Modelling diagnostic error to improve estimation of helminth treatment efficacy, age-specific prevalence and enhance comparison of diagnostic tools

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Carla Marcela Grolimund Guiza

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Erstbetreuerin:	PD Dr. Penelope Vounatsou
Zweitbetreuer:	Prof. Dr. Jürg Utzinger
Externer Experte:	Prof. Dr. Charles Harding King

Prof. Dr. Marcel Mayor
Dekan

Basel, den 15. November 2022

Summary

Background: According to the latest global disease burden estimates roughly 1.1 billion people suffer from neglected tropical diseases (NTDs), from which over a billion are infected with soil-transmitted helminths (STHs) or *Schistosoma* leading to a considerable public health burden. For instance, children mainly suffer from anaemia and growth stunting while adults may develop chronic diseases, which can also result in confined function of affected organs. With financial support from different organisations and donations from pharmaceutical companies, numerous interventions have been implemented to reduce the burden of NTDs. In some cases, specific NTDs have been eliminated. The main interventions are preventive chemotherapy (PC), water, sanitation and hygiene (WASH) and information, education and communication (IEC). However, much remains to be done, and hence, in 2020, the World Health Organization (WHO) put forth a road map for the control and elimination of the NTDs.

To reach the best possible outcomes, control programmes need to be informed about the impact of interventions. This requires prevalence and infection intensity estimates at baseline and following interventions. To assess the prevalence and efficacy of treatments, tools that are widely used lack accuracy, and hence, result in underestimated prevalences and overestimated cure rates (CRs). Highly sensitive diagnostic techniques are available, but rarely applied in the field. It is therefore important to include the diagnostic error to obtain 'true' estimates to accurately inform disease control programmes.

Goal and objectives: The overreaching goal of this PhD thesis was to improve estimation of diagnostic error taking into account variation in egg counts from day-to-day and slide-to-slide to evaluate the performance of diagnostics, disease burden and the efficacy of treatments to better guide control and elimination efforts of NTDs. The specific objectives were to (i) estimate the performance of diagnostic tools against *Schistosoma haematobium*; (ii) translate prevalence thresholds from urine filtration into reagent strip; (iii) assess the efficacy of drug therapies against STHs; (iv) assess the sensitivity of diagnostics for different *Schistosoma* species and STHs; and (v) estimate age-dependent prevalence for *S. mansoni* using Bayesian methods.

Methods: In Chapter 2, I developed a model to compare diagnostic methods for *S. haematobium*, namely urine filtration and reagent strip. Urine filtration results consisted of egg counts, while reagent strip results were semi-quantitative, wherefore two different distributions were assumed. To estimate the prevalence, the infected and non-infected individuals were separated. As the data consist of specimen taken on five consecutive days subjected to two different tests, I was able to take into account diagnostic error and hence, estimate infection intensity-dependent sensitivity. Moreover, by running extensive simulations of hypothetical populations in diverse

transmission settings, we relate WHO prevalence thresholds from urine filtration into reagent strip.

In Chapter 3, I developed a transmission model to conduct a meta-analysis on CR and egg reduction rate (ERR) for an ensemble of drug therapies against hookworm. The prevalence, which is defined as harbouring at least one fertilized female worm, and the CRs were estimated by incorporating a mixture modelling approach. The model was fitted to data from six randomized controlled trials. At baseline and treatment follow-up, two specimen per study participant were collected over consecutive days, which enabled us to take into account diagnostic error and estimate the infection intensity-dependent sensitivity of the Kato-Katz test for hookworm.

In Chapter 4, I extended the egg count model of Chapter 3 and included the density-dependent fecundity to estimate CR and ERR for several drug therapies against *Trichuris trichiura*. Moreover, the infection intensity-dependent sensitivity of the Kato-Katz test was estimated for *T. trichiura*.

