11.90]	1.000

This figure shows the joint posterior predictive distribution of Hb and egg counts based on 20,000 iterations, displayed via the mean of Hb predictions (y-axis) and the geometric mean of egg count predictions (x-axis). The 95% Bayesian Credible Interval (BCI) is solely displayed for the marginal Hb posterior predictive distribution. In absence of hookworm infection, Hb levels in the population are distributed with an estimated geometric mean of 126 g/L (95%-BCI: 124.3 g/L – 127.5 g/L) and a standard deviation of the Hb natural logarithm equal to 0.16 (95%-BCI: 0.15 – 0.17). The estimated parameters of

the logistic function showed that hookworm infection has little effect on Hb levels in the population for intensities up to 1000 epg and that Hb falls below the WHO threshold for anaemia when intensities are above 2000 epg. See **Table 2.2** for detailed parameter estimates.

The posterior predictive checks obtained from the model fit to the data recorded a prevalence of hookworm infection in the population of 54% (95%-BCI: 48%-59%; 52% in data), a M&HI infection prevalence of 4.5% (95%-BCI: 3% - 7%; 4% in data) and a prevalence of overall anaemia of 40% (95%-BCI: 36% - 45%; 41% in data). The posterior distributions of the parameters and σ suggested a baseline prevalence of anaemia (in absence of hookworm infection) in the population of 38% (95%-BCI: 35% - 41%). This represents the prevalence of anaemia that may be attributed to other causes.

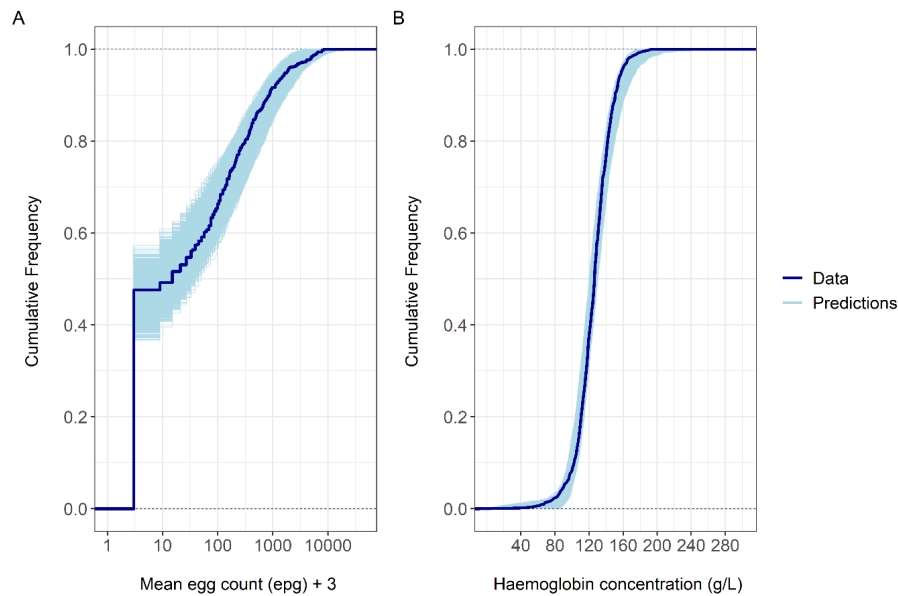


Figure 2.3. Comparison of observed data and model prediction. (A) Full posterior predictive checks for the mean egg counts. Mean egg count data are shifted of +3 epg (i.e. half of the detection limit) to display the zero counts on the logarithmic-scaled axes. (B) Full posterior predictive checks for haemoglobin concentrations. Dark lines represent the corresponding distribution observed in the Ugandan population. Both marginal predictive distributions are displayed through the cumulative distribution function of the predictions based on 20,000 replications (light lines) and compared with observed data.

Full posterior predictive checks for Hb levels and egg counts distributions, based on 20,000 replicated datasets were compared to the original data and

used to assess model fit (**Figure 2.3**). The posterior predictive distributions approximated the observed egg counts and Hb distributions in the population reasonably well.

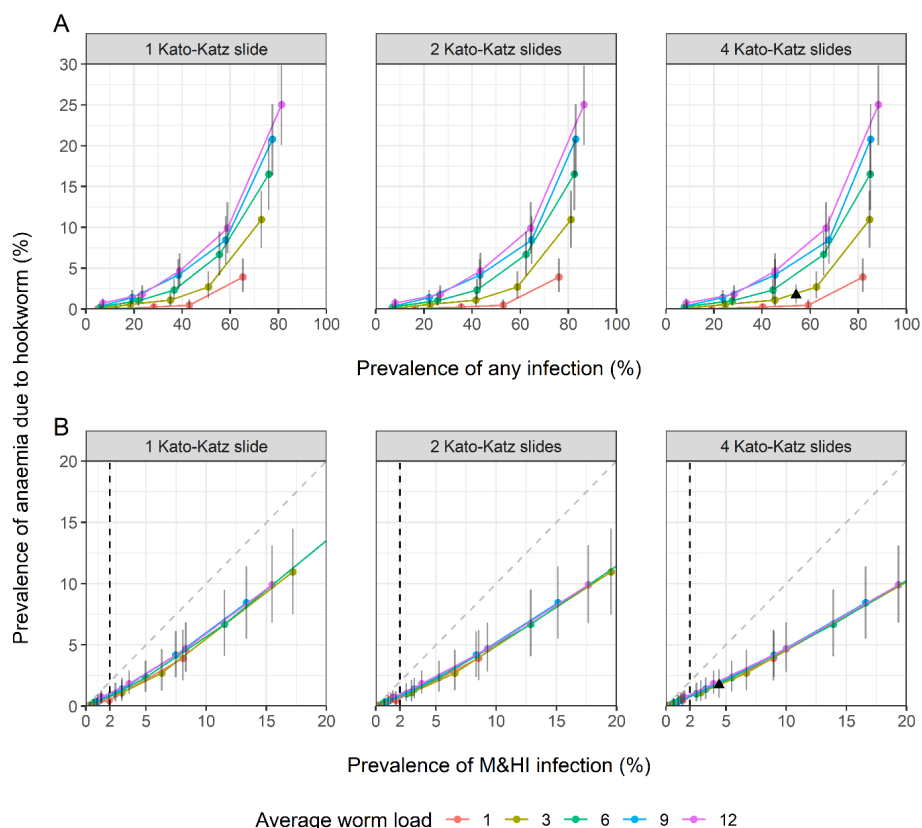


Figure 2.4. Estimated prevalence of anaemia attributable to hookworm in adult populations, for different infection prevalence scenarios. Predictions are displayed for different infection prevalence scenarios, defined by varying the probability p of having zero worms among the five values 0.1, 0.3, 0.5, 0.7, 0.9 (different bullets of the same colour) and the population mean worm burden (different colours). The shape parameter of the worm distribution across infected individuals is fixed to (as estimated from the Ugandan data). From left to right, the prevalence of any hookworm infection (A) and moderate-to-heavy intensity of infection (B) is based on 1, 2, 4 Kato-Katz slides, respectively. Each point (x, y) represents the mean predictions of infection prevalence (x-value) vs. hookworm-anaemia prevalence (y-value). The error band reports the 95% prediction interval (PI) of predicted hookworm-anaemia. The black triangle indicates the predictions (mean and 95%-PI) for the scenario resulting from the fit to the Ugandan dataset. Dashed vertical lines mark the WHO morbidity threshold of 2% moderate-to-heavy intensity prevalence. The bisector in panels (B) is added to visualise the robustness of the prevalence of moderate-to-heavy intensity of infection over the three sampling schemes.

Simulated prevalence of anaemia due to hookworm infection

The posterior distributions obtained for each of the fitted parameters were used for simulating different endemicity scenarios, assuming that the risk of anaemia due to causes other than hookworm infection is the same as in the Ugandan data. The simulated prevalence of anaemia attributable to hookworm is displayed in **Figure 2.4** with its mean and corresponding 95% prediction interval (PI), as a function of infection prevalence (any intensity and M&HI). The figure shows that the prevalence of anaemia attributable to hookworm ranged from 0% to 25% (95%-PI: 20% - 30%) by varying endemicity scenarios and it showed strong association with the prevalence of M&HI infections. In all the simulated scenarios, a 2% prevalence of M&HI infections in adults corresponded to a prevalence of anaemia attributable to hookworm infections lower than 1%.

Our simulations showed that the prevalence of infection is sensitive to the number of KK simulated measurements. However, low values of M&HI infection prevalence (<15%) in a given scenario were relatively consistent over the three sampling schemes (1, 2 or 4 KK simulated measurements).

The endemicity scenarios presented in **Figure 2.4** are based on a fixed value of the shape parameter for the distribution of worms across infected individuals ($\delta = 0.5$, i.e., approximately the value estimated for the Ugandan dataset). Simulations for alternative values of the shape parameter resulted in a similar pattern, with the prevalence of anaemia attributable to hookworm ranging from 0% to 30% (95%-PI: 24% - 36%), by varying endemicity scenarios (**2.S2 Figure**).

2.5. Discussion

The aim of this study was to estimate the prevalence of anaemia attributable to hookworm infection and to evaluate whether the current guidelines for hookworm control properly reflect actual hookworm morbidity. To that end, we used a statistical hierarchical model that estimates the mechanisms of Hb decrease in response to increasing worm burden at individual level. Our analysis show that the estimated hookworm-attributable anaemia is strongly associated to M&HI infections in adults. The current threshold used as an indicator for the elimination of hookworm morbidity (2% of M&HI prevalence in school-aged children as for the 2030 WHO target) corresponds to less than 1% prevalence of anaemia due to hookworm in the simulated endemicity settings. Therefore, our predictions suggest that the current threshold adopted

by the WHO for the elimination of hookworm as a public health problem seems suitable. It should be noted that our results are solely based on Hb values and egg counts from adults, due to limited available data. Even though children show a higher age/sex-variation in the definition of the anaemia thresholds and the underlying Hb distribution, we would expect a similar association between the prevalence of anaemia attributable to hookworm and the prevalence of hookworm infection in adults as in children. In fact, it is known that adults can be infected with hookworm to the same extent as children [22] or even more, with a higher experienced morbidity [23]. In addition, our analysis confirms findings from a previous study in a population of school-aged children in Zanzibar [24] which showed an approximately linear association of intestinal blood loss with intensity of hookworm infection.

Hookworm infections were found to have little effect on Hb levels for intensities up to 1000 epg. In fact, it is known that the uptake of blood by few worms should be easily counterbalanced by stored iron in the host, with some variation depending on individual nutritional reserves [3]. The development of anaemia as a consequence of hookworm infection depends on individual iron balance. At a population level, the threshold in the relationship between intensity of hookworm infection and prevalence of anaemia depends on the underlying iron reserves of the population [24, 25], here incorporated as other sources of anaemia than hookworm infection. Our analysis show that for moderate (≥ 2000 epg) and heavy (≥ 4000 epg) intensity of infection the predicted average Hb drastically drops below the WHO threshold for anaemia. These results are in line with Lwambo *et al.* [9].

The simulated scenarios also show that the predicted KK based prevalence is dependent on the number of repeated measurements, but values of M&HI infection prevalence $< 15\%$ are quite robust over the three simulated sampling schemes (1, 2 or 4 KK) (**Figure 2.4**). Recent work by our team [26] reached similar conclusions, suggesting that 1 slide/sample may be sufficient for determining prevalence of M&HI infection to assess the morbidity target.

Previous modelling studies estimated the prevalence of hookworm morbidity from existing data [3, 9, 27] without explicitly considering anaemia due to other causes. In our model we accounted for an underlying prevalence of anaemia due to other causes such as poor nutritional status or suffering from other infectious diseases, by explicitly modelling individual Hb variation. The latter is mainly governed by the scale parameter σ of the Hb distribution,

defined to be equal for both groups of infected and not infected individuals, thus reflecting an underlying prevalence of anaemia due to other causes in the total population. This approach finds support from a recently published systematic review and meta-analysis [28] which showed that the intensity of hookworm infection and the influence of other sources on the risk of anaemia drive differences in mean Hb concentrations, in hookworm endemic settings.

The Ugandan dataset used to fit our model showed some peculiarities we had to account for in our analysis. The subset of population detected with zero eggs for hookworm reported relatively low average Hb, presumably indicating other abundant sources of anaemia: part of the population was co-infected with *Schistosoma mansoni* [10]. The majority of individuals who tested positive to hookworm was lightly infected (only 4% of M&HI infection prevalence). Therefore, we did not include sex differences in the model, with the aim of gathering enough information about the steepness of the Hb decrease. However, we expect male and female population to show the same decreasing dynamics in response to increasing worm burdens, considering biological differences in how Hb concentrations are distributed in absence of infection between the two groups. The analysed Ugandan population is also heterogeneous with respect to the hookworm species causing the infection. In light of considerable differences between hookworm species in egg production [8], density-dependent fecundity effects [29] and in contribution to morbidity [3, 13, 25], we excluded ten individuals that we assumed to be infected with *A. duodenale* (detected $\text{epg} \geq 10,000$). The differentiation of hookworm species in the present model framework would require a species-specific parametrisation of the parasitological dynamics, which is beyond the information available in the analysed data. Future versions of our statistical model may allow for different species, if sufficiently detailed data of species-specific egg counts (e.g., using qPCR [30]) and haemoglobin become available.

Few individuals infected with *A. duodenale* at lower intensities could not be identified and could well still be part of the analysed data, contributing to a milder estimated slope of the Hb logistic decrease. We nevertheless do not expect those data to have a critical impact on the overall estimation of the relationship between Hb and worm burdens.

The distribution of worms between individuals is commonly described by a negative binomial distribution, parameterised with a mean worm burden and an aggregation parameter regulating the level of over-dispersion. However,

we coded the model in Stan [16] which does not allow the use of a discrete latent variable [16]. Therefore, we used a semi-continuous approximation resulting from a finite mixture of a Weibull distribution and a point mass at zero, that can be interpreted as the level of true infection intensity in the host. The employment of a finite mixture distribution for modelling worm burdens allows discrimination between infected and uninfected individuals, providing a prediction of the true prevalence of infection (i.e., presence of worms). In our model we account for possible false negative results from the KK test, that we assume to be ascribed to an undetectable level of infection (low worm loads) or to the sensitivity of the test (simulated through the over-dispersion parameter of the negative binomial distribution used for modelling egg counts).

In conclusion, this study represents a first step towards better quantifying the prevalence of anaemia due to hookworm infection. Our results support the appropriateness of the current WHO threshold of 2% prevalence of M&HI as a proxy for hookworm morbidity. In addition, a single KK slide may be sufficient for assessing this morbidity target. Further studies are needed to elucidate Hb dynamics pre- and post- mass drug administration, where the infection harbouring time plays an important role [28], ideally using longitudinal data collected in both children and adults.

Acknowledgments

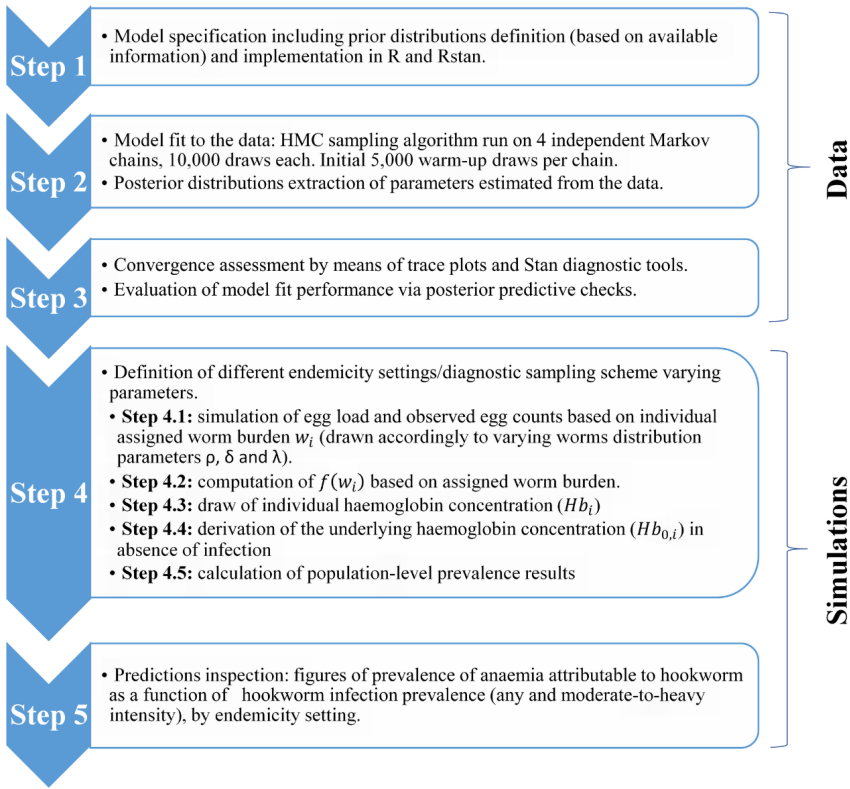
The authors gratefully acknowledge Professor Simon J Brooker (Bill & Melinda Gates Foundation, Seattle, WA, USA), Dr. Rachel L Pullan (Department of Disease Control, London School of Hygiene and Tropical Medicine, London, United Kingdom) and Dr. Narcis B. Kabatereine (Vector Control Division, Ministry of Health, Kampala, Uganda) for collecting and sharing the data. The authors would like to thank Professor Bruno Levecke (Ghent University, Faculty of Veterinary Medicine, Merelbeke, Belgium) for the useful discussions about the differences in egg production and contribution to morbidity among hookworm species.

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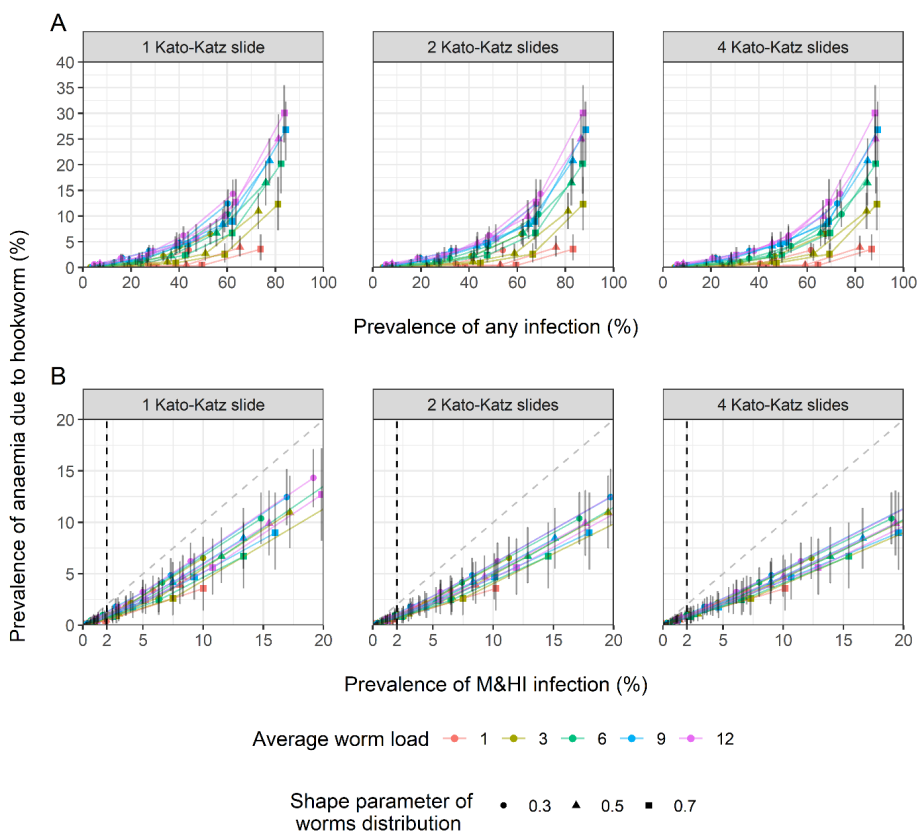
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2.6. Supporting information



2.S1 Figure. Flow diagram summarising the complete process of modelling, fitting and simulation of the statistical analysis for hookworm anaemia.



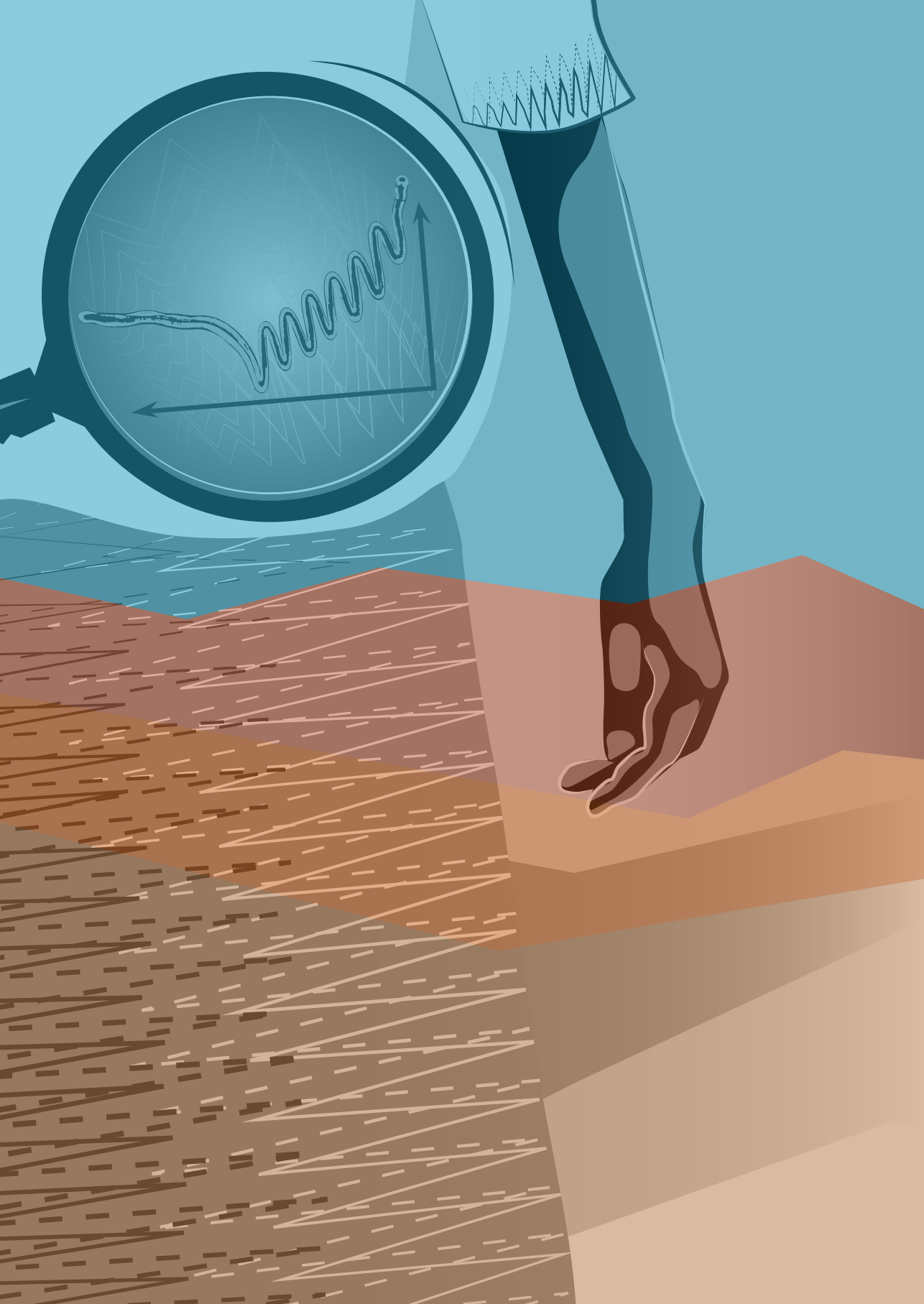
2.S2 Figure. Estimated prevalence of anaemia attributable to hookworm in adult populations, for different infection prevalence scenarios. Predictions are displayed for different infection prevalence scenarios, defined by varying the probability p of having zero worms among the five values 0.1, 0.3, 0.5, 0.7, 0.9 (different points of the same colour), the population mean worm burden (different colours) and the shape parameter δ of worm distribution in infected individuals (different shapes). From left to right, the prevalence of any hookworm infection (A) and moderate-to-heavy intensity of infection (B) is based on 1, 2, 4 Kato-Katz slides, respectively. Each point (x, y) represents the mean predictions of infection prevalence (x-value) vs. hookworm-anaemia prevalence (y-value). The error band reports the 95% Confidence Interval (CI) of predicted hookworm-anaemia. Dashed vertical lines mark the WHO morbidity threshold of 2% moderate-to-heavy intensity prevalence. The bisector in panels (B) is added to visualise the robustness of the prevalence of moderate-to-heavy intensity of infection over the three sampling schemes.

2.S1 Table. The Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD).

Principle	What has been done to satisfy the principle?	Where in the manuscript is this described?
Stakeholder engagement	Work has been approved by the Bill and Melinda Gates Foundation as part of the NTD Modelling Consortium. The work has been presented at the 12 th European Congress on Tropical Medicine and International Health.	-
Complete model documentation	The statistical model implemented and used in this study is described in the manuscript. The full code for calibration of the model and simulations is available in a public repository.[1]	Methods section and References.
Complete description of data used	Data and parameters used are described in the manuscript. Data have been documented in previous publications.[2] The code for data selection and preparation is available in a public repository.[1]	Methods section and References.
Communicating uncertainty	We consider stochastic and parameters' uncertainty in communicated results, via Bayesian Credible Intervals (BCIs) and Prediction Intervals (PIs).	All sections.
Testable model outcomes	The model outcomes can be tested by collecting individual data in different endemicity settings.	Discussion section.

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Chapter 3 Impact of different sampling schemes for decision making in soil-transmitted helminthiasis control programs

This chapter is published as a journal article:

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Keywords. fecal egg counts; Kato-Katz; moderate-to-heavy infection; prevalence; soil-transmitted helminths.

Abstract

Starting and stopping preventive chemotherapy (PC) for soil-transmitted helminthiasis is typically based on the prevalence of infection as measured by Kato-Katz (KK) fecal smears. Kato-Katz-based egg counts can vary highly over repeated stool samples and smears. Consequentially, the sensitivity of KK-based surveys depends on the number of stool samples per person and the number of smears per sample. Given finite resources, collecting multiple samples and/or smears means screening fewer individuals, thereby lowering the statistical precision of prevalence estimates. Using population-level data from various epidemiological settings, we assessed the performance of different sampling schemes executed within the confines of the same budget. We recommend the use of single-slide KK for determining prevalence of moderate-to-heavy intensity infection and policy decisions for starting and continuing PC; more sensitive sampling schemes may be required for policy decisions involving stopping PC. Our findings highlight that guidelines should include specific guidance on sampling schemes.

3.1. Introduction

Soil-transmitted helminthiasis (STH), caused by *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms, affect approximately 1.5 billion people worldwide. The World Health Organization (WHO) has targeted STH for control as a public health problem by 2020 through regular preventive chemotherapy (PC), with control defined as prevalence of moderate-to-heavy (MH) intensity infection $\leq 1\%$ [1–3]. The WHO further recommends that decisions on starting, continuing, and stopping PC are based on estimates of STH prevalence (any intensity) in school-age children as measured by the classic parasitological Kato-Katz (KK) faecal smear [1–3].

Kato-Katz-based egg counts vary highly within individuals over repeated stools samples from different days and between repeated slides based on the same stool sample. Consequently, surveys based on multiple stool samples per individual and/or multiple slides per stool sample typically yield higher prevalence estimates than when examining 1 slide per person [4]. However, increasing the number of slides per sample or the number of stool samples per person (requiring visiting a study site multiple days) means fewer individuals can be tested for the same amount of resources, thereby lowering the statistical precision of prevalence estimates. The trade-off between sensitivity and precision of survey results will be different for prevalence of any versus MH intensity infection, because examining multiple slides increases sensitivity but does not affect estimates of mean intensity of infection [4]. The WHO currently provides a blanket recommendation that prevalence of STH should be evaluated based on a single stool sample per child [2], without any specific recommendation for the number of slides that should be prepared per sample.

In this study, we explore how different sampling schemes used within the confines of the same budget affect the sensitivity of surveys to detect infection (any and MH intensity) and the statistical precision of surveys results. We do so by bootstrap analysis of existing datasets from different epidemiological settings where multiple stool samples were collected and/or stool samples were examined multiple times.

3.2. Methods

Datasets

Four datasets covering 6 countries were analyzed; **Appendix 3.A** provides an overview of characteristics of each dataset, including geographical location, sample size, dominant STH species, and history of control. The first dataset constituted information from a population-based survey conducted in 2008 in a subcounty of eastern Uganda [5]. Members of all households in the subcounty were asked to provide 2 stool samples on 2 consecutive days (26.3% of participants provided only 1 sample); each sample was examined with duplicate KK. The second dataset held baseline data from an epidemiological study in 45 villages in southern India [6], including up to 3 stool samples per individual (10.8% and 6.4% of individuals returned only 1 or 2 stools samples, respectively), each sample examined once with the McMaster egg counting technique (which yields qualitatively similar results to KK [7]) if initial screening with saline and iodine wet preparation was positive. The third dataset constituted baseline data from the TUMIKIA study, a cluster-randomized trial in 120 clusters of villages in Kenya [8, 9], in which 1 individual per household was tested with duplicate KK based on a single stool sample. The fourth dataset contained baseline data from the Starworms study [10–12] in which school-age children in Ethiopia, Lao People’s Democratic Republic, and Tanzania were tested using (among other techniques) duplicate KK performed on a single stool sample. The Starworms study was the only study in which stool samples were homogenized before preparing the fecal smears. Hookworm was the dominant STH species in all sites, except for the Starworms study sites, where roundworm (*A. lumbricoides*) and whipworm (*T. trichiura*) were equally prevalent.

Datasets were prepared in such a way that all individuals within a single dataset had the same number of records by explicitly including incomplete or missing records as missing values, to account for the reality that stool sample collection, slide preparation, and/or slide examination may be incomplete or fail.

Data Analysis

For each dataset, we defined a set of sampling schemes according to which the survey might have been (alternatively) conducted within the confines of the available data. We defined sampling schemes as $a \times b$, where a is the number of stool samples per person, and b is the number of repeated slides per sample. Expected differences in prevalences (absolute and relative, $a \times b = 1 \times 1$

as reference) resulting from different sampling schemes were quantified based on 10000 repeated bootstraps [13]. Within each bootstrap iteration, we started by sampling a number of individuals (with replacement) equal to the original size of the dataset. Then, for each individual, we randomly shuffled stools samples (if more than 1 was available, keeping together repeated slides based on the same sample), and for each stool sample, we randomly shuffled repeated slides (if any). For each sampling scheme $a \times b$, we saved the bootstrapped egg counts from the a first stool samples and b first slides per sample for each individual in the bootstrapped data. This way, within each bootstrap iteration, the first examined slide of each individual included in a multislide sampling scheme was also included in the 1×1 reference scheme, allowing us to directly compare results of the different sampling schemes as if executed on the same set of candidate people.

Results of each sampling scheme were summarized in terms of prevalence of any infection and prevalence of MH intensity infection. Individuals were considered positive if at least 1 of their slides was positive for eggs. Individuals were considered positive for MH intensity infection based on the number of eggs per gram feces (epg) averaged over all slides, using cutoffs for MH intensity infection as defined by WHO [2]: ≥ 2000 epg for hookworm species, ≥ 1000 epg for *T. trichiura*, and ≥ 5000 epg for *A. lumbricoides*. Individuals with all egg counts missing were discarded from the bootstrapped data before calculations, without replacement.

To compare sensitivity and statistical precision of different sampling schemes when executed within the confines of the same budget, we performed a second bootstrap procedure. First, we defined a budget B (range, 50 up to 2000), where the value of B is the number of individuals that can be tested within a 1×1 sampling scheme. Then, for the other schemes, we calculated the number of people that could be tested with the same budget as follows: $N_{a \times b} = B / (S_{a \times b} \times C_b \times a)$. Here, $S_{a \times b}$ is the total number of slides per person in scheme $a \times b$ (eg, 4 for a 2×2 scheme), and C_b is the relative cost per slide for single ($C_1 = 1$) or duplicate slides ($C_2 = \frac{\text{cost per slide}_{1 \times 2}}{\text{cost per slide}_{1 \times 1}} = \frac{2.41/2}{1.94} = 0.621$, based on published cost estimates [14]). The last term a in the denominator is included as a multiplier assuming that collecting a samples per person will increase cost per slide a -fold due to having to visit the study site a days. For instance, given a budget worth the cost of testing 500 individuals in a 1×1 scheme ($B = 500$), the number of individuals that can be tested in a 1×2 scheme ($S_{a \times b} = 2$, $C_b = 0.621$, $a = 1$) would be $N_{1 \times 2} = 500 / (2 \times 0.621 \times 1) = 402$, rounded

down to the nearest integer. Likewise, for a 2×1 scheme ($S_{a \times b} = 2$, $C_b = 1$, $a = 2$), the number of individuals that can be tested would be $N_{2 \times 1} = \frac{500}{2 \times 1 \times 2} = 125$, and for a 2×2 scheme ($S_{a \times b} = 4$, $C_b = 0.621$, $a = 2$) the number of individuals would be $N_{2 \times 2} = 500 / (4 \times 0.621 \times 2) = 100$.

For each value of budget B , we performed 10000 repeated bootstrap iterations. Each bootstrap iteration started by sampling B individuals (with replacement) for the 1×1 scheme and shuffling stools samples and repeated slides (if any) as before. Subsequently, for each non- 1×1 sampling scheme, we selected the $N_{a \times b}$ first people from the bootstrapped dataset, and we selected the first a stool samples per individual and first b slides per sample. This way, again, all individuals included in the non- 1×1 schemes (and their first examined slide) were also included in the 1×1 reference scheme. Prevalences were calculated and compared as in the first bootstrap analysis. Results of the budget-constrained bootstrap analysis were summarized by means of boxplots (illustrating the variation in prevalence of any and/or MH infections), and the proportion of bootstrap iterations in which the estimated prevalence from a non- 1×1 scheme was higher than the corresponding estimate from the 1×1 reference scheme.

3.3. Results

Table 3.1 provides the added value of performing a second slide from the same stool sample. In the Ugandan and Kenyan datasets, this significantly increased the estimated prevalence by a factor of 1.25 for low-endemic settings (prevalence $\leq 5\%$) and 1.10 in highly endemic settings (prevalence $\geq 45\%$), whereas absolute difference in prevalence were highest for more highly endemic settings (see **Table 3.1** for details). For the Starworms data, testing a second slide did not increase estimated prevalences, which was due to the reduced variation between repeated slides resulting from stool homogenization [15]. This is also reflected by the relatively low number of discordant (zero/nonzero) pairs of duplicate egg counts (e.g., 0.8% of pairs in Tanzania hookworm data vs 9.0% in the Ugandan data). This pattern was similar for all 3 STH species and in all 3 countries covered by the Starworms study. **Appendix 3.B** summarizes the added value of collecting additional stool samples per person, which increased prevalences by up to a factor of 1.59 (2×1 scheme) and 1.98 (3×1 scheme). Again, absolute increases in prevalence were highest in more highly endemic settings (see **Appendix 3.B** for details). In

the Indian data, the 3×1 scheme increased prevalence to a lesser extent (1.25 relative to 2×1 scheme) compared with the 2×1 scheme (1.59 relative to 1×1 scheme). In the Ugandan dataset, the increase in prevalence was higher in the 2×1 scheme (1.45) than in the 1×2 scheme (1.19).

Table 3.1. Differences in estimates of prevalence of hookworm infection (any intensity) based on single (1x1) or duplicate slide (1x2) examination of a single stool sample^a.

Dataset	Expected results for 1x1 scheme		Expected difference in prevalence between 1x2 and 1x1 schemes	
	Prevalence of infection (95%-CI)	Mean egg per gram (95%-CI)	Absolute (95%-CI)	Relative (95%-CI)
Mulanda, Tororo, Uganda	23.4 (21.3–25.4)	258 (181–350)	4.5 (3.3–5.5)	1.19 (1.15–1.24)
Kwale, Kenya (TUMIKIA)	16.7 (16.1–17.2)	168 (149–191)	2.4 (2.2–2.6)	1.14 (1.13–1.16)
<i>Prevalence ≤ 5%</i>	2.4 (1.8–2.9)	11 (5–17)	0.6 (0.3–0.9)	1.25 (1.13–1.40)
<i>Prevalence 5–15%</i>	8.8 (8.1–9.5)	81 (62–105)	1.5 (1.2–1.8)	1.17 (1.14–1.21)
<i>Prevalence 15–25%</i>	17.2 (16.1–18.3)	167 (135–200)	2.6 (2.1–3.1)	1.15 (1.12–1.18)
<i>Prevalence 25–35%</i>	26.1 (24.6–27.7)	299 (220–417)	3.9 (3.2–4.7)	1.15 (1.12–1.18)
<i>Prevalence 35–45%</i>	35.5 (33.1–37.8)	381 (295–480)	4.4 (3.3–5.5)	1.12 (1.09–1.16)
<i>Prevalence > 45%</i>	48.1 (45.2–51.2)	465 (381–556)	5.0 (3.6–6.4)	1.10 (1.07–1.14)

Abbreviations: CI, confidence interval.

^a Estimates are based on 10,000 bootstraps of the entire datasets. For the Kenyan data, data were also stratified based on overall prevalence at the cluster level (N = 120). Results for the Starworms data are not shown as differences between the two sampling schemes were non-significant for all of the worm species in all of the countries. Absolute differences are expressed as percentage-points; relative differences are expressed as ratios of 1x2 over 1x1. 95%-CI = 95% confidence interval based on the 2.5th and 97.5th percentiles of bootstrap results.

Prevalence of MH intensity infection did not differ significantly between any of the sampling schemes for any of the datasets, because the 95% confidence intervals for relative differences always included the value 1.0. Only in the Indian data did estimates tend to decline with additional stool samples (again non-significantly), which could be explained by the 2-tiered testing method in which eggs were only counted if initial screening of the sample was positive. The resulting introduction of zero counts (where eggs might have actually been found with the McMaster) caused mean egg counts for individuals to decline when more stool samples were included in the prevalence calculation.

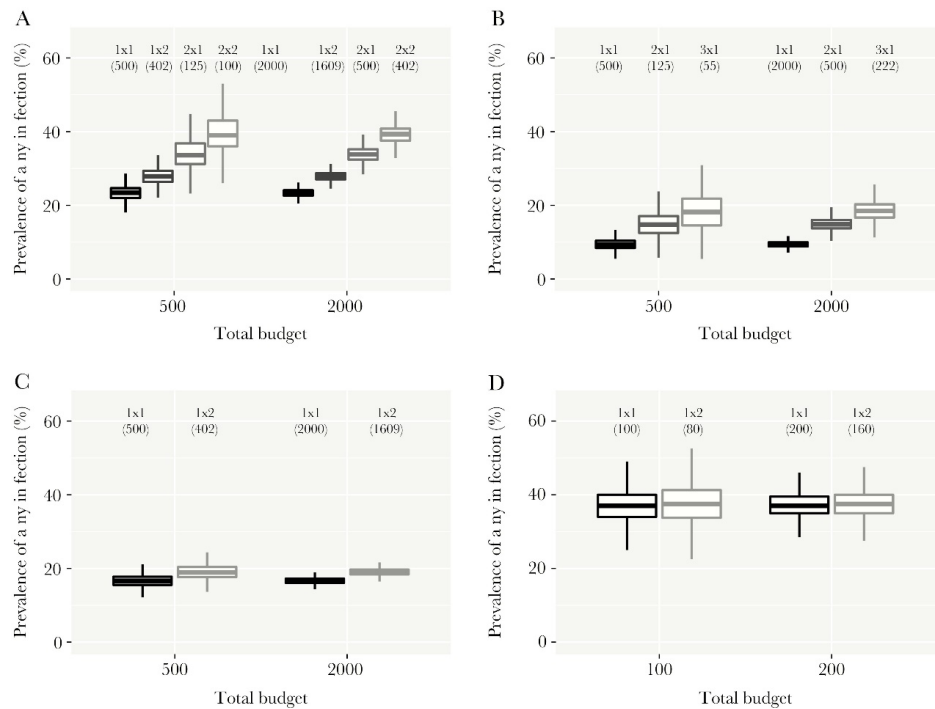


Figure 3.1. Sensitivity and uncertainty of different sampling schemes for detection of moderate-to-heavy intensity hookworm infection in the general population, based on the same overall budget. Budget is expressed as the number of individuals that can be tested in the context of a 1×1 scheme (1 stool sample collected per person and 1 slide tested per sample). Numbers between brackets under the sampling scheme indicators ("1×1", "1×2", etc) represent the number of people who were tested in that scheme, given the budget. Boxes represent the median and interquartile range (25th and 75th percentiles) of the bootstrapped prevalences; whiskers cover the range of bootstrapped values up to a distance of 1.5 times the interquartile range from the outer hinges of the box. Estimated are based on 10 000 bootstraps. (A) Ugandan dataset [5]; (B) Indian dataset [6]; (C) Kenyan data (TUMIKIA) [8,9]; (D) Tanzanian dataset (Starworms) [10–12].

Figure 3.1 shows that when sampling schemes are restrained by the same budget, the reference 1×1 scheme produced survey prevalence estimates with the highest statistical precision, because it included the highest number of people. In general, non-1×1 schemes produced higher prevalence estimates, but with a risk of occasionally finding a lower prevalence than the 1×1 scheme. However, in the Starworms study sites, non-1×1 schemes only increased statistical uncertainty of prevalence estimates without a gain in sensitivity (**Figure 3.1D**; see **Appendix 3.C** for all countries and worm species in the Starworms data). For all datasets but the Starworms data, the risk of accidentally finding a lower prevalence with a non-1×1 scheme decreased with higher budgets. The minimum budget to reduce this risk to $\leq 5\%$ depended on endemicity

(e.g., a budget equivalent to the cost of testing 1030 and 122 individuals in a 1×1 scheme for the lowest and highest endemicity strata in the Kenyan data, **Appendix 3.D**). In the endemicity-stratified analysis of the Kenyan data, the choice of scheme (1×1 vs 1×2) determined the probability that the estimated prevalence of any infection was under or above a policy-relevant threshold value (**Appendix 3.E**). **Figure 3.2** illustrates the impact of sampling scheme on prevalence of MH intensity infection: non- 1×1 schemes only increased statistical uncertainty without a gain in sensitivity. Results were qualitatively similar for all species and sites in the Starworms data (**Appendix 3.F**).

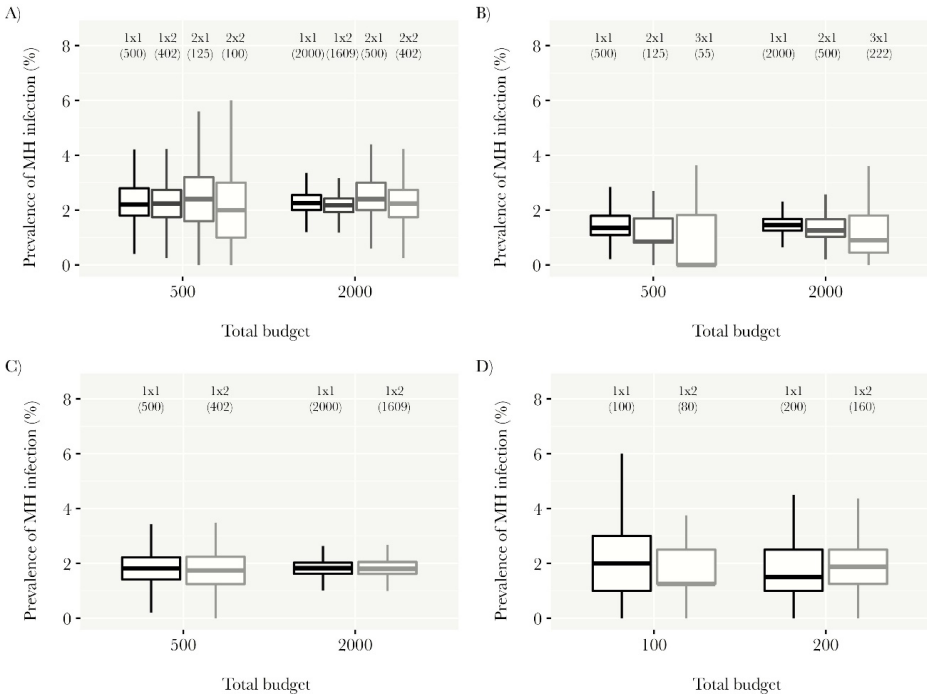


Figure 3.2. Sensitivity and uncertainty of different sampling schemes for detection of moderate-to-heavy intensity hookworm infection in the general population, based on the same overall budget. Budget is expressed as the number of individuals that can be tested in the context of a 1×1 scheme (1 stool sample collected per person and 1 slide tested per sample). Numbers between brackets under the sampling scheme indicators (" 1×1 ", " 1×2 ", etc) represent the number of people who were tested in that scheme, given the budget. Boxes represent the median and interquartile range (25th and 75th percentiles) of the bootstrapped prevalences; whiskers cover the range of bootstrapped values up to a distance of 1.5 times the interquartile range from the outer hinges of the box. Estimated are based on 10 000 bootstraps. (A) Ugandan dataset [5]; (B) Indian dataset [6]; (C) Kenyan data (TUMIKIA) [8, 9]; (D) Tanzanian dataset (Starworms) [10-12].

3.4. Discussion

We show that when designing surveys for assessing the epidemiological situation of STH within a finite budget, a trade-off exists between the sensitivity of the survey to detect infection and the statistical precision of survey results. Importantly, gains in sensitivity only apply to prevalence of infection (any intensity) based on unhomogenized stools and are most pronounced in low-endemic settings (on a relative scale). For prevalence of MH intensity infection, sampling multiple stool samples per person and/or slides per sample only increases statistical uncertainty and not sensitivity.

Because prevalence estimates depend on the choice of sampling scheme, it is important that threshold values for policy decision regarding starting, changing, or stopping PC are defined in conjunction with a clearly specified survey strategy, i.e., with explicit mention of the numbers of samples per person and slides per sample tested. If deviating survey strategies are used, survey results should be translated to the standard scale, using the relative differences (and associated uncertainty) estimated here and elsewhere [4]. Based on our analyses, we recommend that policy decisions for starting and continuing PC are based on a 1×1 sampling scheme, because survey results will then be most stable, ensuring the most consistent policy. However, when deciding whether to stop PC (threshold prevalence of any infection of 2% [2]), sensitivity of the sampling scheme will be particularly important because false-negative findings may lead to stopping PC prematurely. In such situations the higher costs of multiple sampling probably outweigh the costs of potentially having to restart the control program. Schemes based on multiple stool samples per person will be of particular value if a survey using the 1×1 scheme (executed within the confines of the same budget) would require spending multiple days in a site (eg, for large populations), because this would partially negate the additional costs of having to spend multiple days to collect multiple stool samples per person. We further expect that for low-endemic settings, relative gains in sensitivity when using multiple stool samples per person will be higher than estimated here, because prevalence will typically be lower than in the data used here (lowest prevalence of infection approximately 9% in Indian data), and because relative gains in sensitivity increase with declining prevalence (Kenyan data).

A major strength of our analysis and improvement over previous analyses [4] is that we include cost considerations when comparing sampling schemes,

while at the same time accounting for the reality that not all individuals return (all) samples and that slides preparation and examination may fail. Context-dependent costs of sampling schemes [16] can be easily accounted for by multiplying the budget value in our analysis with the cost per slide in a 1×1 scheme in that particular context. Furthermore, context-dependent cost differences between sampling schemes can be easily included by adapting 2 parameters for cost per sample and cost per slide. However, to predict the outcomes of sampling schemes for epidemiological situations far outside the data, such as situations with very low infection levels after a prolonged period of PC, will require either of 2 approaches. The first is the collection of data from those contexts and analyzing them in the same fashion as done here. The ongoing Deworm3 study [17] is expected to generate such data (including a 1×2 KK scheme), in the context of intense school-based and community-based PC for STH after an initial period of community-wide PC for lymphatic filariasis. The second approach is to use transmission models to predict the distribution of infection intensities over time during PC and combine these with a statistical model for the distribution of egg counts in stool samples and slides [15]. This is the subject of ongoing work for both STH and schistosomiasis within the NTD Modelling Consortium, which focuses on the development of transmission models that realistically account for heterogeneity in exposure to transmission and uptake of PC in populations to make policy-relevant predictions of the impact of control efforts [18–24].

Homogenization results in a more Poisson-like distribution of repeated egg counts [15], which has lower variation in contrast to the typically overdispersed, negative binomial distribution of repeated egg counts [25, 26]. This means that for individuals with low or high egg loads (which typically constitute the majority of endemic populations due to overdispersed worm loads), test sensitivity will be maximized with 1 slide per sample, which matches our finding of no increase in sensitivity for multiple-slide KK based on homogenized stools. Repeated slides based on homogenized stools are therefore unlikely to noticeably increase survey sensitivity, but sampling stool samples over multiple days will still increase survey sensitivity. Theoretically, stool homogenization increases the sensitivity of surveys to detect infection, with the highest absolute increase in individuals with moderate to high egg densities [27]. Whether the sensitivity of a single slide based on homogenized stool is higher than that of multiple slides based on unhomogenized stool depends on the overall egg density in a stool sample and therefore the distribution of egg densities in the population. These complexities warrant a

more detailed evaluation of the performance of different sampling strategies in context of control programs, which again requires a combination of transmission models and statistical models.

As for the appropriateness of the WHO-recommended thresholds for STH policy, these cannot be evaluated by this study, because their appropriateness depends on the following: (1) whether they adequately reflect to what extent STH pose a significant public health problem, and (2) whether starting, changing, or stopping PC around the current threshold values actually results in achieving the target of $< 1\%$ prevalence MH intensity infection. The first aspect needs to be addressed by quantifying the association between infection levels and morbidity and their dynamics during control. The second aspect has been partly addressed by a recent modeling study, which suggested that current thresholds for scaling down PC frequency are inappropriate because infection levels will likely bounce back to levels above the current morbidity target [28]. A follow-up modeling study further demonstrated how the positive predictive value of the prevalence of infection (any intensity) in a sample of sentinel villages for having reached the morbidity target in a wider geographical area highly depends on precontrol endemicity, the dominant STH species, number of sentinel villages sampled, and variation in infection levels within the wider geographical area [29].

3.5. Conclusions

In conclusion, we show that different sampling strategies lead to considerable variation in the policies recommended under current WHO guidelines, highlighting the need to link thresholds for decision making to specific sampling schemes. When policy decisions are based on KK, we recommend the use of single slides, unless the decision involves stopping PC, in which case multisample KK is better, in particular in sites where a single-slide survey of the population requires multiple days. Prevalence of MH intensity infection should always be evaluated using a single slide per person.

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3.5. Supplementary data

Appendix 3.A. Overview of datasets and study sites used in the analysis. Only baseline data were used from each of the datasets. All Kato-Katz (KK) faecal smears were based on 41.7 mg of stool.