In Chapter 5, I extended a transmission model and included diagnostic error to estimate age-dependent prevalence curves for *S. mansoni* and predicted the prevalence of adults from the prevalence of school-aged children. The model was fitted to data from Uganda, which was collected by the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) and consists of specimen taken on consecutive days (two days for two years, three days for one year). This enabled estimating the infection intensity-dependent sensitivity of the Kato-Katz test for *S. mansoni*.

Results: The diagnostic accuracy of reagent strip was equivalent to urine filtration data obtained on a single day, when traces were considered negative. A 10% and 50% urine filtration prevalence based on a single day sampling corresponds to 11.2% and 48.6% prevalence by reagent strip, respectively, when traces were considered negative, and 17.6% and 57.7%, respectively, when traces were considered positive.

Taking the diagnostic error into account resulted in considerably lower CRs for drug therapies against hookworm than previously reported. Overall, of all treatments analyzed, mebendazole administered in six dosages of 100 mg each was the most efficacious treatment with a CR of 88% (95% Bayesian credible interval: 79-95%). Diagnostic sensitivity of Kato-Katz for hookworm varied with the infection intensity and sampling effort. For an infection intensity of 50 eggs per gram of stool (EPG), the sensitivity is close to 60%; for two Kato-Katz thick smears it increased to 76%.

The treatment with the highest CR against *T. trichiura* was the combination therapy of albendazole plus pyrantel pamoate plus oxantel pamoate with a CR of 79% and an ERR of 91%. Albendazole plus oxantel pamoate showed the highest ERR of 97% and a CR of 69%. For 24 EPG, the sensitivity was around 50% for a single and increased to almost 70% for duplicate Kato-Katz thick smears.

For 24 EPG, the sensitivity of Kato-Katz for *S.mansoni* was estimated to be 55%, 77% and 99% for simple, duplicate and quadruplicate thick smears.

Conclusions/significance: The main contribution of this PhD thesis to the field of mathematical modelling in public health is the development or extension of modelling frameworks to accurately compare the performance of diagnostics, assess their sensitivity, estimate treatment efficacy and age-specific prevalence. In more detail: (i) reagent strip and urine filtration were compared for detection of *S. haema-*

tobium; (ii) the intensity-dependent sensitivity for different sampling schemes was estimated for aforementioned diagnostic tools as well as the Kato-Katz technique for hookworm and *T. trichiura*; (iii) the efficacy of different treatments against hookworm and *T. trichiura* were assessed; (iv) the age-specific prevalence for *S. mansoni* was estimated; and the prevalence in adults was predicted from the prevalence in school-aged children for *S. mansoni*. The higher accuracy compared to existing studies was achieved by taking into account diagnostic error and the transmission mechanism.

If reagent strip instead of urine filtration would be employed in schistosomiasis control programmes, the costs could be substantially reduced and proceedings would be more efficient. Moreover, the treatment efficacy and infection intensity-dependent sensitivity estimates for different sampling schemes may be considered in aforementioned programmes to make decisions about suitable drug therapies and sampling designs.

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Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Rationale

According to the latest global disease burden estimates, 1,310 million of people worldwide suffer from neglected tropical diseases or malaria, from which 909 million are infected with intestinal nematodes, also known as soil-transmitted helminths and 140 million with *Schistosoma* (Vos et al., 2020). These infections lead to a substantial health burden and therefore, control programmes are implemented to reduce or eliminate these diseases (Lo et al., 2017). The main interventions are preventive chemotherapy (PC), water, sanitation and hygiene (WASH) and information, education and communication (IEC) (Lo et al., 2017). To reach the best possible outcomes, control programmes need to be informed about disease burden as well as impact of interventions.

We developed four Bayesian modelling frameworks, which provide information about cure and egg reduction rates of a substantial number of treatments against different parasites, age-specific prevalence and performance of diagnostic techniques. All models take into account diagnostic error, and hence, provide more accurate results compared to most existing studies. Furthermore, two models also include the transmission mechanism of the parasites, which also increases accuracy of the results.