Location	Study design	Sample size			
		Individuals	Households	Villages	Clusters of villages
Mulanda, Tororo, Uganda	Householdbased census	2,037	469	4	1
Jawadhu Hills, Tamil Nadu, India	Community-based clusterrandomized trial	2,082	824	45	1
Kwale, Kenya (TUMIKIA)	Community-based clusterrandomized trial	19,684	19,674	940	120
Nam Bak, Laos People's Democratic Republic (Starworms)	School-based drug efficacy trial	239	-	-	3 schools
Pemba Island, Tanzania (Starworms)	School-based drug efficacy trial	245	-	-	4 schools
Jimma, Ethiopia (Starworms)	School-based drug efficacy trial	161	-	-	2 schools

^a Three rounds of school-based deworming at 30%-65% coverage during four years preceding the study. ^b Kato-Katz faecal smear based on 41.7 mg of stool, without homogenisation of individual stool samples. ^c Annual mass drug adminsitration with diethylcarbamazine and albendazole since 2007 for control of lymphatic filariasis, with the annual treatment round typically taking place in July. The state-level treatment coverage was reported as 97.3% (data specific to the study area was not available); however, given the hilly terrain of the study area the actual coverage was expected to be much lower. The baseline data used from this study was collected over a period of one year, between October 2013 and November 2014. ^d McMaster was based on 2 grams of stool, as described elsewhere [7], but only on samples in which eggs where detected by saline/iodine wet slide first; samples that scored negative on the saline/iodine wet slide were scores contained zero eggs. ^e The area was subject to four rounds of community-based mass drug administration with albendazole and diethylcarbamazine for lymphatic filariasis (2003, 2005, 2008, and 2011, coverage levels of 62.7% and 58.3% in the last two rounds). The

Age groups sampled	Dominant species	History of control	Parasitological technique	Prevalence of infection (%)		Reference
				Any	Moderate-to-heavy intensity	
6 months and older	Hookworm	Ongoing control	2 repeated KKb on a single sample per day for 2 consecutive days (2x2)	39.2	2.4	[5]
2 to 70 years	Hookworm	Ongoing control	Single McMaster on a single sample per day for up to 3 consecutive days (3x1)	18.5	1.0	[6]
2 years and older	Hookworm	Ongoing control	2 repeated KKb on a single stool sample (1x2)	19.1	1.7	[8,9]
5 to 14 years	Hookworm, whipworm, roundworm	Ongoing control ^f	2 repeated KK on a single stool sample (1x2)	90	25.1	[10–12]
5 to 14 years	Hookworm, whipworm, roundworm	Ongoing control ^f	2 repeated KKg on a single stool sample (1x2)	37	2.0	[10–12]
5 to 14 years	Hookworm, whipworm, roundworm	Ongoing control ^f	2 repeated KKg on a single stool sample (1x2)	41.6	1.2	[10–12]

area further received four rounds of school-based deworming with albendazol for STH between, with programmatic coverage of 82% of pre-school and school-age children (2–14 years) in 2014. The baseline data used from this study was collected between March and May 2015.

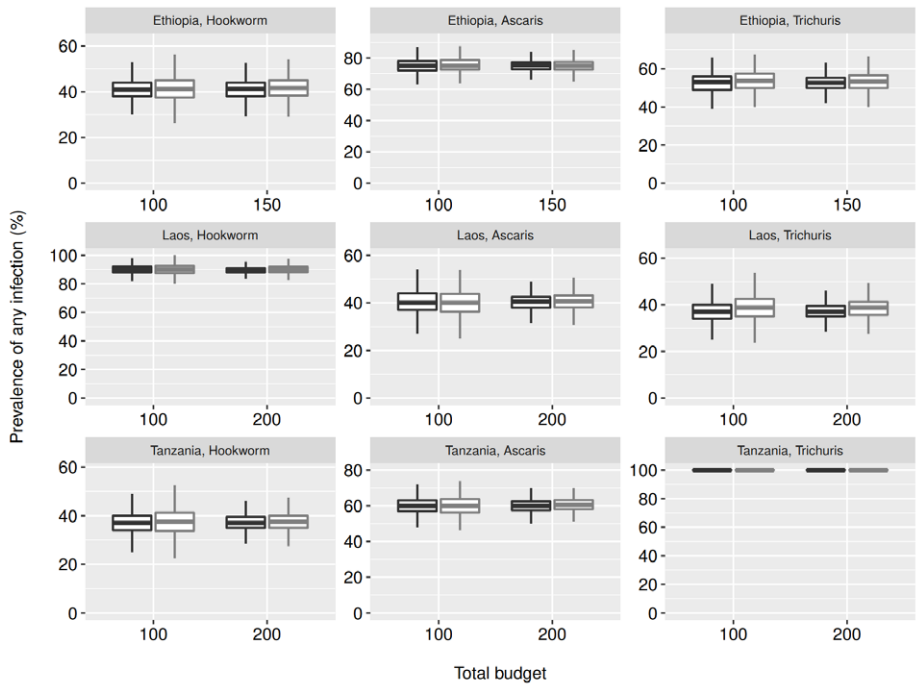
^f Based on the reported national coverage of drug administration to pre-school-age and school-age children for the last 5 years (2009–2014; Preventive Chemotherapy Database of the World Health Organization), the site in Ethiopia was considered to have experienced a low drug exposure (treatment with albendazole since 2015), the site in Lao PDR a medium drug exposure (treatment with mebendazole since 2007), and the site in Pemba (Tanzania) a high drug exposure (treatment with albendazole since 1994) prior to the start of the study.

^g Kato-Katz faecal smear based on 41.7 mg of stool; e individual stool sample was homogenised with a wooden spatula before slide preparation.

Appendix 3.B. Differences in estimates of prevalence of hookworm infection (any intensity) based on single (1x1) or multiple stool samples, examined by means of single (2x1, 3x1) or duplicate slides (2x2). Estimated are based on 10,000 bootstraps of the entire datasets. Absolute differences are expressed as percentage-points; relative differences are expressed as factors. 95%-CI = 95% confidence interval based on the 2.5th and 97.5th percentiles of bootstrap results.

Dataset	Expected results for 1x1 scheme		Average absolute difference in prevalence compared to the 1x1 scheme (95%-CI)			Average relative difference in prevalence compared to the 1x1 scheme (95%-CI)		
	Prevalence of infection (%)	Mean egg count (epg)	2x1	2x2	3x1	2x1	2x2	3x1
Mulanda, Tororo, Uganda	23.4 (21.3–25.4)	258 (181–350)	10.4 (8.9–12.1)	15.8 (14.1–17.7)	-	1.45 (1.36–1.55)	1.68 (1.57–1.80)	-
Jawadhu Hills, Tamil Nadu, India	9.4 (7.8–11.1)	126 (87–181)	5.4 (4.1–6.9)	-	9.1 (7.5–10.5)	1.59 (1.40–1.82)	-	1.98 (1.72–2.3)

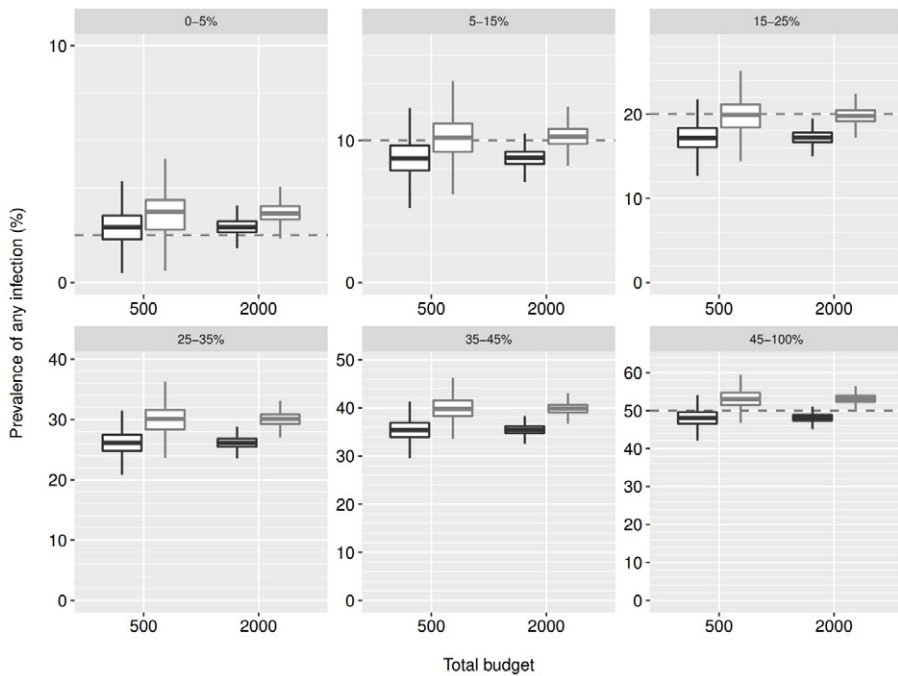
Appendix 3.C. Sensitivity and uncertainty of different sampling schemes of all three soil-transmitted helminth species in school-age children in the Starworms dataset, based on the same budget. Budget is expressed as the number of individuals that can be tested in the context of a 1x1 scheme (one stool sample collected per person and one slide tested per sample). Boxes represent the median and interquartile range (25th and 75th percentiles) of the bootstrapped prevalences; whiskers cover the range of bootstrapped values up to a distance of 1.5 times the interquartile range from the outer hinges of the box. The left (darker) box for each budget value represents the 1x1 sampling scheme, the right (lighter) box represents the 1x2 sampling scheme. Estimated are based on 10,000 bootstraps.



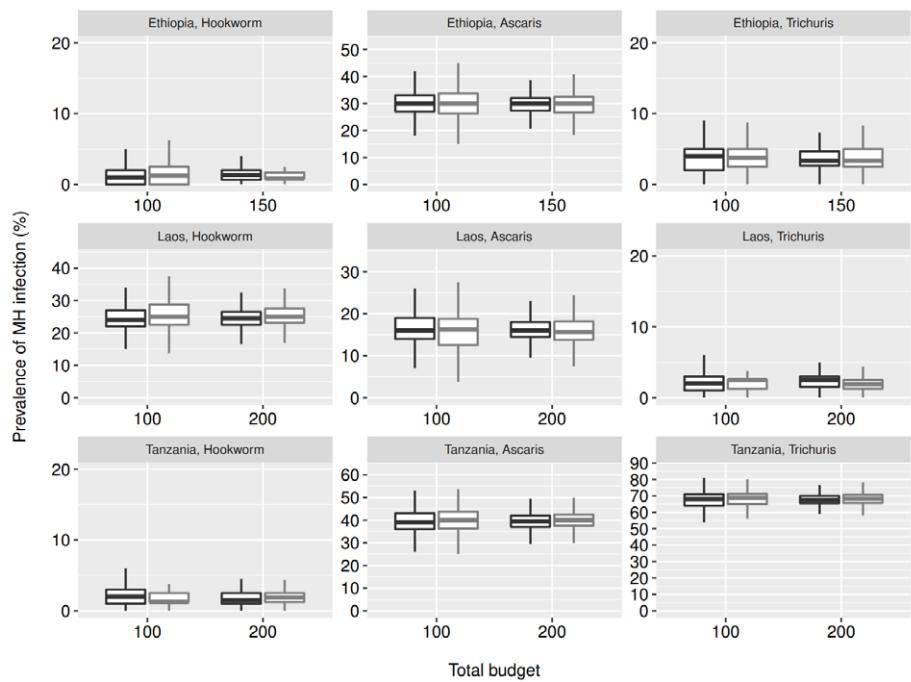
Appendix 3.D. Minimum number of individuals to sample with a non-1x1 scheme for a ≤5% risk of accidentally finding a lower prevalence than in a 1x1 scheme based on the same budget. Associated budget values are indicated in brackets behind minimum number of individuals. Budget values are expressed in terms of the number of individuals that can be sampled within a 1x1 sampling scheme for the same budget. Results for the Starworms data are not shown as non-1x1 sampling schemes did no significantly improve sensitivity for detection of any of the worm species in any of the countries.

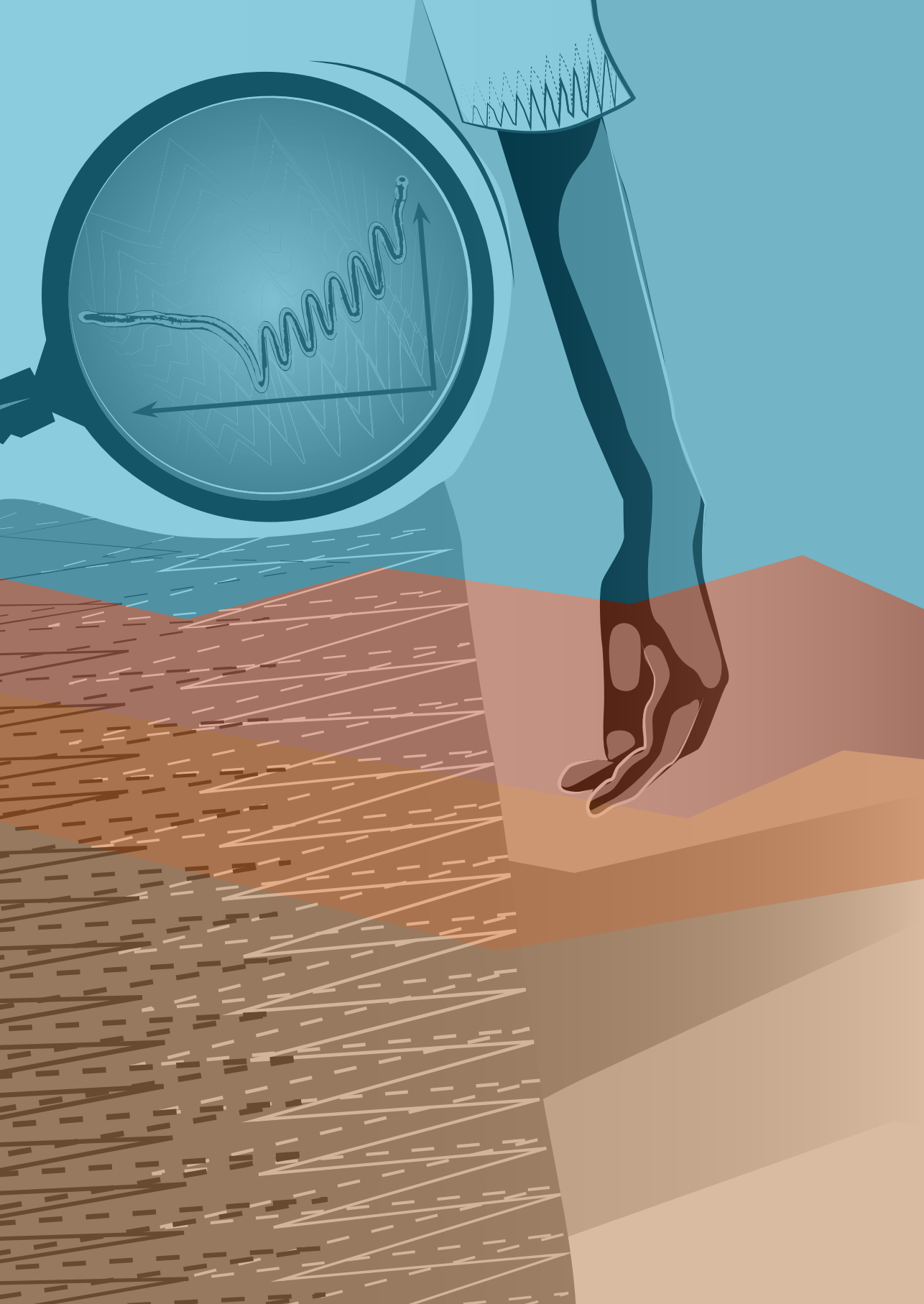
Dataset	Expected results for 1x1 scheme		Minimum number of individuals required to better detect infection with scheme with 95% certainty (budget)			
	Prevalence of infection (%)	Mean egg per gram	1x2	2x1	2x2	3x1
Mulanda, Tororo, Uganda	23.4	258	-	48 (192)	24 (120)	-
Jawadhu Hills, Tamil Nadu, India	9.4	126	-	99 (396)	-	48 (432)
Mulanda, Tororo, Uganda	23.4	258	96 (120)	-	-	-
Kwale, Kenya (TUMIKIA)	16.7	168	235 (292)	-	-	-
Prevalence ≤ 5%						
Prevalence 5-15%	2.4	11	829 (1,030)	-	-	-
Prevalence 15-25%	8.8	81	359 (446)	-	-	-
Prevalence 25-35%	17.2	167	206 (256)	-	-	-
Prevalence 35-45%	26.1	299	122 (152)	-	-	-
Prevalence > 45%	35.5	381	122 (152)	-	-	-
	48.1	465	98 (122)	-	-	-

Appendix 3.E. Sensitivity and uncertainty of different sampling schemes for detection of hookworm infection in the Kenyan data, stratified by endemicity, and when based on the same overall budget. Data were stratified based on the cluster-level ($N = 120$) average prevalence of infection (any intensity). Budget is expressed as the number of individuals that can be tested in the context of a 1x1 scheme (one stool sample collected per person and one slide tested per sample). Boxes represent the median and interquartile range (25th and 75th percentiles) of the bootstrapped prevalences; whiskers cover the range of bootstrapped values up to a distance of 1.5 times the interquartile range from the outer hinges of the box. Horizontal dashed lines represent WHO-recommended threshold values for stopping (1%), starting (20%, 50%), and continuing preventive chemotherapy (10%, 20%, 50%) for soil-transmitted helminths, based on prevalence of infection (any intensity). The left (darker) box for each budget value represents the 1x1 sampling scheme, the right (lighter) box represents the 1x2 sampling scheme. Estimated are based on 10,000 bootstraps.



Appendix 3.F. Sensitivity and uncertainty of different sampling schemes for detection of moderate-to-heavy intensity infection by each of the three soil-transmitted helminth infections in school-age children in the Starworms dataset, based on the same budget. Budget is expressed as the number of individuals that can be tested in the context of a 1x1 scheme (one stool sample collected per person and one slide tested per sample). Boxes represent the median and interquartile range (25th and 75th percentiles) of the bootstrapped prevalences; whiskers cover the range of bootstrapped values up to a distance of 1.5 times the interquartile range from the outer hinges of the box. The left (darker) box for each budget value represents the 1x1 sampling scheme, the right (lighter) box represents the 1x2 sampling scheme. Estimated are based on 10,000 bootstraps.





Chapter 4 Modelling the impact of COVID-19-related control programme interruptions on progress towards the WHO 2030 target for soil-transmitted helminths

This chapter is published as a journal article:

Malizia V, Giardina F, Vegvari C, Bajaj S, McRae-McKee K, Anderson RM, et al. Modelling the impact of COVID-19-related control programme interruptions on progress towards the WHO 2030 target for soil-transmitted helminths. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2021;115(3):253-60.

Keywords: control programmes, COVID-19-related interruption, individual-based models, soil-transmitted helminths, WHO 2030 target

Abstract

Background

On the 1st of April 2020, the World Health Organization (WHO) recommended an interruption of all activities for the control of neglected tropical diseases, including soil-transmitted helminths (STH), in response to the COVID-19 pandemic. This paper investigates the impact of this disruption on the achieved progress towards the WHO 2030 target for STH.

Methods

We used two stochastic individual-based models to simulate the impact of missing one or more preventive chemotherapy (PC) rounds in different endemicity settings. We also investigate the extent to which this impact can be lessened by mitigation strategies, such as semi-annual or community-wide PC.

Results

Both models show that without a mitigation strategy, control programmes will catch up by 2030, assuming coverage is maintained. The catch-up time can be up to 4.5 years after the start of the interruption. Mitigation strategies may reduce this time by up to two years and increase the probability of achieving the 2030 target.

Conclusions

Though a PC interruption will only temporarily impact the progress towards the WHO 2030 target, programmes are encouraged to restart as soon as possible to minimise the impact on morbidity. The implementation of suitable mitigation strategies can turn the interruption into an opportunity to accelerate progress towards reaching the target.

4.1. Introduction

Globally, more than one billion people in developing countries are estimated to be infected with at least one species of soil-transmitted-helminths (STH) [1]. The STH species that mainly affect humans are two species of hookworm (*Necator americanus*, *Ancylostoma duodenale*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*). STH are considered a major cause of morbidity, particularly in children. Common STH-related morbidities are anaemia, growth impairment, respiratory problems and malnutrition due to malabsorption and nutrient loss [2]. More severe morbidity is usually associated with moderate-to-heavy intensity (M&HI) of parasitic infection [1]. The control of morbidity drives the definition of the global target for the elimination of STH as a public health problem (EPHP), that the World Health Organization (WHO) has set by 2030. The target is defined as reaching a prevalence of M&HI infections below 2% in school-age children (SAC) [3]. The current guidelines provided by the WHO to achieve this goal recommend preventive chemotherapy (PC) for pre-SAC (age 2-5 years) and SAC (age 5-15 years) once per year in moderate endemicity settings (20-50% pre-control prevalence of any intensity of infection in SAC) and twice per year in high endemicity settings (>50%). No PC is recommended in areas with low pre-control STH prevalence (<20%) [3].

On the 1st of April 2020, the WHO recommended an interruption of all neglected tropical disease control programmes, including STH, in response to the pandemic caused by the novel coronavirus SARS-CoV-2 [4]. In respect of social distancing, the main public health measure taken to contain the spread of SARS-CoV-2, WHO advised that evaluation activities and PC administration should be postponed until further notice. The impact of this disruption on gains achieved in the control of STH thus far, requires investigation. The time control programmes will take to catch-up with the past and predicted progress will have implications on the time (delay) and feasibility of reaching the target by 2030. To minimise the losses, suitable mitigation strategies may have to be implemented when programmes resume.

We use two independently developed stochastic individual-based models to simulate the impact of missing or postponing one or more PC rounds on the control of STH in different endemicity settings, defined by the pre-control situation, and for all three STH species. We compare the scenario without interruption (baseline scenario) with different "interruption scenarios" which include re-starting the treatment after different interruption lengths, with or without plausible mitigation strategies. For each scenario, we express the

estimated impact in terms of three measures: i) the catch-up time, i.e. the time after the interruption required for the M&HI prevalence to catch up with the scenario without interruption, ii) the probability to reach the control target set by the WHO, and iii) the delay, i.e. how much longer it takes to reach the target with respect to the baseline scenario. We investigate the extent to which these quantities can be improved by suitable mitigation strategies.

4.2. Materials and Methods

Transmission models

We used two stochastic individual-based models independently developed by Erasmus MC (EMC) and Imperial College London (ICL) [5 – 7]. These models are used to simulate the process of transmission of STH in an age-structured human population, through an environmental reservoir of infection (eggs/larvae). Human hosts can be infected and contribute to the reservoir. The life cycle of worms within the human hosts is also modelled. In both models, a single-slide Kato-Katz faecal smear test is simulated, providing egg counts for each individual. Overdispersion of the detected number of eggs (and thus the probability of finding none) is governed by a species-specific parameter. The two models were calibrated in order to reproduce the same endemicity settings at pre-control level, by varying the species-specific parameters regulating the transmission conditions, i.e. the transmission rate (EMC model) or basic reproduction number R_0 (ICL model), as well as the level of exposure heterogeneity, which indicates the extent of aggregation of worms among hosts. Both models assume an effective treatment coverage of 75% of the target population (pre-SAC and SAC or the whole community) in all simulated scenarios. Individual participation in PC is assumed to be random, meaning that at each round a new random fraction of the population participates. The population is treated with albendazole which we assume to kill 94% of hookworm, 99% of *A. lumbricoides* and 60% of *T. trichiura* adult worms [8]. A complete description of the parameters used in both models to run simulations, is available in **4.S1 Table**. All analyses were performed in accordance with the PRIME-NTD criteria [9] (**4.S2 Table**).

Scenarios and mitigation strategies

Two endemicity settings are considered: namely, moderate transmission (20-50% pre-control prevalence evaluated in SAC by single Kato-Katz) and high transmission (pre-control prevalence > 50%). For each species, we ran 500 repeated simulations with both models for each of the six different control

scenarios outlined in **Figure 4.1**, over a timeline of 12 years (2018-2030) where PC is initiated in 2019. The “No-interruption” scenario (baseline) assumes that no interruption occurs, and the PC continues at the same frequency and coverage until 2030. Then, we consider that in 2020 a disruption due to the COVID-19 pandemic causes one or more rounds of PC to be missed and that the programme is resumed normally, after 6, 12 or 18 months. As represented in **Figure 4.1**, according to the endemicity setting and the different “interruption scenarios”, the number of rounds lost is one to three. To mitigate the potential progress lost during the interruption of PC, we also consider scenarios where programmes are resumed one year after the interruption (12-month interruption), with the addition of the following mitigation strategies: i) doubling the frequency of PC for the whole period after the interruption, ii) providing community-wide PC (through mass drug administration or MDA) for only one year after the interruption and then going back to treating only pre-SAC and SAC. In the high endemicity settings, we do not model the scenario of doubling the frequency of PC, because we consider the administration of four PC rounds per year unrealistic/infeasible. Also, the additional impact of more than two rounds per year of PC is negligible, given an assumed expected worms lifespan of 1 (*A. lumbricoides*), 1 (*T. trichiura*), 2-3 (hookworm) years (see **4.S1 Table**).

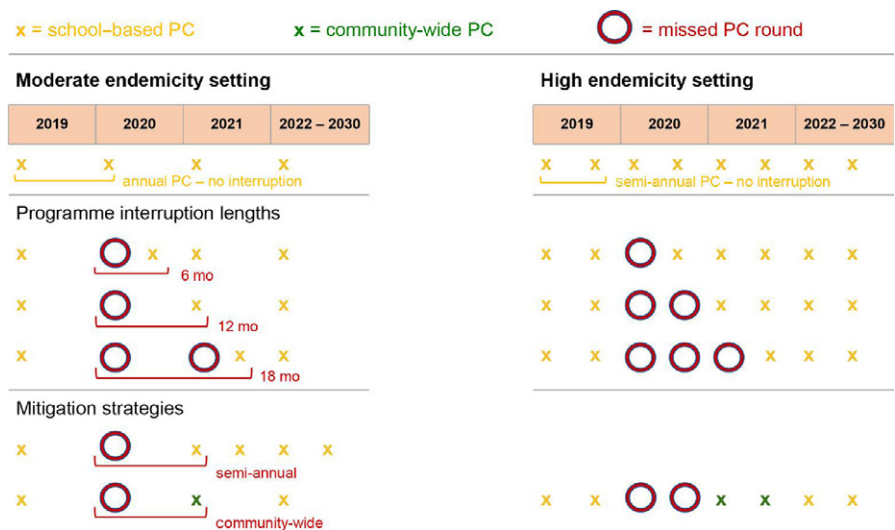


Figure 4.1. Conceptual diagram explaining the frequency of preventive chemotherapy (PC) for each simulated scenario. School-based PC is distributed once per year in moderate endemicity settings and twice per year in the high endemicity settings. Each cross represents one PC round. Each circle represents one missed round. Each green cross represents one round of community-wide PC. Interruption scenarios without mitigation strategies are presented for different interruption lengths, mitigation strategies are assumed to start 12 months after the interruption.

Catch-up times and delays

We predict the impact of PC interruption by comparing the dynamics of the prevalence of M&HI infections in SAC in the different simulated scenarios. The results are expressed in terms of three outcome measures: i) the catch-up time, defined as the time from the interruption, until the M&HI prevalence in SAC becomes equal or lower than the one in the scenario without interruption, based on pair-wise differences between single stochastic simulations; ii) the probability to reach the control target set by the WHO (i.e. the proportion of stochastic simulations showing a M&HI prevalence below 2% at time point 2030); and iii) the delay in reaching the target, which is the additional amount of time needed to reach a M&HI prevalence below 2% (that remains below 2% until 2030) with respect to the scenario without interruptions. The delays are computed based on pair-wise differences between single stochastic simulations that reach the target in the baseline scenario.

4.3. Results

Interruptions without mitigation strategies catch up by 2030

In **Figure 4.2**, we compare the prevalence of M&HI infections in the baseline scenario, i.e. where no interruption occurs, with the interruption scenarios without mitigation strategies, in which up to two PC rounds were missed due to a 6, 12 or 18-month programme interruption, starting in 2020. The figure relates to the moderate endemicity setting and it shows that for all species, after interruption, the prevalence eventually catches up with the prevalence of the baseline scenario, according to both models. This means that at some point after the interruption the M&HI prevalence reaches the same value that would have been observed in absence of interruptions, thus “catching up” with the progress towards the 2030 target that would have otherwise been made. In areas where *A. lumbricoides* is the dominant species it takes slightly longer to recover the progress made by previous control efforts. **4.S1 Figure** shows the analogous results for the high endemicity setting, where the M&HI prevalence of the baseline scenario is compared with the interruption scenarios without mitigations, in which up to three PC rounds were missed. The figure shows that for all species, the prevalence in the interrupted scenarios catches up with the prevalence of the baseline scenario by 2030. The highest impact of interruption on the M&HI prevalence is observed for *T. trichiura*, if an interruption of 12 or 18 months occurs. **Table 4.1** summarises the impact of programme interruptions in terms of estimated catch-up times, i.e. the average time needed for the M&HI prevalence in SAC in the interruption scenarios, to

catch up with the baseline scenario. The values are expressed in years from the start of the interruption. In moderate prevalence settings, if programmes resume after 6 months, the progress in reaching EPHP will be recovered in less than two years (**Table 4.1**) and an interruption of 12 months will require around three years in both moderate and high endemicity settings. Interestingly, in moderate endemicity settings an interruption of 18 months does not increase the time needed to catch up with the baseline scenario, with respect to an interruption of 12 months (**Table 4.1**). **Figure 4.2** shows that this is due to the beneficial effect of having the first PC round after 18 months of interruption, which happens only six months before the following normal-scheduled round (see **Figure 4.1** for the scheme of scenarios), effectively resulting in one year of semi-annual treatment. This pattern is not observed in the high endemicity settings, because all the scenarios already include semi-annual PC (**4.S1 Figure**). In high endemicity settings, the time required for the prevalence to catch up after interruptions of various lengths is limited to on average 2.5 years (hookworm) and on average 3.5 years (*A. lumbricoides*), while *T. trichiura* prevalence requires up to 4.5 years according to both models (**Table 4.1**).

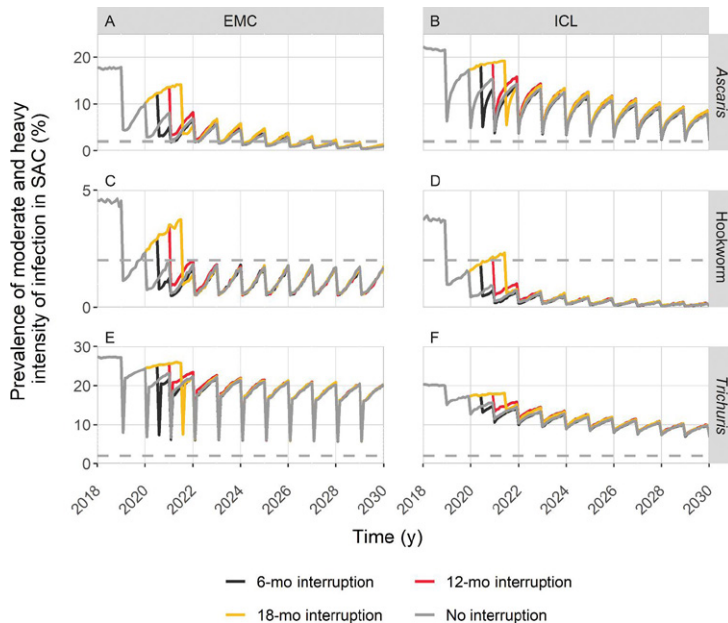


Figure 4.2. Timeline of moderate-to-heavy intensity infections prevalence in moderate endemicity settings for different interruption lengths if programmes resume without mitigation strategies. The comparison between “no interruption” and restarting after 6, 12 or 18 months is presented by line colours. The horizontal dashed line represents the 2% threshold set by the WHO to assess the goal. Results from both the EMC model (A, C, E panels) and the ICL model (B, D, F panels) are shown, for all STH species.

Table 4.1. Model-predicted time (mean number of years since start of interruption [95%-confidence interval]) required to catch up with the progress towards the 2030 target after 6, 12, or 18 months of programme interruption, compared to a scenario without interruption and assuming that no mitigation strategy is implemented. As moments of catch-up always occur right after a PC round, confidence intervals are presented as integers (in case of annual PC) or multiples of 0.5 (semi-annual PC).

Species	Model	Moderate endemicity setting			High endemicity setting		
		6-month interruption	12-month interruption	18-month interruption	6-month interruption	12-month interruption	18-month interruption
<i>A. lumbricoides</i>	ICL	1.35 [0.5; 5]	2.89 [1; 8]	2.78 [2; 8]	1.76 [0.5; 4]	2.69 [1; 6]	3.65 [2; 8.5]
	EMC	1.25 [1; 3]	3.56 [1; 9]	2.80 [2; 8]	1.48 [0.5; 4]	2.14 [1.5; 4]	2.67 [2; 5]
Hookworm	ICL	1.20 [0.5; 3]	2.28 [1; 5]	2.35 [1.5; 5]	1.12 [0.5; 3]	1.67 [1; 3.5]	2.15 [1.5; 4]
	EMC	1.29 [0.5; 4]	2.43 [1; 6]	2.47 [1.5; 6]	1.34 [0.5; 3.5]	1.98 [1; 4]	2.54 [1.5; 5]
<i>T. trichiura</i>	ICL	1.32 [0.5; 5]	2.26 [1; 5]	2.41 [1.5; 6]	1.87 [0.5; 4.5]	3.27 [1.5; 6]	4.65 [2; 10]
	EMC	1.50 [0.5; 5]	2.85 [1; 8]	2.82 [1.5; 7]	2.02 [0.5; 5]	3.31 [1.5; 7.5]	4.47 [2; 9]

Interruptions up to 18 months do not have a strong impact on the probability to reach the WHO target for hookworm, and the time to reach the WHO target will be delayed by between 0.34 (95% CI = [-1; 1]) and 0.49 (95% CI = [-2; 2]) (EMC model) and between 0.39 (95% CI = [-1; 1]) and 1.49 (95% CI = [0; 3]) years (ICL model) (**4.S3 Table**). A negative value means that the moment when the target is reached is anticipated with respect to the baseline scenario. The M&HI prevalence of *A. lumbricoides* is likely to reach levels below 2% with 83.2% (416/500) probability in the baseline scenario (EMC) and 26.2% (131/500) (ICL) (**4.S4 Table**). Interruptions do not affect the probability of reaching the target according to the EMC model, but they can delay the time when the target is reached by 0.5 [-1; 2] (6-month interruption) to 1.4 [0; 3] years (18-month interruption). According to both models, it is not feasible to reach the target by 2030 even without interruptions in settings where *T. trichiura* is the dominant species, due to the relatively low efficacy of albendazole against this STH infection.

Mitigation strategies help recover and speed up the progress

The M&HI prevalence dynamics of the scenarios with two mitigation strategies (semi-annual PC and one round of community-wide PC) are compared for the moderate endemicity setting in **Figure 4.3**. The figure also shows the scenario without any mitigation strategy for comparison. The analogous figure is presented for the high endemicity setting in **4.S2 Figure**. We computed the differences between the catch-up time of each mitigation strategy and the catch-up time of the same interruption's length scenario without mitigations. The values are summarized in **Table 4.2**. With semi-annual PC when resuming programmes in moderate endemicity settings, the catch-up will be speeded up of less than two years with respect of resuming without mitigation strategies for *A. lumbricoides*; of about one year in the cases of hookworm and *T. trichiura*. If control programmes implement a one-year period of community-wide PC and then revert to targeting SAC and pre-SAC, about one year is gained towards the catch-up for *A. lumbricoides* (both models) and *T. trichiura* (EMC model). In the other cases the time required to catch up with past progress is not significantly shorter than resuming without mitigation strategies. In high endemicity settings, mitigation by means of community-wide PC is beneficial in terms of catch-up time only in the case of *T. trichiura*, allowing the prevalence to catch up about one year sooner than if no mitigation is applied, for both models (**Table 4.2**).

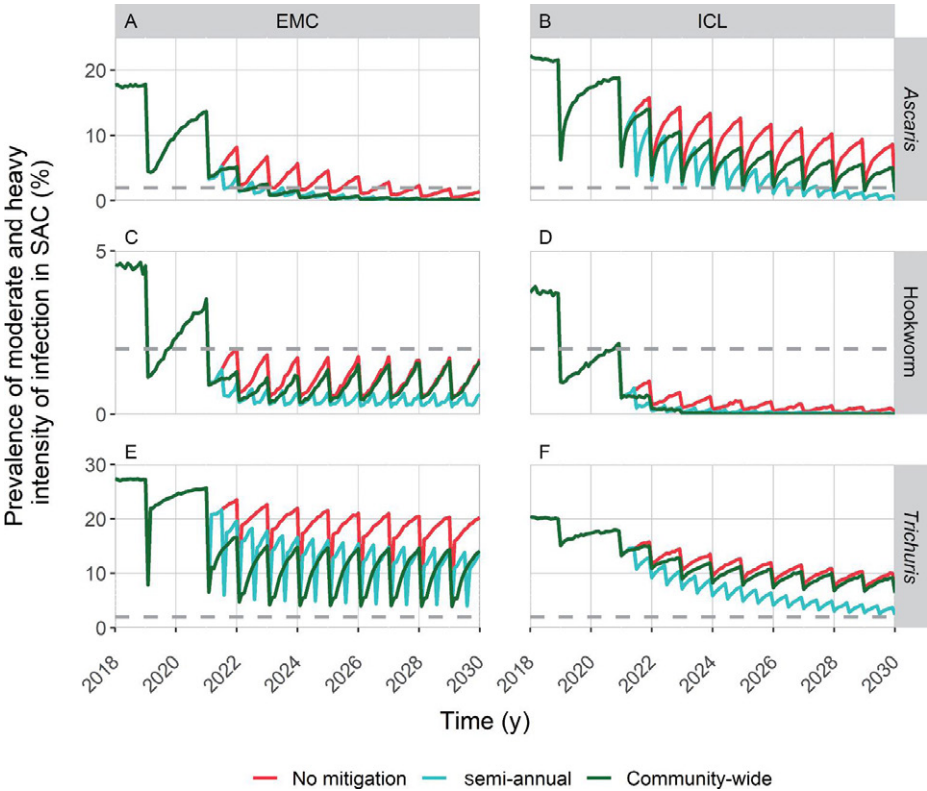


Figure 4.3. Timeline of moderate-to-heavy intensity infections prevalence in moderate endemicity settings, if programmes resume one year after the interruption, i) without mitigation strategies (red line), ii) doubling the frequency (turquoise line) iii) providing a first year of community-wide MDA before going back to the current WHO treatment guidelines (dark green line). The horizontal dashed line represents the 2% threshold set by the WHO to assess the goal. Results from both the EMC model (A, C, E panels) and the ICL model (B, D, F panels) are shown, for all STH species.

The implementation of mitigation strategies can be essential to enhance the chance to reach the WHO target or to speed up the time to the achievement of the target. The 66.6% (333/500) probability (EMC model) to reach the target, observed for hookworm in the baseline scenario, increases to 96.6% (483/500) if a semi-annual PC is implemented when programmes restart, in moderate endemicity settings. The achievement of the target can be anticipated up to a mean of 4.8 years. The ICL model generates slightly more pessimistic results in relation to the predicted impact of interruptions in PC, on the delay to reach the WHO targets for hookworm, by the two mitigation strategies. This is explained by noting that already in absence of interruption (the baseline scenario), the target is reached 0.35 [0; 2] years after the interruption

(**4.S3 Table**). Both models agree that the two mitigation strategies can accelerate the moment when the 2030 target is reached, by on average more than two years for *A. lumbricoides*, that is, even a single community-wide round is sufficient to compensate for the year missed in moderate endemicity settings (**4.S4 Table**). For all three species and for both models, in high endemicity settings we are unlikely to reach the EPHP target by 2030 even without interruption, according to the current guidelines (less than 5% probability), but a single year of community-wide PC (semi-annual) when programmes restart, will be beneficial for *T. trichiura* in speeding up the progress, according to the EMC model. It shows that in those settings, this mitigation could be essential to increase the probability to reach the target from 7.8% (34/500) to 71.4% (357/500). The ICL model results are in reasonable agreement in showing the beneficial effect of community-wide mitigation.

Table 4.2. Model-predicted differences of time (mean number of years [95%-confidence interval]) required for each mitigation strategy (semi-annual or community-wide preventive chemotherapy (PC)), to catch up with progress towards the 2030 target, compared to the catch-up time required if resuming without mitigation strategies. All values relate to the case of a one-year programme interruption. As moments of catch-up always occur right after a PC round, confidence intervals are presented as integers (in case of annual PC) or multiples of 0.5 (semi-annual PC).

Species	Model	Moderate endemicity setting		High endemicity setting
		Semi-annual PC	Community-wide PC	Community-wide PC
<i>A. lumbricoides</i>	ICL	1.26 [0; 6]	0.77 [-1; 5]	0.73 [-1; 4]
	EMC	1.70 [0; 7]	1.32 [-1; 6]	0.39 [-0.5; 2.5]
Hookworm	ICL	0.71 [0; 3]	0.35 [-1; 3]	0.09 [-1; 1.5]
	EMC	0.80 [0; 4]	0.31 [-1.5; 3]	0.24 [-1; 2]
<i>T. trichiura</i>	ICL	0.71 [-1; 4]	0.17 [-2; 3]	0.82 [-1; 4]
	EMC	1.13 [0; 5.5]	1.05 [0; 6]	1.79 [0; 6]

4.4. Discussion

The objective of this study was to investigate the impact of disruptions of STH control programmes by the COVID-19 pandemic, on the progress towards reaching the 2030 morbidity target, and to estimate to what extent that impact can be reduced by mitigation strategies. Two different, and independently developed, stochastic individual-based models of parasite transmission and PC impact, were employed to examine these questions. We assumed that the programmes resume after varying periods of interruption up to 18 months

in length, in order to account for the uncertainties about the duration of the COVID-19 pandemic and the difficulties in resuming control measures. We found that for all STH species, M&HI prevalence catches up before 2030 in both moderate and high endemicity settings, even without implementing a mitigation strategy: catch-up times are limited to 1 – 3 years (moderate endemicity setting) and 1 – 5 years (high endemicity setting). Mitigation strategies reduce the catch-up time by less than one year on average and at most two years. In some case however, they have the benefit of increasing the probability to reach the target by 2030 or reaching it earlier. Thus, mitigation strategies can be an opportunity to enhance progress towards EPHP, especially when reaching the target is not feasible by 2030.

Our results further show that it will always be advantageous to recover the last round missed as soon as possible, e.g. six months after the initially planned date. Our analyses show that it is feasible to reach the target in moderate endemicity contexts where hookworm or *A. lumbricoides* are the dominant species. Different durations of interruption do not have a strong impact on reaching the target but they can introduce a delay up to 1.5 [0; 3] years (ICL, hookworm) and up to 1.4 [0; 3] years (EMC, *A. lumbricoides*).

Although the mitigation strategies considered here have a limited impact on catch-up times, they will help to accelerate the achievement of EPHP by 2030 in moderately *A. lumbricoides* endemic settings. A single community-wide round would therefore be suggested to compensate for a missed year of PC. Mitigation strategies will not help to increase the low probability of reaching the target in the context of *T. trichiura*, but they will enhance the progress by lowering the prevalence of M&HI infections. Both models agree that in highly endemic settings for all three species, the target will not be reached by 2030, even without interruption of PC. For *T. trichiura*, this is mainly due to the relatively low efficacy (60%) of albendazole treatment; dual treatment with ivermectin would be required to reach the target [10]. For high endemicity areas, adding a year of semi-annual community-wide PC (two rounds) as mitigation, proves to be crucial to speed up the progress and enhance the chance to reach the target for *A. lumbricoides* (ICL) and *T. trichiura* (EMC).

The discrepancies observed in the results between the two models can be explained by the different assumptions, such as regarding age patterns in exposure to eggs/larvae in the environment. For instance, the ICL model assumes for hookworm a flat age profile making the exposure to the infection

independent of age. In contrast, in the EMC model it is assumed that exposure increases during the first ten years of life and then stabilises, such that most of the hookworm infection is carried by adults and higher worm burden is observed in adults than in SAC. The two different assumptions about age pattern in exposure, fit previously published age-intensity profiles observed in the field [11, 12], and thus potentially reflect different transmission settings. This difference in assumptions is directly reflected in our results: the probability of reaching the morbidity target in areas with moderate prevalence of hookworm infections is higher in the ICL model, given the current school-based treatment guidelines [7].

COVID-19-related interruptions are affecting several countries with different histories of control. In this study, we decided to implement the first year of treatment for all STH to simulate ongoing PC; the second year is then missed due to COVID-19 preventive measures. We do not investigate the impact of skipping later rounds of PC. However, theoretically, missing PC rounds early in the programme would have a more detrimental impact on current progress and goals to be achieved. As such, our predictions provide a conservative (i.e. pessimistic) foundation on which to base policy decisions. We further assume that control programmes will restart PC with the same coverage as before the interruption (75% random participation among the target population). However, there may be hurdles in reaching the same participation rates, especially in community-wide PC due to logistics, but also fear or stigma of health care workers as indirect effect of COVID-19. However, we expect that school-based PC will be less affected, as long as school attendance will return to pre-COVID rates.

The estimated outcomes of this study can be tested in settings where data of M&HI prevalence was collected before the interruption and where the collection will continue after. The Geshiyaro project [13] and the DeWorm3 [14] focus on the feasibility of interrupting the transmission of parasitic worms by repeated rounds of PC, included STH. In these projects, PC rounds have been delayed by COVID-19 hence they will be a good test of model predictions. Another test of the outcomes proposed with this paper, would require in settings where mitigation strategies are implemented, the assessment if they reach the 2030 target sooner than settings where mitigation strategies have not been implemented. Testable model outcomes fulfil one of the criteria requested by the Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD) (**4.S2 Table**).

Overall, we have shown that STH control programmes may not take too long to catch up after the interruption. However, it is important to minimise the catch-up time and to consider mitigation strategies as soon as possible. There is still paucity of quantifiable evidence and studies to detect direct morbidity from STH, though M&HI infections have been linked to diarrhoea, anaemia, malnutrition, and physical and cognitive impairment [15]. Prolonged intervals without treatment lead to a higher intensity of infection in individuals, increasing the chance for them to develop morbidity. At the population level, this is likely to be reflected in an increase in the proportion of individuals (prevalence) with M&HI infections, therefore a higher prevalence and severity of morbidity. Anaemia, for example, is the main hookworm-related morbidity and it is strongly associated with moderate and heavy hookworm infections. Anthelmintic treatment is an effective means of improving haemoglobin levels [16]. A consistent drop in haemoglobin below the WHO threshold defined for anaemia is estimated to occur starting from 2000 eggs per gram (epg), the value defining moderate infections [17]. It could be, therefore, crucial especially for children to prevent prolonged periods with high M&HI.

We show that even a single year of community-wide treatment after the interruption speeds up the progress towards the morbidity target. In some cases, the target may even be reached sooner than without interruption. Even though community-wide treatment will require extending drug donations to adults as well as children, in specific settings which are far from reaching the target, this can be, not only helpful in speeding up the process, but also offer an opportunity to reach the morbidity target by 2030.

4.5. Conclusions

We estimated that the COVID-19-related interruption of STH control programmes will only temporarily impact the progress towards the EPHP target by 2030, since for all STH species M&HI prevalence after interruption catches up with the prevalence in the scenarios without interruption, recovering the ground lost by 2030. However, after a PC interruption, programmes require a catch-up time (estimated to be less than three years in moderate endemicity settings and less than five years in high endemicity settings) during which endemic areas could attain higher levels of moderate and high infections. We suggest, therefore, to minimise the time without PC and to restart PC as soon as possible, even if that is before the time when the next round of PC would

have been scheduled under normal circumstances. In addition, disruption by COVID-19 could be turned into an opportunity to increase the probability of reaching the target in those settings where it is not feasible with the current guidelines, by implementing suitable mitigation strategies. A one-year period of community-wide treatment after the interruption would speed up the progress towards the morbidity target. In some cases, resuming programmes with a mitigation strategy would be the only possibility to reach the morbidity target by 2030.

Acknowledgements

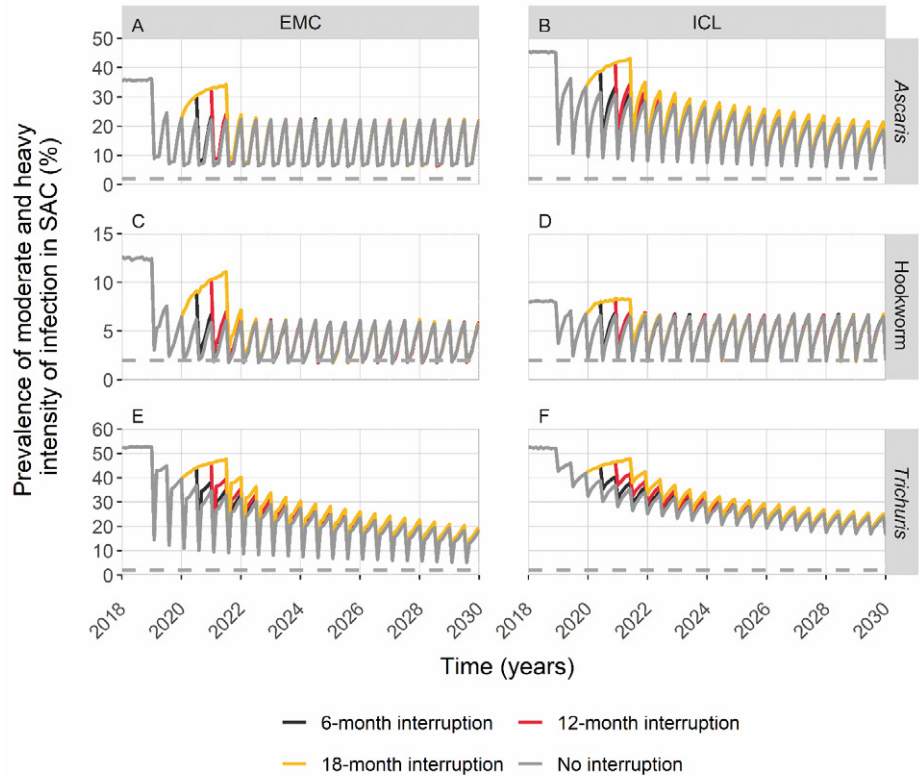
The authors would like to thank all of the NTD Modelling Consortium members.

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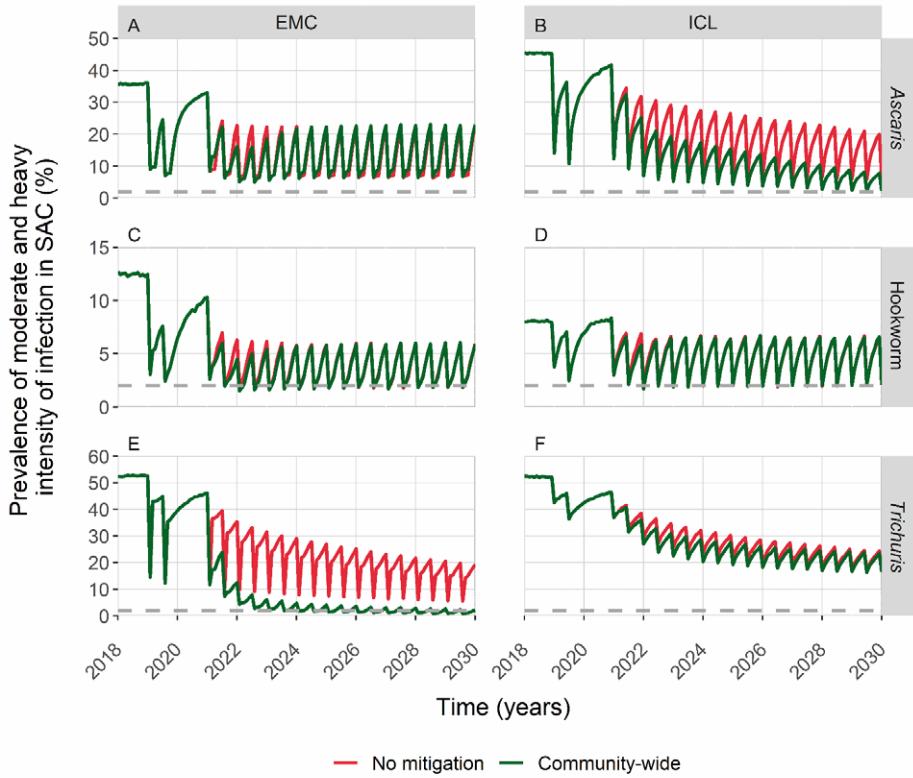
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4.6. Supplementary data



4.S1 Figure. Timeline of moderate-to-heavy intensity infections prevalence in high endemicity settings, if programmes resume without mitigation strategies. The comparison between “no interruption” and restarting after 6, 12 or 18 months is presented by line colours. The horizontal dashed line represents the 2% threshold set by the WHO to assess the goal. Results from both the EMC model (A, C, E panels) and the ICL model (B, D, F panels) are shown, for all STH species.