1.2 Neglected tropical diseases (NTDs)

NTDs are a group of mainly chronic infections, which mostly affect people in low-income countries (Hotez et al., 2020), particularly in Africa, Asia and Latin America (Hotez et al., 2007). In comparison to HIV/AIDS, malaria and tuberculosis, the NTDs have been neglected mainly because of the lower number of deaths (Kindhauser & Organization, 2003). For instance, the latest global burden of disease (GBD) estimates show that in 2019 0.9, 0.6 and 1.2 million people died from HIV/AIDS, malaria, and tuberculosis, respectively, compared to 0.1 million due to NTDs (Vos et al., 2020). Nevertheless, NTDs cause immense health burden, which can be quantified by comparing the estimated years lived with disability (YLD). YLD are calculated as the years lived suffering from a disease multiplied with a weight between zero and one, representing the severity of the disability (Grosse et al., 2009; Struijk et al., 2013). GBD estimates 4.0, 2.6, and 4.3 million YLD for HIV/AIDS, malaria, and tuberculosis, respectively, compared to 11.1 million for NTDs (Vos et al., 2020). Those diseases have also been neglected, as there was no interest in developing drug therapies, diagnostics and vaccines for poor markets (Hotez et al., 2016; Kindhauser & Organization, 2003). The latest developments give hope: with financial support from different organisations and donations from pharmaceutical companies, numerous interventions have been implemented to reduce burden and in some cases already reach elimination (Hotez et al., 2007). For instance, the prevalence of schistosomiasis has been reduced by 58.2% in sub-Saharan Africa over the past 15-20 years (Kokaliaris et al., 2022).

In this work we focus on two NTDs, namely schistosomiasis, 'the most important water-based disease from a global public-health perspective' and soil-transmitted helminthiasis, the most prevalent NTD (Steinmann et al., 2006; Utzinger et al., 2012; Vos et al., 2020). They are both caused by parasitic worms also called helminths.

1.2.1 Schistosomiasis

History

Schistosomiasis, also known as bilharzia, is the disease caused by *Schistosoma* parasites, which infect people since thousands of years (Gryseels et al., 2006). It is not clear where schistosomes evolved and started parasitising humans, but modern genetic analyses suggest an Asian origin and later spread to Africa (Anastasiou et al., 2014; Lawton et al., 2011). In a skeleton from as early as 4500-4000 BC found in the Euphrates, Syria, a schistosome egg was identified. Egyptian medical papyri dating back to 1500 BC describe a disease causing symptoms as they occur with schistosomiasis. Moreover, it was recommended to avoid polluted water to prevent infection, which is a strong indication for *Schistosoma* parasites (Anastasiou et al., 2014). The history of *S. japonicum* goes back to more than 2,000 years ago but it is assumed that it was already prevalent earlier (Utzinger et al., 2005). The first record of a parasitic worm of the genus *Schistosoma* goes back to 1851, when Theodore Maximilian Bilharz and Carl Theodor Ernst conducted autopsies on human bodies in Cairo, Egypt (Jordan, 2000). Several parasites of both sexes were found in the portal system and bladder (Coon, 2005). In honor to the discoverer's name Theodor Maximilian Bilharz, the nowadays called *Schistosoma* parasites (schistosomes) were named bilharzia by English biologist Thomas Spencer Cobbold in 1859 (Cobbold, 1859). In the same year, he discovered that not only humans were affected, when he found a bilharzia parasite in a monkey. In 1902 physician Sir Patrick Manson found a different *Schistosoma* species in a patient living in the Caribbean, showing for the first time that various species exist (Di Bella et al., 2018). The first case of *S. japonicum* was reported in 1905 in the Hunan province (Utzinger et al., 2005).