4.S2 Figure. Timeline of moderate-to-heavy intensity infections prevalence in high endemicity settings, if programmes resume one year after the interruption, i) without mitigation strategies (red line), ii) providing a first year of community-wide MDA before going back to the current WHO treatment guidelines (dark green line). The horizontal dashed line represents the 2% threshold set by the WHO to assess the goal. Results from both the EMC model (A, C, E panels) and the ICL model (B, D, F panels) are shown, for all STH species.

4.S1 Table. Model parameters used to simulate transmission of *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm infections.

Value or assumption	
Parameter	Imperial College London
Human demography	
<i>Hookworm</i>	Demographic data taken from 2003 Kenya Demographic and Health Surveys. ²
<i>Ascariasis</i>	Demographic data taken from 2003 Kenya Demographic and Health Surveys. ²
<i>Trichuris</i>	Demographic data taken from 2003 Kenya Demographic and Health Surveys. ²
Transmission of infection	
Seasonal variation in contribution to reservoir	Stable throughout the year (assumption).
Aggregation of parasites in hosts	
<i>Hookworm</i>	$k_w = 0.35^2$
<i>Ascariasis</i>	$k_w = 0.8^3$
<i>Trichuris</i>	$k_w = 0.38$, in high-prevalence settings fitted to data ⁵ , $k_w = 0.12$ in moderate-prevalence settings.
Variation in exposure and contribution to the environmental reservoir by age and sex	
<i>Hookworm</i>	Relative exposure and contribution to the reservoir are assumed to vary by constant across age groups, assuming no difference between males and females. The values were estimated from baseline data of the Tumikia study ⁷ and unpublished epidemiological data of the DeWorm3 study.

4.S1 Table. Continued

Parameter	Value or assumption
	Imperial College London
<i>Ascariasis</i>	Contribution to the reservoir increases linearly from 0 to 1 between ages 0–10 and is stable thereafter with no difference between males and females (reflecting behaviour related to defaecation and mobility patterns as previously estimated for hookworm ⁶). Exposure to the reservoir is defined as a piece-wise linear function of age that increases linearly from a base level $x_0 = 0.33$ of relative exposure at age zero to a relative exposure of 1.0 at age $a_{peak} = 3$, and then again linearly declines back to the base level x_0 at age 15 and is stable thereafter. This function aims to reflect behaviour leading to ingestion of contaminated matter, which typically peaks in young children. ³
<i>Trichuris</i>	Contribution to the reservoir increases linearly from 0 to 1 between ages 0–10 and is stable thereafter with no difference between males and females (reflecting behaviour related to defaecation and mobility patterns as previously estimated for hookworm ⁶). Exposure to the reservoir is defined as a piece-wise linear function of age that increases linearly from a base level $x_0 = 0.33$ of relative exposure at age zero to a relative exposure of 1.0 at age $a_{peak} = 3$, and then again linearly declines back to the base level at age 15 and is stable thereafter. This function aims to reflect behaviour leading to ingestion of contaminated matter, which typically peaks in young children. ³
Life history and productivity of the parasite in the human host	
Average worm lifespan	2 years ¹¹
Hookworm	1 year ^{8,9,10,12}
Ascariasis	1 year ^{8,9,10,12}
Trichuris	1 year ^{5,11}
Variation in worm lifespan	Exponential distribution; i.e. the mortality rate is constant and independent of worm age.
Pre-patent period	

4.S1 Table. Continued

Value or assumption	
Parameter	Erasmus MC
<i>Hookworm</i>	7 weeks ^{8,9,13,14}
<i>Ascariasis</i>	10 weeks ⁸
<i>Trichuris</i>	10 weeks ⁸
Age-dependent reproductive capacity	Constant over age (assumption).
Female worm fecundity	Density-dependent on total number of female worms in host, assuming hyperbolic saturation. ⁶
	Density-dependent on total number of female worms in host, assuming exponential saturation. Exponential model of saturation with parameter $\gamma = 0.02$ ¹⁵ for hookworm, $\gamma = 0.07$ for ascaris ⁴ and $\gamma = 0.0035$. ^{5,16}
<i>Hookworm</i>	On average 8.3 eggs per female worm per 41.7 mg sample of faeces (200 epg per female worm, as previously reported based on association between number of expulsed adult female worms and egg counts based on Kato-Katz ¹⁷). The average maximum total host output is assumed to be 62.5 eggs per 41.7 mg faeces (1500 epg, as previously assumed ⁶).
<i>Ascariasis</i>	On average 406 eggs per female worm per 41.7 mg sample of faeces (9750 epg per female worm), and maximum total host output of 777 eggs per 41.7 mg faeces on average (18,650 epg). These figures were estimated from pre-control data on number of expulsed adult female worms and egg counts based on a concentration and sedimentation technique using homogenised stools. ³
<i>Trichuris</i>	On average 15.4 eggs per female worm per 41.7 mg sample of faeces (370 epg per female worm), and maximum total host output of 3333.33 eggs per 41.7 mg faeces on average (80,000 epg). These figures were estimated from pre-control data on number of expulsed adult female worms and egg counts based on a concentration and sedimentation technique using homogenised stools. ³

Imperial College London

No pre-patent period used.
No pre-patent period used.
No pre-patent period used.
Constant over age (assumption).

Density-dependent on total number of female worms in host, assuming exponential saturation. Exponential model of saturation with parameter $\gamma = 0.02$ ¹⁵ for hookworm, $\gamma = 0.07$ for ascaris⁴ and $\gamma = 0.0035$.^{5,16}
On average 3 eggs per female worm per 41.7 mg sample of faeces (72 epg per female worm, as previously reported based on association between number of expulsed adult female worms and egg counts based on Kato-Katz¹⁷).
On average 320 eggs per female worm per 41.7 mg sample of faeces (7674 epg per female worm).

On average 5.875 eggs per female worm per 41.7 mg sample of faeces (141 epg per female worm).⁵

4.S1 Table. Continued

Value or assumption	
Parameter	Imperial College London
Host immunity to incoming infections	None (assumption).
Infection dynamics in environmental reservoir	
Survival of infective material in the central reservoir	Exponential survival (assumption).
Hookworm	Exponential survival (assumption). Average lifespan of 30 days. ¹¹
Ascariasis	Average lifespan of two weeks, implemented as a monthly survival probability of (95%-CI: 0.05–7.38 weeks under assumption of exponential survival), based on the notion that average survival time is in the order of weeks. ^{13,14,18} Average lifespan of 1.5 month, implemented as a monthly survival probability of (95%-CI: 0.04–5.53 months under assumption of exponential survival). ^{9,10}
Trichuris	Average lifespan of 20 days implemented as a monthly survival probability of (95%-CI: 0.02–2.46 months under assumption of exponential survival). Lifespan of approximately 2 months. ¹⁹ Lifespan of approximately 20 days. ⁵
Drug treatment	
Proportion of adult worms killed by single dose of albendazole (400 mg), or pyrantel pamoate (10 mg/kg, ascariasis only)	Assumption: proportion killed is equal to the faecal egg reduction rate. Assumption: proportion killed is equal to the faecal egg reduction rate.
Hookworm	0.95 for albendazole. ²⁰
Ascariasis	0.99 for albendazole. ²⁰
Trichuris	0.60 for albendazole. ²⁰
Diagnostic test outcomes	
Variability in measured host load of infective material (eggs per examined sample of faeces)	

4.S1 Table. Continued

Parameter	Value or assumption	
	Erasmus MC	Imperial College London
<i>Hookworm</i>	Kato-Katz: negative binomial distribution with aggregation parameter, estimated separately from repeated individual-level egg count data from Uganda. ²¹	Kato-Katz: negative binomial distribution with aggregation parameter, estimated from unpublished triple egg count data from Tamil Nadu, India
<i>Ascariasis</i>	Kato-Katz: negative binomial distribution with aggregation parameter.	Kato-Katz: negative binomial distribution with aggregation parameter ²²
<i>Trichuris</i>	Kato-Katz: negative binomial distribution with aggregation parameter.	Kato-Katz: negative binomial distribution with aggregation parameter ¹⁶
Cut-offs for no, light, moderate, and heavy infection		
<i>Hookworm</i>	1, 2000, and 4000 epq	1, 2000, and 4000 epq
<i>Ascariasis</i>	1, 5000, and 50,000 epq	1, 5000, and 50,000 epq
<i>Trichuris</i>	1, 1000, and 10,000 epq	1, 1000, and 10,000 epq

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4.S2 Table: The Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD).

Principle	What has been done to satisfy the principle?	Where in the manuscript is this described?
Stakeholder engagement	Work has been presented at the following WHO webinars: (i) Neglected Tropical Diseases and COVID-19: Impact on Programme Implementation; and (ii) A Research Agenda for NTD Programmes Affected by the COVID-19 Pandemic.	-
Complete model documentation	The scenarios modelled in this study are described in the manuscript. Transmission models used are described in the manuscript and fully documented in previous publications. ^{1,2,3}	Methods section and References.
Complete description of data used	Data and parameters used are described in the manuscript and in the supplementary information.	Methods section and Supplementary Table 1.
Communicating uncertainty	We consider stochastic uncertainty in communicated results and we account for quantitative differences between the two models used.	Methods, Results and Discussion sections.
Testable model outcomes	The model outcomes can be tested by collecting data once programmes resume.	Discussion section.

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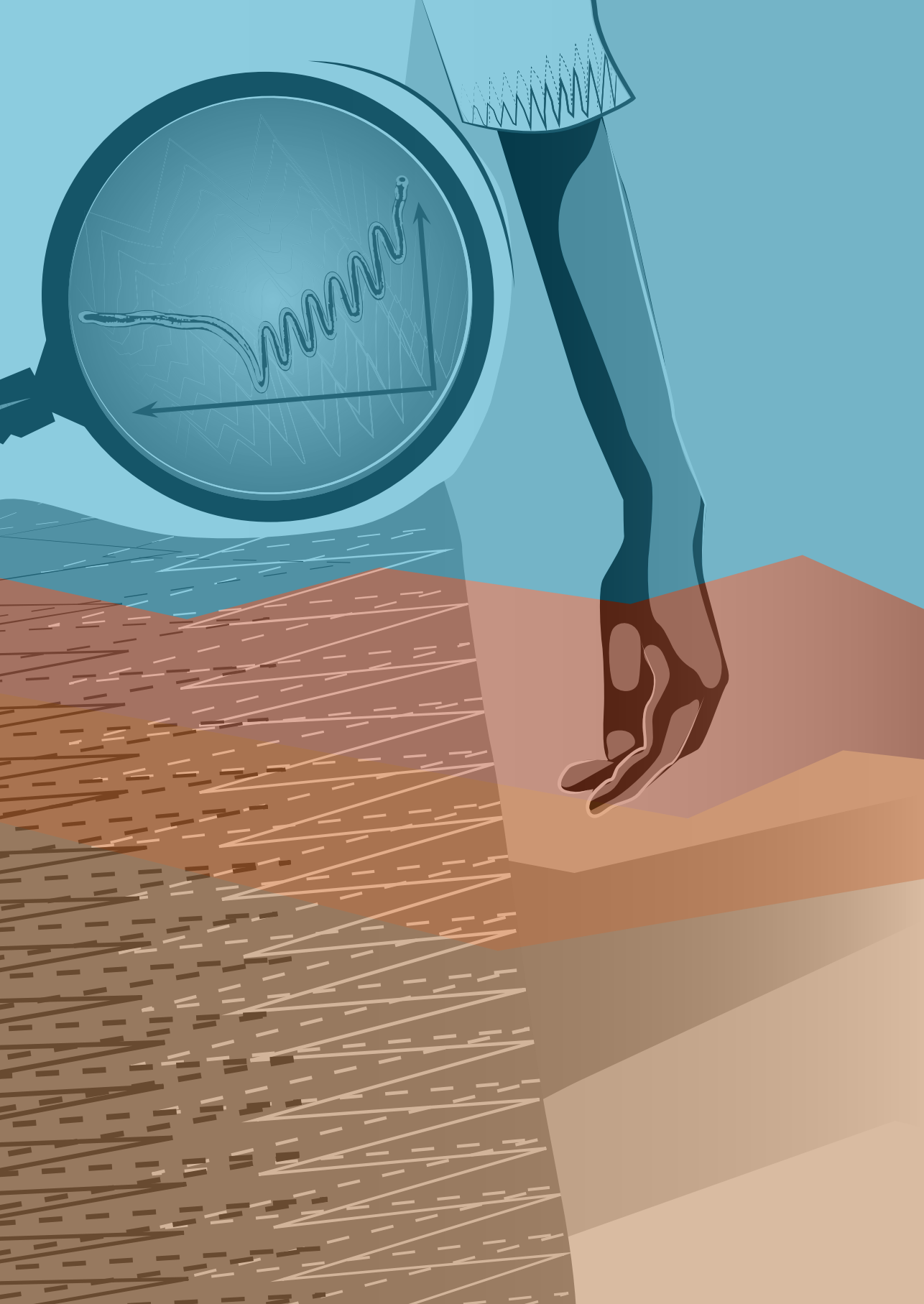
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4.S3 Table. Time (years since the interruption of the control programme) and probability to reach the 2030 target in the baseline scenario (no interruption); introduced delays (years) in reaching the target for each interruption scenario, compared to the baseline scenario. Hookworm, moderate endemicity setting. As moments when the target is reached are evaluated right after a PC round, confidence intervals are presented as integers (in case of annual PC) or multiples of 0.5 (semi-annual PC).

Model	Time (mean [95%CI]) and probability to reach the target in the baseline scenario	Delay from the baseline scenario (mean [95% CI]) (ys)				
		6-month interruption	12-month interruption	18-month interruption	Semi-annual mitigation	Community-wide mitigation
EMC	8.14 [1; 10] 66.6%	0.34 [-2; 2]	0.17 [-2; 2]	0.49 [-2; 2]	-4.76 [-8; -2]	-1.32 [-3; 0]
ICL	0.35 [0; 2] 100%	0.39 [-1; 1]	1.27 [0; 3]	1.49 [0; 3]	1.17 [0; 2]	1.19 [0; 2]

4.S4 Table. Time (years since the interruption of the control programme) and probability to reach the 2030 target in the baseline scenario (no interruption); delays (years) in reaching the target for each interruption scenario, compared to the baseline scenario. A. *Lumbricoides*, moderate endemicity setting. As moments when the target is reached are evaluated right after a PC round, confidence intervals are presented as integers (in case of annual PC) or multiples of 0.5 (semi-annual PC).

Model	Time (mean [95%CI]) and probability to reach the target in the baseline scenario	Delay from the baseline scenario (mean [95% CI]) (ys)				
		6-month interruption	12-month interruption	18-month interruption	Semi-annual mitigation	Community-wide mitigation
EMC	6.37 [2; 10] 83.2%	0.52 [-1; 2]	1.35 [0; 2]	1.40 [0; 3]	-2.30 [-4; -1]	-2.45 [-4; -1]
ICL	7.96 [5; 10] 26.2%	0.85 [-3; 7]	1.90 [-2; 9]	2.44 [-2; 9]	-2.42 [-5; 0]	-1.67 [-5; 2]



Chapter 5 Revisiting the impact of *Schistosoma mansoni* regulating mechanisms on transmission dynamics using SchiSTOP, a novel modelling framework

This chapter is published as a journal article:

Malizia V, de Vlas SJ, Roes KCB, Giardina F (2024) Revisiting the impact of *Schistosoma mansoni* regulating mechanisms on transmission dynamics using SchiSTOP, a novel modelling framework. *PLOS Neglected Tropical Diseases*. 18(9): e0012464.

Abstract

Background

The transmission cycle of *Schistosoma* is remarkably complex, including sexual reproduction in human hosts and asexual reproduction in the intermediate host (freshwater snails). Patterns of rapid recrudescence after treatment and stable low transmission are often observed, hampering the achievement of control targets. Current mathematical models commonly assume regulation of transmission to occur at worm level through density-dependent egg production. However, conclusive evidence on this regulating mechanism is weak, especially for *S. mansoni*. In this study, we explore the interplay of different regulating mechanisms and their ability to explain observed patterns in *S. mansoni* epidemiology.

Methodology/Principal findings

We developed SchiSTOP: a hybrid stochastic agent-based and deterministic modelling framework for *S. mansoni* transmission in an age-structured human population. We implemented different models with regulating mechanisms at: i) worm-level (density-dependent egg production), ii) human-level (anti-reinfection immunity), and iii) snail-level (density-dependent snail dynamics). Additionally, we considered two functional choices for the age-specific relative exposure to infection. We assessed the ability of each model to reproduce observed epidemiological patterns pre- and post-control, and compared successful models in their predictions of the impact of school-based and community-wide treatment.

Simulations confirmed that assuming at least one regulating mechanism is required to reproduce a stable endemic equilibrium. Snail-level regulation was necessary to explain stable low transmission, while models combining snail- and human-level regulation with an age-exposure function informed with water contact data were successful in reproducing a rapid rebound after treatment. However, the predicted probability of reaching the control targets varied largely across models.

Conclusions/Significance

The choice of regulating mechanisms in schistosomiasis modelling largely determines the expected impact of control interventions. Overall, this work suggests that reaching the control targets solely through mass drug administration may be more challenging than currently thought. We highlight the importance of regulating mechanisms to be included in transmission models used for policy.

5.1. Introduction

Schistosomiasis is a neglected tropical disease (NTD) caused by parasitic flatworm (*Schistosoma*) species. Widespread in tropical and sub-tropical regions, schistosomiasis is endemic in 78 countries with an estimated 251.4 million people requiring treatment in 2021 [1]. Responsible for severe morbidity such as complications due to chronic infections of the urinary tract or the intestine, schistosomiasis is considered the deadliest among NTDs [2]. The intestinal form of schistosomiasis is caused by *S. mansoni*, and the urogenital one is caused by *S. haematobium*, two of the main species responsible of human infections [3]. The transmission dynamics of *Schistosoma* between the human host and the water environment are peculiar and remarkably complex, due to the presence of two reproduction phases. The first-stage larvae (free-living miracidia) are released from eggs hatching upon contact with freshwater, which search for certain species of freshwater snails. Asexual reproduction occurs in the snails, leading to the release of second-stage larvae (free-living cercariae). These cercariae can infect humans, where they mature into adult worms, pair and reproduce sexually. Monogamous in their nature, adult pairs of *Schistosoma* release eggs within the human host. Individuals with schistosomiasis contaminate freshwater sources with urine (*S. haematobium*) or faeces (*S. mansoni*) containing parasite eggs. The World Health Organization (WHO) 2030 Roadmap for NTDs delineates two control targets for schistosomiasis: elimination as a public health problem (EPHP) in all endemic countries and interruption of transmission (IOT) in 32% of the endemic countries [1]. EPHP is defined by WHO as achieving a prevalence of heavy intensity infections in school-aged children (SAC) below 1%. Infections are classified as heavy intensity if more than 400 eggs per gram of faeces (epg) are detected for *S. mansoni*, and more than 50 eggs per 10 mL urine for *S. haematobium*. IOT is defined by WHO as having no new autochthonous human cases in a defined geographical area.

Mass drug administration (MDA) to SAC with the anthelmintic drug praziquantel is the primary measure for the control of schistosomiasis. Praziquantel reduces the overall prevalence of infection in the population by killing adult worms within the human hosts [4]. However, the prevalence of infection typically rebounds to pre-control levels quickly after stopping MDA [1,5,6], but we currently lack a clear understanding of rebound pathways. Moreover, maintained transmission at low endemic levels (<10% prevalence in SAC) has been observed [7–9], hampering the achievement of IOT. The WHO

has recently provided a recommendation for additional control measures to prevent rebound of infection, including focal snail control and behavioural change interventions (through education and improvement of hygiene and sanitation standards) in endemic countries [10].

Mathematical models have historically been employed to reproduce and elucidate the transmission dynamics of *Schistosoma* species [11]. Deterministic models have been developed to describe the mean worm burden within humans over time [12–15], while stochastic agent-based models (ABMs) have included individual heterogeneities in transmission, exposure to infection, or adherence to treatment [16–21]. Mathematical models for schistosomiasis require assumptions on mechanisms regulating transmission in order to reproduce a stable endemic equilibrium. In the absence of regulating mechanisms, the number of cercariae in the environment and the burden of worms in humans will grow unbounded, leading to an endemicity setting where the entire population is heavily infected. The assumption of density-dependence in egg production, according to which production of eggs by female worms diminishes with increasing adult worm burdens (density-dependent fecundity), has been largely accepted and employed with the rationale of overcrowding effects within the human host, in analogy with other intestinal parasites [13,22]. However, scientific evidence for this assumption for schistosomiasis has been based on historic human autopsy data [23,24], and the applicability of such data was disputed [25]. The availability of new molecular data analysed via sibship reconstruction [26] has provided some recent evidence of density-dependence in egg production for *S. haematobium* species, but the results were not conclusive for *S. mansoni*, where this question remains unresolved.

Regulating mechanisms at other stages of the transmission cycle occur, however the interplay of such mechanisms has not been generally included in current models used for policy. At the human level, host-acquired immunity has been suggested in antibodies detection studies [27–29] and was included in some deterministic age-structured models [30–32]. However, a clear and conclusive understanding of the processes of acquired immunity (e.g. triggers, rate of development) and the extent to which it may restrain transmission is missing, especially for *S. mansoni* [33]. In addition, modelling studies have shed some light on the role of the intermediate host in the transmission dynamics of schistosomiasis [34–36]. Snails can regulate transmission dynamics in two ways. Firstly, they can amplify transmission due to the parasite asexual reproduction phase occurring within the snail host. Conversely, they can also

limit transmission because of factors such as the depletion of susceptible snails, castration, and increased snail mortality upon infection [37,38]. These factors on their turn are influenced by the overall abundance of snails, which is determined by intraspecific competition for resources [36]. Overall, insufficient attention has been given to describe both host-acquired immunity and the explicit dynamics of the intermediate host in mathematical models employed for guiding policy decisions. There is a need to further understand the extent to which different regulating mechanisms occurring at worm-, human-, and snail-level can explain observed epidemiological patterns and how these affect the estimated impact of control interventions.

The aim of this study is to assess how well different modelling assumptions on the regulating mechanisms of schistosomiasis transmission dynamics can reproduce observed endemicity settings (low, moderate, high) and explain epidemiological patterns observed before, during, and after MDA. We also investigate how such assumptions on regulating mechanisms and their interplay affect the feasibility to reach the control targets set by the WHO, in particular EPHP and IOT, following two MDA strategies: targeting SAC or the whole community. In this work, we focused on *S. mansoni* species and developed SchiSTOP: a hybrid modelling framework for the transmission of *S. mansoni* between humans and snails that combines an agent-based model (ABM) for the human and worm populations, and a deterministic compartmental model for the snail dynamics. We consider the combinations of three assumptions on the regulation occurring at worm-level (density-dependence in egg production), at human-level (anti-reinfection immunity), and at snail-level (density-dependence in snails' population growth).

5.2. Methods

Model structure

We developed SchiSTOP, an agent-based stochastic modelling framework for the transmission dynamics of schistosomiasis between the human hosts and the contaminated water environment via larvae multiplication in the intermediate host (freshwater snails). The dynamics of the snail population are included as an explicit deterministic compartmental model integrated into the ABM.

SchiSTOP consists of five main building blocks: the human population, the parasitic worms living in the human host, the two larval stages living freely

in the contaminated water environment, and the snail population. The models include human, worm, and snail population dynamics via births, aging, and deaths. We focus this section on the definition of the different regulating mechanisms and the simulation scheme. However, thorough specifications of SchiSTOP, including human demography, human and snail infection dynamics, diagnostic procedure, and mass drug administration, are provided in **5.S1 Text**.

The ABM is based on stochastic events updated at discrete time steps t of one month. We assume that the model replicates the transmission dynamics in a rural community, simulating a human population of 1000 individuals, structured by age. The demographic dynamics are governed by a fixed birth rate and an age-specific death probability, informed by the Ugandan Bureau of Statistics [39]. Individuals can also migrate out of the population, according to a rate that results in a stable population size. The population is updated at each time step. Before starting simulations from the transmission model, we simulate the demographic dynamics until reaching an equilibrium for 200 years. The equilibrium age distribution (**Figure 5.1 in 5.S1 Text**) is then used to initialize the transmission model in successive iterations. Infection in humans is then modelled through an age-specific exposure to infection, accounting for individual patterns of contacts with water potentially contaminated with cercariae. Exposure to infection is governed by the overall transmission parameter on humans ζ and the level of worm aggregation k_w . The distribution of worms in the human population is in fact highly aggregated, with most of the population harboring few or no parasites, and a few individuals harboring high worm burden. Maturation, reproduction, and death of worms within the human host are governed by stochastic events. Human hosts contribute to contaminate the water environment through excretion of eggs which hatch and release miracidia, which can infect snails. Infection dynamics in snails is explicitly modelled until the release of cercariae. Diagnostic schemes to assess infection in humans via the Kato-Katz technique, and control interventions via 10 annual rounds of MDA are explicitly modelled, assuming 75% MDA coverage of the target population, selected randomly [10]. This includes a 5% of the targeted population who systematically does not have access to treatment. We assume an imperfect drug efficacy of 86% of adult worms killed by MDA [40]. The full list of models' parameters employed for the simulations of this study can be found in **5.S1 Table**.

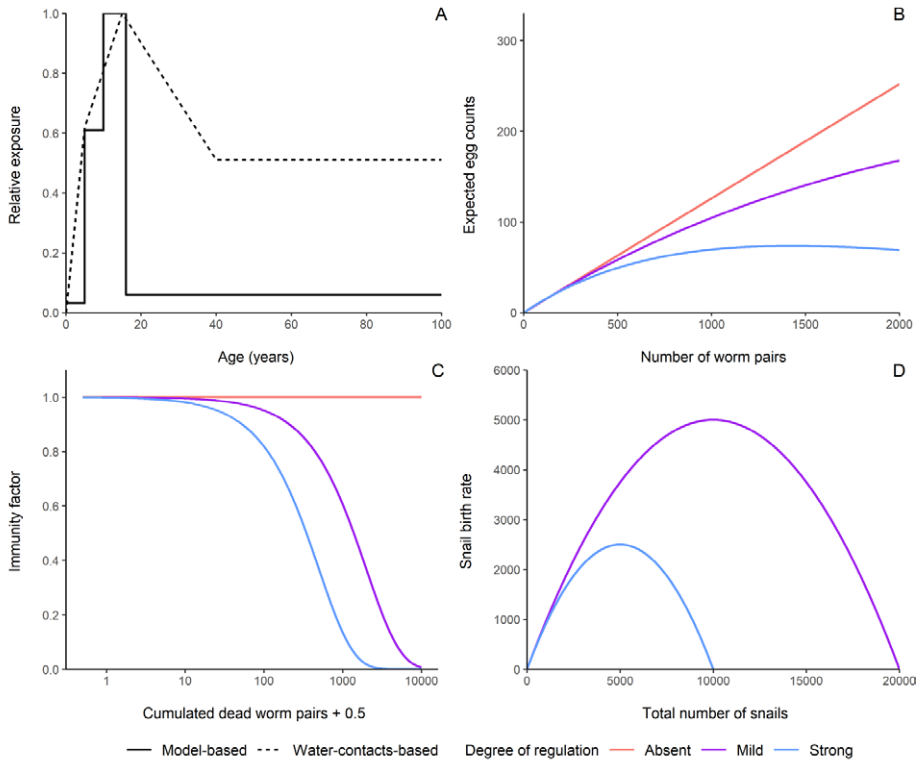


Figure 5.1. Modelling assumptions. (A) Age-exposure functions employed in the models. The functions describe the relative exposure by age of the human host, using 1.0 for the highest value (i.e., at age 15). This is proportional to the individual overall exposure rate. Both functions are interpolations of reported data points: the solid line is a piece-wise constant function representing the relative exposures derived from literature (model-based exposure function) at 0, 5, 10, and 16+ years of age [21]. The dashed line is a piece-wise linear function based on the relative exposures extracted from published water contacts data at 0, 5, 15, and 40+ years of age [41,42]. **(B) Worm-level regulation: density-dependence in egg production.** The expected egg counts are function of the number of mature worms, which are modelled as pairs within the human host. The mean number of eggs per pair per sample α in this figure is set at 0.13 (Absent regulation), 0.13 (Mild regulation), or 0.14 (Strong regulation). The density-dependence parameter z is set at 0 (Absent regulation), 0.00022 (Mild regulation), or 0.0007 (Strong regulation). See text for the parameterization of α and z for different degree of worm-level regulation. **(C) Human-level regulation: (dying-worm driven) anti-reinfection immunity.** The immunity factor is displayed as a function of accumulated dead worms, presented on a logarithmic scale. The immunity coefficient α_{imm} is 0 (Absent), 0.0005 (Mild), or 0.002 (Strong). **(D) Snail-level regulation: density-dependent population growth.** The snail birth rate, following a logistic growth, is displayed as a function of the total number of snails. The snail carrying capacity K is set at 20000 (Mild), or 10000 (Strong). When no regulation at the snail-level is assumed, the model does not include explicit snail dynamics, therefore the corresponding degree is not displayed.

SchiSTOP allows the implementation of different model variants (from here on called models) by varying assumptions on parameters and processes describing the dynamics of the disease. For the scope of this study, we considered and implemented 162 different models that reflect the $3^3 = 27$ combinations of three regulating mechanisms acting at different levels of the transmission cycle (worm, human, and snail) at three intensities (absent, mild, strong), for two different functions to model the age-specific exposure to infection, and three endemicity levels (low, moderate, high). In particular, the three regulating mechanisms act at: i) the worm-level, through density-dependence in egg production, ii) the human-level, through anti-reinfection immunity driven by dying worms, and iii) the snail-level, through the density-dependent growth of snail population. For simplicity, we refer to these three regulating mechanisms as worm-, human-, and snail-level regulation throughout the text. The two functional choices for the relative age-specific exposure are i) a model-based function derived from fitting an established schistosomiasis transmission model [21] to observed age-intensity profiles [40] (model-based), and ii) an alternative age-exposure function that we estimated from published water contact data [41,42] (water-contacts-based). To inform the latter, we extracted frequency of water contacts adjusted for body surface and time of day of contact reported for three age groups (0–9, 10–19, 20+ years old) from an extensive data collection on direct water contact observations in a village in Northern Senegal [41]. To refine the modelling of the exposure in the last age-group (20+), various age-exposure profiles from Kenya [42] were used. Both functions are implemented as relative exposure and displayed in **Figure 5.1A**.

Worm-level regulation: Density-dependent egg production. We consider mature worms to live in pairs within the human host. For each human individual i , the relationship between the expected excreted eggs (μ_i) and the number of carried adult worm pairs (w_i), is implemented as an exponential saturating function, describing density-dependent fecundity of female worms as follows: . In this function, the parameter α represents the maximum fecundity of female worms (i.e., the expected eggs produced per worm pair in absence of density-dependence), z is a parameter dictating the level of saturation in egg production, and therefore the strength of the density-dependent mechanism. The worm-level regulating mechanism for different values of the parameters α and z is displayed in **Figure 5.1B**. The values of α and z were set to numbers available from previous work or tuned to produce a mild or strong regulation. To do so, we first set z and α from literature [17,40,43] to parametrise a strong

worm-level regulation. Secondly, we set z to 0 in absence of worm-level regulation, assuming the expected excreted eggs to linearly depend on the number of adult worm pairs and then tuned α to reproduce the same initial growth as in presence of strong density-dependence. Finally, we tuned both parameters for a mild worm-level regulation.

Human-level regulation: (dying-worm driven) anti-reinfection immunity. The human immunological response, which develops naturally, is assumed to be induced by the death of adult worms, as proposed in published immunological studies [33,44]. Anti-reinfection immunity protects the host from reinfection by hindering the maturation of cercariae into adult worms, and the amount of this immunity increases as a function of the cumulative number of died adult worms. The model describes this behaviour via an immunity factor given by ranging between 0 and 1, which reduces the rate of parasite acquisition by the human host. Here, α_{imm} is the immunity parameter and d is the individual accumulated dead worm burden, defined in terms of worm pairs and inclusive of worms that have undergone either natural mortality or mortality due to MDA. We do not consider decay of immunity within the human lifespan. The human-level regulating mechanism for different values of α_{imm} is displayed in **Figure 5.1C**. The immunity factor is multiplied times the exposure rate, which determines the force of infection acting on humans (FOI_h). In absence of anti-reinfection immunity, we set α_{imm} to 0, implying that the past exposure to infection (and therefore the death of worms) does not affect the chance to acquire new parasites. As a reference for a strong human-level regulation, we derived α_{imm} from literature [32]. We set the parameter to a lower value to define a mild degree of regulation.

Snail-level regulation: density-dependent population growth. The snail phase of the parasite life cycle is explicitly modelled through an ODE-based framework and embedded into the ABM. We employed a deterministic compartmental model to simulate births, deaths, exposure, and infection of snails. Susceptible snails $S(t)$ reproduce according to a logistic growth with birth rate $\beta(t)$ due to competition for resources:

$$\beta(t) = \beta_0 \left(1 - \frac{N_s(t)}{K}\right) (S(t) + E(t))$$

Here, β_0 is the maximum reproduction rate in absence of competition [36], $N_s(t)$ the total snail population size, and K the carrying capacity. The birth rate of snails, dictating the degree of the snail-level regulating mechanism, is displayed

in **Figure 5.1D** for different values of K . The carrying capacity K was tuned to parametrise a mild or strong degree of snail-level regulation.

Susceptible snails can be invaded by miracidia present in the water environment after egg excretion by human hosts, and become exposed ($E(t)$), i.e., infected but not infectious. The force of infection FOI_s acting on snails is proportional to the abundance of miracidia, through a coefficient η representing the transmission parameter on snails. Miracidia live in exposed snails for a period during which they mature and asexually reproduce into cercariae. Susceptible and exposed snails undergo natural mortality, according to a per-capita mortality rate v [36]. When the parasites are mature, the snails move to the infected compartment $I(t)$ at a rate τ equal to the inverse of the assumed parasites' maturation period [17,45]. Infection on snails causes an increased mortality (vI) and castration [36]. Therefore, only susceptible and exposed snails contribute to reproduction (see formulation of $\beta(t)$). The depletion of susceptible snails and the effects of infection on the snail population growth, regulate the transmission of schistosomiasis at this stage of the transmission cycle. Infected snails shed cercariae $C(t)$ into the environment, according to a cercarial per capita production rate λ [36]. The abundance of shed cercariae determines the force of infection acting on humans FOI_h . Cercariae naturally die with a mortality rate γ before infecting humans. The dynamics of this module are thus described by the following system of ordinary differential equations:

$$\frac{dS(t)}{dt} = \beta - (v + FOI_s) S(t)$$

$$\frac{dE(t)}{dt} = FOI_s S(t) - (v + \tau) E(t)$$

$$\frac{dI(t)}{dt} = \tau E(t) - v I(t)$$

$$\frac{dC(t)}{dt} = \lambda I(t) - \gamma C(t)$$

The system of ODEs is defined in continuous time with events governed by daily rates. At each time step of the agent-based model (discrete and set to one month), we simulate from the system of ODEs over a 1-month time horizon. The results from these simulations then serve as starting values for the following ABM time step (details in **5.S1 Text**).

In the scenario where no regulation at the snail-level is considered, the infection dynamics in the snail population are not explicitly modelled. We assume instead that the cercarial uptake by the environment at time t is equal to the number of miracidia shed at the previous time step, which coincides with the maturation period into the intermediate host (1 month). The full list of parameters can be found in **5.S1 Table**. The specifications of the snails' infection dynamics can be found in **5.S1 Text, Intermediate host**.

Simulations

Three parameters, namely the overall transmission parameter on humans ζ , the level of worm aggregation k_w , and the transmission parameter on snails η , were varied within a grid search framework with the aim of allowing all models to reproduce the same initial setting of either low, moderate, or high endemicity. The initial settings were defined on the basis of three prevalence indicators and their targets informed from literature: the infection prevalence in SAC, as per WHO definition (average of 10%, 30%, 60%, in low, moderate, and high endemicity, respectively) [10], the prevalence of heavy infections in SAC (average of 0%, 6%, 20%) [46], and the prevalence of infection in snails (average of 6% in all settings) [37]. First, a visual inspection of the three prevalence indicators allowed refining the search. The prevalence of infection in snails is mostly influenced by the parameter η , about which very little information is available. We therefore varied the parameter η until the models reproduced a prevalence in snails in the range $6\% \pm 1\%$. Afterwards, we performed the grid search for the three transmission parameters jointly in the reduced space and identified for each model the parameters' values minimising the root mean squared error (RMSE) between the predicted and desired targets. The RMSE was computed combining and scaling the three target indicators with most of the weight assigned to the prevalence of any infection in SAC, which was allowed to vary in relative terms about $\pm 10\%$ with respect to the corresponding desired threshold ($10 \pm 1\%$, $30 \pm 3\%$, $60 \pm 6\%$, in low, moderate, and high endemicity, respectively). The file with selected parameters for each model and the full code is publicly available at https://github.com/VeronicaMalizia/SchiSTOP_model. SchiSTOP was implemented and run using R programming language 4.2.2 [47].

After the selection of parameters, we ran 100 stochastic simulations for each model to capture inherent models' variability and used the average trends for comparison. We assessed and compared the ability of each model to explain three observable patterns: i) the age-intensity profiles expressed as mean

detected eggs per gram (epg) of faeces as a function of age, ii) the effect of 10 annual rounds of MDA administered to SAC, iii) the rebound of prevalence after treatment. The number of eggs per gram of faeces (epg) is expressed as geometric mean across age groups (see **5.S1 Text, Human Demography**) and stochastic realizations of the models. Although geometric means lead to biased estimators of the true mean, they have traditionally been used in the analysis of data from field studies [48]. We defined models as successful when they could i) reproduce a convex age-intensity curve with a typical peak of intensity of infection in adolescents, ii) bring the prevalence of infection in the human population down of at least 20% of their pre-control levels after 10 years of MDA administered to SAC, and iii) result in a rebound of prevalence to values close to pre-control levels, after stopping MDA (10 annual rounds to SAC), even in low endemicity settings [1,49–51]. After stopping MDA, we expect that the prevalence of infection in SAC should go back to pre-control levels within 20 years. In order to parametrise the model and define the above-mentioned criteria for model plausibility, we undertook an expert elicitation process that involved multiple steps. We first identified experts in the field of schistosomiasis, ranging from parasitology, epidemiology, experimental and field research. All experts had a strong publication record, practical experience, and a deep understanding of the disease dynamics. All experts were informed about the purpose of the elicitation process, the goals of our research, and the specific areas in which we sought expertise. The experts involved are acknowledged at the end of this paper. In particular, we conducted structured interviews and one workshop, all organized within the SchiSTOP project [52]. We asked questions related to 1) the role of the intermediate host and how to interpret malacological surveys, 2) exposure and mechanisms of immunity in terms of triggers, protection, and decay and 3) prevalence patterns before and after control.

Lastly, we used the successful models to compare the predicted probabilities (based on 100 repeated simulation runs) to meet the control targets of EPHP and IOT, considering two different treatment strategies: 10 rounds of annual MDA administered to SAC (school-based), and 10 rounds of annual MDA administered to all individuals older than 2 (community-wide), as per the most recent WHO guidelines towards the 2030 targets [10]. EPHP is reached when the prevalence of heavy intensity of infections in SAC is below 1%, and IOT when the prevalence of any intensity of infection in SAC is 0%. We define a stochastic run to have met the target if the prevalence indicator is still below the control threshold 20 years after the end of the MDA programme.

5.3. Results

Reproducing initial settings

The defined initial settings of low, moderate, and high endemicity were reproducible only with a subset of models (147 out of 162). Clearly, the presence of at least one regulating mechanism is required to reproduce a stable endemic equilibrium for all three endemicity settings. In addition, adopting the model-based age-exposure function, worm- or human-level regulation alone was not sufficient to reproduce a stable, low endemic equilibrium ($\leq 10\%$ prevalence of any infection in SAC). Explicit snail population dynamics at any intensity of regulation is essential for reaching low stable endemic equilibria. With the alternative definition of age-exposure function based on water contacts we found that any regulating mechanism can initiate the model in a low endemicity setting. In particular, snail-level regulation allows very low endemic equilibria.

When the system does not reach the required endemic equilibrium, the number of simulated cercariae in the environment and the average worm load in humans can either grow without upper limits, leading quickly to an endemicity setting where the entire human population is infected, or die out, leading to a disease-free situation. Models without any regulating mechanism and models without snail-level regulation combined with the model-based exposure function are not successful in reproducing stable equilibria for all endemic settings and have therefore been excluded from the assessment of further results. Only exception to this exclusion is the model with strong worm-level regulation alone and model-based exposure function. Although this model does not allow to generate steady initial settings with low endemicity, it is included for reference in further comparisons, as current models for policy use the same assumptions.

Reproducing observed epidemiological patterns

Age-intensity profiles. The assumptions on human-level regulation via anti-reinfection immunity and on the age-exposure functions have the largest impact on the resulting shape of the age-intensity profiles, whereas varying assumptions on regulation occurring at worm- and snail-level has a minor effect. **Figure 5.2** compares the age-intensity profiles for different degrees of regulation in humans (anti-reinfection immunity, by colours) and both age-exposure functions, for all three endemicity settings. The figure shows that the peak in intensity of infection reproduced by all models is followed by i) a steep

drop for adults with the model-based exposure function, and ii) a smoother decline in adults leading to higher egg counts, using the exposure function based on water contacts. In the latter, implementing human-level regulation from absent to strong, shifts the peak from 20 to 10 years old on average and considerably decreases the mean intensity in adults. Interestingly, despite a relatively high exposure in adults assumed by the water contacts-based exposure function, a strong regulation in humans can explain the low intensity of infection in adults (20+) that is sometimes observed in specific exposure settings (**Figure 5.2D** and **5.2F**). The effect of anti-reinfection immunity on the intensity of infection is not seen in low endemicities, because the accumulation of dead parasites in human hosts is too low to trigger an immune response.

Observed age-intensity profiles from three Kenyan villages, published elsewhere [53], are plotted in **Figure 5.2** (black lines) for comparison with simulated profiles. The model-based exposure function can replicate age-intensity profiles in high endemicity settings reasonably well. However, at lower endemicities, the decline in intensity of infection among older ages may result in very low average epg, compared to the observed data. The alternative age-exposure function based on water contacts better reproduces different age-intensity profiles. With some degree of regulation in humans, it also replicates low intensity of infection in adults in high endemicity settings. The age-intensity profiles disaggregated for all models are displayed in **5.S1 Appendix**.

Effectiveness of MDA and prevalence bounce-back. All models reproduce similar decreasing trends of prevalence during MDA (**Figure 5.3**). Assumptions on human-level regulation and the chosen age-exposure function are the main determinants of the drop in SAC prevalence due to treatment, depending on the endemicity setting. With a model-based exposure function, MDA has a stronger effect on prevalence in SAC. The prevalence drops to lower levels after 5 MDA rounds if compared to the results obtained by using the exposure function based on water contacts. This can be explained by the fact that the simulated control strategy targets the SAC group, where most of the exposure occurs, particularly when using the model-based exposure function. A strong regulation in humans also predicts a more effective treatment with respect to assuming absent or mild regulation. In fact, MDA itself contributes to the development of anti-reinfection immunity by its acting mechanisms that kills adult worms [29].

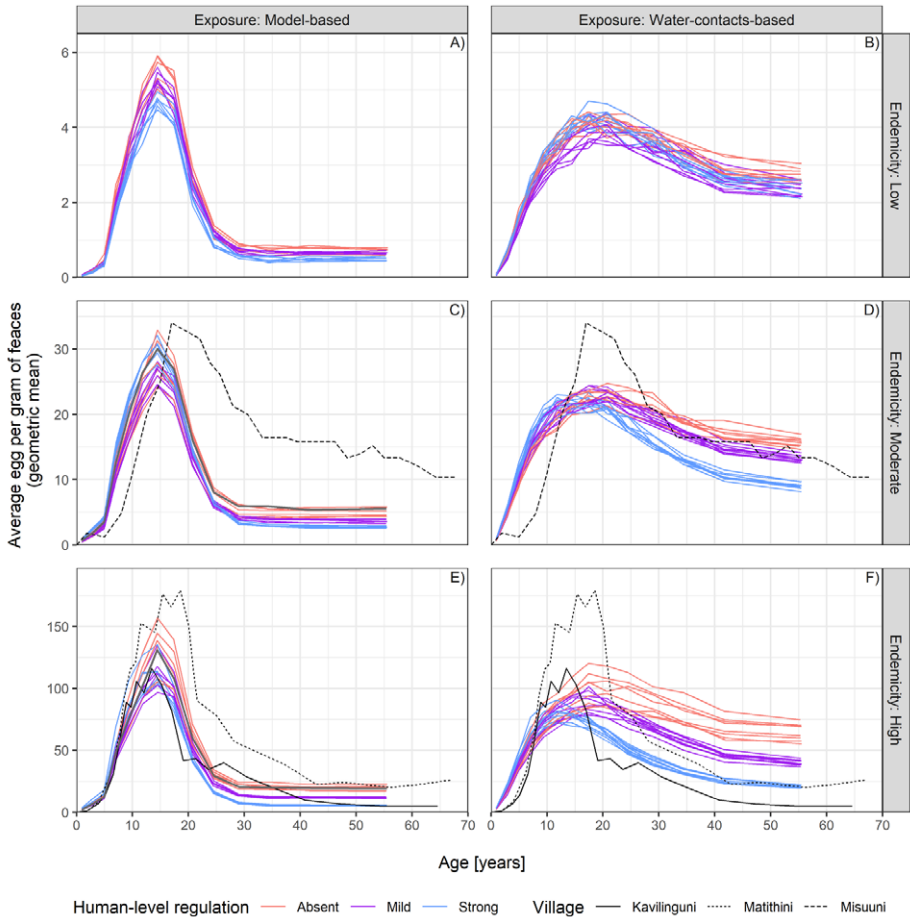


Figure 5.2. Age-intensity profiles by varying assumptions on age-exposure and anti-reinfection immunity mechanism. For each choice of the age-exposure function (columns) and different endemicity settings (rows), a single panel shows the simulated egg counts on the y-axis (mean egg is displayed, over age group and 100 stochastic realizations of the models) by age on the x-axis. The age-intensity profiles are displayed at pre-control, for all models that could successfully reproduce all three endemicity settings. Each line depicts results from a single model. The degree of regulation assumed at human level via anti-reinfection immunity is highlighted with different colours, from Absent to Strong, according to the legend in the figure. Lines of the same colour within a single panel are due to combinations ($3 \times 3 = 9$) of worm- and snail-level regulation, given the same choice of immunity (colour), age-exposure function (column), and endemicity (row). Age bins are defined as to have the same number of individuals in each bin. The grey line in the left-hand-panels (C and E) represents a model with strong worm-level regulation only and the model-based exposure function. This model does not allow to generate stable initial settings with low endemicity, but it is included here for reference, as current models for policy use the same assumptions. The black lines indicate age-intensity profiles observed in three Kenyan villages and published elsewhere [53].

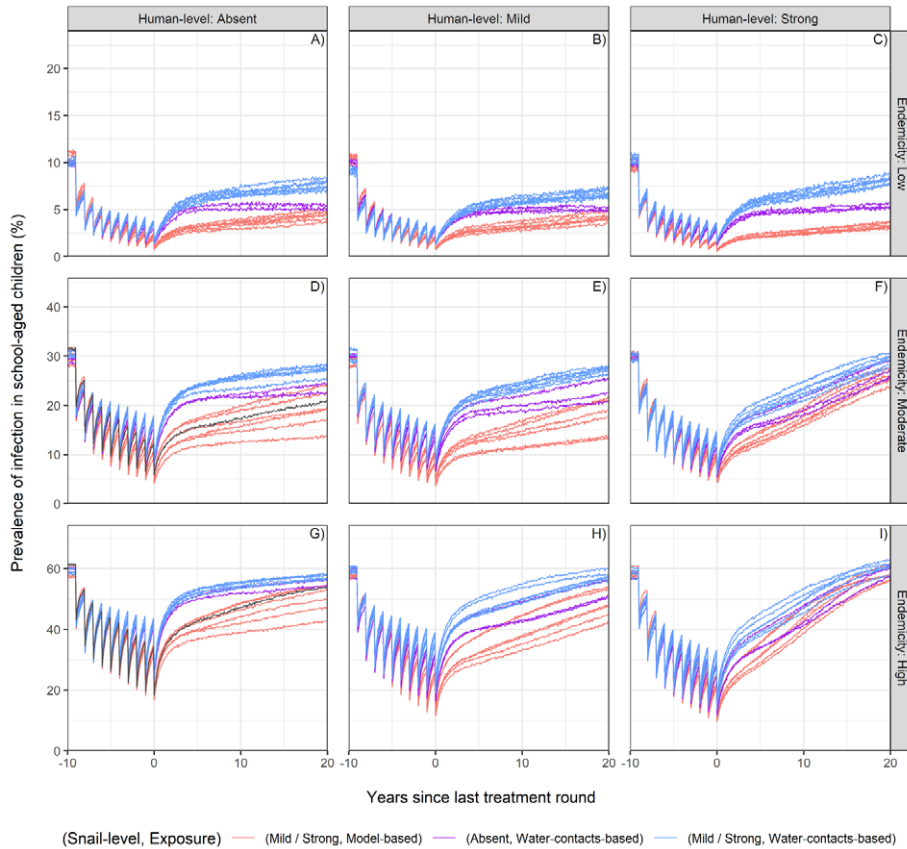


Figure 5.3. Prevalence timelines in SAC during and after treatment. For different degree of human-level regulation via anti-reinfection immunity ("Human-level", by columns) and different endemicity settings ("Endemicity", by rows), single panels show the infection prevalence in school-aged children on the y-axis (mean of 100 stochastic realizations of the model) by years since the last treatment round on the x-axis, for all models that could successfully reproduce all three endemicity settings. Each line depicts results from a single model. Lines of the same colour represent groups of models as indicated in the legend of the figure. "Snail-level" refers to the different assumptions of snail-level regulation. The grey line in panels D) and G) represents a model with a strong worm-level regulation only and the model-based exposure function. The model is excluded from the analyses because it does not allow stable initial settings with low endemicity, but it is added here for reference as current models for policy use the same assumptions. For all models, treatment is annually administered to 5–15 years old individuals with a coverage of 75% of the target population, 5% of target population systematically untreated, and a drug efficacy of 86%.

The ability of each model to reproduce the natural prevalence bounce-back is further shown in **Figure 5.3**, by the prevalence trends up until 20 years after the last MDA round. The figure shows that the combination of the age-exposure

function based on water contacts and a mild or strong degree of regulation in snails is essential to reproduce a bounce-back of prevalence close to pre-control levels in all endemicity settings, within 20 years after termination of the MDA programme. The rationale for this result lies in a reduced impact of treatment as a consequence of the water contact-based exposure function, as previously explained, in addition to higher values of transmission parameters required if considering snail- or human-level regulation, in order to reproduce the initial endemicity settings. By assuming a strong regulation at human level in fact, the bounce-back is much more prominent, although the prevalence drops to lower values during treatment with respect to assuming the regulation to be absent or mild. The models found successful in explaining a plausible rebound of prevalence after treatment are not significantly influenced by the degree of worm-level regulation.