Key facts

At present, six *Schistosoma* species are known. Five of them cause intestinal schistosomiasis (*S. mansoni, S. japonicum, S. mekongi, S. guineensis*, and *S. intercalatum*) and one urogenital schistosomiasis (*S. haematobium*) (WHO, 2018). The latter is prevalent in Africa, the Middle East and France (Corsica) (Berry et al., 2014), while intestinal schistosomiasis is distributed across Africa, Asia and the Americas. In more detail, *S. mansoni* is prevalent in Africa, the Middle East, Brazil, Venezuela, the Caribbean and Suriname, while *S. japonicum* is found only in Asia, specifically in China, Indonesia and the Philippines. *S. mekongi* is prevalent in Cambodia and Lao People's Democratic Republic and *S. guineensis* and *S. intercalatum* in the rain forests of central Africa. Fig. 1.1 depicts the distribution across sub-Saharan Africa for the two most prevalent species. The most widespread *Schistosoma* species are *S. mansoni, S. haematobium* and *S. japonicum* (Gryseels et al., 2006). According to the latest estimates, 140 million people suffer from a schistosomal infection, leading to approximately 1.6 million disability-adjusted life years (DALYs) and 12,000 deaths per year (Vos et al., 2020).

Life cycle

The life cycle of schistosomes involves snails as intermediate host. Depending on the schistosome, the species of the snail varies (see Fig. 1.2). The cycle works as follows. Cercariae, which are the larval form of the parasites, penetrate the skin when humans

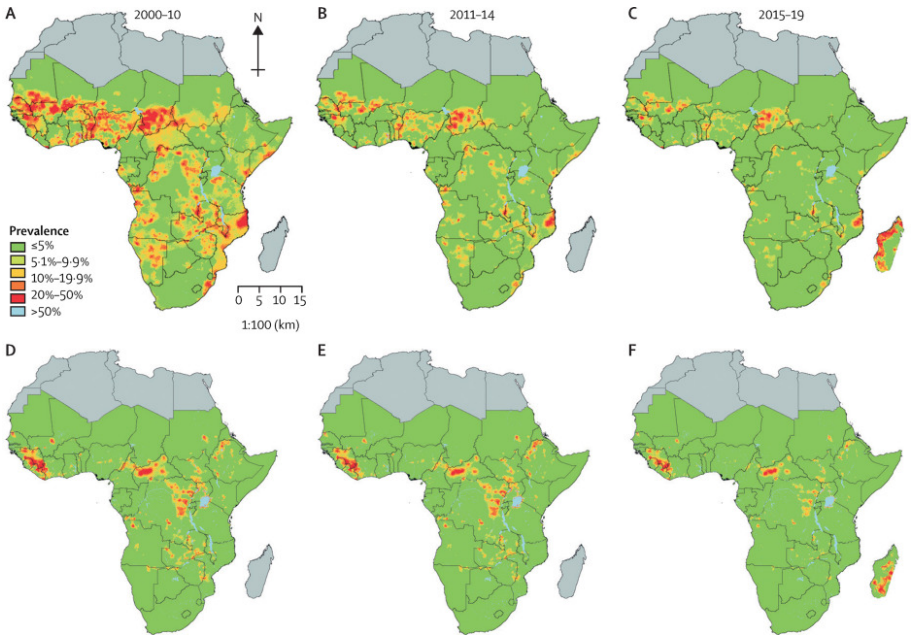

Figure 1.1: Estimated schistosomiasis prevalence across sub-Saharan Africa, in 2000-2010, 2011-2014 and 2015-2019. **A-C** *Schistosoma haematobium*; **D-F** *Schistosoma mansoni* (source: Kokaliaris et al., 2022)

have contact with infested water (Combes et al., 1994). While entering the human body, they shed their tail and become schistosomulae (still a larval stage) and travel through the veins to the lungs (CDC, 2019b). They pass through the heart and mature to worms in the liver. Male and female worms pair and females lay eggs in the mesentric vessels of the bowel in the case of *S. mansoni, S. japonicum, S. mekongi, S. guineensis* or the bladder for *S. haematobium* (CDC, 2019b; McManus et al., 2018). The eggs are excreated in the faeces or urine, respectively. As soon as the eggs are exposed to water, miracidia hatch and penetrate the snail. In the snail they transform into cercariae, which are released into the water, closing the cycle.

Symptoms and clinical manifestations

Acute symptoms may start when the larvae penetrate the skin causing a rash, also named 'swimmers itch'. Individuals who are exposed for the first time can develop 'Katayama fever', experiencing stronger fever in the afternoon among other symptoms, which resolves after two to eight weeks (Ross et al., 2007). If schistosomulae survive in the human host and male and female worms pair, the host may develop an inflammation of the tissue due to the entrapped eggs. This in turn may lead to fibrosis and confine the function of affected organs. For instance, gastrointestinal as wells as genitourinary complications can arise and the liver, heart, lung and central nervous system can be affected. *S. mansoni* is normally responsible for gastrointestinal complications, while *S. haematobium* causes genitourinary complications (Coon, 2005). These often show as blood in urine or faeces, respectively. Infected children may suffer from anaemia, growth stunting, reduced ability to learn and comprised physical fitness, resulting in substandard school performance (Colley et al., 2014a; McManus et al., 2018; WHO, 2018). Adults with chronic infections may not be able to work as usual, which reduces economic productivity (McManus et al., 2018;

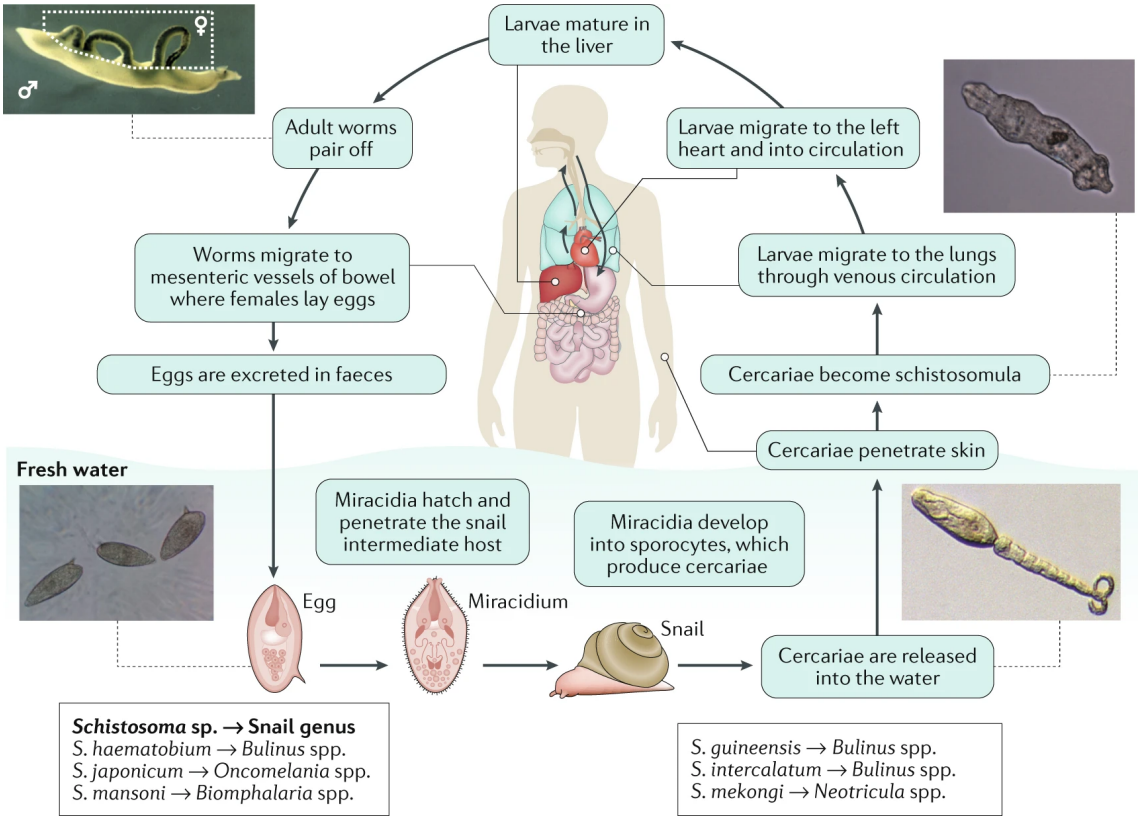

Figure 1.2: Life cycle of *Schistosoma* on the example of *S. mansoni* (source: (McManus et al., 2018)).