In conclusion, the models that were successful in explaining observed patterns (blue lines in second and third columns in **Figure 5.3**) were those that combined an age-exposure function based on water contacts with a mild or strong degree of regulation at both snail- and human- level. Selected successful models could explain observed patterns both in terms of pre-control age-intensity profiles and bounce-back of prevalence after treatment. The timelines of SAC prevalence during and after the MDA programme disaggregated for all models are displayed in **5.S2 Appendix**.

Feasibility to reach the control targets

Despite reproducing similar epidemiological patterns, successful models can still differ in their predictions of the probability to reach the control targets. Results that follow include only such selected models, with the exception of the model with only strong worm-level regulation and model-based exposure function, as current models for policy use the same assumptions.

Reaching control targets with 10-year annual MDA to school-aged children.

We found that all successful models agree that treating SAC only with 10 years of annual MDA will not allow reaching the EPHP in high or moderate endemicity settings. In low endemicities, the target of interest is the IOT and none of the models predict a positive probability to reach this target despite 10 rounds of annual MDA to SAC. Results are different for the model assuming only strong worm-level regulation and a model-based exposure function, used here as reference for common assumptions, which predicts a 73% probability to reach EPHP in a moderate endemicity setting.

The impact of community-wide annual MDA. Expanding the 10-year annual MDA programme to all individuals older than 2 years of age, leads to EPHP in moderate endemicity settings according to all successful models with a mild human-level regulation (**Figure 5.4**). The mechanism of (dying-worm driven) anti-reinfection immunity (human-level regulation) has the highest impact on the probability to reach EPHP: a strong human-level regulation decreases the probability to a range between 32% and 98% if combined with another regulating mechanism (snail or worm) (**Figure 5.4**). In fact, in order to reproduce moderate and high endemicity settings in the presence of a strong human-level regulation, transmission rates in human hosts need to reach high values (input files with transmission parameters can be found in the public repository https://github.com/VeronicaMalizia/SchiSTOP_model). These high transmission rates cause infection prevalence to rebound more quickly compared to scenarios with mild or absent human-level regulation. Remarkably, with community-wide MDA, the treatment-induced death of worms during MDA, and the consequent stronger anti-reinfection immunity response, cannot compensate for this effect. In high endemicity settings, it is still feasible to reach EPHP with a probability ranging between 72%– 95% if human-level regulation is mild and worm-level regulation is absent or mild (**Figure 5.4**). The probability shows a decreasing trend with increasing degree of worm-level regulation, dropping to a range of 4% - 9% if strong worm-level regulation is assumed. In fact, strong worm-level regulating mechanism decreases here the impact of MDA in high endemicity settings, as individuals with high worm loads will still have a similar egg output after treatment because of release of density-dependent intraspecific competition, therefore keeping their contribution to transmission. Consequently, prevalence rebounds much earlier than in models without worm-level regulation (absence of density-dependency in egg production, thus a linear relationship between worm burdens and expected egg counts). According to all other models, the probability to reach EPHP is zero in high endemicity settings (**Figure 5.4**). The probability to reach EPHP was found to be higher (100%) when using assumptions as employed in current models used for policy (marked by *).

Community-wide MDA also increases the chances of reaching IOT in low endemicity settings, with respect of only treating SAC. Here, the probability of interrupting transmission jumps from 0% (if treating only SAC) to a range of 32%– 66% across the different models (**Figure 5.5**).

Probability to elimination as a public health problem

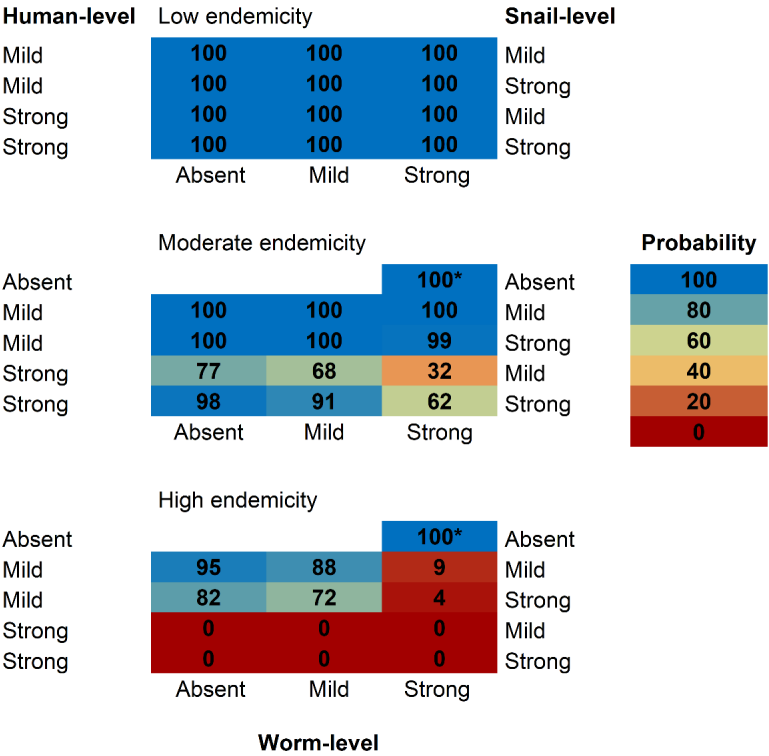


Figure 5.4. Probability to reach elimination as a public health problem with a 10-year annual MDA to all individuals older than 2. The figure reports predictions for the probability (portion of the 100 stochastic runs monitored at 20 years after end of treatment) of reaching elimination as a public health problem (EPHP, prevalence of heavy infections in school-aged children < 10%), across models successful in reproducing all observed patterns for schistosomiasis. Successful models assume an age-exposure function based on water contacts. Regulating mechanisms can be at human-level ("Human-level", left side, via anti-reinfection immunity), snail-level ("Snail-level", right side, via density-dependence in population growth), and worm-level ("Worm-level", bottom, via density-dependence in egg production). *This model assumes a strong worm-level regulation only and the model-based age-exposure function. It was not successful in reproducing observed patterns within our modelling framework but it is added here for reference as current models for policy use the same assumptions. For all models, treatment is annually administered to 2+ years old individuals with a 75% coverage of the target population, 5% of target population systematically untreated, and a drug efficacy of 86%.

Probability to interruption of transmission

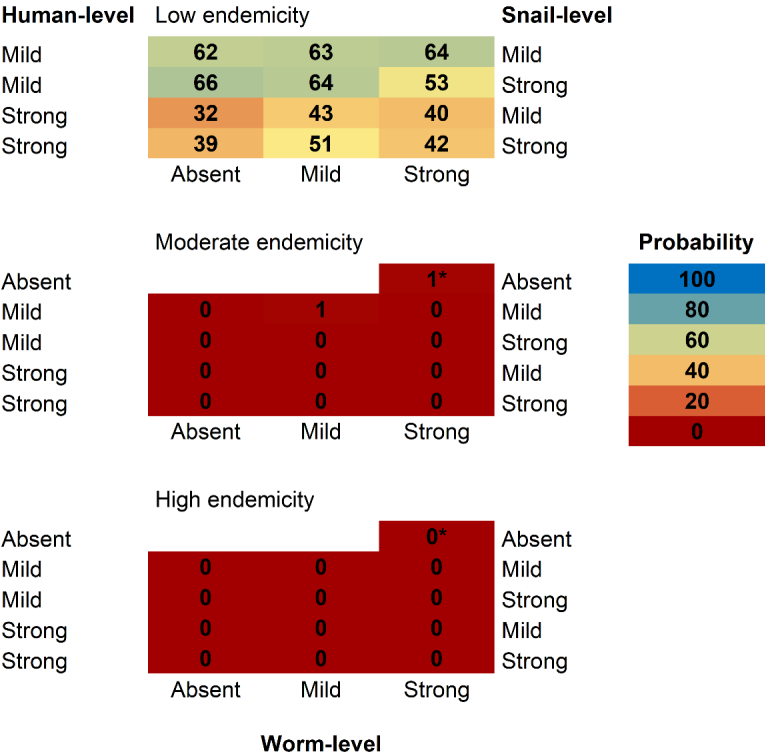


Figure 5.5. Probability to reach interruption of transmission by 10-year annual MDA to all individuals older than 2. The figure reports predictions for the probability (portion of the 100 stochastic runs monitored at 20 years after end of treatment) of reaching interruption of transmission (0% prevalence of any infection in school-aged children), across models successful in reproducing all observed patterns for schistosomiasis. Successful models assume an age-exposure function based on water contacts. Regulating mechanisms can be at human-level ("Human-level", left side, via anti-reinfection immunity), snail-level ("Snail-level", right side, via density-dependence in population growth), and worm-level ("Worm-level", bottom, via density-dependence in egg production). *This model assumes a strong worm-level regulation only and the model-based age-exposure function. It was not successful in reproducing observed patterns within our modelling framework, but it is added here for reference as current models for policy use the same assumptions. For all models, treatment is annually administered to 2+ years old individuals with a 75% coverage of the target population, 5% of target population systematically untreated, and a drug efficacy of 86%.

5.4. Discussion

The objective of our study was to revisit the modelling assumptions on the regulating mechanisms for the transmission of *S. mansoni* and to investigate the impact of such assumptions on the feasibility to reach the WHO control targets. To do so, we developed SchiSTOP, a new modelling framework for the transmission dynamics of *S. mansoni*. SchiSTOP was used to run a large number of simulations, varying the assumptions on the regulating mechanisms and the age-exposure to infection.

Overall, our results show that a degree of regulation at the snail-level and at the human-level, combined with the water contacts-based exposure function is needed to reproduce the defined endemicity settings (low, moderate, high) and to explain pre- and post-control observed patterns, i.e. the expected age-intensity profiles and a plausible rebound of prevalence after termination of an MDA programme. In particular, we found that without regulating mechanisms, the system leads quickly to settings where the entire population is highly infected, as previously demonstrated in other modelling studies [54]. Moreover, stable low endemic equilibria (prevalence of infection in SAC $\leq 10\%$) cannot be reproduced with the modelling assumptions on age-exposure and only worm-level regulation that are considered in current models used for policy. To our knowledge, there are no schistosomiasis modelling studies in the literature that aim to focus on low transmission settings. We found that snail-level regulation is crucial to reproduce very low stable endemic equilibria, within SchiSTOP. In fact, explicit snail dynamics with a varying carrying capacity can stabilise the system providing a continuous reservoir of infection even at very low transmission levels in humans, thanks to the force of infection acting on snails which contributes to maintain transmission.

The assumptions made on the regulating mechanisms are particularly relevant when the models are used for policy recommendations. In fact, the predicted probabilities to reach the control targets differ largely across successful models, and they are overall lower compared to the predictions obtained under the regulating assumptions of current models used for policy recommendations. Results show that according to all successful models, it is unlikely to meet EPHP and IOT when treating SAC only. If MDA is expanded to community-wide treatment of all individuals older than 2, the feasibility increases, even for IOT in low endemicity. This is in line with previous studies [55].

The present work also highlights the importance of informing the age-exposure function with water contact data. In fact, the model-based age-

exposure function only performs well in reproducing age-intensity profiles in high endemicity settings, while the drop in intensity of infection at older ages may be too strong in lower endemicities. This is because this function was derived from fitting a transmission model solely considering regulation at worm-level to the age-intensity profiles from different African villages, all characterized by high endemicity [11,15,17,56,57]. Available data show that age-intensity profiles, although generally peaking in 10–20 years old, can appear differently in older ages describing heterogeneities in endemicity, exposure, and regional-specific settings [48]. The alternative age-exposure function based on water contacts effectively reproduces the variation in age-intensity profiles. Using this function, our results additionally indicate that the impact of (dying-worm driven) anti-reinfection immunity on population age-intensity profiles aligns with findings from previous studies [58] showing a peak shift to lower ages and reduced intensity in adults. We further explored the interaction of anti-reinfection immunity for *S. mansoni* with other regulating mechanisms and assessed their implications for control programs and expected impact of interventions. Our findings suggest that some degree of human-level regulation via (dying-worm driven) anti-reinfection immunity is necessary to explain observed age-intensity relationships in high endemicity settings. A recently published review provided evidence for water contacts being robustly associated with infection in both children and adults, across heterogeneous settings [59]. These findings shed light on the definition of at-risk populations and therefore requiring treatment and highlighted the need of standardised tools for exposure measurements. However, how to properly define and quantify exposure to infection on the basis of observable data such as number of contacts with contaminated water, duration of contact and area of the body exposed, remains a challenge.

Overall, the modelling assumptions commonly employed in schistosomiasis modelling and used for informing control strategies (i.e., in terms of age-exposure and only worm-level regulation) are found not adequate to reproduce low endemic pre-control settings and rebound of prevalence after MDA, within SchiSTOP. Predictions to reach EPHP under those assumptions are generally more optimistic compared to the same predictions for the successful models in our study. This is because i) with a model-based function, the MDA has a stronger effect on prevalence in SAC, ii) the assumption of a strong worm-level regulation requires lower transmission parameters and a higher heterogeneity of worms to represent moderate and high endemicity scenarios, compared to those required by other regulating mechanisms.

Our modelling framework, SchiSTOP, has some limitations, mainly related to the limited knowledge and reliability of data available to more precisely parametrise regulating mechanisms. In particular, we assumed that acquired immunity leads to a protective effect towards repeated infections, as suggested for *S. mansoni* [33]. However, the long-term dynamics of immunity still constitute a research and data gap [33]. While the current understanding points towards a slow development of immunity triggered by the death of adult worms (both naturally and by praziquantel therapy) [60], not much is known about the duration of such protection. We chose not to account for a decay of anti-reinfection immunity for the scope of these analyses. In addition, some studies suggest that the main effect of acquired immunity is a decrease in worm fecundity. This has been proposed for *S. haematobium* [61,62], but does not seem to be the case for *S. mansoni* [33,63]. The assessment of infection in snails is also subject to uncertainty due to sampling procedures, and diagnostic methods to assess infection. Field and laboratory data have shown that the detected prevalence of infected snails (thus shedding cercariae) is usually quite low [37,64–67], but exhaustive explanation of such low prevalence is lacking and no evidence of correlation between infection rates in snails and humans has been identified. We chose a fixed 6% prevalence of infection in snails to define all three endemicity initial settings. Molecular tools and genetic data are further necessary to deepen our understanding of variations in susceptibility to schistosome species by specific intermediate host snails.

Furthermore, we compute probability of IOT as the number of stochastic runs that meet the target up to 20 years after termination of the MDA programme to ensure capturing pathways of late recrudescence, despite monitoring and evaluation in the field are likely to occur within shorter time intervals [10]. A rebound after elimination, as well as maintained low transmission, can nevertheless occur via other mechanisms like movement of infected individuals [68] or cercariae/snail movement through water stream. Although human movement, particularly rural-to-urban migration, is likely to contribute to the re-emergence of the disease through importation of infection [69], SchiSTOP does not take movement of individuals into account. We assume a close population reproducing the size of a rural village, and we consider human movement to play a minor role for schistosomiasis, given its very focal nature [3].

We assume treatment by MDA to kill 86% of adult worms, in line with other existing models [17,21,40,70]. This value originates from a field study [71] where drug efficacy is determined by the observed egg reduction rate (ERR)

due to praziquantel, defined as the relative reduction in the group mean egg output after treatment compared to pre-treatment levels [72]. The observed ERR does not translate directly into the worm killing rate because of the high individual variation in egg counts, and this difference is dependent on our assumptions on worm-level regulation. However, our analysis shows that the 86% reduction in adult worms results in a mean ERR (based on single Kato-Katz slide) after one round of MDA that varies in a small range (between 81% and 83% across absent, mild, and strong worm-level regulation). It is important to mention that the sampling methods used for the field assessment of ERR likely lead to an overestimation of efficacy due to the fact that egg-negative individuals at baseline are excluded, but light infections might have missed [73]. Therefore, we chose a constant portion of 86% of worms killed by MDA, for the scope of our analysis and we performed a sensitivity analysis by varying such parameter between 80% and 90% (**5.S3 Appendix**). Even in the case of 90% of worms killed by MDA, none of the successful models predict a probability to reach the control targets greater than 0 when treating only SAC. In the case of community-wide treatment instead, although absolute predictions to achieve control targets vary according to a higher or lower worm killing rate, the trend across regulating scenarios remains unchanged.

SchiSTOP integrates an ODE module to describe the explicit snail dynamics into an ABM framework capturing dynamics and complexities of transmission in the human host. SchiSTOP considers limited snail population growth, in line with commonly-made assumptions of resource competition [36]. The depletion of susceptible snails and increased mortality of infected snails are thus responsible of regulating transmission. Other aspects in snail transmission dynamics have been considered in the literature and have been shown to play an important role in transmission on humans, and therefore in the expected impact of interventions, such as MDA. Some examples are: the effect of seasonality, temperature and annual rainfalls [34], snail age structure [74], and saturating force of infection for snails [35]. Here, we mainly focus on exploring the role of snail dynamics in interaction with other regulating mechanisms such as (dying-worm driven) anti-reinfection immunity and density-dependence in egg production.

In this work, SchiSTOP has been used to revisit the assumptions of regulating mechanisms for *S. mansoni* transmission. However, its formulation is suitable to answer diverse research questions about the epidemiology and control of schistosomiasis. For instance, the presence of a specific module for the

dynamics in snails allows for a thorough assessment of the impact of snail control interventions.

In conclusion, the present work highlights the importance of considering regulating mechanisms at different levels of the transmission cycle in models for schistosomiasis transmission and control, as they largely determine the predicted impact of interventions. We showed that some degree of regulation in both snail- and human-level is required to explain commonly observed epidemiological patterns for schistosomiasis. Our findings support the current WHO guidelines, recommending community-wide treatment to all individuals > 2 years old. This control strategy greatly enhances the probability to reach the control targets, also in high endemicity settings. However, the probability to reach these targets is likely not as high as predicted by the currently used models that only assume worm-level regulation. We stress on the need for a better understanding of the mechanisms regulating transmission and persistence of schistosomiasis in endemic settings.

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5.5. Supporting information

5.S1 Text Introduction

This document contains full specification of the modelling framework SchiSTOP, including functions and parameters employed for the simulations. We implemented an agent-based stochastic model (ABM) to reproduce the transmission dynamics of schistosomiasis between the human hosts and the contaminated water environment, via larvae multiplication in the intermediate host, namely freshwater snails. The dynamics of the snail population are explicitly included via a deterministic model consisting of a system of ordinary differential equations (ODEs), integrated into the ABM. The five main building blocks of SchiSTOP are: the human population, the parasitic worms living in the human host, the two parasitic larval stages living in the contaminated water environment, and the snail population.

The ABM is based on stochastic events updated at discrete time steps t of 1 month. The ODEs system is defined at continuous time scale and a daily time step t' . Events are governed by daily rates, considering the short lived larval stages of *Schistosoma mansoni*. At each time step t of the ABM, we simulate from the system of ODEs over a time horizon h equal to 1 month. Afterwards, the results from these simulations serve as initial conditions for the next ABM-time step $t + 1$.

The model is written in R programming language, version 4.2.2 [1] and the code is available for consultation and downloading at the public online repository https://github.com/VeronicaMalizia/SchiSTOP_model.

Here on, we refer the subscript i to the i -th human individual alive at time t . The human population at each time step t is tracked as a matrix $N \times m$ where N is the number of alive individuals (i.e., the current population size) and m the columns storing the following individual characteristics: age, sex, individual susceptibility to infection, parasite acquisition rate, number of juvenile worms, number of adult worm pairs, cumulative dead worm pairs, and observed egg counts. All parameters employed in the model and mentioned in the next sections of this document are listed and documented in 5.S1 Table.

Human demography

The human population is governed by births, deaths, aging, and migration. The human demography is parameterised to follow the age-distribution in Uganda as reported by the Ugandan bureau of statistics [2].

The number of newborn individuals is deterministically obtained with a fixed birth rate. People at birth have zero worm/egg loads and their sex is assigned as a random draw with probability 0.5.

Individuals migrate according to a fixed monthly net migration rate, which is tuned to reach an equilibrium population size of $N = 1000$, assuming the model replicates the transmission dynamics in a rural community. Individuals of age between 5 and 55 years are eligible for migration.

Each month individuals can die according to an age- and sex- specific death probability. In case of death, the individual is removed from the population matrix.

The population is accordingly updated and aged of a period equal to t . The demographic dynamics are run to the equilibrium for 200 years and the final age distribution is used to initialise the transmission model (**Figure 5.S1.1**).

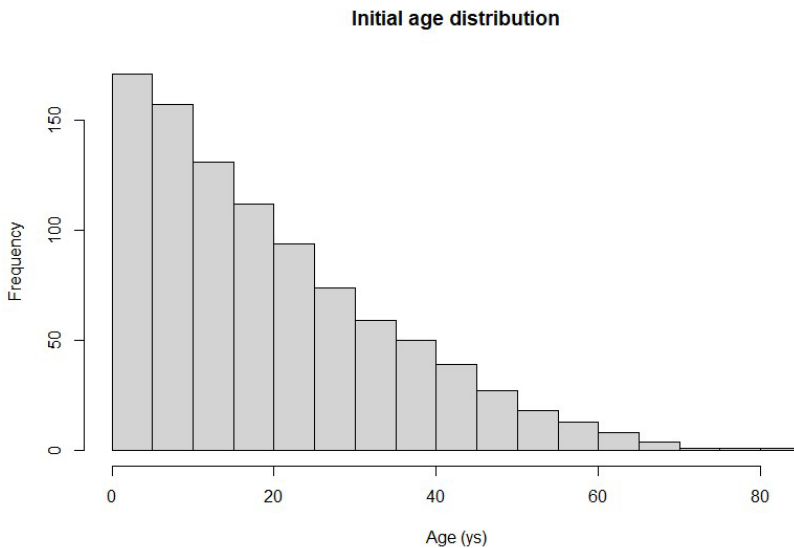


Figure 5.S1.1. Initial age distribution. The histogram represents the age distribution used to run the simulations for the present work. This distribution is extracted after running the demographic dynamics to the equilibrium with no presence of infection dynamics, for a total of 200 years. The human demography is parameterised to follow the age-distribution of Uganda as estimated by the Ugandan bureau of statistics [2].

Infection dynamics

The transmission cycle of *S. mansoni* occurs between the human host and the contaminated water environment, mediated by freshwater snails acting

as intermediate host. The first-stage larvae (free-living miracidia) are released from eggs hatching upon contact with freshwater, which search for certain species of freshwater snails. Asexual reproduction occurs in the snails, leading to the release of second-stage larvae (free-living cercariae). These cercariae can infect humans, where they mature into adult worms, pair and reproduce sexually. Individuals infected with *S. mansoni* contribute to the water environment with their excreta containing parasite eggs, thereby maintaining transmission.

Human exposure to infection

The force of infection acting on each human host is defined as follows:

$$FOI_{Hi}(t) = \phi_i(t) \exp(-\alpha_{imm} d_i(t))$$

where $\phi_i(t)$ describes the parasite acquisition rate, multiplied by an exponential factor describing the effect of human-level regulation implemented as (dying-worm driven) anti-reinfection immunity: this dictates the level of protection from consecutive reinfections. The immunity coefficient α_{imm} is a function of the dead adult worm pairs accumulated up to the current time step $d_i(t)$. The value assumed for the immunity coefficient α_{imm} modulates the degree of the regulating mechanism in humans.

The parasite acquisition rate ϕ in each human host is defined as a function of the current amount of cercariae in the environment ($C(t)$), the overall transmission parameter on humans ζ and the relative exposure to infection x_i :

$$\phi_i(t) = \frac{C(t) \zeta x_i}{\sum_{i=1}^N x_i}$$

The individual relative exposure to infection is $x_i = Ex(a_i) s_i$, where:

$Ex(a_i)$ is the relative exposure of an individual with age a , defined as a piece-wise function of user-defined exposure rates, for a finite set of ages. This incorporates the age-specific pattern of exposure to the contaminated water;

s_i : individual susceptibility to infection, which captures personal factors influencing the chance to get exposed to infection, e.g., contacts with water due to occupation. This parameter is assumed to follow a gamma distribution with mean 1.0 and shape and rate (or 1/scale) equal to k_w . The individual susceptibility of a person is assigned at birth and remains constant throughout lifetime.

Subsequently, each human host acquires new juvenile worms $j_i(t)$ according to a Poisson process with a rate given by the $FOI_{Hh}(t)$. The process of worms acquisition is therefore a Poisson-Gamma mixture, namely the individual worm burden follows a negative binomial distribution with aggregation parameter k_w . Such distribution has been shown to be adequate for describing the overdispersion of worms around the mean [3].

Newly acquired worms are assumed to be juveniles for a given pre-patent period. Juvenile worms do not mate nor reproduce. Mortality of juvenile worms is neglected. Once the pre-patent period is over, juvenile worms are randomly assigned sex according to a fixed probability of 0.5 and considered mature and patent to pair and reproduce.

Worm life within the human host

In the model, mature worms live in pairs. Individual worm pairs $w_i(t)$ are defined as the minimum number between female and male juvenile worms (all possible pairs are formed). Worms which do not pair will not survive the next time step. In the rest of the transmission cycle, mature worm pairs are considered as infective units for simplicity, supported by the monogamous nature of *Schistosoma*. Similarly to the assumptions used by previous models [4], the adult worms' lifespans follow an Erlang distribution with a rate r and a shape equal to a specified number of stages throughout which the worm pairs are distributed within each human host. The newly paired worms enter the first stage and are subsequently aged through all the remaining stages before they die. In each stage, the portion of worm pairs aging to the next step is given by $\psi = e^{-r} = e^{-(s/T_w)}$, hence assuming exponential survival within each stage. Here, s is the number of considered stages and T_w the adult worm lifespan.

Worm pairs are expected to reproduce and to pass eggs into the human intestine. The eggs will be released into the environment through the faeces. The model accounts for egg detection via the Kato-Katz diagnostic test, that uses stool smear samples of 41.7 mg for egg counting. Assuming that all paired worms reproduce within a time step of one month, we define the individual expected number of eggs observed in a stool sample as: $\mu_i(t) = \alpha w_i(t) e^{-z w_i(t)}$. Here, the parameter α represents the fecundity parameter (i.e. the expected number of eggs / worm pair / stool sample, in absence of density dependence in egg production) and z is a density-dependency factor regulating the level of saturation in egg production, therefore tuning the regulating mechanism at worm level. In a modelling setting without regulation occurring at worm

level (meaning in absence of density-dependence in egg production), we set $z = 0$ assuming the produced egg load to linearly depend on the number of worm pairs.

Diagnostic test

SchiSTOP simulates results of a single Kato-Katz diagnostic tests, at pre-defined moments along the simulation. The result of the diagnostic test is drawn from a negative binomial distribution with mean equal to $\mu_i(t)$ at the current time step, and aggregation parameter k_e . If multiple tests by individual are desired by the user, the results are averaged per person.

Human contribution to the water environment

The number of eggs (e_i) by which each individual contributes to the water environment is given by multiplying the quantity ($\mu_i \times 24$), which translate into eggs per gram of faeces, by the daily average of excreted quantity of faeces expressed in grams. We define the individual contributions (o_i) as:

$$o_i(t) = e_i(t) \text{Con}(a_i)$$

where $\text{Con}(a_i)$ indicates the relative contribution of an individual with age a , defined as a piece-wise function of user-defined contribution rates, for a finite set of ages. This accounts for any age-specific pattern in human contribution to infection. For the scope of the current work, we set a flat relative contribution function, that we assume to be independent on age.

We assume that all excreted eggs hatch in the water and mature into miracidia in a negligible simulation time. We can therefore immediately update the total miracidial uptake into the water environment $M(t)$ as the sum of individual contributions:

$$M(t) = \sum_{i=1}^N o_i(t)$$

Intermediate host**Implicit intermediate snail host.** In the simplest model formulation, no regulating mechanism is assumed to act at snail level. In such model variant, the dynamics in the intermediate host are implicitly modelled as maturation of miracidia into cercariae. The miracidia released in the water environment will simply mature into cercariae in a period h which approximates the maturation period within the intermediate host, i.e., $C(t) = M(t - h)$.

Explicit intermediate snail host. SchiSTOP allows explicit modelling of the intermediate host, by means of a separate module for the simulation of infection dynamics within the snail population. The module consists of a deterministic equation-based model that represents the role of snails and their interaction with the human population.

The deterministic module is implemented as a compartmental model [5] where births, deaths, exposure, and infection of snails occur. Finally, cercariae are shed in the water environment. The course of events is governed by daily rates. See **Figure 5.S1.2** for a schematic representation of the snail transmission dynamics. The state of the system ($S(t')$, $E(t')$, $I(t')$, $C(t')$) describes in order: the amount of susceptible, exposed, infected snails, and cercariae available at ODE-time step t' . The dynamics between compartments are described by the following system of ordinary differential equations with given initial conditions.

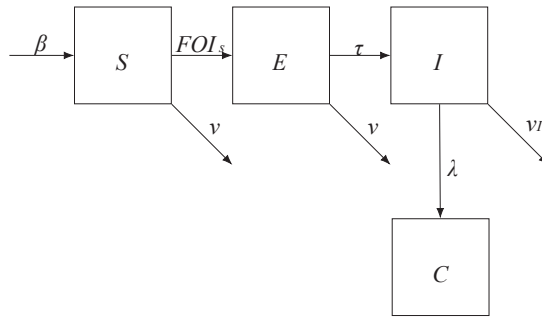


Figure 5.S1.2. Compartmental module simulating the transmission dynamics in the snail population and the cercarial production.

$$dS(t')/dt' = \beta - (\nu + FOI_s(t)) S(t')$$

$$dE(t')/dt' = FOI_s(t) S(t') - (\nu + \tau) E(t')$$

$$dI(t')/dt' = \tau E(t') - \nu_I I(t')$$

$$dC(t')/dt' = \lambda I(t') - \gamma C(t')$$

Newly born snails are susceptible to schistosomiasis infection. Susceptible snails reproduce with a birth rate $\beta(t')$, according to a logistic growth due to competition for resources:

$$\beta(t') = \beta_0 \left(1 - \frac{N_s(t')}{K} \right) (S(t') + E(t'))$$

Here, β_0 is the maximum reproduction rate in absence of competition, $N_s(t')$ the total snail population size, and K the carrying capacity. K is tuned to parameterise a mild or strong degree of snail-level regulating mechanism. Only susceptible $S(t')$ and exposed $E(t')$ snails are assumed to contribute to reproduction, due to castration upon parasitic infection.

Susceptible snails can encounter invasion of miracidia released in the water environment after egg excretion by human hosts and become exposed according to a linear force of infection $FOI_s(t) = \eta M(t)$ where η is the transmission parameter on snails. Since the miracidial input $M(t)$ is a quantity obtained by the ABM simulation, the $FOI_s(t)$ is considered a constant parameter within the time horizon of the compartmental module.

Miracidia live in exposed snails for a maturation period h , after which cercariae are released. Susceptible and exposed snails undergo natural mortality, according to a mortality rate v . When the parasites are patent, the hosting snails move to the infected stage $I(t')$ with a rate $\tau = \frac{1}{h}$. Infected snails experience increased mortality (v_i) and castration. Infected snails shed cercariae ($C(t')$) into the environment, according to a cercarial per capita production rate λ . Cercariae can naturally die with a rate γ before infecting humans.

At each ABM-time step t , the ODEs module is run for a period equal to h , with the aim to approximate the miracidial maturation in the intermediate host. The state $(S(h), E(h), I(h))$ is then set as initial conditions for the ODE system at the following ABM-time step $t + 1$. Similarly, the cercarial amount is updated as and it will contribute to the definition of the $FOI_h(t + 1)$.

Mass drug administration

SchiSTOP allows the incorporation of control activities such as Mass drug administration (MDA). MDA with praziquantel is implemented as a process that causes the death of adult worms (with a certain probability) in the treated individuals. Several parameters can be varied to reflect different options of treatment campaigns and efficacy.

- Length, namely how many years the MDA campaign last for
- Frequency, in terms of how often MDA campaigns implemented e.g. every second year, every year, twice a year
- Target population eligible for the treatment, e.g. school-aged children only or the whole community
- Coverage: portion of the target population actually reached by the treatment
- Target population systematically untreated: fraction of the target population that is not reached by MDA over consecutive rounds
- Drug efficacy: fraction of killed adult worms (pairs) per each human host

It is important to note that only adult worms die with praziquantel. Killed worms contribute to the amount of accumulated dead worms that in turn act as a trigger for the development of anti-reinfection immunity in our model.

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5.S1 Table: Parameters employed in the model.

Parameter	Value	Source
Human demography		
Population size (N)	1000	Assumption
Birth rate [annual, per 1000 individuals]	36.5	[1]
Emigration rate [annual, per 1000 individuals]	18.6	Tuned
Eligible age group for migration [years old]	[5 – 55]	[2]
Death probabilities by age	[0 – 1]	[1] and avail. at SchiSTOP
Parasite life within human host		
Aggregation of worms ($kw > 0$)	-	Available at SchiSTOP
Transmission parameter on humans ($\zeta > 0$)	-	Available at SchiSTOP
Age specific relative exposures	<i>Model-based</i> : Piece-wise constant. (0.032, 0.61, 1, 0.06) for ages (0-4, 5-9, 10-15, 16+). <i>Based on water contacts</i> : Piece-wise linear. (0, 0.62, 1, 0.51, 0.51) for ages (0, 5, 15, 40+).	[3-6]
External force of infection	Value = [0.5 - 5] worms Duration = [0.5 - 2] years	Assumption
Average lifespan of adult worms within the human host [months]	60	[7]
Pre-patent period [constant, months]	3	[7]
Egg production		
Expected number of eggs per sample ($a > 0$) [eggs/worm pair/sample]	[0.12 - 0.14]	[8, 9] and Methods main text
Density dependence in egg production (z) [/ worm pair]	(Absent) 0, (Mild) 0.00022, (Strong) 0.0007	[10] and Methods main text
Daily grams of stool produced by each human individual [gr]	150	[9]
Aggregation of observed egg counts ($ke > 0$)	0.87	[9]
Anti-reinfection immunity		
Immunity coefficient ($a_{imm} > 0$)	(Absent) 0, (Mild) 0.0005, (Strong) 0.002	[11] and Methods main text

5.S1 Table: Continued

Parameter	Value	Source
Snail population module		
Maximum reproduction rate ($\beta_0 > 0$) [1 / days]	1	[12]
Carrying capacity ($k > 0$) [number of snails]	(Absent) -, (Mild) 20000, (Strong) 10000	Varying
Natural mortality of snails ($v > 0$) [1 / days]		[12]
Mortality of snails upon infection ($v_i > 0$) [1 / days]		[12]
Snail transmission parameter ($\eta > 0$)	-	Available at SchiSTOP
Worm maturation period within the snail ($h > 0$) [days]	30	[10, 13]
Cercarial production rate ($\lambda > 0$) [1/days]	50	[12]
Mortality rate of cercariae ($\gamma > 0$) [1/days]	1	[12]
Mass drug administration		
Target population	5 – 15 or 2+ years old	Assumption
Duration	10 years	Assumption
Frequency	Annual	Assumption
Coverage (% of target population reached by treatment)	75%	[14]
Efficacy (% of killed adult worm pairs)	86%	[4]
Fraction systematically untreated	5% of target population	[4]

References

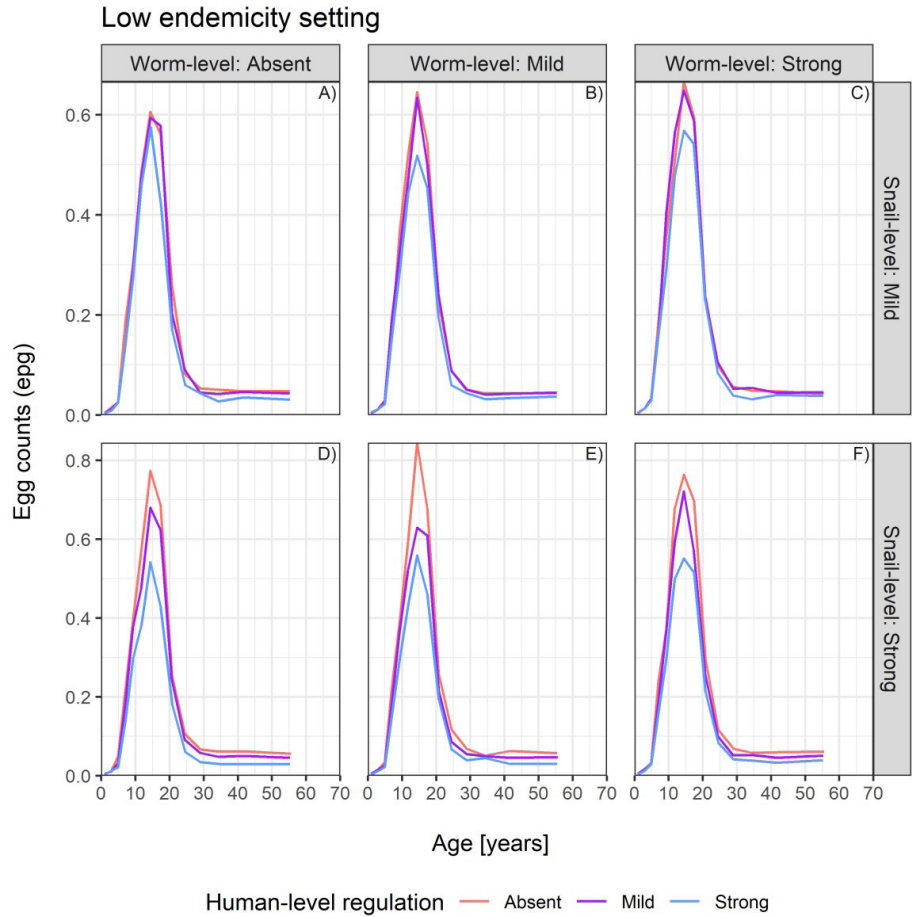
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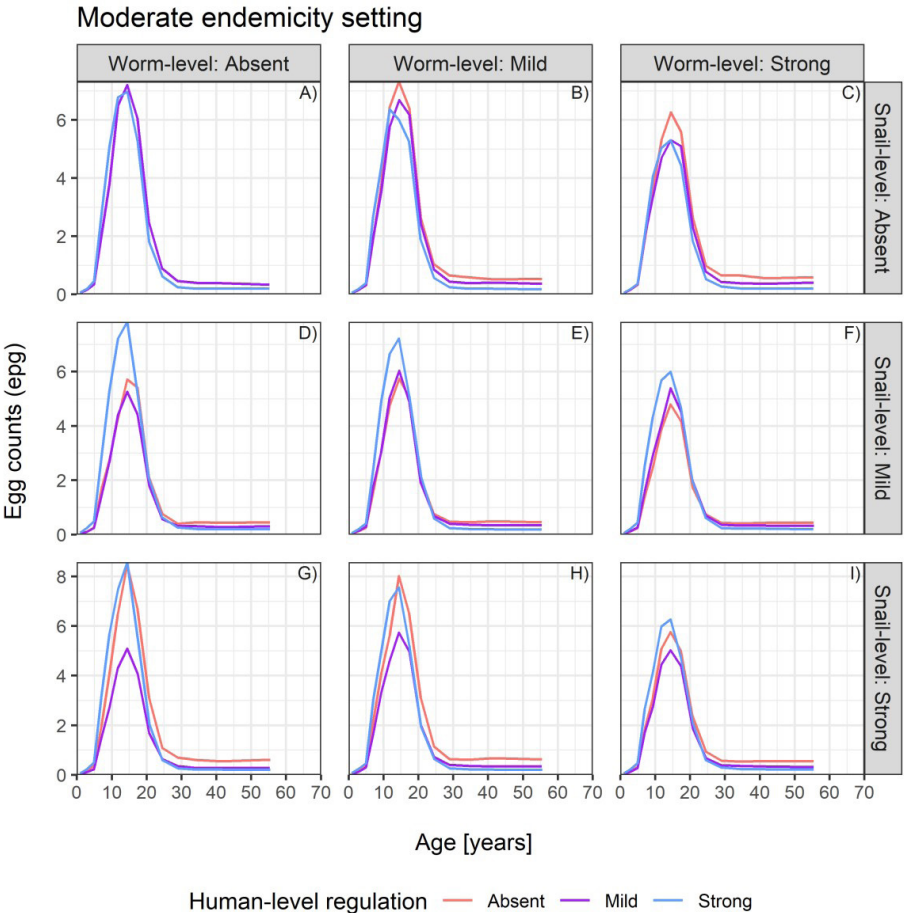
5.S1 Appendix

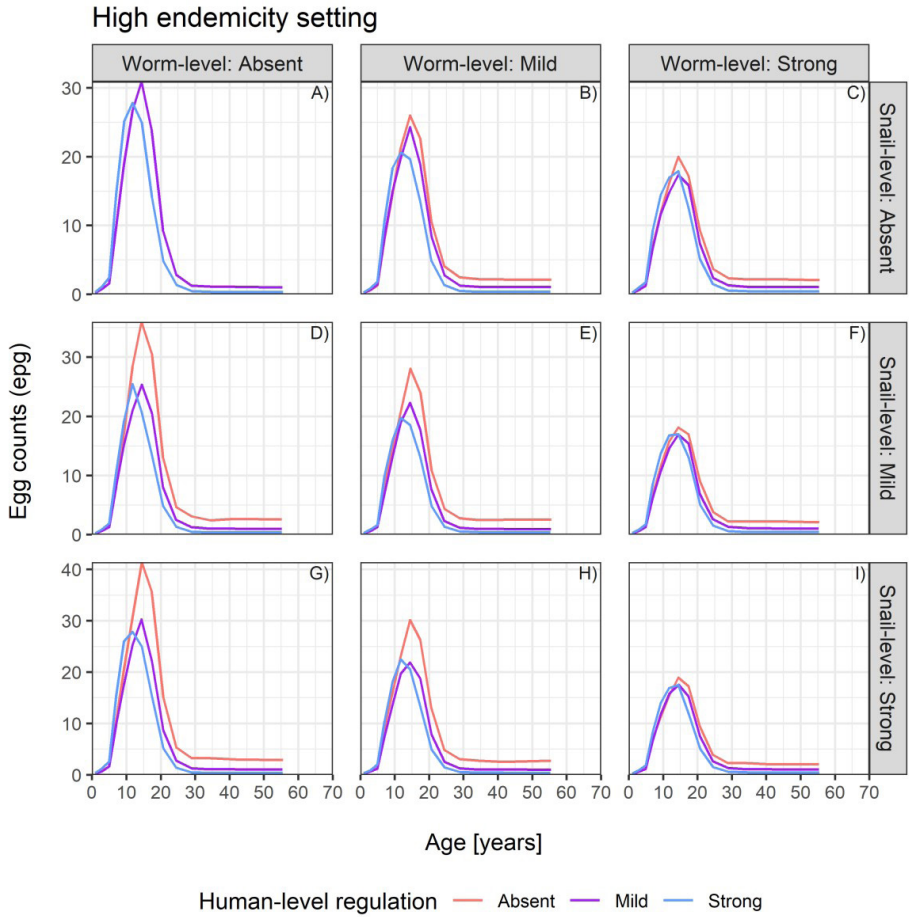
Age-intensity profiles

Age-intensity profiles for the complete set of modelling scenarios. For each choice of the ageexposure function and each endemicity setting (titles), single panels refer to a given combination of the assumptions of worm-level regulation via density-dependence in egg production ("Wormlevel", columns) and snail-level regulation via explicit snail modelling ("Snail-level", rows). Each line depicts results from a single model. The degree of regulation assumed at human level via anti-reinfection immunity ("Human-level") is highlighted with different colours, from Absent to Strong, according to the legend above each figure. A single panel shows the simulated egg counts on the y-axis (mean epg, over age group and 100 stochastic realizations of the model) by age on the x-axis. Age bins are defined as to all be equally sized.

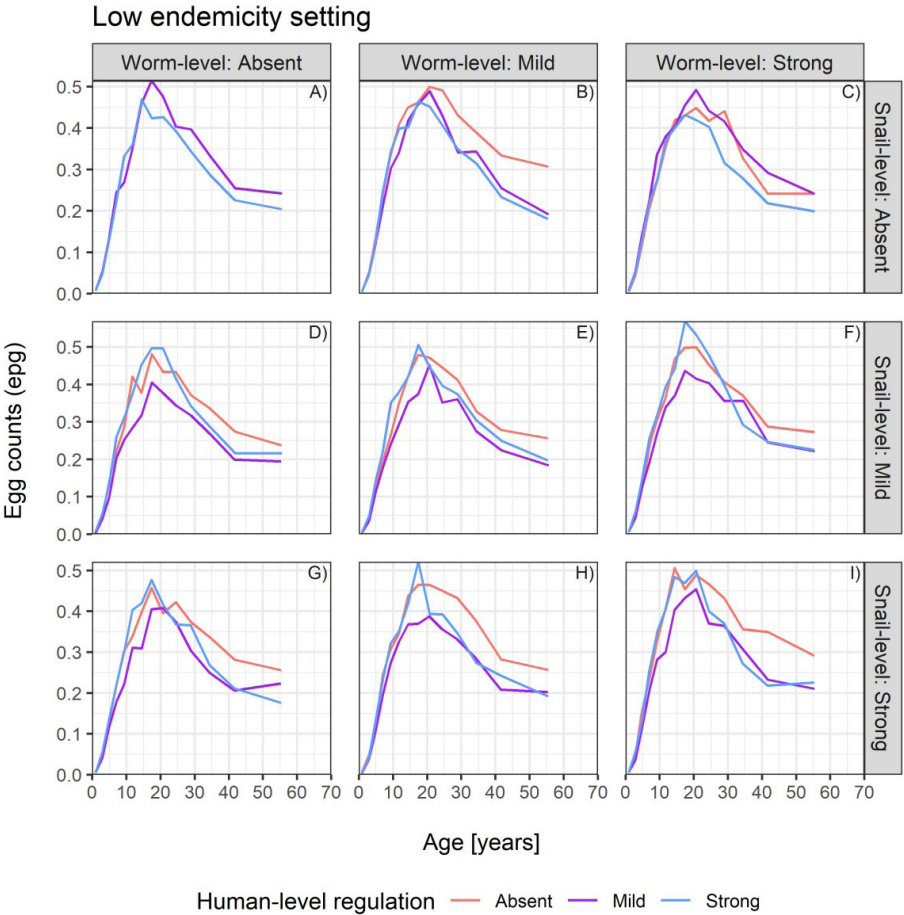
1. Assumption for the age-exposure function: "Model-based"

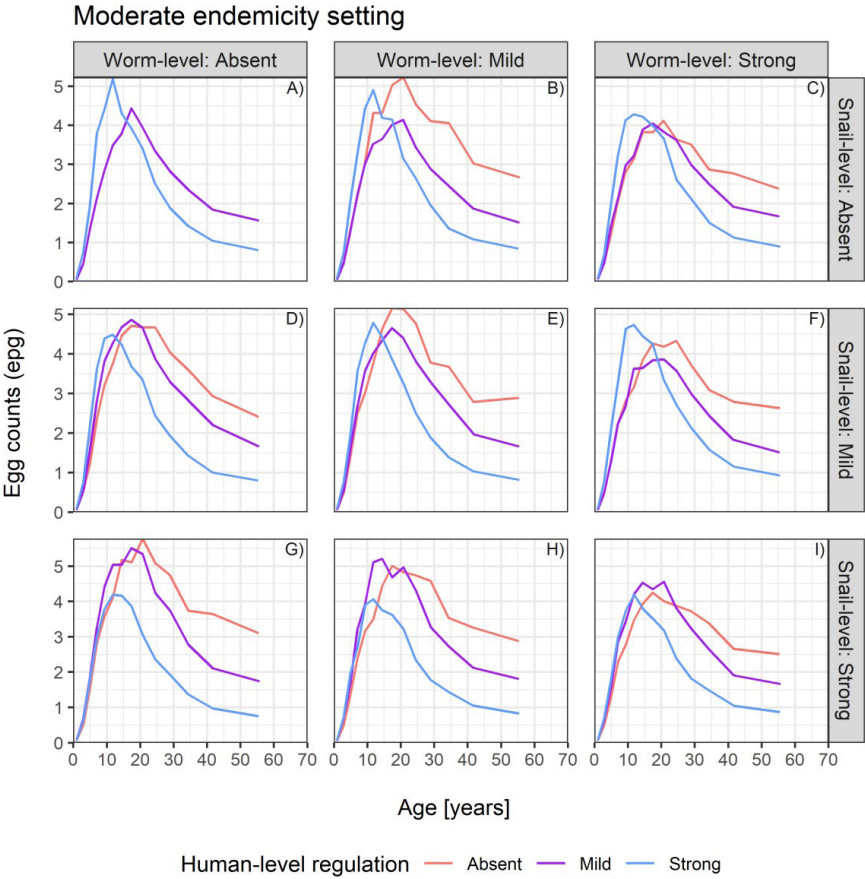


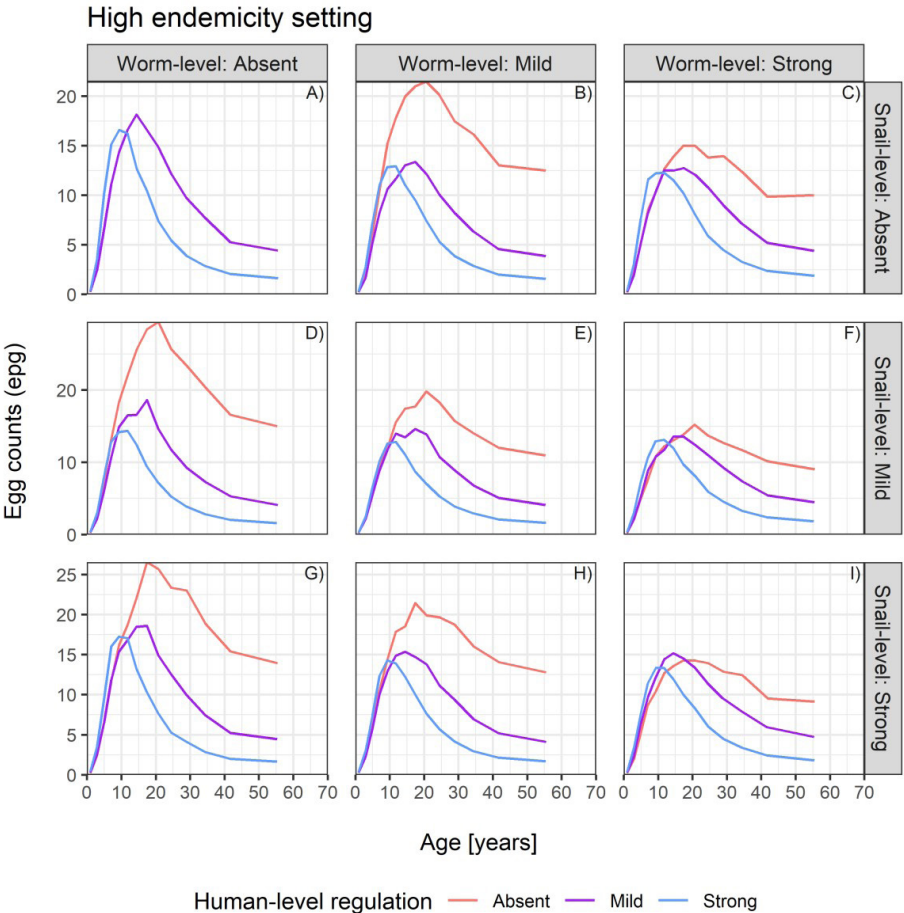




2. Assumption for the age-exposure function: "Based on water contacts"







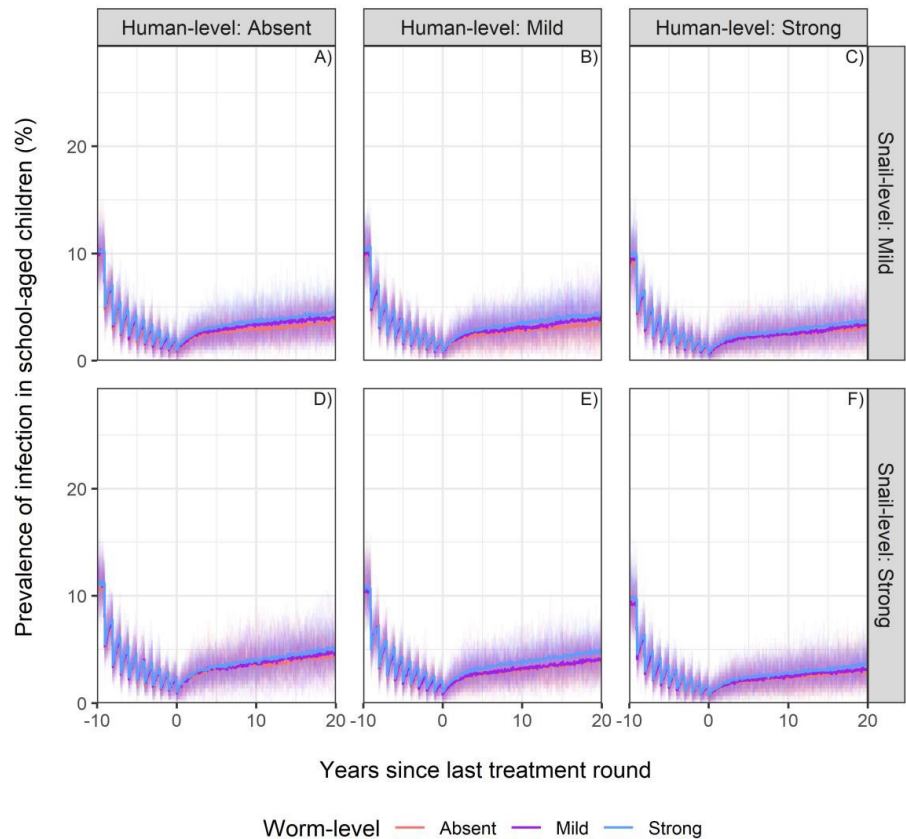
5.S2 Appendix

Effectiveness of treatment and prevalence bounce-back

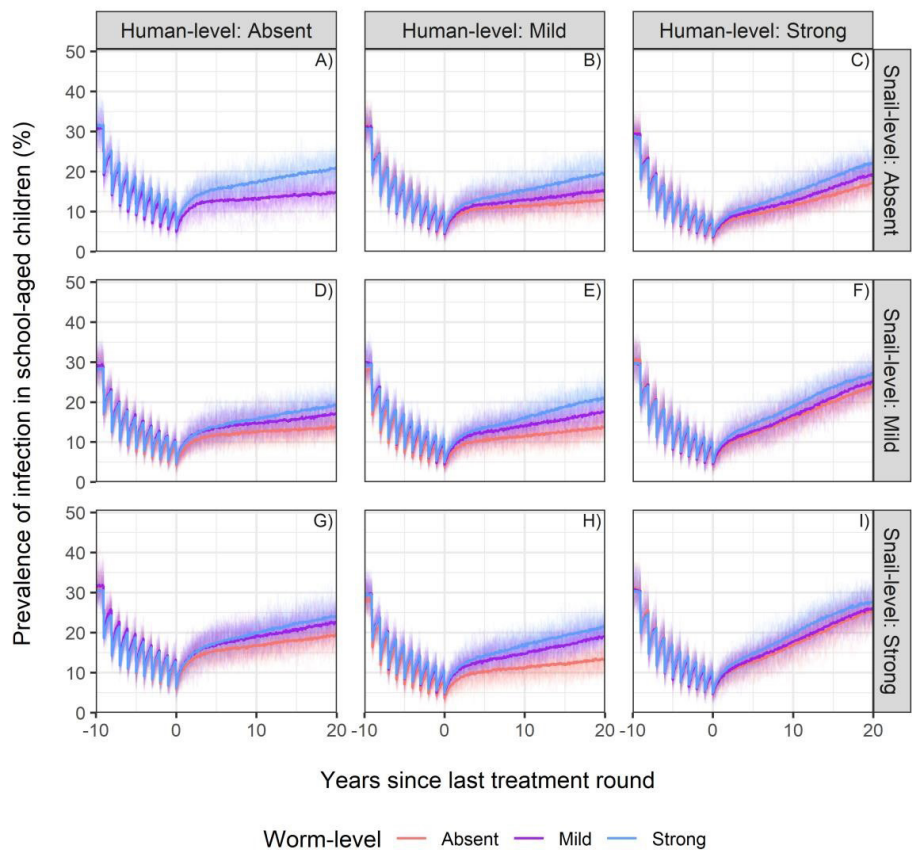
Prevalence timelines in SAC during and after treatment. For each choice of the age-exposure function and endemicity setting (titles), single panels refer to a given combination of the assumptions of human-level regulation via anti-reinfection immunity ("Human-level", columns) and snail-level regulation via explicit snail modelling ("Snail-level", rows). The degree of regulation assumed at worm level density-dependence in egg production ("Worm-level") is highlighted with different colours, from Absent to Strong, according to the legend above each figure. A single panel shows the infection prevalence in school-aged children on the y-axis (mean of 100 stochastic realizations of the model, single runs as shaded lines) by round of treatment on the x-axis. For all scenarios, treatment is annually administered to 5-15 years old individuals with 10 repeated rounds, a coverage of 75% of the target population, 5% of target population systematically untreated, and a drug efficacy of 86%.

1. Assumption for the age-exposure function: "Model-based"

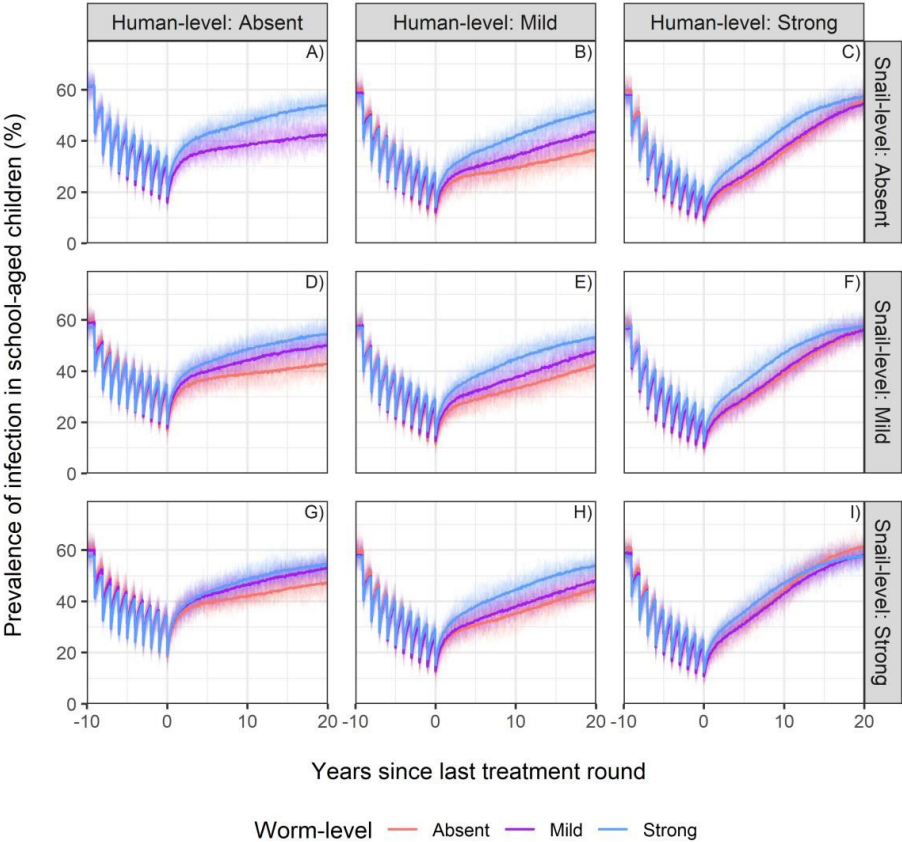
Low endemicity setting



Moderate endemicity setting

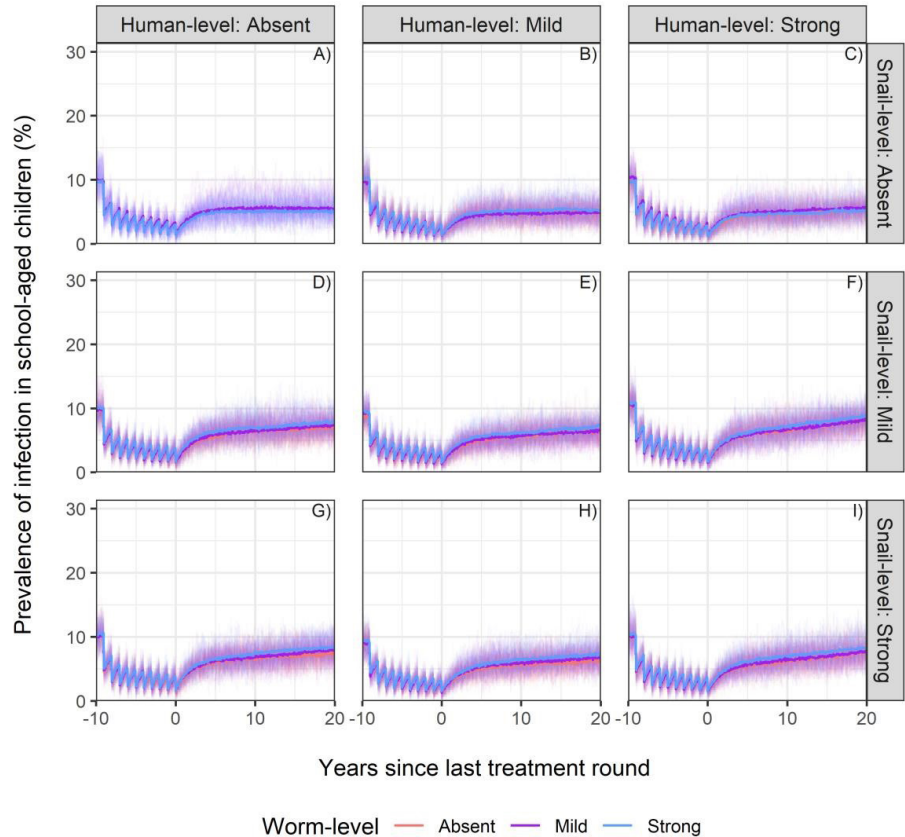


High endemicity setting

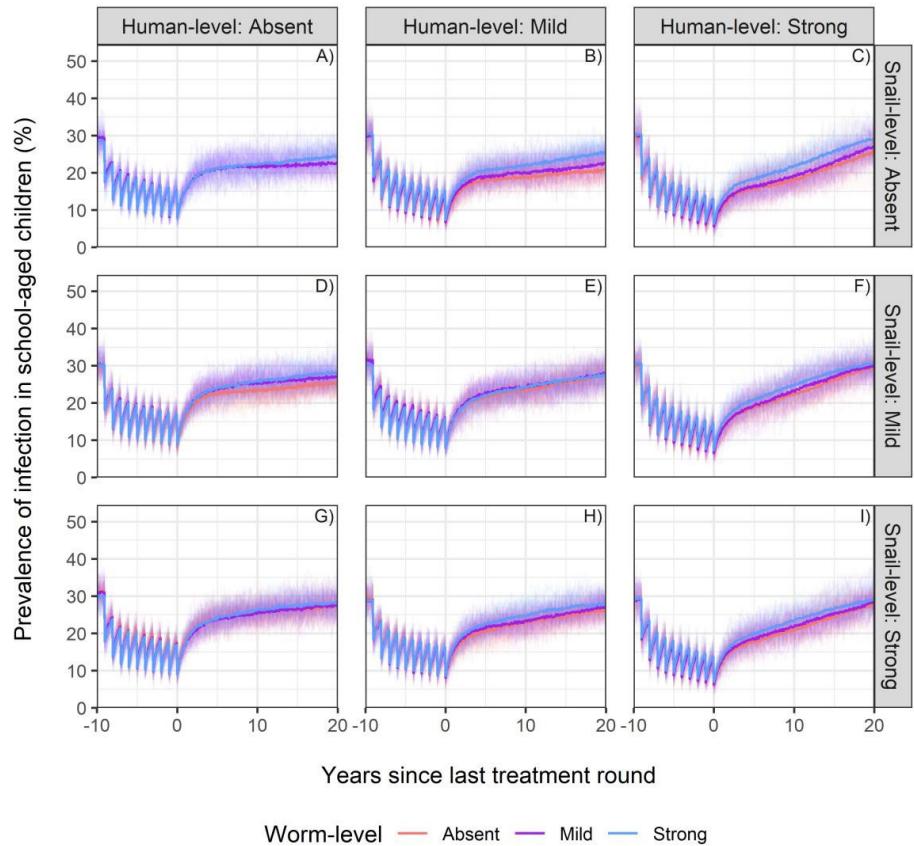


2. Assumption for the age-exposure function: “Based on water contacts”

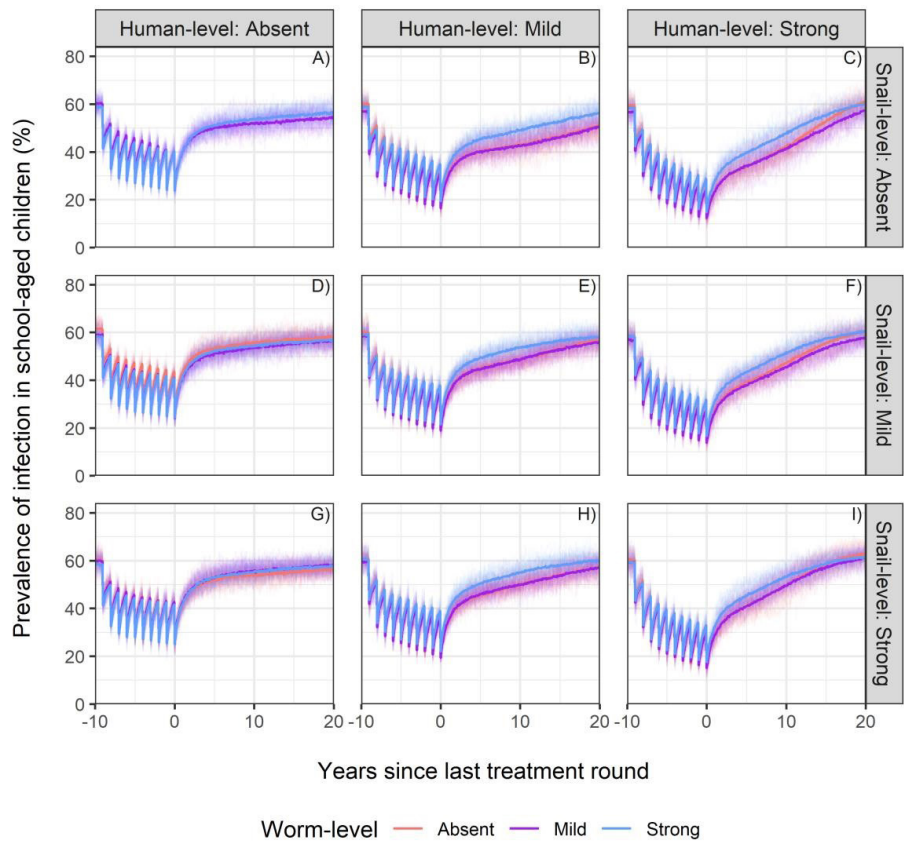
Low endemicity setting



Moderate endemicity setting



High endemicity setting



5.S3 Appendix

Sensitivity analysis varying drug efficacy

We performed a sensitivity analysis of the drug efficacy (in the model defined as portion of adult worms killed by MDA with praziquantel), by varying the parameter between two values: 80% and 90%. The value of 86% used for the main analysis falls in this range.

For each choice of the parameter, we ran all the models as described in the “Simulations” section of the main text. We further computed the probability for each model to reach elimination as a public health problem (EHP) and interruption of transmission.

Feasibility to reach the control targets

In line with the results described in the main text, successful models can still differ in their predictions of probability to reach the control targets, despite reproducing similar epidemiological patterns in terms of pre-control age-intensity profiles and bounce-back of prevalence after treatment. Results that follow include only such selected successful models (i.e. those that combined an age-exposure function based on water contacts with a mild or strong degree of regulation at both snail- and human- level), with the exception of the model based on only strong worm-level regulation and model-based exposure function, as current models for policy use the same assumptions.

Reaching control targets with 10-year annual MDA to school-aged children

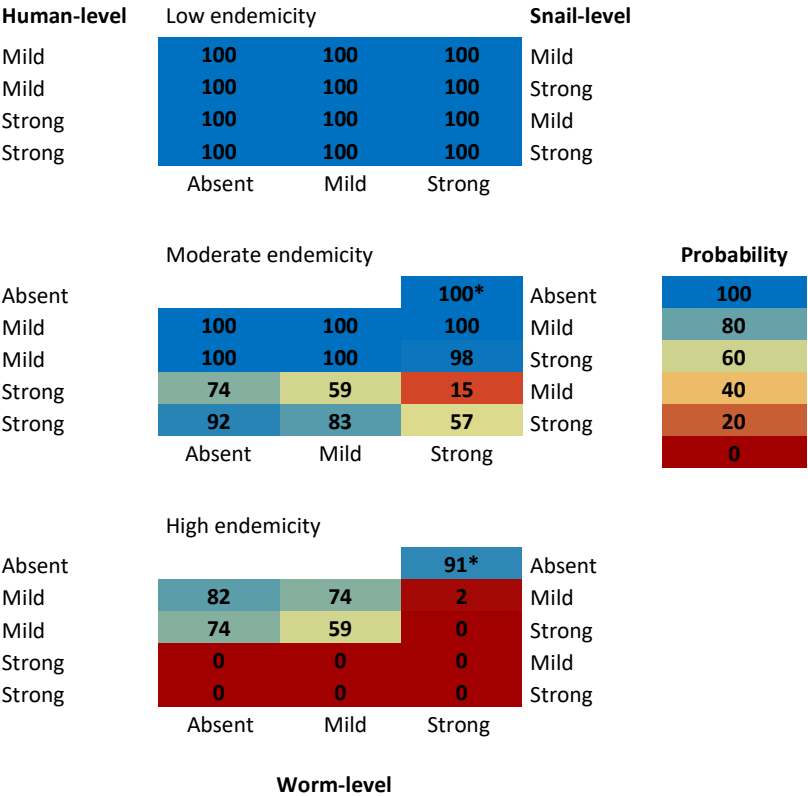
We found that all successful models agree that treating SAC only with 10 years of annual MDA will not allow to reach the EHP in high or moderate endemicity settings, irrespective of the value set for the drug efficacy. In low endemicities, we start from a setting where the prevalence of high intensity infection in SAC is already below 10% (EHP has already been met). Here, the target of interest is the IOT and none of the models predict a positive probability to reach this target despite 10 rounds of annual MDA to SAC. Results are different for the model assuming only strong worm-level regulation and the model-based exposure function, used here as reference for common assumptions. In fact, this model predicts a probability of 76% to reach EHP in moderate endemicity setting, if drug efficacy is 90%.

The impact of community-wide annual MDA

The figures below report the predictions to the control targets assuming a strategy of community-wide annual MDA, by varying the parameter of drug efficacy. The main effect of varying the drug efficacy is a decline or an improvement of the MDA effectiveness. This is reflected in the absolute predictions which can differ from the figures in the main text. However, the trend across models with varying regulating assumptions is not impacted, supporting the main message of this study.

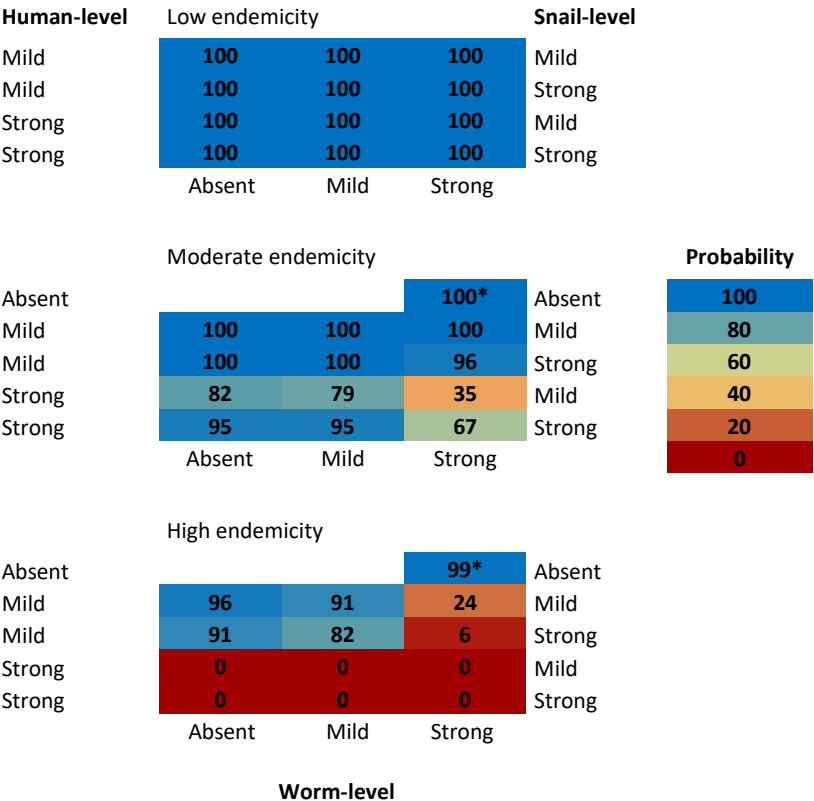
Worm killing rate = 0.8

Probability to elimination as a public health problem



Worm killing rate = 0.9

Probability to elimination as a public health problem



Probability to reach elimination as a public health problem with a 10-year annual MDA to all individuals older than 2. The figure reports predictions for the probability (portion of the 100 stochastic runs monitored at 20 years after end of treatment) of reaching elimination as a public health problem (EPHP, prevalence of heavy infections in school-aged children < 10%), across models successful in reproducing all observed patterns for schistosomiasis. Successful models assume an age-exposure function based on water contacts. Regulating mechanisms can be at human-level ("Human-level", left side, via anti-reinfection immunity), snail-level ("Snail-level", right side, via density-dependence in population growth), and worm-level ("Worm-level", bottom, via density-dependence in egg production). *This model assumes a strong worm-level regulation only and the model-based age-exposure function. It was not successful in reproducing observed patterns within our modelling framework, but it is added here for reference as current models for policy use the same assumptions. For all models, treatment is annually administered to 2+ years old individuals with a 75% coverage of the target population, 5% of target population systematically untreated, and a drug efficacy of 80% and 90% in the top and bottom figure, respectively.

Worm killing rate = 0.8

Probability to interruption of transmission

Human-level	Low endemicity			Snail-level
Mild	57	51	50	Mild
Mild	62	55	45	Strong
Strong	34	32	27	Mild
Strong	45	31	35	Strong
	Absent	Mild	Strong	

Moderate endemicity			
Absent			1*
Mild	0	0	0
Mild	0	0	0
Strong	0	0	0
Strong	0	0	0
	Absent	Mild	Strong

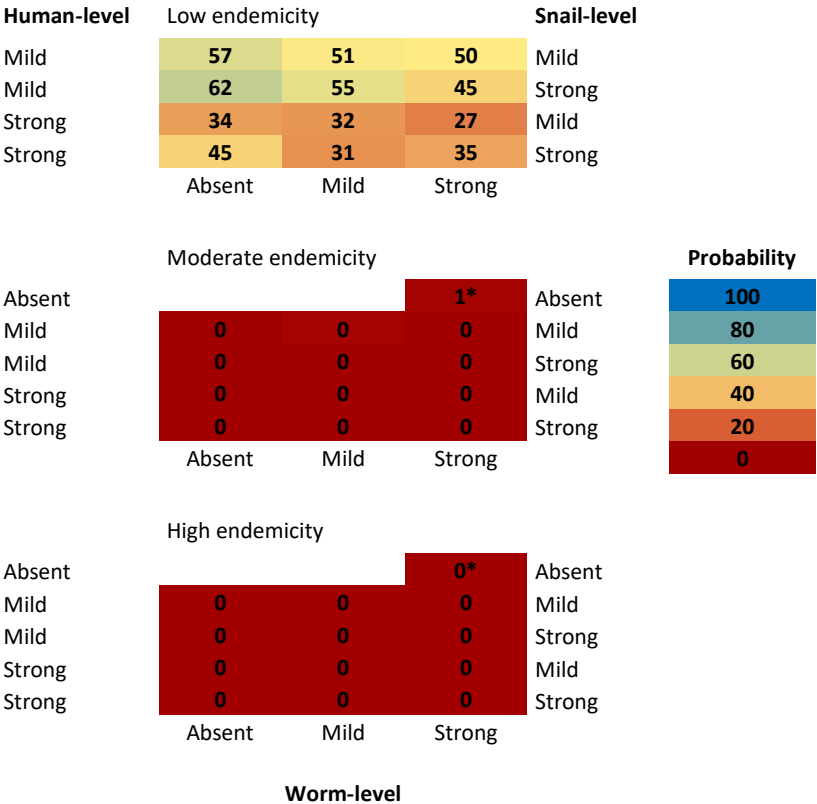
Probability	
Absent	100
Mild	80
Strong	60
Mild	40
Strong	20
	0

High endemicity			
Absent			0*
Mild	0	0	0
Mild	0	0	0
Strong	0	0	0
Strong	0	0	0
	Absent	Mild	Strong

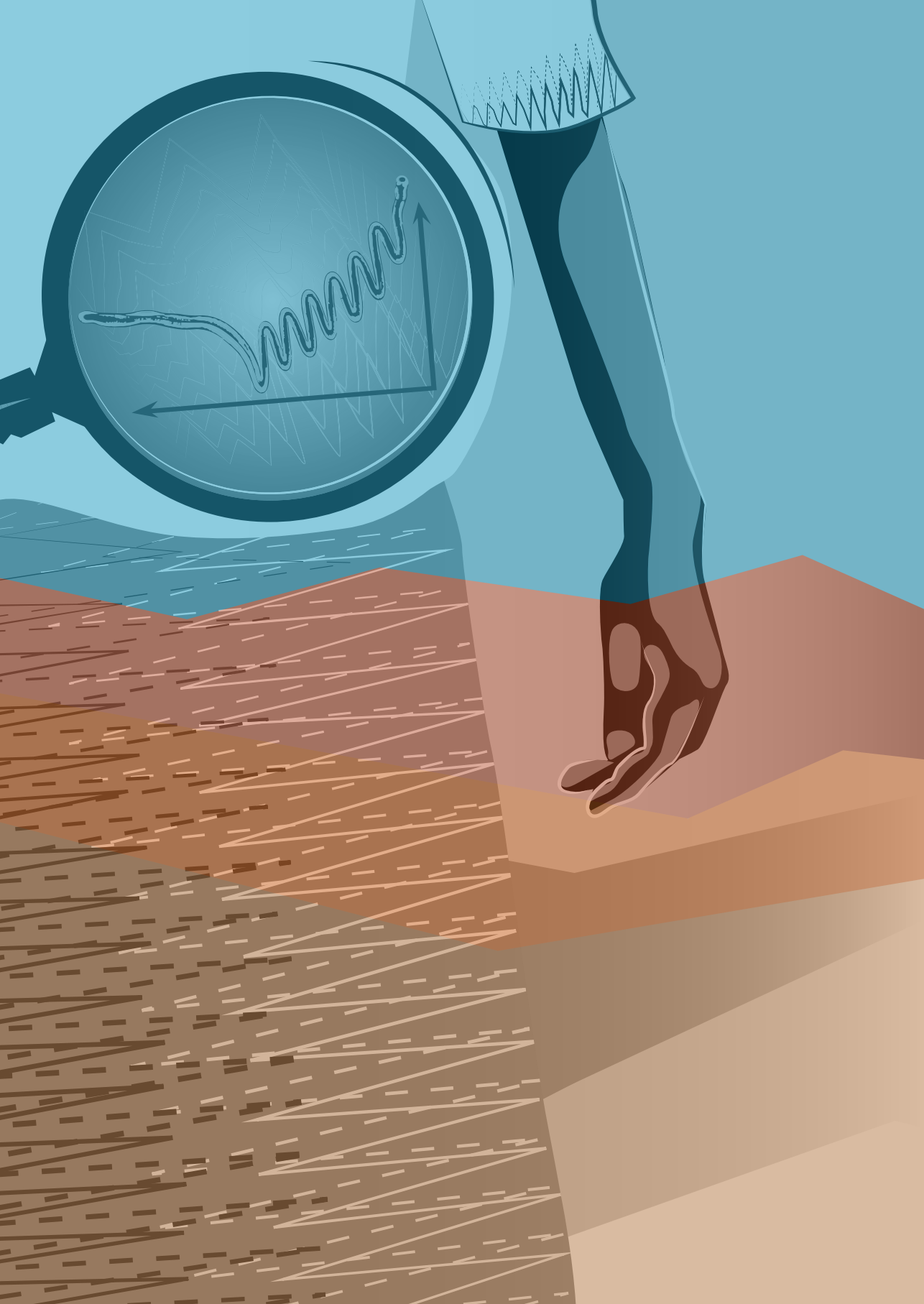
Worm-level

Worm killing rate = 0.8

Probability to interruption of transmission



Probability to reach interruption of transmission by 10-year annual MDA to all individuals older than 2. The figure reports predictions for the probability (portion of the 100 stochastic runs monitored at 20 years after end of treatment) of reaching interruption of transmission (0% prevalence of any infection in school-aged children), across models successful in reproducing all observed patterns for schistosomiasis. Successful models assume an age-exposure function based on water contacts. Regulating mechanisms can be at human-level ("Human-level", left side, via anti-reinfection immunity), snail-level ("Snail-level", right side, via density-dependence in population growth), and worm-level ("Worm-level", bottom, via density-dependence in egg production). *This model assumes a strong worm-level regulation only and the model-based age-exposure function. It was not successful in reproducing observed patterns within our modelling framework, but it is added here for reference as current models for policy use the same assumptions. For all models, treatment is annually administered to 2+ years old individuals with a 75% coverage of the target population, 5% of target population systematically untreated, and a drug efficacy of 80% and 90% in the top and bottom figure, respectively.



Chapter 6 Challenges of calibrating complex models of schistosomiasis: applying history matching with emulation to SchiSTOP

This chapter is in preparation for submission:

Veronica Malizia, Danny Scarponi, Maurice Mutro Nigo, Patrick Hunziker, Kit C.B. Roes, Federica Giardina

Abstract

Calibration of infectious disease models is crucial for improving accuracy of model predictions and delineation of public health interventions. Mathematical models have been historically used to support policy guidelines for the control of helminths infections. SchiSTOP, a stochastic agent-based model simulating the transmission dynamics of *Schistosoma mansoni*, provides a detailed representation of the parasitic infection dynamics involving human hosts and intermediate hosts, i.e. freshwater snails. However, its computational complexity, typical of stochastic agent-based approaches, poses significant challenges for parameter calibration, especially when the parameter space is large. This study applies history matching with emulation to SchiSTOP to efficiently explore the parameter space, while limiting computational demands and accounting for various sources of uncertainty. History matching is a calibration method that makes use of simplified surrogate models (emulators), trained to reproduce inputs-outputs from the full model to iteratively narrow down parameter spaces, until a non-implausible region of parameters is possibly identified.

We applied history matching with emulation to SchiSTOP to match epidemiological data from the Ituri Province, Democratic Republic of Congo. We first provided aggregated data on school-aged children (SAC) to explore the parameter space and then incorporated data over the whole population aggregated by five age groups. The reason for this choice was to investigate what types of data are most informative for improving parameter estimation and therefore accuracy of model predictions. The method identified key parameters, such as transmission rates and degrees of regulating mechanisms as primary drivers of emulators for model outputs. Although the results highlight the challenges in fully identifying the full set of parameters, we show how the model behaves across a large parameter space, which parts of the parameter space are definitely inconsistent with the data, and how the uncertainty in model parameters is propagated into model outcomes. Age-stratified data was crucial for reducing the uncertainty of the emulators and the non-implausible parameter region, therefore improving model predictions of prevalence and intensity at older ages.

Our findings underscore the challenges of efficient calibration of computationally intensive ABMs, like SchiSTOP. The study also illustrates the critical role of data richness, collected beyond SAC, and systematic calibration

frameworks to improve the reliability of schistosomiasis transmission models used for policy support. Future work should consider calibration on pre- and post-control data to further enhance SchiSTOP applicability in public health decision-making.

6.1. Introduction

Mathematical models are widely employed for elucidating the dynamics of infectious diseases and guiding public health interventions. By simulating transmission dynamics, and intervention strategies, these models provide insights that can inform policy decisions and optimize control programmes. Infectious disease modelling has been particularly beneficial in the fight against schistosomiasis, a major neglected tropical disease (NTD) caused by the intestinal parasite of the *Schistosoma* species [1]. This disease of poverty has a significant impact on global health, despite the limited resources for prevention and treatment available in some endemic areas. With 251.4 million of individuals requiring treatment in 2021 [1], close to 800 million are considered to be at risk [2]. Over time mathematical modelling has contributed to reproduce and understand the complicated transmission cycle of schistosomiasis, and to predict the impact of interventions such as campaigns of mass drug administration (MDA), as well as the probability to reach control targets [3]. Modelling results have been included in the most recent World Health Organisation (WHO) guidelines for schistosomiasis control [4] to evaluate the level of scientific evidence supporting each recommendation.

One class of models that has gained prominence in recent years is agent-based models (ABMs). ABMs offer a flexible and detailed framework for simulating the behaviour of individual agents (e.g., hosts, vectors, or pathogens) and their interactions within an environment, allowing for more realistic representations of disease transmission dynamics. This is particularly valuable for modelling diseases such as schistosomiasis, where transmission depends on heterogeneous interactions between humans and contaminated water bodies. Moreover, the transmission cycle is complicated by the presence of an intermediate host, namely freshwater snails [5]. The individual burden of worms harboured in the human intestine is the variable of interest to track the intensity of the disease in the human population, which is only indirectly observed via expulsion of parasites' eggs in the human excreta. ABMs have proven ideal to track individual worm burdens in age-structured populations and to include individual heterogeneities in exposure and contribution to infection [6-8]. Intervention scenarios targeted at specific age groups and subcategories can be directly modeled with the aim to provide scenario-specific probabilities to reach the WHO control targets [9-11].

However, the power and credibility of these models hinge on accurate parameter estimation, which can be extremely challenging due to the inherent

complexity of disease dynamics and the stochastic nature of many processes leading to transmission [12]. The large number of parameters, often related to biological and epidemiological processes, combined with the computational demands of running such models, make the calibration task computationally expensive. A recent systematic review has screened calibration methods of ABMs [13] used in epidemiological research on HIV, tuberculosis, and malaria. They have found that less than half of the studies employed formal, reproducible calibration methods, with the remaining studies relying on informal or non-reproducible approaches.

A major obstacle in calibrating complex models like stochastic ABMs is the absence of an explicit likelihood function, which prevents the direct application of classical statistical methods such as maximum likelihood estimation or fully Bayesian inference. To address this problem, several calibration techniques have been developed to either approximate the likelihood or circumvent it altogether, such as Approximate Bayesian Computation [14-16]. Moreover, complex stochastic models drag various sources of uncertainty inherent in the model stochasticity, in the model's imperfect approximation of reality, as well as observational uncertainty associated to the observed data. Uncertainty Quantification (UQ) is the discipline concerned with the identification, propagation, and analysis of uncertainties in models and data, and with assessing how these uncertainties affect model predictions and decisions [17]. Model calibration is a component of UQ, where observational data are used to quantify uncertainty in the model parameters. UQ methods through emulation reduce computational costs by approximating the model with a simpler surrogate model (emulator) trained on runs from the original simulator [18]. Among these innovative approaches, history matching with emulation has been proposed as a robust method for calibrating complex models, to favour parameter exploration when the likelihood is intractable, or the parameter space is too vast [19].

History matching with emulation, first introduced in the context of galaxy formation [20], is a method that iteratively narrows down the parameter space by comparing model outputs to observed data and discarding implausible parameter sets. Unlike traditional calibration methods that focus on finding a single "best-fit" set of parameters (quantify and constraint uncertainty), history matching with emulation works by systematically eliminating parameter combinations that are inconsistent with the data (eliminate implausible uncertainty), reducing the parameter space and returning a region of not-implausible values. This technique has been applied successfully

in various fields, including epidemiology [18, 21-23], where it has shown promising results in identifying non-implausible parameter sets via emulation, and improving model performance.

In this paper, we apply history matching with emulation to SchiSTOP [11], an agent-based modelling framework developed by our team to simulate the transmission dynamics of *Schistosoma mansoni*, the parasitic worm responsible for the intestinal form of schistosomiasis. While SchiSTOP has previously been used to investigate the influence of regulating mechanisms such as host immunity and snail ecology [11], its formulation is suitable to respond to diverse epidemiological research questions. However, several key epidemiological parameters remain uncertain, particularly those driving and limiting transmission. Many of these parameters are loosely informed by literature or expert opinion. Such uncertainty on the parameters and on available epidemiological data raises important research questions. How can observed epidemiological data be used to identify and exclude disease transmission scenarios that are incompatible with reality, in order to improve the accuracy of agent-based models used for public-health decision-making?

We address this research question by using history matching with emulation, implemented via the *hmer* R package, to match SchiSTOP to age-stratified epidemiological data. We aim to explore the model behaviour across the large parameter space and to understand how increasing data richness affects the identifiability of non-implausible parameters. We generate sets of non-implausible parameter combinations and assess how uncertainty in these parameters propagates through the model to affect predictions of intervention impact.

In doing so, we demonstrate how the calibration process itself, and the information available to inform it, can shape the credibility of model-based policy recommendations. Our findings also help identify which types of data (e.g., age-stratified infection prevalence and intensities) are most valuable for reducing predictive uncertainty. This aligns with recent calls to strengthen data collection for neglected tropical diseases, particularly through more granular and targeted surveillance that better supports modelling and intervention planning [24]. More broadly, this work illustrates how advanced UQ methods such as history matching with emulation can support the translation from mechanistic model development and outputs to actionable insights for schistosomiasis control programmes, while simultaneously informing strategies for more targeted and efficient data collection.

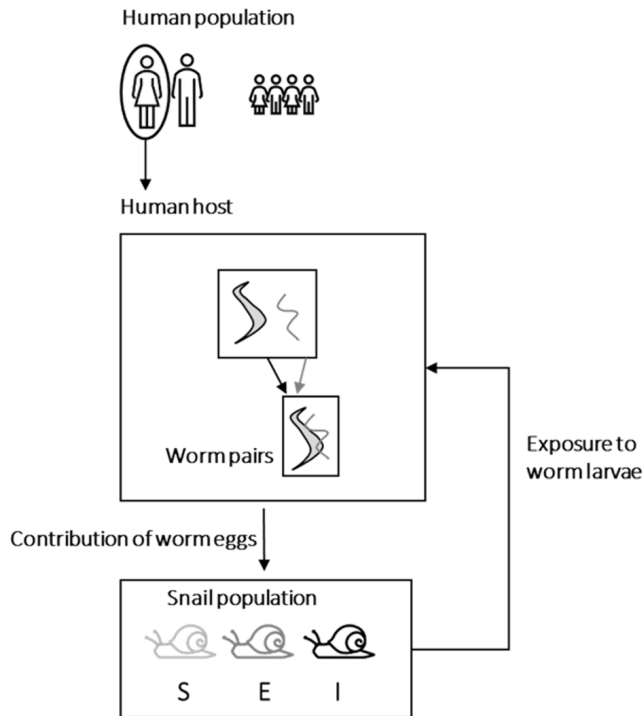


Figure 6.1. Schematic representation of SchiSTOP. An agent-based framework describes the age-structured human population that interacts with contaminated water environments. Humans are exposed to infection via parasitic larvae shed by infected snails, and further contribute to infection by excreting eggs that will hatch and infect snails. Life of worms is tracked within each human agent, including maturation, pairing, and reproduction. The infection dynamics within the intermediate host, i.e. freshwater snails, are described by a deterministic compartmental module according to a Susceptible-Exposure-Infected structure.

6.2. Methods

The transmission model - SchiSTOP

SchiSTOP is an agent-based stochastic modelling framework that replicates the transmission dynamics of *S. mansoni* between the human hosts and the contaminated water environment via larvae multiplication in the intermediate host (freshwater snails). In fact, the life cycle of this parasite is peculiarly complex, due to the presence of two reproduction phases. The first-stage larvae (free-living miracidia) contaminate water environments and invade certain species of freshwater snails. Asexual reproduction occurs in the snails, leading to the release of second-stage larvae (free-living cercariae). Humans

exposed to contaminated water can be infected by these cercariae through skin penetration. In humans, the parasites mature into adult worms, pair and reproduce sexually. Adult *S. mansoni* release eggs within the human host, which are then excreted through human faeces. The eggs released in the proximity of water sources hatch into miracidia and the cycle continues. The ecology of the snail population is explicitly modelled through a deterministic compartmental model that is integrated into the ABM. For a thorough description of the inner structure of SchiSTOP and the infection processes we refer elsewhere [11]. We focus this section on the core building blocks of the model and the delineation of the calibration task.

SchiSTOP is structured around five core components: the human population, the parasitic worms living in human hosts, two free-living larval stages in the contaminated water environment, and the snail population. A schematic representation of the model is displayed in **Figure 6.1**. The model incorporates dynamics of the human, worm, and snail populations through births, aging, and mortality. The ABM framework can capture sources of heterogeneities such as the process of worms' acquisition from the human host, an age-specific exposure to infection that accounts for individual patterns of contacts with water, and specific target groups for interventions. The distribution of worms in the human population is highly aggregated, with most of the population harbouring few or no parasites, and a few individuals harbouring high worm burden. The worm load in humans can be adequately described by a negative binomial distribution [25] with aggregation parameter capturing the overdispersion of worms. Worm pairs reproduce within the human host and their eggs are then released into the environment through faeces and contribute to the force of infection acting on snails. Diagnosis is commonly determined by examining stool samples for egg counts. The distribution of eggs shows high variation within (and between) stool samples. This distribution is also well represented by a negative binomial with aggregation parameter . SchiSTOP accounts for different mechanisms regulating *S. mansoni* transmission, acting at the level of the: i) parasite, ii) definitive host (human), iii) intermediate host (snail). Regulation at the parasite levels is assumed through the mechanism of density-dependence in egg production, where egg production by female worms decreases as adult worm burdens increase. At the level of the human host, the development of anti-reinfection immunity driven by dying worms regulates the intensity of the disease and therefore the transmission. Last, regulation is assumed at the level of the intermediate host, through explicit simulation of the snail dynamics via the

ODE system [11]. The implied depletion of susceptible snails and the assumed density-dependent population growth via the carrying capacity K , regulate transmission. The function describing the host exposure to infection by age is estimated using water contacts data and adapted from previous work [11] to align with recent empirical data from a large-scale study aimed to understand the complexity of water contacts [26]. The resulting function is described in **6.S1 Table** and plotted as **6.S1 Fig**. A full list of parameters employed in the simulations can be found in **6.S1 Table**.

The calibration method - History matching with emulation

History matching with emulation is a powerful iterative technique for complex models designed to systematically identify regions of the parameter space that are consistent with observed data. These will be defined as *non-implausible* up to the present iteration [22]. The method is particularly advantageous for computationally expensive models, as it reduces the need for extensive simulations by leveraging statistical emulators. These emulators must be seen as surrogate models that can approximate the behaviour of the model (the simulator), providing rapid predictions of outputs across the parameter space and quantifying associated uncertainties. We followed Goldstein approach [27] to build the emulators, i.e. using Bayes Linear statistics. The predictions produced by the emulators and the uncertainties are then utilized to compute a measure of implausibility for the model output at each parameter set. The implausibility measure quantifies the distance between the data and emulated model output by incorporating three terms of uncertainty: the emulator variance, the data variance (provided with the targets), the ensemble variability (the stochastic nature of the model), and a structural model discrepancy term (reflecting discrepancies between the observed reality and the mathematical approximation) [12]. The implausibility measure is used to discriminate non-implausible points in the parameter space.

The key steps of the algorithm are as follows for each iteration, here called *wave*:

1. **Defining the initial parameter space:** the process begins by specifying an initial plausible range for each parameter, informed by prior knowledge or expert opinion, determining an initial parameter space that is considered potentially consistent with the observed data. Worth of mention, history matching does not assume a probability density over the space, so the parameters ranges are treated as non-probabilistic bounds, not as prior distributions.

2. **Producing the training and validation set:** a representative sample of parameter combinations is drawn from the initial parameter space using a space-filling design, such as a Latin Hypercube or Sobol sequence. The full model (the simulator) is then executed for each of these parameter combinations, generating outputs that are used to train the emulator. The input-output data frame is split in training and validation set to build the emulators, ensuring adequate exploration of the parameter space.
3. **Building the emulator:** a statistical emulator is trained to approximate the relationship between input parameters and model outputs. The emulator provides fast predictions of both a mean and a variance for the model outputs, for any given set of parameters, significantly reducing the computational burden of exploring the parameter space.
4. **Emulator diagnostic:** the emulators are validated to ensure they accurately approximate the model outputs. Emulators that do not meet the diagnostic criteria are either adjusted to be more conservative or excluded from the current wave.
5. **Generating non-implausible parameter combinations:** the trained emulators are evaluated on a large number of parameter combinations in order to generate a set of non-implausible parameter sets. The algorithm discards the points with an implausibility measure above a chosen threshold, as considered implausible. This step systematically reduces the parameter space, focusing subsequent waves on regions of the parameter space more likely to produce outputs consistent with the observed data.
6. **Iterative step:** the reduced parameter space from one wave becomes the basis for the next. Steps 2 – 5 are repeated, with the training set updated and the emulator retrained as the parameter space becomes progressively smaller. Each wave refines the emulator's accuracy within the narrowed space, allowing for increasingly precise approximations of the model outputs.
7. **Convergence:** the process continues until the parameter space converges to a region where we get enough non-implausible parameters (i.e. matching all the targets) or until no further reductions can be made. After stopping criterion is reached, we run the full model for the parameter combinations within the remaining space and we select only those matching all targets to be used for analyses and prediction of reality.

We refer to technical documentation for detailed implementation of history matching with emulation, the structure of the Bayesian linear emulators, the available space-filling designs, and explanation of the stopping criteria [20, 21, 29, 30].

SchiSTOP calibration

Epidemiological data

This study made use of existent individual-level data collected in a field study from the Ituri province in the Democratic Republic of Congo. The data have been used and described in a previous publication [31]. We filtered the data from the two community-based studies carried on in 2017, which comprised 707 participants from 12 randomly selected villages in Ituri Province. The data selected for the scope of this study report the age of participants, geographical information, and the two individual *S. mansoni* egg counts measured using two smears from one stool sample per participant, then analysed via the Kato-Katz (KK) diagnostic method.

Parameters and prior ranges

For the calibration task, we identified 8 input parameters that were to be varied within the history matching algorithm according to ranges informed by literature, previous analyses, or data-driven (**Table 6.1**). Among the eight input parameters, three are transmission parameters which can be tuned to identify different endemicity levels [11]: the overall transmission parameter ζ , which is proportional to the force of infection acting on humans, the level of worm aggregation k_w in humans, and a transmission parameter η acting on snails. Furthermore, three input parameters modulate the strength of the regulating mechanisms: the level of exponential saturation z of eggs production, the anti-reinfection immunity coefficient α_{imm} which dictates the level of protection from consecutive reinfections, and the snail carrying capacity K driving the regulation due to the snail population dynamics. The remaining input parameters are the worm fecundity parameter α , which defines the expected number of eggs/worm pair/stool sample, and the level of aggregation (k_e) for the distribution of observed egg counts upon diagnostic. To inform the range of k_e to be explored by history matching, we used a data-driven approach. To this aim, we replicated the process of egg production in a simple Bayesian hierarchical model implemented in JAGS [32], describing how observed egg counts are linked to the latent worm burdens. For each individual, the (unobserved) number of worms is modelled with a negative binomial distribution that allows overdispersion across hosts. Egg counts are then linked to worm burden through a fecundity parameter. Each egg count observation is modelled as a negative binomial draw with its own overdispersion parameter to capture extra variability in counts observed in a duplicate sample per individual. By combining weakly informative priors on

the parameters and the negative binomial likelihood for worm burdens and egg counts, JAGS uses Markov Chain Monte Carlo to generate samples from the posterior distribution and quantifies uncertainty in the estimated parameters. The estimate of the (within-individual) variability in egg counts is then used to inform the range of for history matching (**Table 6.1**). For detailed information on the model specification and the role of the parameters we refer to a previous study presenting SchiSTOP [11].

Table 6.1. Input parameters for history matching. For each parameter, the table reports the range explored by history matching and used to construct the initial hypercube defining the region of parameters.

Parameter	Range	Source
Transmission parameter on humans ($\zeta > 0$)	[1e-05, 1]	[11]
Aggregation of worms ($kw > 0$)	[0.1, 1]	[11, 33, 34]
Snail transmission parameter ($\eta > 0$)	[5e-11, 5e-09]	[11]
Density dependence in egg production (z) [/ worm pair]	[0, 0.001]	[6, 11]
Immunity coefficient ($\alpha_{imm} > 0$)	[0, 0.1]	[11, 35]
Snail carrying capacity ($K > 0$) [number of snails]	[5000, 40000]	[11]
Expected number of eggs per sample ($\alpha > 0$) [eggs/worm pair/sample]	[0.05, 0.5]	[11, 34, 36]
Aggregation of observed egg counts ($ke > 0$)	[0.1, 10]	Data-driven

The calibration targets

We defined 21 calibration targets, provided to the algorithm with increasing information on the age of human individuals. One calibration target is the prevalence of infected snails. The rest of the targets, that are all related to the human population, describe: i) the prevalence of infection, ii) the prevalence of heavy intensity of infection (i.e. portion of individuals with more than 400 eggs per gram of faeces as detected by KK), iii) the average egg count, and iv) the average of the individual-level variance between the two KK measurements. These targets are defined for each age group. We considered five age groups: 0 – 4 years old (pre-school-aged children (pSAC)), 5 – 14 years old (school-aged children (SAC)), 15 – 29 years old, 30 – 49 years old, and 50+ years old.

For each target, we specified an interval for the algorithm to match (**6.S2 Table**). The intervals for the 21 calibration targets provide to history matching the observational uncertainty, they are to be interpreted as non-probabilistic bounds and were calculated as follows. For the 10 targets that describe a

prevalence measurement in humans, we calculated the Clopper–Pearson exact confidence interval, which is based on the binomial distribution and particularly useful when sample sizes are small or proportions are near 0 or 1 [37]. For the 10 targets that describe the within-group average of mean and variance egg counts, non-parametric confidence intervals were obtained by bootstrap resampling. Specifically, for each target, 1000 bootstrap samples were generated by sampling separately the individual-level mean egg counts and the variance egg counts with replacement, and calculating the mean for each resample. The 95% confidence interval was then defined as the 2.5th and 97.5th percentiles of the resulting bootstrap distribution of means. This approach does not assume normality of the underlying data and is suitable for small sample sizes. Eventually, the interval for the prevalence of infected snails was arbitrarily informed as used in a previous study [11]. In history matching, parameter sets were considered to match the targets if all the corresponding outcomes were between the upper and lower bounds of these targets. Description of each target and corresponding values can be found in **6.S2 Table**.

Use of the hmer package and training of the emulators

To perform history matching with emulation on SchiSTOP we used the R package *hmer* version 1.6.0 [29, 38]. We defined the initial parameter space by sampling 120 input points through Latin Hypercube sampling procedure [39]. We ran the full model for the 120 input points, considering 25 stochastic replications per each point and collated results to generate an input-output data frame further employed to build the emulators. Two-thirds of these points were designated as training points to build the emulators, while the remaining third served as a set of validation points to assess emulator performance and diagnostics. For each target, we built two emulators: one to estimate the expected value of the target (expectation emulator) and another to estimate its variance across stochastic runs (variance emulator). Capturing the stochasticity generated by SchiSTOP is a key objective. Providing multiple replications for each input point is essential to effectively train the variance emulators, which are used to better train the expectation emulators, by informing the component of the emulator uncertainty that reflects the stochasticity of the model. The well-trained expectation emulators are then used to generate a new set of non-implausible points, which serve as input for the subsequent wave. The algorithm generates these points using a Latin Hypercube Design, enhanced with line sampling to thoroughly explore the boundaries of the parameter space, and importance sampling to refine the search [22].

Across subsequent waves we progressively increased the number of input points up to 360 (see **6.S3 Table** for quantitative details about each wave) and the number of the stochastic repetitions up to 100 for each input point. This is shown to be an effective strategy to build increasingly precise emulators, which are trained on a progressively reduced parameter space. The input-output data frame was split such that 80% of the points were used to train the emulators of each calibration target, and 20% to validate them. History matching was iterated for a total of 17 waves, with increasing age-stratified information in the targets provided to the algorithm. Specifically, the first 8 waves were dedicated to build the emulators for the subset of 5 targets that include: epidemiological measures (prevalence and intensity of infection) in SAC, and prevalence of infection in snails. In the eighth wave, a total of 36,000 model simulations were run to produce the input-output data frame used to construct the emulators. The validation of the emulators was performed using the emulator diagnostics as described above. Visual inspection of such diagnostics allowed the discrimination of well-trained emulators (**6.S1 Appendix**). From a technical perspective, the validation of the emulators after seven waves revealed that only two points exceeded the threshold for the implausibility measure. This indicated that the non-implausible region would not undergo significant further reduction, as no more than these points would have been excluded in a next wave (**Fig. A1, 6.S1 Appendix**). From here, the decision to proceed by providing additional calibration targets followed. This was done in a gradual procedure, first excluding those targets for which history matching returned high values of implausibility measure, to allow the algorithm to zoom into the non-implausible parameter space, until all 21 targets were included. The training of the emulators was iterated from the parameter space already reduced and deemed non-implausible through the waves conducted in the calibration setting with fewer targets. In fact, the 5 targets used in the first waves represent a subset of the complete set of targets. The initial waves are then expected to include parameter points that are potentially fitting all 21 targets. Following this reasoning, the parameter region already refined based on the target intervals of the first setting should not exclude points that could be deemed non-implausible in the second scenario. However, one specific target, i.e. the mean of the individual-level variance of two egg counts in the age group [0, 5) (pre-SAC), remained problematic also at later waves, and therefore excluded from final inference. The quantity is in fact observed to be near 0 in pre-SAC, where most of the infections are of light intensity, this causing the algorithm to hardly extract information from the data to train the emulators for such target. After 17 waves we stopped the iterations. By

inspecting the diagnostics (**Fig. A2, 6.S1 Appendix**) and uncertainty of the expectation emulators, we concluded that additional waves would not have been beneficial. In fact, the emulators' uncertainty was not substantially reducing since the previous wave. Moreover, for the majority of the targets, the uncertainty of the emulators was lower than the uncertainty in the targets. In the last 9 waves, a total of 36,000 model simulations were run for each wave to produce the input-output data frame used to construct the emulators.

At the end of the last wave, the non-implausible region of points generated by the emulators was extracted. In this region, it was not possible for the algorithm to find full-fitting points, i.e. input points that produced outputs matching simultaneously all 20 desired targets. Given the high number of calibration targets, we then relaxed the intervals with a noise of ± 0.3 around the target bounds, and generated 136 non-implausible points (38%) that fall in such range, for further investigation with SchiSTOP. Specifically, we investigated the corresponding model outcomes in terms of the age-intensity function (i.e. mean number of egg observed per each age group), and timelines of prevalence pre-, during-, and post-control interventions. We assumed interventions to be deployed as mass drug administration to SAC, annually, with a 75% coverage of the target population and 5% of target population systematically untreated. The drug kills adult worm pairs within the human host with efficacy of 86%.

The analyses with the *hmer* package were run in R 4.4.1 [40], this included all the steps aforementioned, except for the running of the simulator (SchiSTOP). Simulations with SchiSTOP were needed i) in the calibration procedure, to produce the input-output data frame to train and validate the emulators at each wave), ii) to make inference on the simulation outputs produced by the non-implausible parameters. SchiSTOP was run on a single node on the SURF Snellius supercomputer [41], utilizing the Rome partition. The Rome partition is equipped with AMD EPYC 7742 processors, featuring 128 cores per node, and a base clock speed of 2.25 GHz, designed for high-performance parallel computing tasks. This configuration enabled efficient parallel execution of the computationally intensive model runs required for the study. The full code for the analyses is published online at <https://github.com/VeronicaMalizia/Efficient-calibration-ABM/tree/v1.0>. The repository includes the scripts to analyse data and calculate both the ranges of the parameters and the targets, the algorithm for history matching with emulation, the full specification of SchiSTOP adapted to run on HPC, the manipulation and plotting of the outcomes.

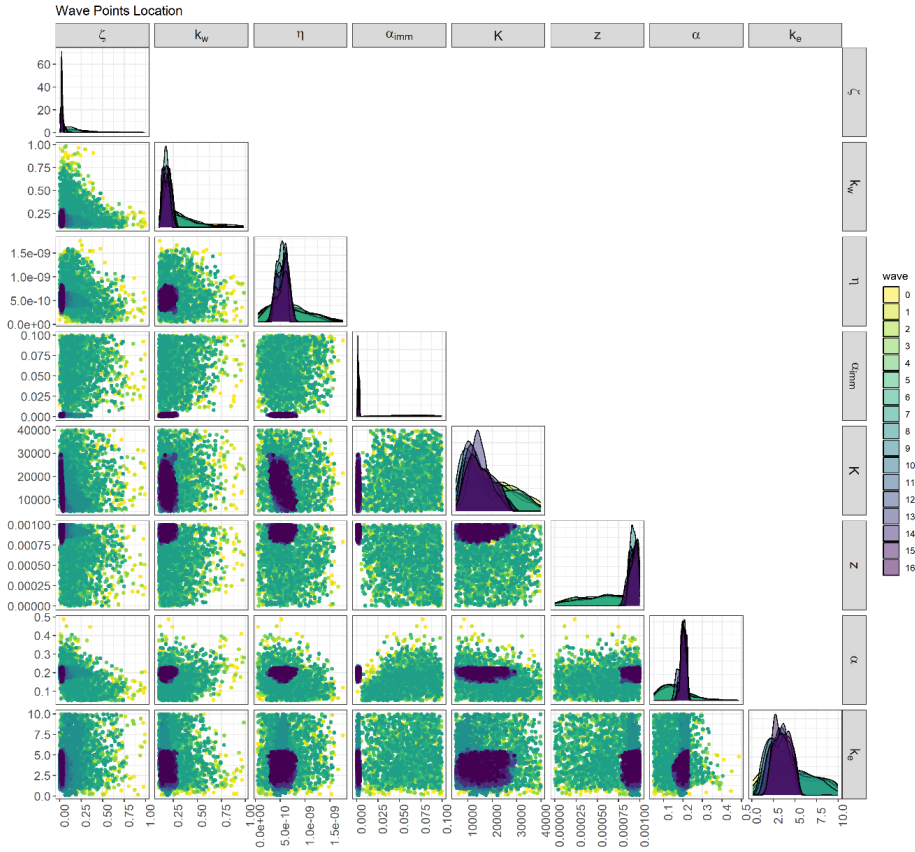


Figure 6.2. Scatterplot of input parameters, coloured by wave of history matching. Each group of points with the same colour represents the non-implausible region of parameters identified in the corresponding wave of history matching.

6.3. Results

Performance of the emulators

In general, the emulation process highlighted aspects of the model that reflect in most cases biological intuitions of the infection dynamics. We investigated in fact the relative contributions of all parameters to the expectation emulator, for each specific output, i.e. the regression surface (**6.S2 – 6.S4 Figure**). Results show that the transmission parameters (on humans ζ and on snails η) have a strong influence on all targets. This is not surprising, given their major role in driving transmission. Among the parameters reflecting the regulating

mechanisms, the carrying capacity of snails K (directly) and the immunity factor α_{imm} (inversely) contribute to the construction of the emulators for the prevalence and heavy prevalence across all age groups. As far as concerns the targets of mean and variance of egg counts instead, K and α_{imm} were found to mostly influence the emulators for the age groups of SAC and young adults (15 – 29 years old). The immunity mechanism has a major role in shaping the age-intensity profile at later ages, in the case where the age-exposure function is kept fixed, as in this exercise. To continue, the parameter of eggs aggregation k_e mostly contributes to the variance of the egg counts, especially in the age groups of SAC and young adults where most of the egg variability is captured. The rest of the parameters have minor influence on the construction of the emulators, with the level of exponential saturation z of eggs production ranking last. This suggests that the level of density-dependence in egg production has a minor contribution compared to the other regulating mechanisms considered here.

Analysis of the non-implausible region

The structure of the non-implausible final region after 17 waves is displayed in **Figure 6.2**. The figure shows the extent to which the input parameters are most restricted across the waves, as well as possible correlations. “Wave 0” refers to the initial space-filling sampling within the initial ranges, when the algorithm had not any knowledge about the data. For simplicity, we will call the waves with the number assigned by history matching, as in **Figure 6.2**. It can be noticed that history matching does not exclude any substantial region from the parameter space in the first 8 waves. Here, the emulators were built for the subset of five targets, i.e. the prevalence in snails, the prevalence and heavy prevalence in SAC, and the mean and variance of egg counts observed in SAC. This result implies that several combinations of parameters, which span over the whole region defined by the initial ranges, were all able to plausibly explain the given targets. The addition of information about the age groups other than SAC was crucial in extensively reducing the non-implausible region during waves from number 8 to 16. The three parameters driving the regulating mechanisms (α_{imm} , z , and K) spanned values that imply regulation from weak to strong, for each mechanism. At later waves, the algorithm excludes a large part of the region (higher values of α_{imm} and lower values of z) that would produce an extremely strong immunity mechanism and a too weak worm-level regulation (density-dependence in egg production). The favoured combinations results to better explain the relatively sustained peak of prevalence and intensity in the age groups [15-30) and [30-50) (repeated infections), while keeping low

high intensity prevalence (regulation in egg production). Moreover, we have previously shown that absent or weak immunity, given a fixed age-exposure function, not only implies sustained intensity at older ages, but a peak shift of egg counts to older ages [11]. The parameters controlling worm aggregation (k_w) and mean egg production (α) are usually well informed by the empirical literature. Accordingly, the ranges found with calibration (k_w : 0.11–0.27; α : 0.15–0.23) are consistent with values commonly used in previous modelling studies. The parameter describing the aggregation in egg counts is likely to fall in a range [1.44 – 5.44] that might be different than what currently found in modelling literature and what was used in the previous SchiSTOP study [11]. In fact, estimation of is here data-driven and only represents the variability between a duplicate KK test within the same stool sample, as available in the data used for the analyses. The within-sample variability is known to be much less if compared with the combination of within and between stool sample variability [34], as commonly captured in simulation studies. Overall, the final non-implausible region suggests that various combinations of parameters and interplay of regulating mechanisms can match the targets, with exclusion of combinations that would generate extremely strong immunity mechanism and a weak worm-level regulation.

Figure 6.3 is a visual representation of the simulator evaluations (the outputs generated with SchiSTOP) at points deemed non-implausible in the current wave. The plot illustrates how the simulator behaves across the range of input parameters, as the waves progress. Lines are coloured by wave of history matching and a single line represents the average of multiple stochastic replications (**6.S3 Table**), given the same input parameters. Calibration targets are included as grey bars for direct comparison. The waves are split in panels A) and B) according to the calibration setting with five or all targets, respectively. Due to high output variability and different scales, the targets are all displayed on a logarithmic scale. As the wave number increases, the ensemble of simulator runs from non-implausible points converges more closely towards the targets. Panel A) shows how the search moves from the initial region (wave 0, yellow lines) to match the first five targets until the end of wave 6. By gradually incorporating additional information from the remaining age groups, history matching further explored the non-implausible parameter space identified at the end of wave 6 to better align with the new targets. This process is illustrated in panel B), where the simulator outputs visibly converge toward the target ranges. In the initial waves of this panel (waves 7–10), the simulator tended to overestimate most of the targets, particularly the mean

and the variance of egg counts. As the process continued, the simulator outputs progressively narrowed towards the target ranges, initially underestimating them, before finally converging around the targets in the last two waves of history matching. In both panels, we note a flat line to vary low values. This represents the average of a simulation where all stochastic runs faded out. We also note lines that are consistently below the trend of the lines belonging to the same wave. These represent the average of model simulations where only part of the stochastic runs faded out. If the corresponding parameter set is considered non-implausible (e.g. because the simulator output does not cross any of the targets), the algorithm will exclude it from the next wave.

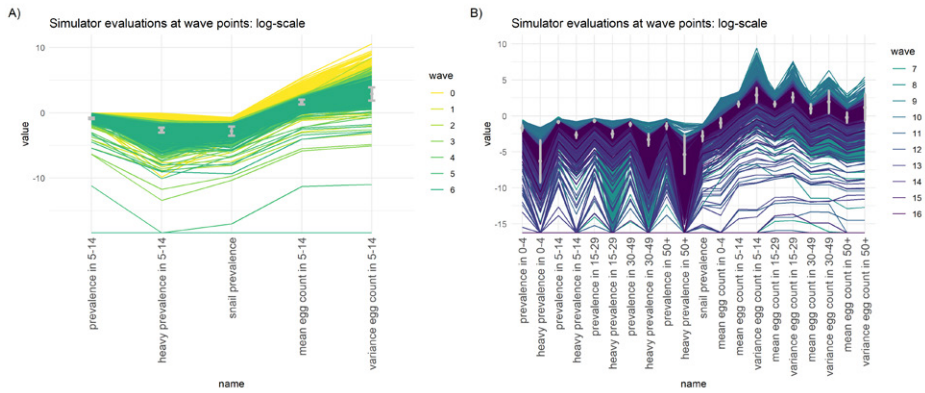


Figure 6.3. Simulator evaluations by wave. Outputs of model simulations, in terms of prevalence, and mean and variance of egg counts in specific age groups, coloured by wave. Each line represents the average of multiple stochastic seeds, up to 100. The first 7 waves of history matching are run with 5 targets and displayed in panel A). The following 10 waves, run with 20 targets, are displayed in panel B). All outputs are log-transformed for plotting.

Full-fitting points are defined as those parameter sets that produce simulator evaluations crossing simultaneously the ranges of all targets. At the end of the 17 waves, full-fitting points could not be found, i.e. none of the darkest blue lines in **Figure 6.3** simultaneously cross all targets ranges. The number of targets simultaneously hit per each evaluation was at most 17 out of 20 targets. However, the waves provided insights on which targets are more difficult to match or which targets are mutually incompatible under the current SchISTOP structure. A pairwise compatibility analysis is shown in **Figure 6.4** to assess which targets are mutually incompatible, revealing potential structural constraints in the model or data-model mismatches that can drive model or calibration refinements. The figure is a heatmap which displays the portion of model runs that, in wave 16, hit simultaneously target i and target j ,

where spanned over the full set of calibration targets used in the last wave. The heavy prevalence in the 30–49 age group resulted the most difficult to match in combination with all the other targets. The heavy prevalence in 50+ proved difficult to match in combination with the variance of egg counts in the 15–29 age group. Specifically, when the model matched the variance, the heavy prevalence in the older age groups tended to be underestimated; conversely, when matching the heavy prevalence, the variance was overestimated. This behaviour is in line with biological interpretation. In fact, mean higher variance in individual duplicate egg counts would result in a lower prevalence of heavy infections (i.e. individuals with a mean of duplicate egg counts > 400 epg). Conversely, a lower variance, given a relatively high mean egg counts reported in the data, would result in higher prevalence of heavy infections. Eventually, prevalence and heavy prevalence in older age groups (30–49 and 50+) seems incompatible with the prevalence at younger ages (5–15 and 15–29).

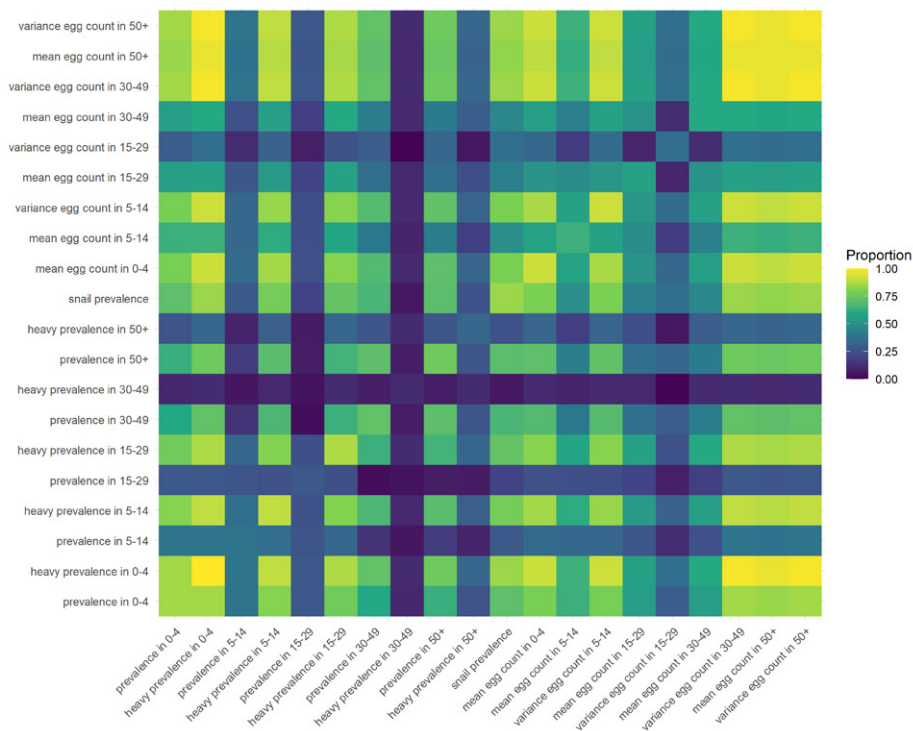


Figure 6.4. Heatmap of pairwise joint calibration across prevalence targets. For each pair of calibration targets, the colour intensity represents the proportion of model runs whose outputs fall within both corresponding target ranges. Diagonal cells report marginal acceptance rates for individual targets, indicating which targets might be problematic to identify full fitting points. Off-diagonal cells quantify simultaneous match of target pairs.

Predictions with SchiSTOP

To run predictions with SchiSTOP, we extracted 136 points from the non-implausible region generated in the last wave of history matching, which produce outputs close to the targets. These points constituted the input region of the parameters passed to SchiSTOP for simulations. The resulting region is displayed in **Figure 6.5** as pairs of parameters. On the diagonal, the density for each parameter is plotted, although it should be used for orientation only. History matching does not provide posterior distributions nor statistical summary, rather a multidimensional region of the estimated parameters. Each of these points was used to run 100 stochastic replications with SchiSTOP.

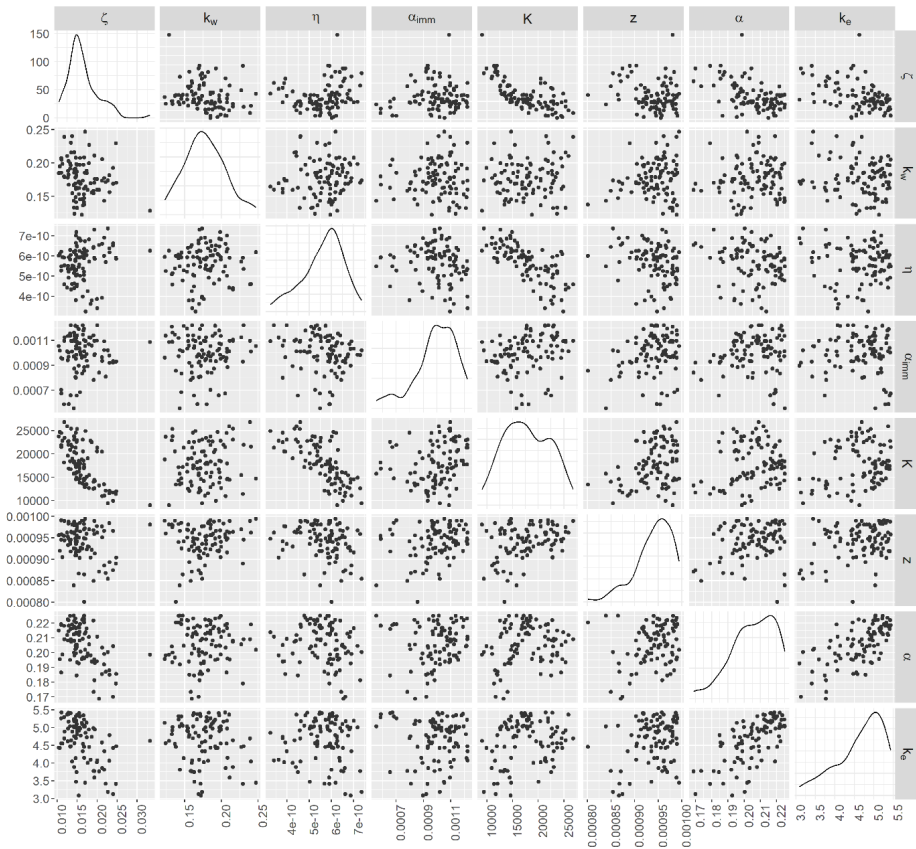


Figure 6.5. Region of input points used for predictions. The 136 input point provided to SchiSTOP for predictions are presented as pairs of observations. These are extracted from the non-implausible region generated during the final wave of history matching. Each point represents an input parameter set used for running 100 stochastic simulations with SchiSTOP.

We inspected the model behaviour across the space of the input parameters. Specifically, we plotted in **Figure 6.6** the mean egg counts simulated with SchiSTOP for each input point. The figure shows the age-intensity profile, i.e. the intensity of infection (arithmetic mean of egg counts) by age group. Each coloured line represents the average of 100 stochastic runs for a single input point. The black bars represent the target ranges (mean egg count per age group) used for history matching in this calibration setting. As said, target ranges in the context of history matching should be interpreted as a pure interval to match which incorporates observational uncertainty, without probabilistic assumptions. Overall, the input parameters reproduced the expected pattern, with infection intensity peaking in the 5–14 and 15–29 age groups, followed by a decline at older ages and reaching very low levels in the 50+ group. Although all simulations captured the general increasing–decreasing trend, some variability is observed around the peak: in some simulations, the peak occurred in the 5–14 age group, while in others it shifted to 15–29 years old.

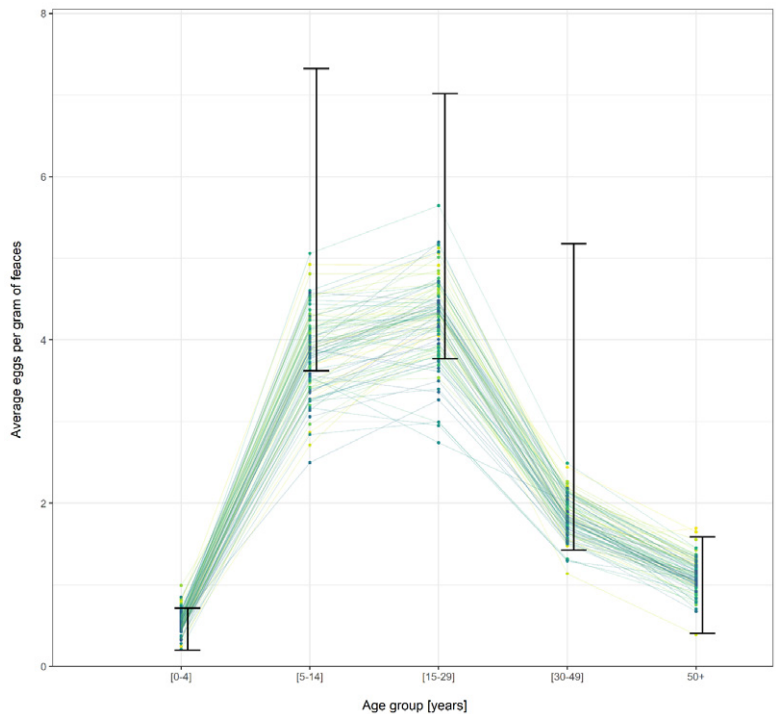


Figure 6.6. Age-intensity profiles for the complete input region. The arithmetic mean of observed egg counts (y-axis) are plotted by age group (x-axis), for all the non-implausible parameters extracted for predictions. Each line represents the average of 100 stochastic runs for a single input point. The black bar shows the targets ranges (mean egg count by age group) provided to history matching to generate non-implausible input points.

Furthermore, we examined the performance of SchiSTOP in terms of the prevalence of any infection and of heavy-intensity infection across age groups, as these were the targets used in the calibration task with history matching. The timelines for any and heavy prevalence by age group are shown in **Figure 6.7** and **6.S4 Fig**, respectively, plotted against time (expressed as years since the last treatment round). The figure shows the extent to which the outcomes generated by the non-improbable points cross the target ranges. Each line represents the mean of multiple stochastic simulations for a single parameter set (input point), while the black bars indicate the target ranges provided to history matching. For visualization purposes, the plotted average across stochastic simulations is computed only between the runs (out of 100) that bounce back after end of treatment, therefore not including those runs that reach elimination as a public health problem (EHP). The control target of EHP is assessed in the model as heavy intensity prevalence in SAC $\leq 1\%$ after 20 years since the end of treatment. However, the histogram of the probability to EHP, i.e. portion of stochastic runs that reach EHP across the parameter sets, is included in **Figure 6.7**, bottom-right panel. Overall, the simulations reproduced a plausible epidemiological setting to explain the observed data. The prevalence of infection in the age group [15-29] revealed the most difficult to match, with an overall underestimation by the model. A possible explanation is the constraint given by the age-exposure function used in the model, where the exposure declines after the peak at 15 years old, while a sustained high intensity of infection and prevalence is observed in young adults [15-29 years old] in the current dataset. As discussed earlier, one way for history matching to reproduce the relatively high prevalence and intensity in the 15-29 age group, which equals the measures observed in SAC, is to reduce the contribution of anti-reinfection immunity, while moving to high degree of worm-level regulation (density-dependence in egg production). These behaviours may help explain the slow rebound in prevalence observed after the end of treatment, a behaviour that has been explored in a previous study [11]. Overall, the predicted probability to EHP is high, as shown in the histogram. Despite the endemicity setting is moderate in this study (simulated SAC prevalence 30 – 45%, target range 38 – 47%, observed 42%), a relatively low prevalence of heavy intensity is reported in SAC (simulated 5 – 12%, target range 5 – 10%, observed 7%) at pre-control (**S3 Figure**). This, combined with a limited effect of human-level regulation via immunity, made the chance to reach EHP high. It is interesting to notice that, despite the parameter sets generated comparable trends in age-intensity profiles and prevalence timelines, they still produced a skewed distribution of probabilities to reach EHP.

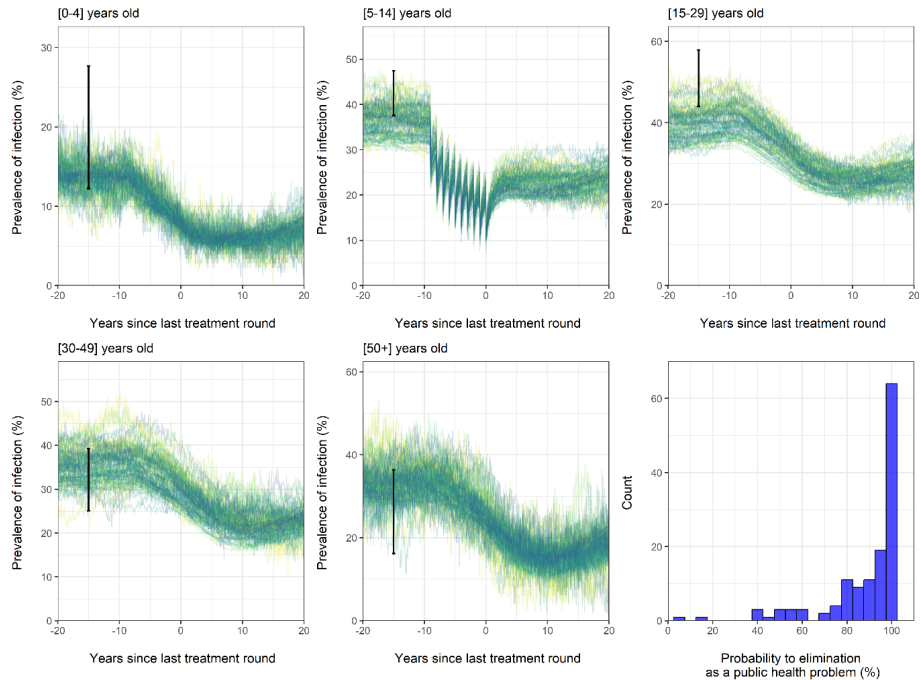


Figure 6.7. Timelines of prevalence of infection in different age groups. The timelines of prevalence pre-, during-, and post-control is plotted by age group, for all the non-implausible parameters extracted for predictions. Each line represents, for a single parameter set, the average of the portion of solely those stochastic runs (out of 100) that do not reach elimination as a public health problem (EPHP, i.e. heavy intensity prevalence in age group [5-14] $\leq 1\%$) after 20 years since the last treatment round. The black bars show the targets' range (prevalence of heavy infection per age group) provided to history matching to generate non-implausible input points. The bottom-right panel shows the histogram of the probability to EPHP, i.e. portion of stochastic runs that reach EPHP, across each of the parameter sets.

6.4. Discussion

This work presents a calibration exercise of SchiSTOP, an agent-based model (ABM) that reproduces transmission dynamics of *S. mansoni* in humans through explicit modelling of the intermediate host (freshwater snails). This study addresses parameterization challenges for complex models, such as ABMs, by exploring high-dimensional parameter space while limiting the heavy computational demand. The aim is to investigate which types of data and level of data aggregation are informative to identify and exclude regions of the parameter space that would generate model-data incompatibilities. The calibration task included parameters that are known to drive transmission,

but also epidemiological parameters commonly informed by literature. In fact, numerous processes are considered in ABMs for schistosomiasis, which combined with the aggregated nature of the age-specific data available and the highly overdispersed distribution of egg counts in the faeces, pose significant challenges for parameter identifiability. Eventually, the study explores the accuracy of model predictions across the space of the estimated parameters. To address these points, we used history matching with emulation as a calibration method to fit SchiSTOP on observed epidemiological data [31]. We then used the region of the parameters deemed by history matching as non-implausible to match reality, to run predictions with SchiSTOP.

Results demonstrated that the transmission parameters driving the force of infection (on snail η and on humans ζ) have an influence on model outputs stronger than other parameters shaping transmission, such as the aggregation of worms k_w and the mean worm egg output α . The transmission parameters are commonly tuned in simulation studies to reproduce transmission settings, while η and α usually have good empirical support. Our explorations showed that non-implausible values for k_w and α align with figures used in [11] and described in literature [34, 36]. Among the parameters describing the regulating mechanisms, the immunity factor α_{imm} and the carrying capacity of snails K are found to influence how well the emulators can be trained to reproduce the model outputs. Conversely, the parameter z responsible for worm-level regulation (density-dependence in egg production) has less influence on the performance of the emulators. History matching showed that multiple combinations of the parameters and various interplay of regulating mechanisms can reproduce the main epidemiological patterns of the study setting, but only after including age-specific information beyond SAC did the non-implausible region substantially restrict. The calibration favoured parameter sets with weak-to-strong anti-reinfection immunity and relatively strong worm-level density dependence, which jointly helped reproduce the sustained prevalence and intensity in young adults other than SAC, while maintaining low overall heavy-infection prevalence. Conversely, the non-implausible range for the egg-count aggregation parameter (k_e) differed from values commonly assumed, reflecting the fact that in this exercise the parameter is constrained by within-sample variability only.

We fitted the model on prevalence and intensity of infection, and variance in egg counts across duplicates on one Kato-Katz (KK) sample. The targets were first matched in the school-aged children (SAC) group, and then gradually

provided for the rest of the population. Surveillance data for schistosomiasis are commonly collected among SAC, a group that is easier reached through school-based programmes [42]. However, more specific granular data is recommended for informing schistosomiasis mathematical models [24, 43]. When information aggregated by age groups beyond SAC was incorporated, history matching could exclude significant regions of the parameter space not compatible with real data. To align with the sustained peak of prevalence and intensity that is observed in young adults other than SAC in this specific field study, the algorithm favoured a region where the regulation at human level due to anti-reinfection immunity is limited. In fact, two primary mechanisms influence the patterns of prevalence and intensity of infection at older ages [26]: i) the age-exposure function, which describes age-specific human exposure to infection [11], and ii) the anti-reinfection immunity, triggered by the accumulation of dead worms in the human body, producing an immunological response that protects against future reinfections [44, 45]. In this calibration study, the age-exposure function was fixed (**S1 Figure**) and not estimated, making the immunity parameter the primary variable adjusted by the algorithm. This can explain why the algorithm could not fully match the targets for infection intensity and prevalence in young adults aged 15–29, and heavy prevalence in age 30–49. This constraint in the model implementation of exposure to infection further explains the mutual incompatibility found between the prevalence and heavy prevalence in older age groups (30–49 and 50+) with the prevalence at younger ages (5–15 and 15–29). On the other hand, the overall intensity of infection in the population is relatively low (6% observed prevalence of heavy infections, 7% in SAC, 8% in young adults) moving the algorithm to regions of stronger degree of worm-level regulation, as this would limit the worm egg production. Overall, the regulating mechanisms remain difficult to fully parametrise, as multiple parameter combinations produce similar results, suggesting that not a dominant mechanism but an interplay of all would explain observed patterns. The degree of such interplay is influenced by the epidemiological setting and patterns of exposure to infection. However, calibration results can guide refinements on the initial ranges for the parameters. Mutual incompatibilities between calibration targets, e.g. heavy prevalence in 50+ in combination with the variance of egg counts in the 15–29 age group, together with model-data mismatches suggest expanding the initial range for the parameter z . This regulates the degree of worm-level regulation. Overall, the input parameter sets deemed non-implausible at the end of history matching generated comparable model outcomes in terms of age-intensity profiles, the impact of treatment, and the rebound of prevalence, whereas still differing in predicted probability to elimination as a public health problem.

Some limitations of this study warrant discussion. We have shown in a previous work [11] that the age-exposure function, which should reflect heterogeneities in human interactions with water bodies, plays a major role in shaping pre- and post-control endemicity patterns. The choice of the age-exposure function was found to influence the strength of the immunity mechanism in modulating infection intensity at older ages. The relationship between the exposure function and the immunity mechanism is in line with recent findings [33], suggesting that exposure patterns largely drive the observed age-infection profiles, while acquired immunity may have subtle and long-term effects on transmission dynamics. The fixed age-exposure function considered in the model for this calibration task may oversimplify real-world exposure dynamics or prevent the exploration of exposure parameters reflecting regional-specific settings. This simplification might have limited the model's ability to simultaneously match age-intensity profiles across all age groups, especially in this setting where the intensity peak is observed in both SAC and young adults.

The calibration was performed on a single epidemic setting of moderate endemicity and relatively low intensity of infection [31]. The choice of the dataset was driven by the granular information available at individual level, including both prevalence of infection and duplicate egg counts, well suitable for the scope of this study. However, the data only refer to a pre-control setting and the model is not fitted to post-control epidemiological data. Performing history matching incorporating longitudinal data pre- and post-control enables the exploration of the parameter region that can capture reinfection and bounce-back of prevalence, leading to more reliable projections and effective control strategies [43, 46].

A bimodal behaviour of the model, characterized by divergent outcomes across multiple stochastic simulations, is observed in some regions of the parameter space. Specifically, certain simulations converge to a stable prevalence of infection, while others result in complete disease fade-out, with no infections persisting in the population. In this work, such input points were deemed implausible because the average across the stochastic runs would fall far from the targets. However, recent developments of history matching allows the construction of emulators that can be trained to capture a bimodal behaviour [38], which reflects the inherent stochasticity and sensitivity of the system to initial conditions and parameter configurations. This might be of high relevance especially in future calibration tasks that are aimed to fit the model to low endemicity settings (SAC prevalence < 10%), where a bimodal

behaviour of the transmission model is commonly observed. Here, parameters that generate bimodal outcomes might still be crucial to capture, for accurate predictions of probability to elimination of transmission.

History matching offers several advantages over conventional calibration methods, particularly in addressing the inherent limitations of models and data, by incorporating various sources of uncertainty in the definition of the implausibility measure. By explicitly acknowledging that models are imperfect representations of the real world through inclusion of a structural model discrepancy term, history matching reduces the risk of overfitting to past data and enhances the reliability of future predictions [12]. This approach systematically excludes implausible parameter sets, facilitated by fast emulators, whose accuracy is progressively improved, ensuring a more precise exploration of the parameter space while minimizing computational demands. History matching with emulation proved to be an efficient approach for Uncertainty Quantification in computationally intensive models like SchiSTOP, where direct exploration of the entire parameter space would be infeasible. We have explored more than 3,500 parameter combinations that allowed to understand which interplay of mechanisms are incompatible with observed data under the architecture of SchiSTOP. We generated 136 non-implausible points that can all explain similar epidemiological patterns. The non-implausible points helped to understand how the variability in model inputs propagates on the model outcomes, and to compare the behaviour of SchiSTOP in terms of predictions to elimination. Future improvements in the calibration task might help in guiding history matching to identify full-fitting points. The high number of targets, and therefore constraints, might have hindered zooming in some specific regions of the parameter space. This is likely to suggest defining an even more gradual approach to incorporate the calibration targets, based on biological interpretation and performance of the emulators. We further understood that parameters with strong empirical support remained within literature ranges, supporting the decision to keep them fixed and allow the algorithm to better explore the rest of the space. As discussed, estimating the shape of the exposure function at older ages and building emulators that can capture bimodal simulations might further improve the performance of history matching with SchiSTOP.

Unlike traditional calibration methods that focus on identifying a single best-fit parameter set, history matching provides a comprehensive understanding of the resulting non-implausible parameter space, which can also be returned

as empty. Emulator-based calibration can guide model refinement, such as model adjustment in the implementation of the exposure function, or the redefinition of some calibration targets. History matching does not produce posterior distributions of the parameters, that however can help interpretation of the calibration results and understand the extent to which each parameter influences the predictions. To help this, the *hmer* package includes visualisations to quantify the influence of each parameter on the emulator for each target. However, conventional sampling methods such as ABC or other Bayesian calibration methods that might have failed if applied to very large input region, can be then applied on the reduced space identified with history matching, to produce probabilistic statements of the parameters [21, 39].

Our study reinforces the importance of efficient and systematic calibration practices in enhancing the accuracy of complex model predictions. A recent review [13] has highlighted variability in calibration methodologies across the field of infectious disease modelling, with only one-third of the reviewed articles quantifying parameter uncertainty. The study emphasized a lack of standardization in the field, as only 17% of articles provided a clear rationale for their choice of calibration method, and just 37% reported model validation. These findings underscore the need for improved calibration practices, including the use of algorithmic calibration methods and better documentation, to enhance the reliability and reproducibility of complex epidemiological models.

In summary, this study addresses key challenges in calibrating complex ABMs for schistosomiasis by applying history matching with emulation to the SchiSTOP model. We found that: (i) parameters shaping the force of infection and the regulating mechanisms meaningfully influenced calibration performance and outputs. This reinforces the importance of considering and understanding the interplay of regulating mechanisms in models used to guide policy decisions. Parameters commonly considered as fixed (e.g. worm aggregation and egg production) contribute actively to the training of the emulators but the calibration naturally constrained them within literature ranges. (ii) History matching with emulation proved able to explore a large, high-dimensional parameter space under the computational constraints of a stochastic ABM, as SchiSTOP. (iii) Age-specific data beyond SAC were crucial to exclude those regions of the parameter space that would generate too strong human-level regulation (anti-reinfection immunity) and too weak worm-level regulation (density dependence in egg production). These combinations were

deemed implausible to explain the observed epidemiological setting. Our results reinforce the new WHO monitoring recommendations, which emphasise the need to expand beyond SAC-only surveys [43]. Finally, (iv) across the non-implausible sets, projections of prevalence and impact of interventions still varied, despite reproducing comparable patterns, this demonstrating that parameter uncertainty propagates into uncertainty in policy-relevant outcomes. Enhanced calibration frameworks, paired with granular data collection efforts, will be instrumental in advancing infectious disease modelling to better inform public health policy and optimize control strategies.

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6.5. Supporting Information

Supplementary tables

6.S1 Table: Parameters employed in the model.

Parameter	Value	Source
Human demography		
Population size (N)	1000	Assumption
Birth rate [annual, per 1000 individuals]	36.5	[1]
Emigration rate [annual, per 1000 individuals]	18.6	Tuned
Eligible age group for migration [years old]	[5 – 55]	[2]
Death probabilities by age	[0 – 1]	[1, 2]
Parasite life within human host		
Aggregation of worms ($k_w > 0$)		Calibrated
Transmission parameter on humans ($\zeta > 0$)		Calibrated
Age specific relative exposures	Piece-wise linear. (0, 0.62, 1, 0.51, 0.1) for ages (0, 5, 15, 40, 100).	[3–6]
External force of infection	Value = [0.5 – 5] worms Duration = [0.5 – 2] years	Assumption
Average lifespan of adult worms within the human host [months]	60	[7]
Pre-patent period [constant, months]	3	[7]
Egg production		
Expected number of eggs per sample ($\alpha > 0$) [eggs/worm pair/sample]		Calibrated
Density dependence in egg production (z) [/ worm pair]		Calibrated
Daily grams of stool produced by each human individual [gr]	150	[8]
Aggregation of observed egg counts ($k_e > 0$)		Calibrated
Anti-reinfection immunity		
Immunity coefficient ($\alpha_{imm} > 0$)		Calibrated
Snail population module		
Maximum reproduction rate ($\beta_0 > 0$) [1 / days]	1	[9]
Carrying capacity ($k > 0$) [number of snails]		Calibrated
Natural mortality of snails ($\nu > 0$) [1/days]	0.01	[9]
Mortality of snails upon infection ($\nu_i > 0$) [1/days]	0.033	[9]
Snail transmission parameter ($\eta > 0$)		Calibrated
Worm maturation period within the snail ($h > 0$) [days]	30	[10, 11]
Cercarial production rate ($\lambda > 0$) [1/days]	50	[9]
Mortality rate of cercariae ($\gamma > 0$) [1/days]	1	[9]

6.S1 Table: Continued

Mass drug administration		
Target population	5 – 15 years old	Assumption
Duration	10 years	Assumption
Frequency	Annual	Assumption
Coverage (% of target population reached by treatment)	75%	[12]
Efficacy (% of killed adult worm pairs)	86%	[4]
Fraction systematically untreated	5% of target population	[4]

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6.S2 Table: Calibration targets passed to history matching. Each target is defined for every age group and provided to history matching with an upper and lower non-probabilistic bound.

Age group	N	Prevalence of infection	Prevalence of high intensity infection (> 400 epg)	Mean of mean egg counts	Mean of variance egg counts	Prevalence of infection in snails
[0,5)	110	0.12 - 0.28	0 - 0.30	0.20 - 0.71	0.09 - 0.25	0.03 - 0.12
[5,15)	405	0.38 - 0.47	0.05 - 0.10	3.62 - 7.32	6.40 - 48.51	
[15,30)	210	0.44 - 0.58	0.05 - 0.13	3.77 - 7.01	6.96 - 24.36	
[30,50)	176	0.25 - 0.39	0.02 - 0.08	1.43 - 5.18	1.47 - 33.08	
[50,100]	79	0.16 - 0.36	$3.2e^{-4}$ - 0.07	0.41 - 1.59	0.49 - 21.11	

6.S3 Table. Number of non-implausible points generated at each wave of history matching (HM). The non-implausible points generated by the emulators at each specific wave, were provided as input parameter sets to the full transmission model SchiSTOP, for evaluation and generation of model outputs. The last column reports the number of stochastic replications run by SchiSTOP for a single parameter set.

	Wave	Number of non-implausible points generated with HM	Number of stochastic replications evaluated with SchiSTOP
Calibration setting 1	0	120	25
	1	120	25
	2	120	50
	3	160	75
	4	160	100
	5	160	100
	6	240	100
	7	360	100
Calibration setting 2	8 to 17	360	100

6.S1 Appendix

Validation of the emulators

The statistical emulators are trained to approximate the relationship between input parameters and model outputs. The emulator provides fast predictions of model outputs for any given set of parameters, significantly reducing the computational burden of exploring the parameter space. After building the emulators using the training set of points, the emulators must be validated to ensure they accurately approximate the model outputs. Emulators that do not meet the diagnostic criteria are either adjusted to be more conservative or excluded from the current wave.

Validation of the emulators and diagnostics

The R package *hmer* provides the `validation_diagnostic` function, which can be used to perform three types of diagnostics, for each emulated output. These allow to inspect:

- the performance of the emulator predictions
- the emulator implausibility
- the standardised errors of the emulator outputs in light of the model output

We applied such diagnostics both to the emulators for the expectation, and the emulators for the variance of the model outputs. In fact, we built two emulators for each model output (target): one to estimate the expected value and another to reproduce the variance across stochastic runs. More details can be found in the Methods section of the main text. Well-trained emulators for the variance across stochastic runs are valuable tools to capture the stochasticity of the model and give a measure of the stochasticity to the mean emulator uncertainties. Diagnostics of such emulators give an indication of whether the variance emulators can be trusted, or possible inaccuracies in the model. However, only the emulators of the expectation are then used to generate a new set of non-implausible points, which will serve as input for the subsequent wave. Therefore, discrimination of well-trained emulators and decisions to stop or not the waves, were based on the diagnostics of the expectation emulators.

At every wave of the calibration process, diagnostics of the emulators were checked and emulators accordingly adjusted if needed. In **Figure A1** we show the diagnostics for the expectation emulators of wave 7 (the last wave based on a subset of 5 calibration targets) as an example. The first column presents

the emulator outputs (expected value) compared to the model output, for each validation point, represented by black dots. The emulator's uncertainty at each validation point is displayed as a vertical interval spanning around the emulator expectation, where σ denotes the emulator variance at that point. The green diagonal line represents a perfect emulator. Any parameter set where the emulator prediction deviates by more than 3σ from the model output is highlighted in red. The second column compares the emulator and simulator implausibility measure. For more details on the definition of the measure we refer to the official documentation. The implausibility comparison is displayed in a confusion matrix-fashion to evaluate the performance of the emulator in classifying the validation points. The bottom-left and top-right quadrants report concordant classification: non-implausible if below the threshold of 3 (the corresponding parameter set will be kept in the next wave), implausible above (the parameter set will be discarded in the next wave). The top-left quadrant is also fine: the emulator classifies a parameter set as non-implausible, although the model rules it out. The emulators will gradually improve their accuracy on subsequent waves and these sets may be removed as the parameter space is reduced. More careful consideration should be given to the bottom-right quadrant: the emulator rules out a parameter set, but this has a low implausibility, when we calculate this directly using the simulator. If more than 5% of the points fall in this quadrant we might consider removing the specific emulator from the present wave, because it is ruling out regions of the parameter space that are good for the model.

The third column shows the standardised error of the emulator outputs versus the model outputs.

For details about each diagnostic and a thorough interpretation, we refer to the *hmer* package documentation. **Figure A1** shows that at the end of the 7th wave all our emulators performed well in reproducing the model output, with only two points highlighted in red (first column) for the prevalence in snails. However, the deviation was not concerning. The second diagnostic showed that all the emulators produced classification of the validation points concordant with the model. Moreover, only two points exceeded the threshold for the implausibility measure. This was indication that the non-implausible region would not undergo significant reduction, and therefore we decided to stop the process and continue by increasing the number of calibration targets.

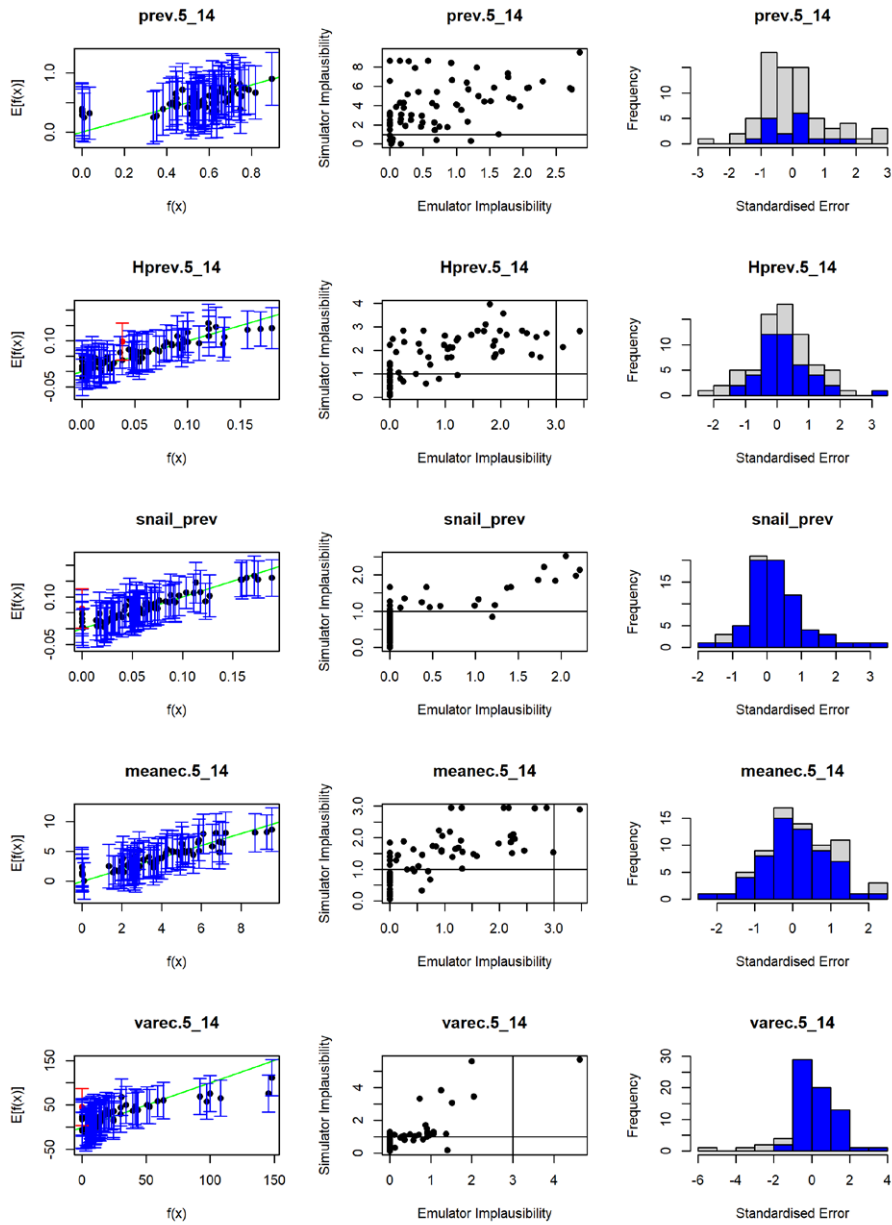


Figure A1. Emulator diagnostics performed on each emulated output, calibration setting with 5 targets. The 7th wave is shown as example.

The diagnostics for the expectation emulators, relative to the full calibration setting are displayed in **Figure A2**. The emulators of the last wave of history matching (17th wave) are shown as example. After 17 waves, 20 out of 21 emulators successfully reproduced the model outputs. In fact, the calibration target for the variance between two egg counts in the age group [0,4) was excluded from the inference, because problematic for the construction of the relative emulator. The second diagnostic (second column) showed that the emulators produced a classification of the validation points concordant with the model. Some calibration targets show an emulator implausibility very close to zero. The behaviour can be explained with the definition of the implausibility measure, where all sources of uncertainty go at the denominator. The emulators showing such small implausibility thus reflect high observational uncertainty and therefore poor information from the data to build better emulators. The results of such diagnostic should be interpreted as an indication that the specific emulator is not able to rule out any other point, based on the information provided. Differently, the implausibility diagnostic of the emulator for the heavy intensity prevalence and the variance in egg counts in the age group 30-49 showed that a large part of the validation points are classified as implausible (implausibility > 3) by both the emulator and the model (upper-right quadrant). These targets were more problematic for the emulation process, and might have hindered the generation of full-fitting points, i.e. parameter sets that could match all the given targets. Exploration on these targets and other challenges highlighted by history matching are elaborated in the Results and Discussion sections of the main text.

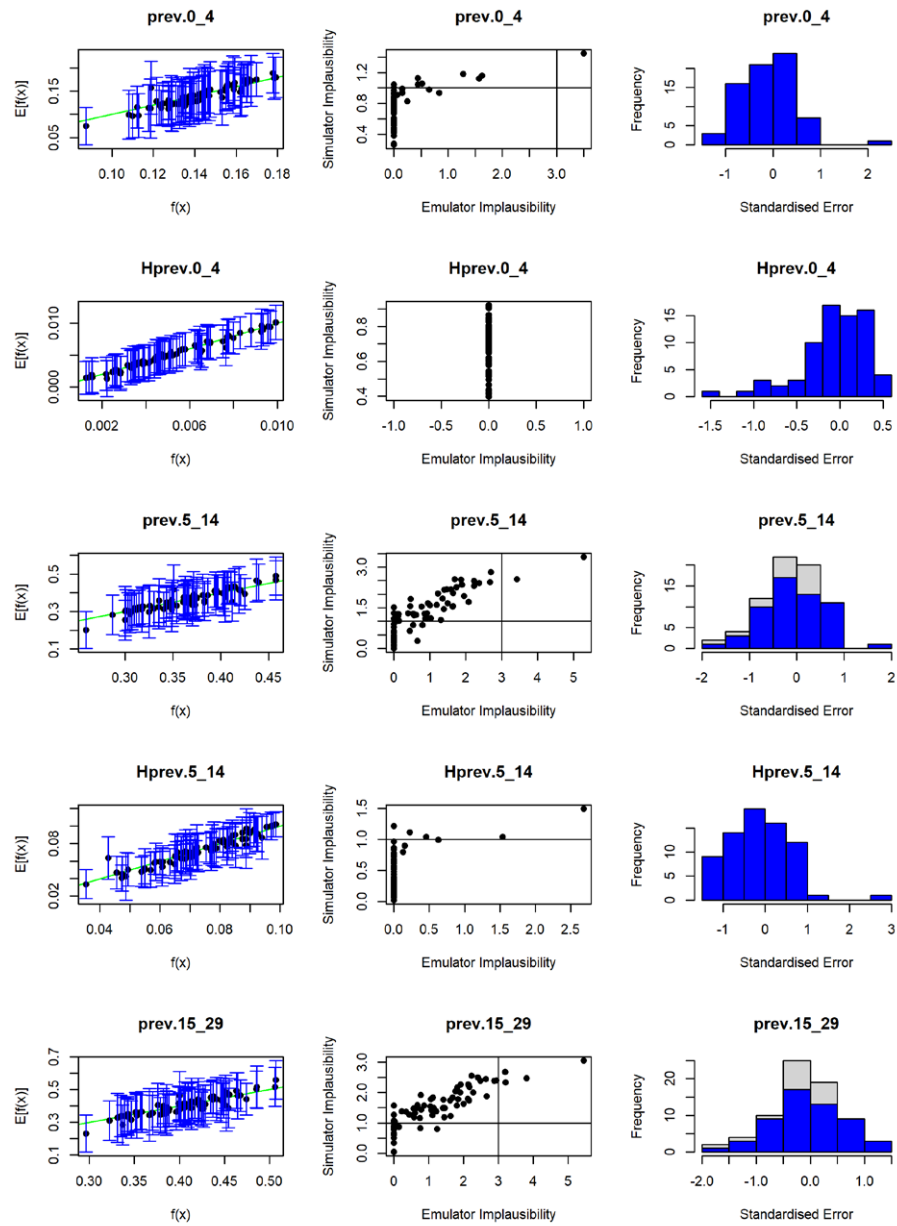


Figure A2. Emulator diagnostics performed on each emulated output, calibration setting with 20 targets. The 17th wave is shown as example.

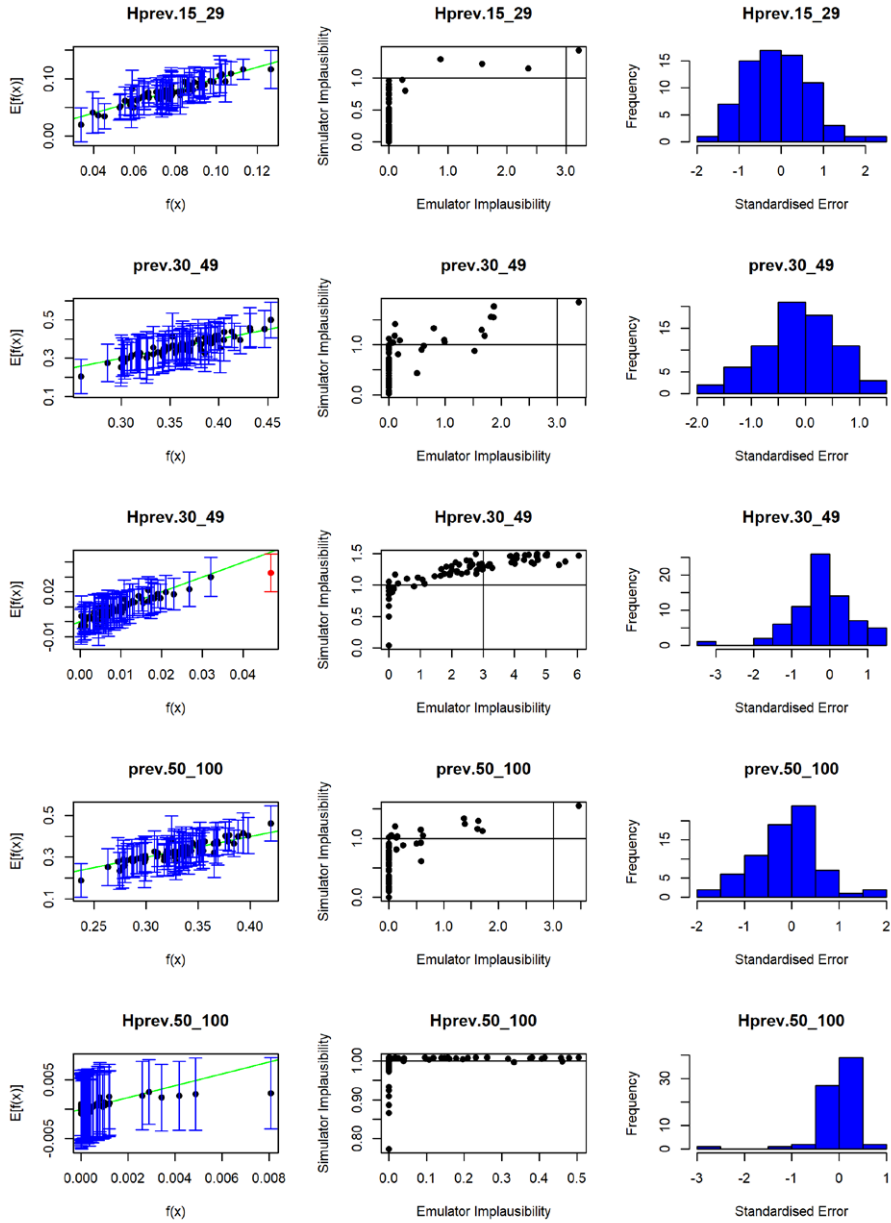


Figure A2. (continued) Emulator diagnostics performed on each emulated output, calibration setting with 20 targets. The 17th wave is shown as example.

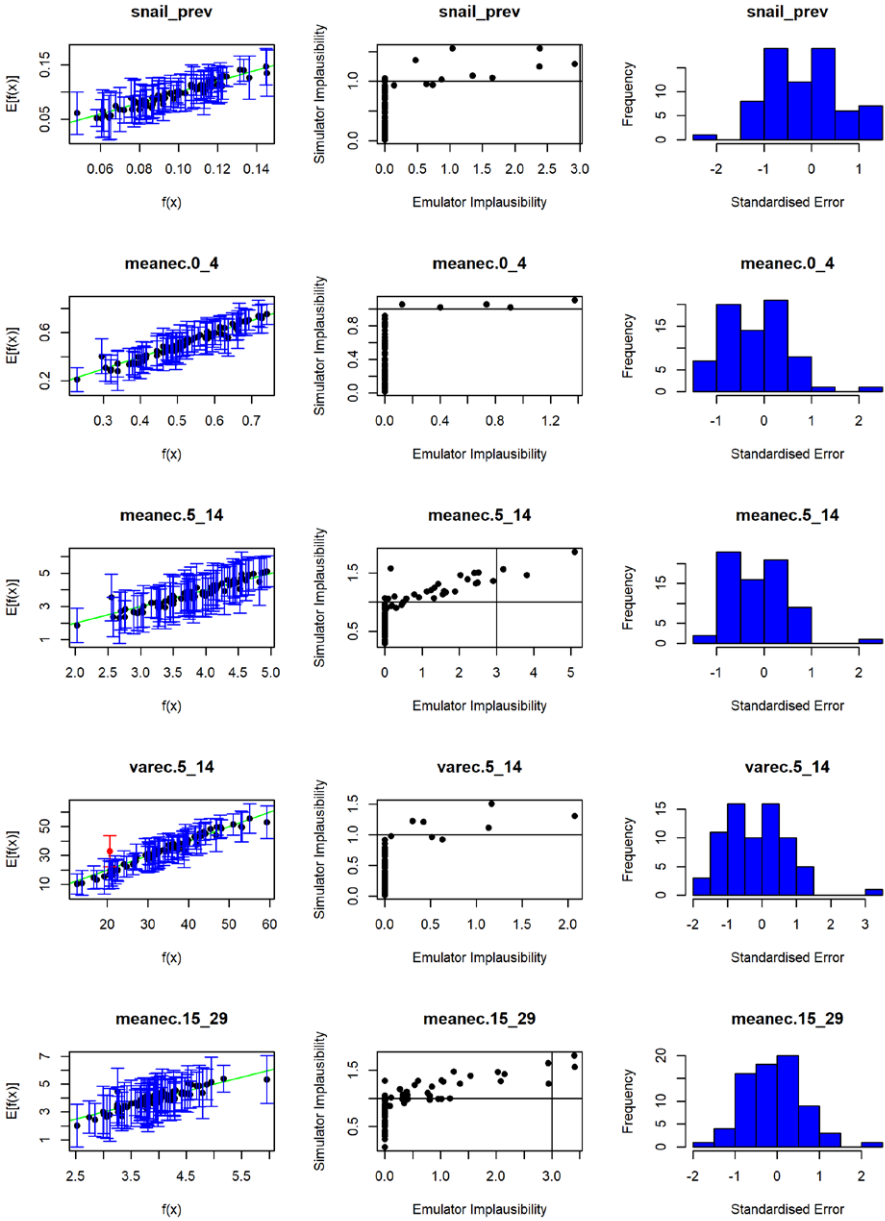


Figure A2. (continued) Emulator diagnostics performed on each emulated output, calibration setting with 20 targets. The 17th wave is shown as example.

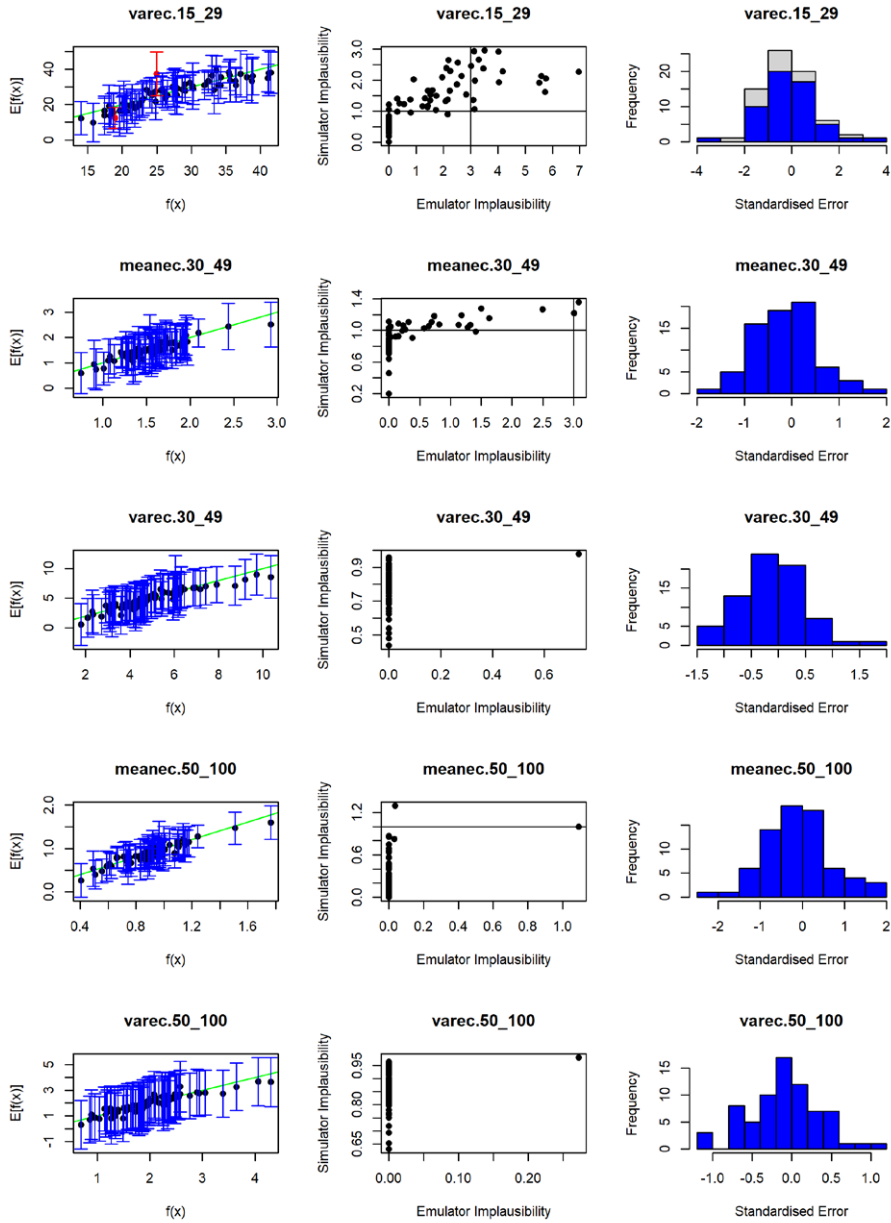
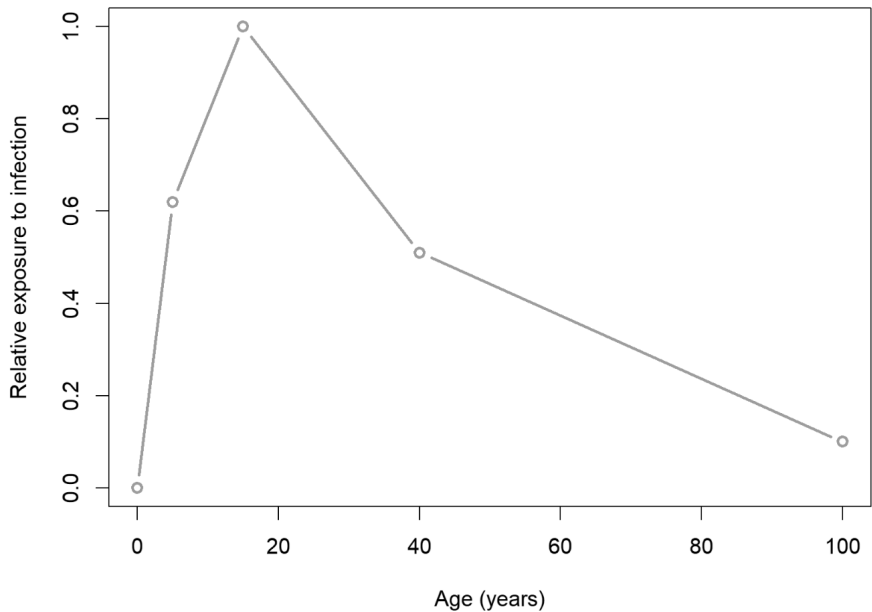
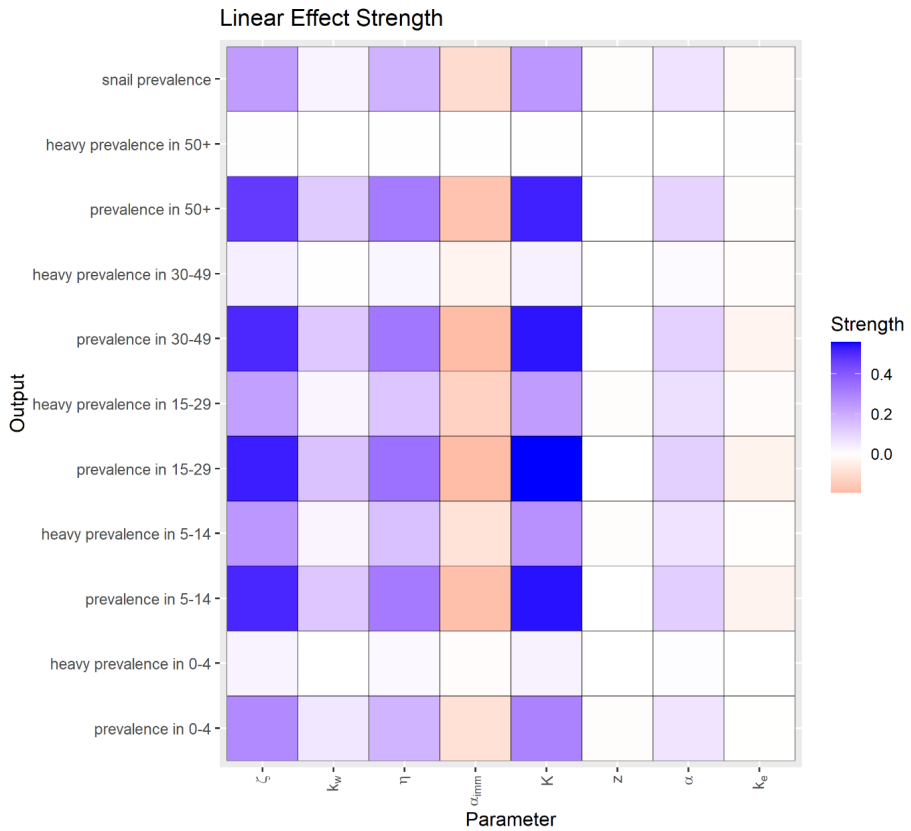


Figure A2. (continued) Emulator diagnostics performed on each emulated output, calibration setting with 20 targets. The 17th wave is shown as example.

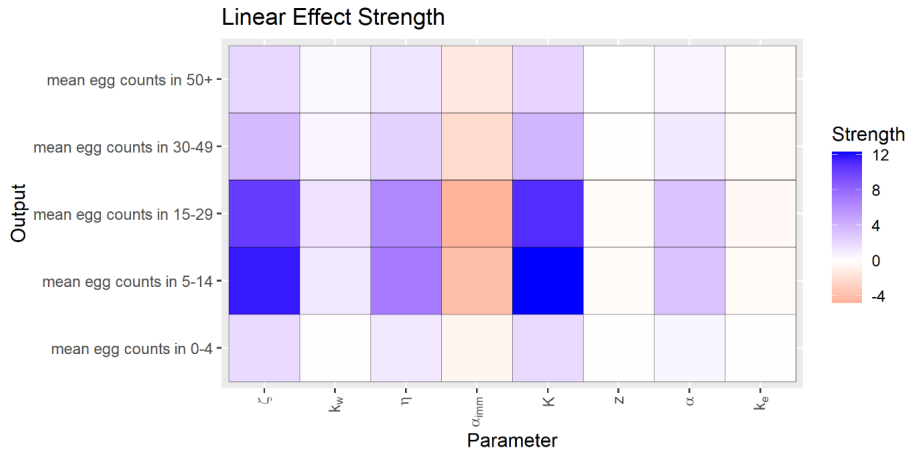
Supplementary figures



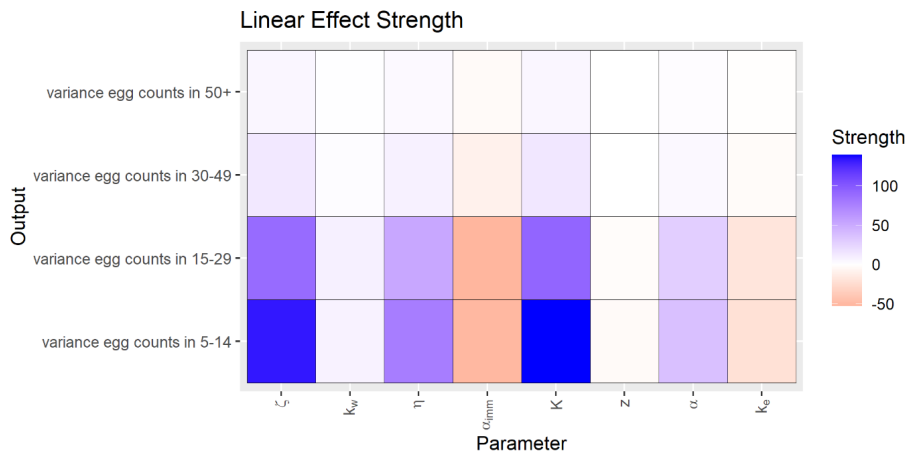
6.S1 Figure. Age-exposure functions employed in the model. The function describes the relative exposure by age of the human host, using 1.0 for the highest value (i.e., at age 15). This is proportional to the individual overall exposure rate. The function is a piece-wise linear function adapted from previous work.



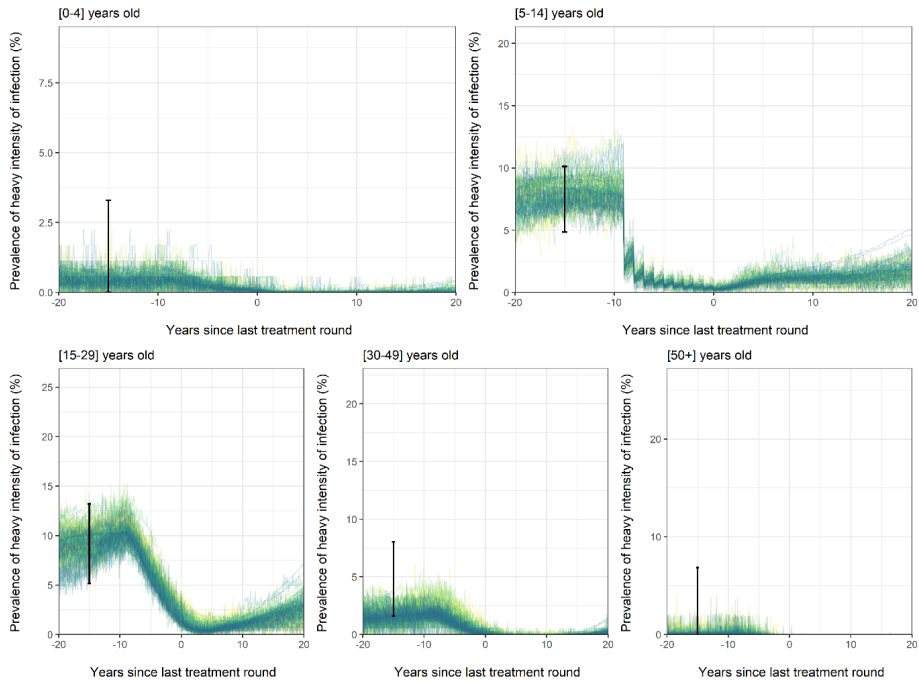
6.S2 Figure. Active regression variables and their influence on last-wave emulators of prevalence and high intensity prevalence over age, are summarized. The prevalence of infection on snails is included in the first row. Each row represents a model output, while each column corresponds to a parameter. The intensity of blue and red shading indicates the strength of the response, with stronger shadows denoting more significant positive (blue) or negative (red) effects.



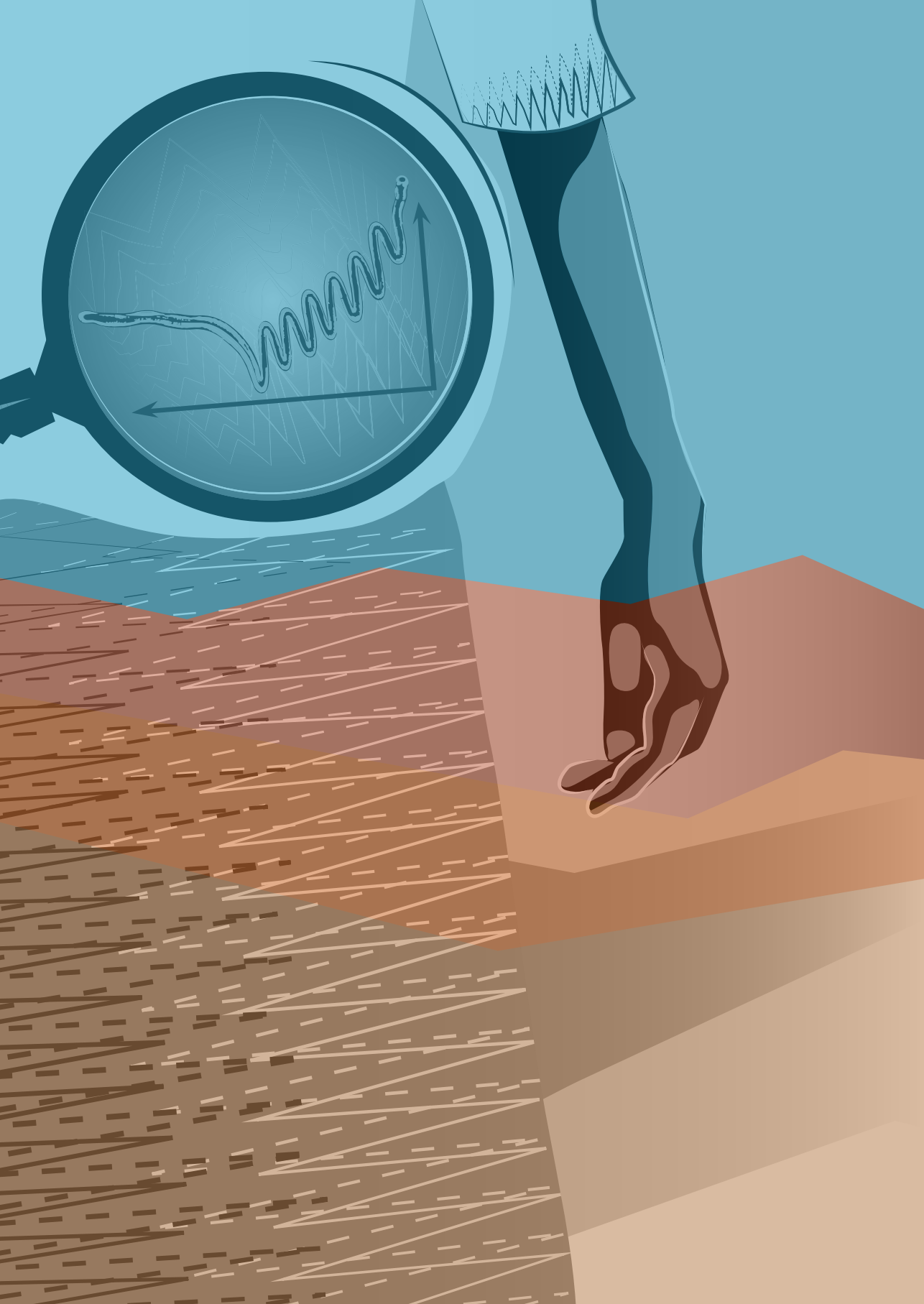
6.S3 Figure. Active regression variables and their influence on last-wave emulators of the mean observed egg counts in faeces over age, are summarized. Each row represents a model output, while each column corresponds to a parameter. The intensity of blue and red shading indicates the strength of the response, with stronger shadows denoting more significant positive (blue) or negative (red) effects.



6.S4 Figure. Active regression variables and their influence on last-wave emulators of individual-level variance between duplicate egg counts averaged over age, are summarized. Each row represents a model output, while each column corresponds to a parameter. The intensity of blue and red shading indicates the strength of the response, with stronger shadows denoting more significant positive (blue) or negative (red) effects.



6.55 Figure. Timelines of prevalence of heavy infections across different age groups. The timelines of heavy prevalence pre-, during-, and post-control is plotted by age group, for all the non-implausible parameters extracted for predictions. Each line represents, for a single parameter set, the average of the portion of stochastic runs (out of 100) that do not reach elimination as a public health problem (heavy intensity prevalence in age group [5-14] $\leq 1\%$) after 20 years since the last treatment round. The black bars show the targets' range (prevalence of heavy infection per age group) provided to history matching to generate non-implausible input points.



Chapter 7 General discussion

7.1. Core findings

In this thesis, I presented statistical and mathematical models that were developed to help informing guidelines for policy decisions about the control of soil-transmitted helminths (STH) and *Schistosoma mansoni*, at different levels of the decision-making process. Policy decision-making involves a multi-step, evidence-based process that guides the development and implementation of effective control and elimination programmes. A starting point is the proper definition of epidemiological indicators and related thresholds. For both STH and *S. mansoni*, prevalence and intensity of infection, typically assessed through school-based parasitological surveys using stool samples, are the indicators used to make decisions on the frequency and continuation of mass drug administration (MDA). Thresholds for these indicators mark the achievement of the control targets. Once indicators and thresholds are defined, monitoring of progresses and evaluation of the feasibility of achieving the control targets ensures more evidence-based and strategic planning. My thesis showed how modelling can be used to assist policy decisions, in terms of the definition of control targets (**Chapters 2 and 3**), and the feasibility of reaching the control targets according to different biological assumptions and control strategies (**Chapters 4 and 5**). The challenges and benefits of efficiently calibrating such complex models for accurate prediction and optimal data collection is addressed in **Chapter 6**.

Thus, the key outcomes of the thesis can be summarized as follows:

1. **Assessing the appropriateness of the WHO indicator threshold for defining the STH morbidity targets.**

The current WHO threshold of 2% prevalence of moderate and heavy intensity (M&HI) infection is appropriate for defining the morbidity target for STH, i.e. elimination as a public health problem (EPHP).

Hookworm-attributable morbidity is mainly associated to prevalence of M&HI infection. A single Kato-Katz (KK) slide is recommended for policy decisions determined by measures of M&HI prevalence.

2. **Estimating the effectiveness of various MDA strategies and feasibility to reach the WHO 2030 targets for STH in the exceptional situation of COVID-19-related interruption of deployment of control programmes.**

*EPHP is possible by 2030 in moderate endemicity settings for *A. lumbricoides* and hookworm, under the current WHO treatment guidelines, while the target*

is more challenging for the same species in high endemicity settings, or for T. trichiura in all endemicity settings. Temporary interruptions due to COVID-19 pandemic do not disrupt the progress to the targets, assuming that coverage is maintained when resuming the programmes.

3. Revisiting the modelling assumptions of regulating mechanisms of *S. mansoni* to assess their impact on the control targets.

The interplay of regulating mechanisms acting at worm-, human-, and snail-level provides a coherent explanation of observed epidemiological patterns of S.mansoni. The choice of regulating mechanisms in schistosomiasis modelling largely determines the expected impact of control interventions and feasibility to reach control targets. Reaching the control targets solely targeting school-aged children (SAC) is challenging, particularly in moderate- and high-endemicity settings. Expanding MDA to the entire community increases the chances to reach EPHP in such settings, and improves the prospects for interrupting transmission in low endemicity settings.

4. Assessing data needs and model adequacy through emulator-based calibration.

Emulator-based calibration demonstrates that several parameter combinations can reproduce similar epidemiological patterns, particularly for mechanisms regulating transmission. Data limited to school-aged children are insufficient to substantially restrict the parameter space. In contrast, incorporating age-stratified data on both prevalence and intensity of infection helps narrowing the non-implausible parameter space and better captures observed patterns. Although no parameter set is found to match all targets simultaneously, the calibration process clarifies where incompatibilities arise between targets and model assumptions, helping to disentangle parameter uncertainty from potential structural limitations. History matching with emulation enables this systematic exploration while limiting the high computational demand of the agent-based model and guides model refinement.

In the General Discussion, I put these key outcomes in the perspective of their use for policy and decision-making and reflect on key challenges and limitations in the modelling studies. I also elaborate on future developments and proposed research.

7.2. Discussing core findings

In this thesis I explored how different statistical and mathematical models were implemented and used as potential tools for enhancing evidence-based decision-making in the control of STH and *S. mansoni*, while also highlighting implementation challenges.

Models support evidence-based policy

Definition of epidemiological indicators

I proposed two statistical tools to support the decision-making process in the step of the assessment of epidemiological indicators and thresholds that define the control targets. The statistical hierarchical model defined at individual level, presented in **Chapter 2**, studies the association between individual Hb values and hookworm egg counts (observable) via a latent variable representing the worm burden within each human host (invisible). The model captures the overdispersion of worm burdens in the population, as well as the overdispersion of observed egg counts, underscoring the importance of individual-level data. This method adds to the modelling literature estimating hookworm morbidity [1-3] by accounting for an underlying prevalence of anaemia, which is common in hookworm endemic settings due to malnutrition and coinfections. In fact, to assess the appropriateness of the WHO indicator that monitors the STH morbidity target, it is important to estimate the prevalence of anaemia that is attributable to hookworm. By predicting the latent burden of worms after which a consistent decrease in haemoglobin is observed, the model helps understanding whether the prevalence of hookworm anaemia is actually associated with M&HI infections. The results support the WHO threshold of 2% M&HI prevalence to evaluate EPHP for hookworm, as was found to correspond to a prevalence of hookworm anaemia < 1%.

The same epidemiological dataset is analysed in **Chapter 3**, together with other three datasets covering overall 6 countries. The aim is to assess the performance of different sampling schemes. In the study, bootstrap iterations are employed as a resampling technique to evaluate the robustness and variability of the sampling schemes used for assessing STH infections. Results support policy by estimating the uncertainty of indicators used for decision-making (prevalence of any and M&HI infection) with respect to the diagnostic sampling scheme used to assess infection. The key message supports aligning WHO thresholds for decision-making with specific guidelines on the sampling

schemes to be used. In fact, different sampling procedures lead to considerable variation in the indicators used for policy, under the current WHO guidelines. A major improvement of the presented approach over existing analyses [4] is the consideration of the budget constraints when comparing sampling schemes, to reflect country-specific needs of resource allocation. After the study presented in this thesis, other modelling analyses have been published to expand beyond KK sampling-scheme comparisons [5, 6] which lead to similar results: KK is cost-effective for monitoring and evaluation of STH control programmes, combined with a recommended “no screen” survey design (all enrolled individuals are followed up) [6]. By integrating data for three faecal egg count methods, cost, and simulations of different survey designs, **Chapter 3** and the later studies support the use of modelling to provide evidence-based guidance for various policy decisions in large-scale STH deworming programmes.

Monitoring and evaluation

I have focused on the use of stochastic agent-based models (ABMs) to evaluate the feasibility of reaching the control targets. In addition to their use in long-term strategic planning, I also experienced how mathematical models play an important role in addressing urgent public health questions where real-time decisions are needed. The ability to simulate and compare hypothetical scenarios makes them particularly valuable when empirical data are limited or when rapid action is required. A key example is the use of models during the COVID-19 pandemic, when many NTD control activities, including MDA for STH and schistosomiasis, were disrupted [7]. Promptly quantifying the impact on the progress to elimination was considered important to know [8]. To this aim, I used an existing stochastic ABM that simulates the process of STH transmission in an age-structured human population [9, 10]. In absence of empirical data and due to time constraints, the approach was to tune the species-specific transmission parameters to reproduce a moderate and a high endemicity setting, as typically observed (**Chapter 4**). Various MDA scenarios with 0 to 18-month interruption were simulated, considering resuming the programmes with and without mitigation strategies. Findings show that the impact on the progress is limited if programmes would have resumed within 18-month interruption with the strategy in use, assuming that treatment coverage remained as before. However, mitigation strategies can halve catch-up time with pre-endemic prevalence levels and mitigate morbidity in settings that are far from targets under normal conditions.

The work in **Chapter 4**, as part of a joint modelling effort of several researchers within the NTD Modelling Consortium (<https://www.ntdmodelling.org/>),

responded to the WHO urgent appeal to quantify the impact of the COVID-19 pandemic on multiple NTDs, and to help formulating mitigation strategies that could enhance programmes' catch-up with the targets. Different modelling approaches, all with a common objective: to simulate several interruption scenarios and predict the negative impact on the progress, for each disease, towards the WHO disease-specific control targets. The results of these extensive modelling analyses [8] constituted the content of the WHO report to inform and guide decision-making in the resumption of the community-based activities for seven NTDs, including STH and schistosomiasis [11].

SchiSTOP, the ABM developed in **Chapter 5**, shows that the modelling assumptions of mechanisms regulating transmission influence predictions about the impact of control strategies: models that include regulation at both the snail and human levels better reproduce observed patterns of stable low transmission and post-treatment rebound than those that assume only density-dependent egg production in worms, which is common in models currently used to inform policy. As a result, the study indicates that relying solely on MDA, particularly school-based treatments, may be less effective than currently thought. This finding supports the current WHO recommendation of policy shifting toward community-wide treatment and underscores the importance for models that more realistically capture ecological and immunological processes to guide decision-making.

Models enhance the understanding of biological assumptions

Mathematical models are useful to enhance the understanding of underlying biological assumptions, while highlighting data needs. Models strongly rely on epidemiological data, such as prevalence and intensity of infection, in the process of model calibration. The prevalence and intensity of infection, in relation to the control history, characterise an observed endemicity setting. Although the intensity is generally observed to peak in school-aged children, larger variability is observed in the intensity at older ages, that is likely to reflect regional specific contexts. Model calibration for estimation of parameters is a component of the Uncertainty Quantification (UQ) framework. UQ refers to the process of identifying and analysing uncertainties in models and predictions [12, 13] to quantify their impact of model outcomes. In the context of epidemic modelling, UQ involves considering and evaluating different sources of uncertainty, specifically at i) data-level (data usually imperfectly observed), ii) model-level (differences in model outcomes arising from the choice of methodology or assumptions, acknowledging that models are an imperfect reproduction of reality), iii) parameter-level (uncertain

knowledge about key parameters) [12, 13]. The primary goal of UQ is not to eliminate uncertainty but to make its impact on the outcomes explicit, enabling that predictions are robust, reproducible, and reflective of real-world complexities [14]. However, the application of the framework to epidemic modelling still poses several challenges (**section 7.3**) in parameter estimation, model selection and validation, and requires interdisciplinary efforts [14].

The analyses presented in **Chapter 6** elaborate on the process of calibrating SchiSTOP and on the challenges arising with parameter estimation, mainly related to limitations in the available data, and the complexity of the model processes. Epidemiological data are often incomplete and subject to random noise. Knowledge on the interplay between some biological mechanisms, such as regulating mechanisms, is incomplete, leading to vague prior information on the driving parameters. **Chapter 5** already showed how uncertainty in modelling assumptions and parameters is propagated on the predicted outcomes. In fact, models that reproduce similar epidemiological patterns can differ largely in the predicted probabilities to achieve the control targets, emphasizing the importance of considering the right assumptions in mathematical models used for policy and highlighting data needs. I address parameter identifiability of SchiSTOP in **Chapter 6**, as a case study of a complex ABM, by exploring a large parameter space despite the heavy computational demand of the model, including parameters that are commonly informed by literature. SchiSTOP is calibrated by means of history matching with emulation, an efficient calibration method that systematically rules out regions of parameter space that are inconsistent with observed data. It is especially useful for high-dimensional or computationally expensive models through the use of emulators: i.e., statistical surrogates that approximate the input-outputs behaviour of a computationally expensive model, across the parameter space without running the full model repeatedly. It is clear that multiple combinations of parameters can successfully match the targets of infection prevalence and intensity. Of importance, providing epidemiological data aggregated over multiple age groups (prevalence and intensity of infection, and variance across duplicate samples) was crucial to restrict the region of parameters deemed as non-implausible to match the calibration targets.

7.3. Quantitative challenges and limitations

A fundamental difficulty in modelling intestinal parasitic worm infections lies in the need to estimate invisible quantities: specifically, the worm burden within

human hosts. Generally, models heavily rely on epidemiological knowledge and data to accurately inform the underlying assumptions, as well as to estimate the parameters that can generate real settings. This thesis showed and discussed how the predictions of transmission models are sensitive to the different modelling assumptions about parasite biology and human behaviour. The challenges and the limitations of this thesis mainly reflect limitations in the data or decisions to simplify the modelling of the epidemiological processes. Overall, the challenges encountered in model implementation and parametrisation can and should be used to highlight research priorities, possible model improvements, and (additional) data needs.

In this thesis, I mostly employed stochastic ABMs (**Chapters 3 – 6**). The choice is driven by the purpose of explicitly tracking individual hosts and life of worms within the human host, incorporating individual heterogeneities in exposure behaviour and treatment uptake. Intervention scenarios tailored to population subgroups are simulated by varying duration, frequency, coverage, or treatment compliance. In modelling literature, ABMs have proven especially useful when evaluating uncertainty, such as the probability of prevalence resurgence after cessation of MDA [10, 15-19], or assessing the likelihood of reaching elimination targets under different intervention scenarios. Nevertheless, stochastic ABMs are computationally intensive, require granular data for efficient calibration, and need multiple simulation runs to interpret probabilistic outcomes, which led me to face quantitative challenges during implementation and parametrisation.

The analyses to estimate the impact of COVID-19-related interruptions on the progress towards WHO 2030 targets for STH (**Chapter 4**) were compared with a second ABM transmission model developed elsewhere [20], within the NTD Modelling Consortium initiative. We observed some discrepancies in the results between the two models, which could be explained by different modelling assumptions, such as age-exposure patterns of humans to eggs/larvae in the environment. This led to a follow-up study that examined how uncertainties in the biological and behavioural aspects of STH can influence the effectiveness of control programmes, using the same two models [21]. Specifically, the study considers the assumptions on the aggregation of worms within hosts and the age-exposure profile of infection, as well as the functional form of density-dependent fecundity of adult female worms. The prevalence estimates based on measurements of faecal samples were found to highly depend on the combinations of such assumptions. This sensitivity highlights how uncertainty

in STH biology and human behaviour can be used to inform setting-specific data collection strategies. For example, infection intensity data collected prior and at the end of MDA programmes provide accurate information on age-intensity patterns, especially at older ages where more variability is observed to reflect different behavioural settings. When combined with prevalence data, intensity measurements help estimate the degree of worm aggregation within hosts, a key transmission parameter to accurately predicted the impact of MDA. Additionally, worm expulsion data offer direct insight into the relationship between faecal egg counts and underlying worm burdens, allowing calibration of diagnostic measures and informing assumptions on density-dependent fecundity of adult female worms. Such data are especially valuable in high-prevalence settings, where the effect of density-dependent fecundity on the egg output is more pronounced.

Schistosomiasis is another good case study to elaborate on the challenges faced to accurately formulate the biological assumptions in the complex disease transmission cycle, where the understanding is still poor and the availability of direct observations difficult to collect. In the General Introduction (**Chapter 1.3**), I have explained how mechanisms regulating transmission operate at different levels of the parasite life cycle. These include density dependence in egg production at the worm level, anti-reinfection immunity in the human host, and depletion of susceptible snails at the snail level. Snail abundance is assumed to be limited by carrying capacity, reflecting the assumption of competition for resources [22, 23]. The interplay of such mechanisms lacks full understanding. In some cases, direct observations might be difficult to collect, e.g. malacological data facing the hurdles of snail sampling and snail infection detection, and behavioural data of human exposure to water bodies, which are highly variable and resource-requiring. When calibrating SchiSTOP to a specific regional endemic setting of moderate endemicity with low prevalence of heavily infected individuals (**Chapter 6**), I allowed the parameters which drive the regulating mechanisms to vary on large parameter space. The bounds of the parameter space were informed by previous search (**Chapter 5**). Exploring such large space of parameters proved computationally expensive, requiring use of High-Performance Computing environments. History matching with the help of emulators allowed to estimate more than 36,000 parameter combinations in a unit time of weeks, that would have been unfeasible without the emulation process. However, good prior knowledge on the initial parameter space would optimise the search i) by avoiding leaving out important regions in the initial input space, ii) facilitating

the algorithm to zoom in and exclude implausible regions. An optimised search can better identify points fully fitting all the calibration targets.

In fact, the hurdles encountered by history matching in the calibration process shed light on poor knowledge and limited data around specific targets, such as the prevalence of infection detected in snails, as well as around mechanisms influencing the age patterns of infection intensity. The latter include the development of anti-reinfection immunity, i.e. regulation at human-level, and the human exposure behaviour to contaminated water environments. The relationship between the age-exposure function and the immunity mechanism has been studied in a recent work [24], highlighting the difficulty to disentangle the relative contributions of immunity and exposure to the age-infection profiles. Here, the authors use immunoglobulin E (IgE) as an indicator of (long-term) acquired immunity, that comes with limitations. IgE correlate with protection and recent immune boosting, but current human and modelling data do not justify using IgE levels alone as a quantitative marker of how fast protective immunity to schistosomiasis decays [25, 26]. The rate of immune decay further contributes to the magnitude of the anti-reinfection protection, but the mechanism of waning of immunity is not fully understood for *S. mansoni* and therefore not yet included in SchiSTOP. Field studies that quantify the immunological response are essential for generating the parameters that support accurate transmission models [25]. Moreover, there is need to better parameterise the exposure function in transmission models used for policy predictions, implying a standardised approach to collect water contact data and definitions of exposure scores [27]. However, standard interpretation of water contact data is inherently challenging, as exposure depends on multiple factors, including frequency and duration of contact, body surface area exposed, type of activity, and temporal variation in cercarial shedding throughout the day. In addition, these factors are known to be highly context-specific, varying across ecological and social settings. Efficient model calibration is an opportunity to identify which exposure components are most influential for transmission dynamics and prioritise these data needs.

7.4. Developments and future research

Some of the aspects discussed in this thesis have since been expanded by more recent studies, whereas other aspects point to important directions for future investigation.

Infection-related morbidity

In **Chapter 2**, anaemia has been used as a proxy for hookworm-related morbidity to assess how the prevalence of morbidity relates to infection prevalence. For schistosomiasis, clinical examination of morbidity is more challenging, and a morbidity module is not commonly included in transmission models. A recent study has been conducted for schistosomiasis to study the relationship between infection intensity categories and morbidity in SAC affected by schistosomiasis [28]. Similarly to the work of **Chapter 2**, the authors developed a statistical model to investigate to which extent infection intensity categories for *S. haematobium* and *S. mansoni* correlate with morbidity prevalence and assessed the appropriateness of infection intensity thresholds as indicators of morbidity in SAC. They found that for *S. haematobium*, infection intensity categories can serve as reliable indicators of morbidity in SAC. In contrast, for *S. mansoni*, these categories do not appropriately reflect morbidity levels, indicating a need for alternative assessment methods of the morbidity target.

The association between intensity of infection and morbidity due to parasitic infections can help to incorporate the morbidity mechanism into transmission models. Implementing a disease morbidity module would require understanding the process of accumulation of damage over time, as a function of current infection (worm burden). An approach of this type has been developed for the onchocerciasis parasitic disease [29]. For schistosomiasis it is important to distinguish between reversible morbidity (the individual can recover if worm burden decreases), and chronic morbidity (only partially reversible). Variations in individual susceptibility to clinical manifestations should be included as well. All these processes introduce parameters that rely on epidemiological and empirical data for formulation and calibration. The predictions of models incorporating the accumulation of damage can advance the understanding of morbidity dynamics pre- and post-control, and how they respond to changes in worm burdens, ideally using longitudinal data collected in both children and adults.

Diagnostic technique

The Kato-Katz (KK) test is the simulated diagnostic technique in the models presented here, as it is the standard mode to detect STH and *S. mansoni* infection. The most recent WHO guidelines consider the use of qPCR as a sensitive and specific diagnostic tool to monitor low-intensity infections and to support control and elimination programmes, although challenges in standardization and implementation remain [30]. The impact of sampling schemes based on the KK diagnostic technique explored in **Chapter 3** for

STH has been complemented by more recent studies [31] that focussed on the impact of diagnostics schemes on stopping decisions for control of schistosomiasis, while considering new techniques such as qPCR. The authors found that the potential value of more sensitive diagnostics can reduce survey-related costs, although integrating new diagnostics into control programmes requires careful consideration of decision criteria to balance health benefits and programme sustainability. Thus far, alternative diagnostic procedures have not been systematically used in practice nor included in transmission models used for policy. Addressing this gap supports evidence-based criteria for control decisions and ensures that policy recommendations remain robust as diagnostic practices evolve.

Expansion of SchiSTOP

SchiSTOP in its present formulation is already suitable for future research in the epidemiology and control of schistosomiasis. For instance, the presence of a specific module for the dynamics in snails enables a possible detailed evaluation of the effectiveness of molluscicide-based snail control interventions. The impact of a reduction in snail abundance on the force of infection acting on humans can be directly measured. Multiple KK slides can also be simulated, with multiple purposes: e.g. comparing the prevalence estimate and the achievement of the WHO targets across different sampling schemes. Also, the effectiveness of potential alternative pharmaceutical interventions may be tested, i.e. the administration of praziquantel to pre-school-aged-children (pSAC), whose dosing and safety is still under investigation [32-34], or novel drugs aimed to reduce the egg-production of the worms [35, 36].

SchiSTOP can be further expanded to include behavioural interventions, such as WASH, for example by incorporating individual heterogeneities relevant to hygiene practices, or access to clean water and adequate sanitation. Expansions of the model may further incorporate the process of morbidity development in the human population as discussed above, to quantify how morbidity responds to changes in worm burdens pre-, during- and after-control interventions. Finally, expansion of the specific snail module might be beneficial to incorporate differentiated susceptibilities in snails to elucidate if and how genetic variability within snail populations might play a role in maintaining transmission [37] or explaining the very low infection prevalence usually observed in snails [38]. Various aspects of snail transmission dynamics which have been already explored in snail-modelling literature, such as effects

of seasonality, temperature, and annual rainfall [39], snail age structure [40], and a saturating force of infection in snails, can also be considered to be further studied in the complex interplay of snail-environment-human transmission.

7.5. Concluding remarks

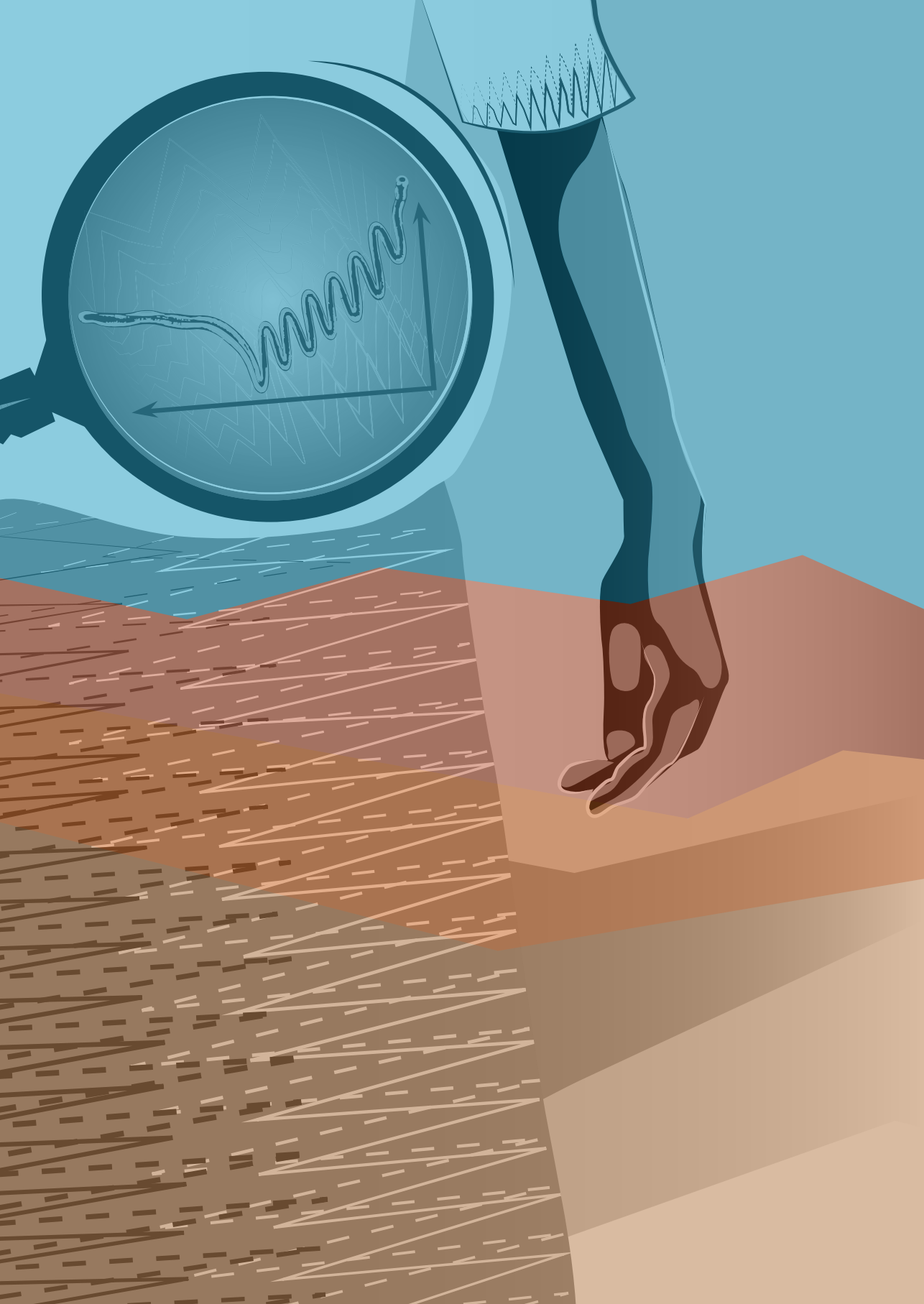
In this thesis, I proposed several tools and diverse methodologies to improve our understanding of helminth transmission dynamics and better inform control interventions, contributing to the broader goal of guiding policy for public health. These tools include statistical models that capture associations in the data, as well as complex stochastic agent-based transmission models tailored to simulate long-term epidemiological trends under various intervention scenarios. The latter are particularly valuable for assessing the feasibility of meeting control targets, such as those set by the WHO for 2030. Despite their advantages, complex models require efficient calibration and validation to ensure reliability and practical relevance, although the calibration of such models poses significant challenges due to their high computational demands. Thus, continued research efforts in data collection and methodology remain essential to advance helminth control. By combining several modelling tools with real-world data, this thesis demonstrates the critical role of modelling in quantifying the invisible, for better control of intestinal parasitic worms.

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Chapter 8 Summaries

8.1. English summary

This thesis provides statistical and mathematical models that contribute to inform policy guidelines for the control of STH and schistosomiasis, at different levels of the decision-making process. Specifically, it aims: i) to assess the epidemiological indicator and threshold for the definition of control targets, ii) the feasibility to reach such targets, and iii) the role of modelling as an opportunity to bridge knowledge gaps in the biology of the disease, as well as prioritise data needs.

The **Chapter 1** of the thesis provides a general introduction on soil-transmitted helminths (STH) and schistosomiasis, two of the most prevalent and important neglected tropical diseases (NTDs), particularly in tropical and subtropical regions characterised by poor health system and hygiene. These parasitic infections, spread through contaminated soil or water, cause a range of morbidities, such as anaemia (particularly from hookworm) and organ damage from schistosomiasis, are diagnosed by detecting parasite eggs in human excreta. Traditional tools like the Kato-Katz (KK) test can, while cost-effective, lack sensitivity, especially for light infections. The chapter discusses the evolution of global control efforts, including mass drug administration (MDA), the promotion of WASH (Water, Sanitation, and Hygiene) interventions, and the setting of WHO targets for morbidity control and transmission elimination by 2030.

A major focus of the chapter is the critical role of mathematical and statistical models in improving our understanding of helminth transmission and informing public health policy. Models help capture the intensity-based nature of helminth infections, where disease outcomes and transmission reflect the number of parasites an individual harbours. Worm burden and egg output are commonly linked using the Negative Binomial distribution to represent parasite aggregation in human populations. More complex models, such as agent-based models (ABMs), simulate individual-level infection dynamics, incorporating heterogeneities in host behaviour, exposure, susceptibility, and response to interventions.

Models can be also used to simulate the performance of diagnostic tools, test the effectiveness of different MDA strategies, and evaluate whether current WHO control targets are appropriate. For example, models have shown that achieving targets may require tailored strategies depending on endemicity level, population structure, and treatment coverage. In schistosomiasis,

modelling has highlighted the importance of accounting for snail intermediate hosts, environmental conditions, and potential regulatory mechanisms like density-dependent fecundity or host immunity, though many aspects remain poorly understood.

Crucially, models not only help interpret existing data but also identify data and knowledge gaps (e.g., snail ecology or environmental contamination) and can guide future data collection for more accurate predictions. Overall, mathematical and statistical modelling is a powerful tool in the global fight against helminthiases, with this thesis aiming to contribute to the modelling literature and enhance their utility in shaping evidence-based control policies.

In **Chapter 2** the suitability of the WHO threshold for morbidity control of STH is assessed (M&HI prevalence in children < 2%) to reflect morbidity attributable to hookworms (one of the three STH species). The focus is on anaemia as primary morbidity associated to hookworm infections, caused by adult worms attaching to the intestinal mucosa of the human host to feed on blood. A hierarchical statistical model to simulate individual haemoglobin levels is presented, incorporating the effects of hookworm burden while accounting for other potential causes of low haemoglobin, such as malnutrition and malaria. The modelling analysis addresses the challenge to disentangle the burden of anaemia that is actually attributable to hookworm, in settings of significant underlying anaemia. This results in estimates of the prevalence of anaemia attributable to hookworm in relationship with prevalence of infection, across various endemicity scenarios and diagnostic sampling schemes. The chapter shows that in all the simulated scenarios, a 2% prevalence of M&HI infections corresponds to a prevalence of anaemia attributable to hookworm infections lower than 1%, therefore supporting the appropriateness of the WHO indicator threshold. Although the prevalence of infection is found sensitive to the number of KK simulated measurements, low values of M&HI infection prevalence (relevant range for morbidity target) are relatively consistent over the three sampling schemes. In this case, the use of single KK slide for determining M&HI infection prevalence reveals cost-effective.

The impact of different sampling schemes on WHO indicators for STH control targets is further expanded in **Chapter 3**. Decision-making for STH is typically based on prevalence indicators measures by KK slides, without a clear protocol about the number of samples and slides per sample to be analysed. KK egg count measurements can vary significantly across repeated stool

samples and smears per sample, affecting survey sensitivity. However, with limited resources, collecting more samples or smears reduces the number of individuals screened, thereby decreasing the statistical precision of prevalence estimates. Using data from diverse epidemiological settings, the work in this chapter evaluates the performance of different sampling strategies under the constraint of a fixed budget, to optimize the balance between sensitivity and precision. To do so, bootstrap iterations are employed as a resampling technique to evaluate the robustness and variability of the sampling schemes used for assessing STH infections. Specifically, multiple resampled datasets are generated by randomly sampling with replacement from the original data. Each resampled dataset retains the same sample size as the original dataset but potentially included repeated data points while excluding others. The procedure is structured to define a set of alternative sampling schemes (combinations of varying number of slides and samples per slide) according to which the survey might have been conducted, but considering the confines of the available resources, meaning less individuals where sampled if more slides were required. The prevalence of any intensity of infection is found sensitive to increasing number of measurements. Sensitivity especially increases if multiple stool samples are examined. Conversely, not much gain in sensitivity is obtained if comparing the M&HI prevalence across sampling schemes. recommended that evaluation of progress towards EPHP, which entails measurement of M&HI prevalence, and policy decisions involving starting and continuing MDA are based on the single KK scheme, ensuring optimal allocation for resources. The decision to stop treatment based on a low threshold prevalence of any infection of 2% would require instead more sensitive sampling. In such cases, the increased costs associated with multiple sampling are likely justified by the potential expense of stopping the programme prematurely.

Chapter 4 shows a case study where a modelling analysis responds to urgent public health questions. A stochastic ABM is used to simulate the impact of missing one or more rounds of MDA against STH, in moderate and in high endemicity settings. This was needed in response to an abrupt interruption of all activities for the control of neglected tropical diseases in endemic countries, in April 2020, due to the COVID-19 pandemic. I investigate the impact of this disruption on the progress towards the WHO 2030 target for STH, and whether the effects can be mitigated by additional strategies, such as more frequent treatment or targeting the whole community. The analysis shows that the impact on the progress is limited if programmes would resume

with the strategy in use, assuming to maintain treatment coverage. The time for the prevalence to catch up with the no-interruption scenario is estimated up to 4.5 years after the start of the interruption. Mitigation strategies reduce this time by up to 2 years and increase the probability of achieving the 2030 target. These can thus be seen as an opportunity to limit morbidity and accelerate progress, for those species and endemicity settings deemed far from targets' achievement even in normal situation. However, the time constraints for this overview did not allow cost-effectiveness considerations and the practical implementation of the mitigation strategies was not investigated.

The impact of different MDA intervention strategies is studied for schistosomiasis in **Chapter 5**, in relation to varying modelling assumptions. The chapter contains the specification and description of a novel modelling framework, SchiSTOP: a stochastic ABM for *S. mansoni* transmission in an age-structured human population, incorporating an explicit deterministic compartmental component to model infection dynamics in snails. The snails are modelled with a Susceptible-Exposed-Infected (SEI) structure to account for the latent period during which the hosts are Exposed to the infection (i.e. the snail has been invaded by the parasite), but they are not able yet to shed the larvae. Shedding snails are considered Infected because they contribute to populate the environmental infective reservoir with larvae that are infective for humans. Using SchiSTOP, I explore the interplay of different regulating mechanisms assumed at worm- (density dependence in egg production), human- (anti-reinfection immunity), and snail-level (depletion of susceptible snails), combined with two different functional choices for describing the age-specific human exposure to infection. I consider 162 different combinations of modelling assumptions, varying degree of regulating mechanisms, endemicity settings, and age-exposure function. For each combination, the ability to explain observed epidemiological patterns for *S. mansoni* is assessed, such as an age-intensity profile peaking in adolescents and a rapid rebound of prevalence after end of treatment. The chapter links to the publicly available code of SchiSTOP, whose formulation is suitable to answer diverse research questions about the epidemiology and control of schistosomiasis. The results support the new schistosomiasis guidelines that prioritise additional control measures, such as behavioural interventions (WASH) and snail control, e.g. through molluscicides, to enhance the progress. According to models identified suitable to reproduce observed patterns for schistosomiasis, it is unlikely to meet the control targets when treating SAC only. If MDA is expanded to community-wide treatment, the feasibility increases both for

EPHP in moderate and high endemicity and interruption of transmission in low endemicity settings.

Chapter 6 provides a methodology to efficiently calibrating SchiSTOP. It describes history matching with emulation, a calibration method to explore the parameter space, while limiting computational demands of complex models. History matching makes use of simplified surrogate models (emulators), trained to reproduce the inputs-outputs behaviour of the full model, to iteratively narrow down parameter space until a non-implausible region of parameters is possibly identified. The chapter shows how history matching is applied to fit SchiSTOP on field intensity and prevalence data, provided at increasing level of information by age groups. The chapter aims to investigate what types of data are most informative for improving parameter estimation and therefore accuracy of model predictions. Overall, the chapter emphasises that efficient calibration frameworks, combined with age-stratified data collection, are crucial to provide accurate model predictions that enable more robust public health policy recommendations and targeted control strategies.

Finally, a discussion of the main findings and the methods of this thesis makes the content of **Chapter 7**. The main aims of the thesis are addressed and recommendations from this thesis are presented. The chapter elaborates on the use of statistical and mathematical models to inform strategic decision-making for the control of STH and schistosomiasis. The strengths and limitations of different modelling approaches are discussed, highlighting their utility in simulating complex transmission dynamics, as well as the challenges of calibrating such models, especially with limited or imperfect data. It emphasizes how modelling both reveals data gaps and helps prioritize future data collection needs. The chapter concludes by outlining limitations of the thesis and proposing future research directions.

8.2. Nederlandse samenvatting

Dit proefschrift onderzoekt statistische en wiskundige modellen die bijdragen aan het onderbouwen van beleidsrichtlijnen voor de bestrijding van STH (soil-transmitted helminths; door de bodem overgedragen worminfecties) en schistosomiasis, op verschillende niveaus van het besluitvormingsproces. Het proefschrift heeft specifiek tot doel: i) de epidemiologische indicator en drempelwaarde voor het definiëren van controledoelen te evalueren, ii) de haalbaarheid van het bereiken van deze doelen te onderzoeken, en iii) de rol van modellering als middel om kennislacunes in de biologie van de ziekte te onderzoeken, en prioriteiten voor data verzameling vast te stellen.

Hoofdstuk 1 is een algemene introductie van soil-transmitted helminths (STH) en schistosomiasis, twee van de meest voorkomende verwaarloosde tropische ziekten (NTD), met name in tropische en subtropische regio's die worden gekenmerkt door zwakke gezondheidssystemen en gebrekkige hygiëne. Deze parasitaire infecties, die worden overgedragen via verontreinigde bodem of water, veroorzaken verschillende gezondheidsproblemen, zoals anemie (met name door haakworm infecties) en orgaanschade bij schistosomiasis. De diagnose gebeurt doorgaans door het aantonen van parasieteneieren in humane excretie. Traditionele diagnostische methoden zoals de Kato-Katz (KK)-test zijn kosteneffectief, maar hebben een beperkte sensitiviteit, vooral bij lichte infecties. Het hoofdstuk bespreekt de ontwikkeling van wereldwijde bestrijdingsprogramma's, waaronder massale medicatietoediening (MDA), de bevordering van WASH-interventies (Water, Sanitatie en Hygiëne), en de vaststelling van WHO-doelstellingen voor beheersing van gezondheidsschade en transmissie-eliminatie tegen 2030.

Een belangrijk thema in dit hoofdstuk is de cruciale rol van wiskundige en statistische modellen in het verbeteren van ons begrip van de transmissie van worminfecties en in het ondersteunen van volksgezondheidsbeleid. Modellen maken het mogelijk om het intensiteit-gebonden karakter van worminfecties te beschrijven, waarbij ziekte uitkomsten en transmissie samenhangen met het aantal parasieten dat een individu draagt. De worm last en productie van eitjes worden vaak gemodelleerd met behulp van de negatieve binomiale verdeling om aggregatie van parasieten binnen populaties weer te geven. Complexere modellen, zoals agent-based modellen (ABM), simuleren infectiedynamiek op individueel niveau en houden rekening met heterogeniteit in gedrag, blootstelling, vatbaarheid en respons op interventies.

Modellen kunnen tevens worden gebruikt om de prestaties van diagnostische tests te simuleren, de effectiviteit van verschillende MDA-strategieën te testen en te evalueren of de huidige WHO-doelen haalbaar zijn. Zo tonen modellen aan dat voor het behalen van doelstellingen strategieën op maat nodig zijn, afhankelijk van endemisch niveau, populatiestructuur en in hoe volledig de dekking van behandeling is. Voor schistosomiasis heeft modellering het belang aangetoond van het meenemen van de intermediaire host (zoetwaterslakken), omgevingsfactoren en mogelijke regulerende mechanismen zoals dichtheidsafhankelijke fecunditeit of hostimmunitet, hoewel veel aspecten nog onvoldoende begrepen blijven.

Cruciaal is dat modellen niet alleen gebruikt worden voor het interpreteren van bestaande data, maar ook kennislacunes kunnen identificeren (bijvoorbeeld omtrent de rol van slakken ecologie of verontreiniging van de omgeving) en richting geven aan toekomstige dataverzameling voor nauwkeurigere voorspellingen. Wiskundige en statistische modellen vormen een krachtig instrument in de wereldwijde bestrijding van worminfecties, en dit proefschrift beoogt bij te dragen aan de wetenschappelijke basis van modellen en het vergroten van hun bruikbaarheid voor evidence-based beleidsvorming.

In **Hoofdstuk 2** wordt de WHO-drempel voor morbiditeitscontrole van STH (prevalentie van matige en zware infecties (M&HI) < 2% bij kinderen) geëvalueerd als indicator voor morbiditeit toe te schrijven aan mijnworminfecties (één van de drie STH-soorten). De focus ligt op anemie geassocieerd met mijnworm, veroorzaakt doordat volwassen wormen zich hechten aan het darmslijmvlies en bloed opnemen. De basis is een hiërarchisch statistisch model om individuele hemoglobinewaarden te simuleren, waarbij rekening wordt gehouden met de invloed van wormlast en met andere oorzaken van lage hemoglobinewaarden, zoals ondervoeding en malaria. De analyse richt zich op het deel van de anemielast dat daadwerkelijk aan mijnworm kan worden toegeschreven te onderscheiden in situaties met een hoge achtergrondprevalentie van anemie. Dit leidt tot schattingen van de prevalentie van aan mijnworm toe te schrijven anemie in relatie tot infectieprevalentie onder verschillende endemische scenario's en strategieën voor bemonstering. De resultaten tonen aan dat in alle gesimuleerde scenario's een M&HI-prevalentie van 2% overeenkomt met een prevalentie van aan mijnworm toe te schrijven anemie van minder dan 1%, wat de geschiktheid van de WHO-drempel ondersteunt. Hoewel de infectieprevalentie gevoelig blijkt (in de simulaties) voor het aantal KK-metingen, blijven lage M&HI-prevalenties (relevant voor het morbiditeitsdoel) relatief consistent

over drie bemonsteringsschema's. In dit geval blijkt het gebruik van één enkele KK-preparaat kosteneffectief voor het bepalen van M&HI-prevalentie.

In **Hoofdstuk 3** wordt de impact van verschillende bemonsteringsschema's op WHO-indicatoren voor STH-controle verder onderzocht. Beleidsbeslissingen zijn doorgaans gebaseerd op prevalentie-indicatoren gemeten met KK-preparaten, zonder een duidelijk protocol voor het aantal monsters en uitstrijkjes per monster. Tellingen van eitjes kunnen aanzienlijk variëren tussen herhaalde monsters en uitstrijkjes, wat de sensitiviteit van de bemonsteringen beïnvloedt. Bij beperkte middelen leidt het verzamelen van meer monsters of uitstrijkjes echter tot minder gescreende individuen en dus tot lagere statistische precisie. Op basis van gegevens uit epidemiologisch verschillende settings wordt de prestatie van verschillende strategieën voor bemonstering geëvalueerd onder een vast budget, met als doel een optimale balans tussen sensitiviteit en precisie te vinden. Bootstrap-iteraties worden toegepast als techniek om de robuustheid en variabiliteit van bemonsteringsschema's te beoordelen. De resultaten tonen aan dat de schatting van prevalentie van infecties van welke intensiteit dan ook gevoelig is voor een toename van het aantal metingen, vooral wanneer meerdere monsters per individu worden onderzocht. Daarentegen is er weinig winst in sensitiviteit bij vergelijking van M&HI-prevalentie tussen schema's. Daarom wordt aanbevolen om de evaluatie van voortgang richting EPHP (eliminatie van een volksgezondheidsprobleem), gebaseerd op M&HI-prevalentie, en beslissingen over het starten of voortzetten van MDA te baseren op het schema met één enkele KK-meting. Het stoppen van behandeling op basis van een lage drempel (2% prevalentie van eender welke infectie) vereist echter bemonstering met grotere sensitiviteit; in dat geval kunnen de hogere kosten gerechtvaardigd zijn om voortijdige beëindiging van programma's te voorkomen.

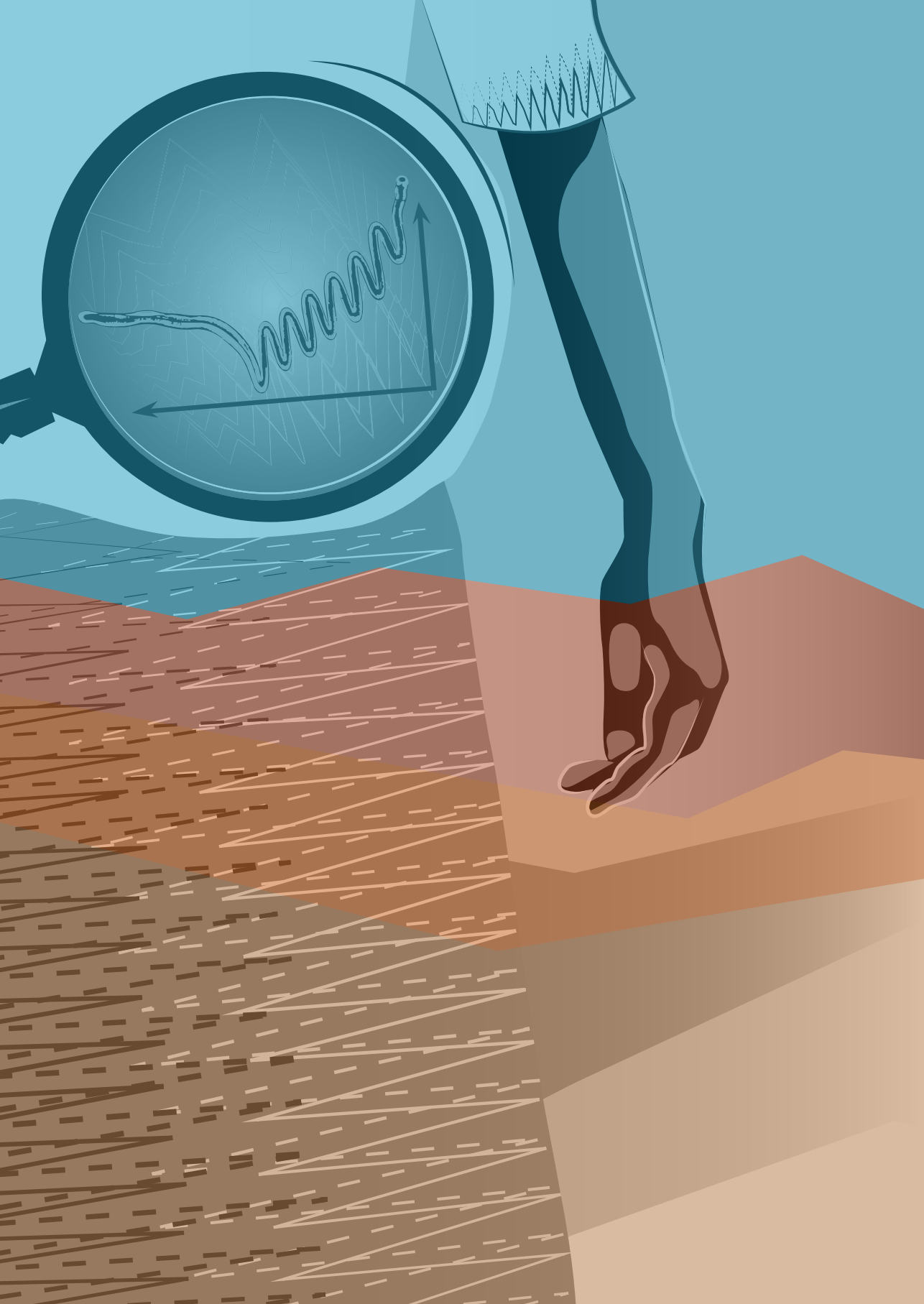
Hoofdstuk 4 presenteert een case studie waarin modellering wordt ingezet om volksgezondheidsvragen met urgentie te beantwoorden. Een stochastisch ABM wordt gebruikt om de impact te simuleren van het missen van één of meerdere MDA-rondes tegen STH in matig en hoog endemische settings. Dit was noodzakelijk na de plotselinge onderbreking van NTD-controleactiviteiten in april 2020 als gevolg van de COVID-19-pandemie. De impact van deze verstoring op de voortgang richting de WHO 2030-doelstelling voor STH wordt onderzocht, evenals de vraag of aanvullende strategieën (zoals frequentere behandeling of populatie brede behandeling) de effecten kunnen beperken. De analyse toont aan dat de impact beperkt blijft indien programma's worden

hervat met behoud van de dekking van de populatie. De tijd tot herstel naar het scenario zonder onderbreking wordt geschat op maximaal 4,5 jaar na de start van de onderbreking. Mitigatiestrategieën kunnen deze periode met maximaal twee jaar verkorten en verhogen de kans op het behalen van de 2030-doelstelling. Kosten-effectiviteitsanalyses en praktische implementatie werden niet onderzocht.

In **Hoofdstuk 5** wordt de impact van verschillende MDA-strategieën voor schistosomiasis onderzocht in relatie tot een reeks van modelaannames. Het hoofdstuk beschrijft een nieuw model framework, SchiSTOP: een stochastisch ABM voor de transmissie van *S. mansoni* in een leeftijd gestructureerde humane populatie, gecombineerd met een deterministisch compartimentenmodel voor de infectie dynamiek in slakken. De slakkenpopulatie wordt gemodelleerd met een Susceptible-Exposed-Infected (SEI)-structuur om de latente periode te beschrijven waarin slakken wel geïnfecteerd maar nog niet infectieus zijn. Met SchiSTOP worden verschillende regulerende mechanismen onderzocht op wormniveau (dichtheidsafhankelijke eiproductie), humaan niveau (anti-herinfectie immuniteit) en slakkenniveau (uitputting van vatbare slakken), gecombineerd met twee functies voor leeftijdsafhankelijke blootstelling. In totaal worden 162 combinaties van aannames geëvalueerd. De resultaten ondersteunen nieuwe richtlijnen die aanvullende controlemaatregelen, zoals gedragsinterventies (WASH) en slakkenbestrijding (bijvoorbeeld met mollusciciden), prioriteren. Volgens de passende modellen is het onwaarschijnlijk dat controledoelen worden bereikt wanneer enkel schoolgaande kinderen worden behandeld. Gemeenschap brede MDA vergroot de haalbaarheid van EPHP in matig en hoog-endemische settings en van transmissieonderbreking in laag-endemische settings.

Hoofdstuk 6 beschrijft een methode om SchiSTOP efficiënt te kalibreren via "history matching" met emulatie. Deze methode maakt gebruik van vereenvoudigde surrogaatmodellen (emulators) om het gedrag van het volledige model te benaderen en iteratief de parameter-ruimte te verkleinen tot een niet-onwaarschijnlijke regio is geïdentificeerd. De toepassing op veldgegevens van prevalentie en intensiteit, gestratificeerd naar leeftijd, toont welke datatypen het meest informatief zijn voor het schatten van model parameters en de nauwkeurigheid van het model. Goed gedefinieerde en praktisch haalbare kaders voor kalibratie van modellen, in combinatie met leeftijd gestratificeerde dataverzameling, zijn essentieel voor robuuste beleidsaanbevelingen.

Tot slot bevat **Hoofdstuk 7** een algemene discussie van de belangrijkste bevindingen en methoden. De sterke en zwakke punten van verschillende modelleringsbenaderingen worden besproken, evenals de uitdagingen van kalibratie bij beperkte of onvolledige data. Het hoofdstuk benadrukt hoe modellering datalacunes blootlegt en toekomstige dataverzameling kan sturen. Het proefschrift sluit af met een bespreking van beperkingen en aanbevelingen voor toekomstig onderzoek.



Appendices

Research Data Management

List of publications

Curriculum Vitae

Acknowledgments

PhD Portfolio

Research Data Management

This thesis consists of statistical and data analyses that only make use of already published and anonymised data.

Ethics and privacy

This thesis is based on the results of research that did not involve collection or creation of new data. When using published data involving human participants, the privacy of the participants in these studies was warranted by the use of fully anonymous data.

Data collection and storage

For Chapter 2, the data employed in the statistical analysis have been collected and described for previous publication in Pullan R.L., Kabatereine N.B., *et al.* (2010). The anonymised data were shared with us by the authors. The original study protocol was approved by the Makerere University Faculty of Medicine Research and Ethics Committee (#2008-043), the Uganda National Council of Science and Technology (#HS 476) and the London School of Hygiene and Tropical Medicine Ethics Committee (#5261). All analyses of Chapter 2 were performed in accordance with the Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD) criteria.

For Chapter 3, four different datasets were analysed. All datasets have been collected within already existent projects. We did not access the raw data. We obtained only a selection of variables on anonymised data, relevant to the study. The first dataset is the same as described for Chapter 2. The second dataset held baseline data from an epidemiological study described and published in Sarkar R., Rose A. *et al.* (2017). The authors report approval by the Institutional Review Board (IRB) of CMC, Vellore, India and registration in the Clinical Trials Registry - India (CTRI: <http://ctri.nic.in>) under registration number CTRI/2013/05/003676. Written informed consent was obtained from all participants prior to participation. The third dataset constituted baseline data from the TUMIKIA study, a comparative-effectiveness study implemented by Kenya Medical Research Institute (KEMRI) and founded by the Bill & Melinda Gates Foundation. Detailed information on the project, the participation criteria, and the publications attained within the project is available at <https://www.cor-ntd.org/research-outcomes/studies/tumikia-project> and at <https://clinicaltrials.gov/study/NCT02397772?tab=study>. The fourth dataset contained baseline data from the Starworms (STop Anthelminthic Resistant

WORMS) study, a Bill & Melinda Gates Foundation funded project that unites three WHO Collaborating Centres. Information and details on the project can be found at <https://www.starworms.org/> and the official study protocol is published in Vlamincck J., Cools P. *et al.* (2018). Full acknowledgements for data sharing for use in Chapter 3 of this thesis is included in the Chapter.

Chapter 4 constitutes a simulation study based on existent mathematical models, that did not comprise field data. The model parameters were informed via published literature. The simulation results reflect hypothetical scenarios and ethical approval or data management statement was not required. All analyses were performed in accordance with the Policy-Relevant Items for Reporting Models in Epidemiology of Neglected Tropical Diseases (PRIME-NTD) criteria, further described in Chapter 4.

Chapter 5 presents a modelling framework that did not make use of collected and reported field data. The model parameters were informed via published literature.

For Chapter 6, existent field data were filtered and analysed. The data have been published and described in Nigo M.M., Odermatt P., *et al.* (2021). The authors report approval by the Swiss Ethical Commission (Ethikkommission Nordwest und Zentralschweiz [EKNZ], Ref. No. UBE-15/78) and the University of Kisangani's Research Ethical Commission (Ref No: CER/003/GEAK/2016). Research authorization was granted by the Nyankunde Higher Institute of Medical Techniques (Ref No 70/ISTM-N/SGAC/2017), Bunia, DRC. Permission for field work was obtained from Ituri Provincial Health Division (Ref. 054/433/DPS/IT/06/2016 and Ref. 054/472/DPS/IT/06/2017) and from all relevant health districts. Written informed consent was obtained from all study participants aged 15 years or older. The anonymised data were shared with us by the authors Maurice Mutro Nigo and Patrick Hunziker who are also co-authors of the study constituting Chapter 6 of this thesis.

Data sharing according to the FAIR principles

Chapters 2 to 5 of this thesis are published open access. Chapter 6 is not published and is in preparation for submission.

The data used for Chapter 2 and the full code for data selection, statistical analysis and simulations are publicly available at https://github.com/VeronicaMalizia/Hookworm_anaemia

All relevant data for Chapter 3 and 4 are within the published manuscripts and their Supporting Information files.

For Chapter 5, the full source code for model implementation, simulations, and preparation of figures, is publicly available at
https://github.com/VeronicaMalizia/SchiSTOP_model

For Chapter 6, the full code for the analyses generating the results of Chapter 6 are published online at
<https://github.com/VeronicaMalizia/Efficient-calibration-ABM/tree/v1.0>

List of publications (2019 – 2024)

Publications from this thesis

1. Coffeng LE, **Malizia V**, Vegvari C, Cools P, Halliday KE, Levecke B, *et al.* (2020). Impact of different sampling schemes for decision making in soil-transmitted helminthiasis control programs. *The Journal of Infectious Diseases*, 221(Suppl. 5), S531–S538.
2. **Malizia V**, Giardina F, Vegvari C, Bajaj S, McRae-McKee K, Anderson RM, *et al.* (2021). Modelling the impact of COVID-19-related control programme interruptions on progress towards the WHO 2030 target for soil-transmitted helminths. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 115.
3. **Malizia V**, Giardina F, de Vlas SJ, Coffeng LE. (2022). Appropriateness of the current parasitological control target for hookworm morbidity: A statistical analysis of individual-level data. *PLOS Neglected Tropical Diseases*, 16(6), e0010279.
4. **Malizia V**, de Vlas SJ, Roes KCB, Giardina F. (2024). Revisiting the impact of *Schistosoma mansoni* regulating mechanisms on transmission dynamics using SchiSTOP, a novel modelling framework. *PLOS Neglected Tropical Diseases*, 18(9), e0012464.

Other publications

1. Imtiaz R, Campbell SJ, Vegvari C, Giardina F, **Malizia V**, de Vlas SJ, *et al.* (2019). Insights from quantitative analysis and mathematical modelling on the proposed WHO 2030 goals for soil-transmitted helminths. *Gates Open Research*, 3, 1632.
2. Vegvari C, Giardina F, **Malizia V**, de Vlas SJ, Coffeng LE, Anderson RM. (2021). Impact of key assumptions about the population biology of soil-transmitted helminths on the sustainable control of morbidity. *Clinical Infectious Diseases*, 72 (Suppl. 3), S188–S194.
3. Vegvari C, Giardina F, Bajaj S, **Malizia V**, Hardwick RJ, Truscott JE, *et al.* (2021). Deworming women of reproductive age during adolescence and pregnancy: what is the impact on morbidity from soil-transmitted helminths infection? *Parasites & Vectors*, 14, 220.
4. Toor J, Adams ER, Aliee M, Amoah B, Anderson RM, Ayabina D, *et al.* (2021). Predicted impact of COVID-19 on neglected tropical disease programs and the opportunity for innovation. *Clinical Infectious Diseases*, 72(8), 1463–1466.

5. Borlase A, Le Rutte EA, Castaño S, Blok DJ, Toor J, Giardina F, **et al.** (2022). Evaluating and mitigating the potential indirect effect of COVID-19 on control programmes for seven neglected tropical diseases: a modelling study. *The Lancet Global Health*, 10(11), e1600–e1611.

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I believe that completing a PhD is a journey of successes and failures, professional and personal growth. My track, in particular, was not standard. I had the great opportunity to begin as a Junior Researcher with an international project, without secured funding for the continuation of the PhD. Then, the possibility to start another project, in a new group, in a new city, where I could build on and expand on what I had started. All of this was made possible by my supervisors, who accompanied me throughout this journey, with expert eyes.

Dr. Federica Giardina, I remember our first call during the recruiting process, when I had just graduated, and I was trying to fit in a brand new role as a consultant in a very hot Milan. But my hopes were for a job in scientific research and infectious disease modelling, which I really liked during my studies. We spoke in English, I was still not really sure whether you had Italian nationality too. Honestly, that was my first professional call in English and I realised it only afterwards. I still did not know, but your call was about to change my life: the hiring news did not only mean work, but also the begin of my Dutch part of life. Although I start with acknowledging the opportunity you gave me and the funding you secured for the completion of my PhD, I would like to further thank you for the trust you placed in me, for the support, for the feedback, and the career guidance. Even in the moments of disagreements or challenges during the PhD, our discussions valuably helped my professional growth.

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every working day. It feels now almost unbearable, but only good memories actually comes to my mind about that period. Although too many to list all names, I sincerely thank you every single member of the "Worms' club" for all the stimulating scientific discussions, thank you Luc for guiding me through my first scientific paper and for all the valuable help you have always provided to me. Thank you Thomas, Zoë for sharing science and dramas of the PhD life. Thank you to all the juniors I met, for lightening the working days with lunch breaks, social activities, and overtime in the office for playing soccer table.

I was not less lucky when I moved to Radboud UMC. Thank you to all the colleagues of the Biostatistics team and to all the PhDs and other employees that I met at the (originally HEV) department. Despite I was coming to the office only once per week due to the long commuting, you always made me feel part of the group. I appreciated how much attention and importance was given to every individual personality. Thank you Scott, Jo, for stimulating my self-confidence and sharing with me many PhD experiences and suggestions.

Although this work covered the period up to 2024, I believe that my current MOD team (and other colleagues) at RIVM is worth of acknowledgements. Thank you all for supporting me, despite the administration of this PhD was still not finalised. I love the job here, where I can see how excellent science translates into tangible impact on society.

Fabio, avrai notato che il tuo nome non viene esplicitamente menzionato tra il gruppo Erasmus. Hai pensato anche solo per un secondo che fosse stata una svista? Sei stato così tante cose per me, che sarebbe difficile piazzarti in un solo gruppo, ecco perciò che avrai il tuo paragrafo. Grazie per essere stato un mio collega, abbiamo condiviso scienza, alti e bassi lavorativi, e sapevo che ogni giornata sarebbe iniziata con un selfie nell'ascensore dell'EMC. Grazie per essere stato un mio coinquilino, appena messo piede a Rotterdam io mi sono sentita a casa. Abbiamo condiviso maratone TV, cene, e certamente tanto disagio. Ma anche in questi momenti non ci siamo mai trascurati. Grazie per essere un mio amico, la mia vita a Rotterdam sarebbe stata certamente diversa se non ti avessi incontrato. Hai riposto subito fiducia e simpatia in me, gettandomi nel mondo internazionale di Rotterdam, ci siamo divertiti tanto e la gioventù ci permetteva di uscire tutte le sere. Grazie per essere stato il celebrante del mio matrimonio, perché come una persona di famiglia, hai partecipato all'evolversi della mia vita sentimentale. Grazie per avermi permesso di essere tua 'paranimf', così da accompagnarti nel giorno che tante

volte ci siamo immaginati insieme. Ed infine manca solo una cosa... grazie per essere il mio 'paranimf'! Perché sì, se penso a due persone che possano conoscere il contenuto scientifico ed emotivo del mio dottorato quasi quanto me, potete essere solo tu e Marco.

To the Rotterdammers crew, all the current and ex Rotterdammers, the Nonnen in Pasten, I refer every day of you as my Dutch family, and I mean it deeply. Living abroad brings joy and enlightening experiences, but family and sense of community is what is missed the most. Thank you for always having each other for smiles, for tears, for (unfortunately) growing up. The Drambuie crew and the nights in Witte de Withstraat, the Nederlandse familie and all our little trips in the middle of nowhere, the lovely Gooses and the screams just to remind ourselves that we are happy, Ranu and Matte e i nostri pranzi della Domenica, all of you are the reason why I can forever call the Netherlands home. À Oriane aussi, merci pour le temps qu'on a vécu ensemble, parce que la pandémie nous a forcés à rester à la maison presque 24/7, et alors on a créé une routine familiale de travail, master chef, séries, et Backstreet Boys.

Then I moved to Utrecht. Although I was moving for love, coming here was not without a little shock: all my friends were elsewhere and I was not working in the city. But like always in my life, my personality which recharges among people and not solo, helped me to meet lovely friends. A Lorenza, grazie per essere stata la prima persona in assoluto che si è fermata a parlarmi solo perché avevi sentito la lingua italiana, ti abbiamo chiesto il numero di telefono in mezzo alla strada e non sei scappata via. Da quel momento, tutto è andato in discesa per me. Federico, Aureliana, Sigo, Valeria, Gianmarco, grazie per le infinite conversazioni incoraggianti sul PhD, anche quando non ne vedevo la luce. Thank to every other friend I met in Utrecht, and the No Apoya no folla big group, for making this crazy life fun despite the 'agenda'.

To all friends far away, thank you for being with me in all the important milestones of my life, despite the thousands kilometres between us. Bruzzo, Giulio, Laura, Elisabetta, abbiamo superato insieme quelli che ai tempi ci sembravano gli ostacoli più insormontabili per diventare grandi: gli esami universitari. Ma poi ci siamo visti effettivamente diventare grandi, dai banchi alle conferenze scientifiche, navigando l'incertezza del futuro. Grazie per essere ancora in contatto e per le rimpatriate di scienza e di divertimento. A tutti i cari amici che ho lasciato tra Trento e Bologna tra i gruppi salsa e le coinqui Anna e Giulia, mi sento così fortunata ad avervi ancora con me. Non

abbiamo condiviso scienza, ma avete contribuito a formare e nutrire la me che è arrivata fin qui, camminando insieme attraverso ogni cambiamento. A Elena, Floriana, Rita, Kira, Marta, Chiara, un grazie infinito per essere da sempre delle costanti nella mia vita. Anche quando ho fatto le valigie e sono partita, anche quando i momenti di vita diversi hanno allontanato i nostri interessi, anche quando la routine rende difficile sentirci. Grazie per aver sempre fatto grandi sforzi per poter gioire insieme a me di ogni traguardo.

Nederland verdient ook mijn dank, 'dat hele kleine stukje aarde', zoals een oud liedje klinkt. We zijn nu verliefd. Bedankt voor de uitstekende carrière-mogelijkheden die je aan buitenlanders biedt. Wat je denkt is waar: ik mis de zon, de zee, de olijfolie, mijn familie, de spontaniteit in ontmoetingen. Maar hier voel ik me vrij en onafhankelijk. In mijn bubbel heb je me de cultuur van tolerantie, inclusiviteit, en openheid ten opzichte van diversiteit geleerd. Ik geniet hier van mijn werk en tegelijkertijd heb ik de mogelijkheid om te reizen wanneer ik daar even aan wil ontsnappen. Ten slotte, speel je de belangrijkste rol in mijn leven: ik heb jou gekozen als het land waar mijn dochter geboren zal worden!

Alla mia famiglia non sarò mai abbastanza grata per il privilegio donatomi di aver sempre potuto scegliere ciò che mi piaceva, sentendomi sempre accompagnata. Ringrazio la famiglia allargata: zii, cognati, suoceri per mostrare sempre interesse in ciò che faccio, o per avermi chiesto di descrivere il mio lavoro in dieci parole così da poterlo raccontare, ma poi spesso riassumerlo in "lavora al computer". Alle mie vecchiette, perché ad ogni abbraccio prima di partire portavo via con me un po' di voi, e adesso ci siete in ogni espressione che uso, in ogni piatto che cucino, in ogni ricordo, in ogni risveglio. Un ringraziamento speciale a babbo, mamma, Marta, zia Carla. Mi avete visto fare la valigia per la prima volta a 18 anni e forse voi sapevate già che sarebbe stato un cambiamento a lungo termine. Io no, ancora non me ne rendevo conto. Credo che uno dei gesti di amore più grandi sia quello di un genitore che lascia partire un proprio figlio, per donargli la libertà di trovare il suo posto, anche se a parole ti augura solo buona fortuna. Grazie per avermi cresciuta con i valori di rispetto, curiosità, responsabilità, che credo nel loro insieme mi abbiano avvicinata alla scienza. Grazie per aver festeggiato con me tutti i raggiungimenti, e per aver fatto chilometri quando invece andava male, così da poter saltare insieme.

The love of family, this I would like to transmit to my daughter. To my daughter, a mia figlia, aan mijn dochter, thank you for letting me experience a depth of love that I never thought I was capable of bearing. At the moment of writing these acknowledgements you are still unborn, we share a body and we are deeply connected. In every effort I make to finalise the PhD defence, I think of you being with me on that day. I did not plan it when I started, then life has its own flow. I wish for you to be independent, to be free and find your passions, to value yourself and your ideas. I wish for you to embrace the immense privilege of simply being born here and now, and choose to use it in every way possible to help create a kinder, fairer, and more equal world.

Negli articoli scientifici, l'ultimo nome ricopre il ruolo di supervisore senior che guida il progetto e si assicura della sua riuscita. Grazie a mio marito e 'paranimf', Marco, Qu, al quale lascio l'ultimo nome in questi Ringraziamenti. Posso pensarti proprio così, un faro guida nel nostro progetto di vita, ed anche nel mio dottorato. Grazie per le serate che mi hai dedicato nell'aiutarmi a calcolare probabilità, a risolvere errori nel mio codice, ad utilizzare GitHub. Grazie per tutte le ore in cui mi hai ascoltata raccontarti la mia giornata: mi hai co-regolato le emozioni con un abbraccio quando mi hai trovata stressata o in lacrime per eventi che non andavano come previsto, e hai lanciato un brindisi per ogni piccolo e grande successo. Percepisco il valore che dai alla mia persona ed alla mia figura professionale quando racconti del mio lavoro. Credo davvero che tu sia in grado di rispondere ad ogni domanda che riguarda questo libro. Un libro che in fin dei conti è cresciuto con noi: dall'incertezza e inesperienza degli inizi, alla maturazione di un progetto non perfetto, ma definito e consapevole. Grazie per essere questo progetto. Grazie per chiederci ogni giorno "raccontami tutto di come è andata oggi", grazie per intraprendere a breve con me un progetto più grande di ogni idea immaginabile e che non avrà mai data di scadenza, o meglio, 'finché, il più tardi possibile, i nostri atomi torneranno a danzare nell'universo'.

Curriculum Vitae

Veronica Malizia is an infectious disease modeller whose research focuses on the development and application of mathematical and computational models to support public health decision-making. Her work combines mathematical biology, infectious disease modelling, and epidemiology to better understand the transmission dynamics of infectious diseases and to evaluate the impact of control and elimination strategies.



Veronica was born on 25 December 1993 in San Benedetto del Tronto, Italy. She left her hometown on the seacoast for university studies in the north of Italy. She obtained her Bachelor's degree in Mathematics from the University of Bologna, Italy, in 2016. She subsequently pursued a Master's degree in Mathematics for Life and Data Science at the University of Trento, graduating in 2018.

During her Master's studies, she developed a strong interest in the application of mathematical modelling to biological systems and public health. Her Master's thesis, as a result of a Research Internship carried out at Fondazione Bruno Kessler (FBK) in Trento, focused on modelling the transmission dynamics of healthcare-associated infections caused by antibiotic-resistant pathogens, in a low-incidence Italian hospital.

In 2019 the decision to leave Italy to pursue a career in interdisciplinary research. Veronica joined, in that year, the Department of Public Health at Erasmus MC in Rotterdam as a Junior Scientific Researcher. There, she worked on mathematical modelling for neglected tropical diseases, contributing to research on the control and elimination of intestinal parasites. As part of her project, she was a member of the NTD Modelling Consortium: a group of modelers responding urgent neglected tropical diseases (NTD) policy issues and providing quantitative support to policy decision makers, major donors, and organizations. Her work supported the evaluation of intervention strategies and informed international discussions on the World Health Organization's 2030 targets for neglected tropical diseases.

In July 2021, she started her PhD at the Department of IQ Healthcare, Biostatistics Section, Radboud University Medical Center in Nijmegen. Her doctoral research built upon the work carried out at the Erasmus MC. She

developed mathematical and agent-based models to study the transmission dynamics of schistosomiasis, with the aim of improving the understanding of the parasite transmission and supporting evidence-based control and elimination strategies.

After completing her PhD, Veronica continued as a postdoctoral researcher at RadboudUMC. Here, she worked on a one-year project focused on mathematical modelling to support equitable and effective responses to epidemics, by integrating epidemiological evidence with quantitative modelling approaches.

Since January 2025, Veronica has been working as a Scientific Researcher at the Dutch National Institute for Public Health and the Environment (RIVM), within the Centre for Epidemiology and Surveillance of Infectious Diseases. She develops mathematical models that integrate behavioural sciences and data into infectious disease modelling to strengthen public health policy advice.

Throughout her career, she has published in leading journals and attended international conferences for science dissemination and networking. During her time at Erasmus MC and RadboudUMC she was involved in departmental initiatives, including co-authoring the Junior newsletter or development and maintenance of the team website.

Veronica enjoys working in multidisciplinary and international research environments. Outside science, she is passionate about dance, theatre, travelling, and discovering new cultures and languages.



PhD portfolio of Veronica Malizia

Department: IQ Health
PhD period: 01/07/2021 – 31/12/2024
PhD Supervisor(s): prof. dr. C.B. Roes
prof. dr. S.J. De Vlas
PhD Co-supervisor(s): dr. F. Giardina

Training activities	Hours
Courses	
• RIHS - Introduction course for PhD candidates (2021)	15.00
• Radboudumc - Introduction day (2021)	6.00
• Digital Research Environment for beginners (2022)	10.00
• RU - Writing Scientific Articles (2022)	96.00
• Summer School in Infectious disease modelling and Health economics (2022)	35.00
• RU - Open Science for PhD candidates (2022)	20.00
• Seminar Mathematical Epidemiology (2022)	110.00
• Radboudumc - Scientific integrity (2023)	20.00
• Meet the Expert - Bridge the gap between the scientific community and the general public (2024)	2.00
• Cluster computing for social scientists with R (2024)	8.00
• Getting ready for your first grant application (2024)	32.00
• Radboudumc - Career development for PhD candidates & postdocs "The next step in my career" (2024)	20.00
Seminars	
• RIHS PhD Retreat (2022)	12.00
• Modern Mixed Models (2022)	4.50
• PhD Day 2022 (2022)	6.00
• RIHS PhD Retreat (2022)	7.00
• Personal Grant Info meeting 2022 (2022)	2.00
• Mini-symposium on models and methods for infectious diseases (2023)	10.00
• Meet the Expert - Prepare your defense (2023)	2.00
• Malaria mini-symposium (2024)	8.00
Conferences	
• European Congress on Tropical Medicine and International Health (ECTMIH) (2021)	49.00
• Science day - Radboud Center for Infectious diseases / research theme Infectious Diseases & Global Health (2022)	23.00
• CaRe Days (2022)	15.00
• WEON 2022 (2022)	40.00
• NCOH Annual Scientific Meeting (2023)	8.00

Conferences (continued)	
• WEON 2023 (2023)	14.00
• European Congress of Tropical Medicine and Hhygiene (ECTMIH) (2023)	28.00
• EPIDEMICS9 (2023)	32.00
• WEON 2024 (2024)	16.00
• Symposium: Paradigm shifts for Global One Health (2024)	24.00
• NCOH Annual Scientific Meeting (2024)	8.00
• Congress on Pandemic & Disaster Preparedness (2024)	9.00
Teaching	
• 'Meet the PhD' project (2022)	56.00
• Design and Analysis of experiments (BMS14) (2022)	12.00
• Introduction to R for PhD (2023)	21.00
• Bootcamp statistics (2024)	28.00
Other	
• Reviewing a scientific article (2021)	16.00
• Reviewing a scientific article (2023)	24.00
• Developing and maintaining website of Biostatistics Research team (2024)	52.00
Total hours	900.50

About the author