Rinaldo et al., 2021).

1.2.2 Soil-transmitted helminths

History

Reports suggest that hookworms were already prevalent in the Middle ages. Yet, the first record of a hookworm dates back to 1838 when Angelo Dubini conducted a human autopsy. He named the roundworm *Ancylostoma duodenale*. The relation of anaemia and hookworm was discovered by Edoardo Perroncito in 1880 while conducting autopsies on bodies of workers building the St Gotthard tunnel in Switzerland. The life cycle of *A. duodenale* was determined around 1898 by parasitology professor Arthur Looss in Cairo, Egypt (Looss, 1908). Four years later zoologist and parasitologist Charles W. Stiles discovered the second hookworm species *Necator americanus* in Puerto Rico (Power, 2001).

In 1761 a new worm species was reported by J. G. Roederer, who named the genus of the whipworms *Trichuris*, which means 'hair tail' ("American Society of Parasitologists: Sixteenth Annual Meeting, Philadelphia, Pa.", 1941). Nevertheless, he was mistaken regarding the morphology, wherefore 21 years later Goeze renamed it *Trichocephalos*, meaning 'hair head'. A few years later Schrank adapted the name to *Trichocephalus*. The Committee on Nomenclature of the American Society of Parasitologists prioritised the name *Trichuris* (Bundy & Cooper, 1989). Newer reasearch showed that *T. trichiura* was already parasitising humans much earlier,

when fossilised faeces from as early as 7,100 BC were found containing *T. trichiura* eggs (Doyle et al., 2022).

The Romans, including Celsus, knew about the existence of *Ascaris lumbricoides* in the first century. The genus *Ascaris* and its infections were described by Paulus Aeginata in the 7th century. It was Linnaeus, who described and named the species of roundworms *A. lumbricoides* in 1758 (Cox, 2002; Despommier et al., 1995). Almost 100 years later, Henry Ransom found eggs in faeces. In the following years several experiments were done, where individuals were infected with eggs. An intermediate host could not be found until, in 1916, Major F. H. Stewart assumed that it was a rat (Lane, 1917). Finally, in 1922 Shimesu Koino confirmed that the life cycle of *A. lumbricoides* did not involve an intermediate host by eating eggs and finding larvae in his sputum a few days later (Koino et al., 1922). New research shows that as early as 2,277 BC *A. lumbricoides* parasitised humans as eggs have been found in human fossilized faeces in Peru (Cox, 2002).

Nowadays, it is known that the history of *A. lumbricoides, T. trichiura* and *A. duodenale* goes back to more than 400,000 years ago. The three species are so called 'heirloom parasites' as they coevolved with humans (species of the *Homo* lineage) (Araujo et al., 2008). Eggs found in ancient sites indicate that they evolved in the tropical and subtropical regions of the Old World, while three theories exist of how they migrated to the New World.

Key facts

Soil-transmitted helminths (STHs) are, as the name suggests, mainly transmitted through contaminated soil and are distributed throughout the world (Feasey et al., 2010; Organization et al., 2018) (see Fig. 1.4). Most infections are found in tropical and subtropical areas, mainly in sub-Saharan Africa, the Americas, China and East Asia (WHO, 2019a). At present, 909 million people suffer from soil-transmitted helminthiasis, leading to 1.97 million DALYs (Vos et al., 2020). Children are at highest risk as they generally harbour most worms and are more susceptible to the consequences of soil-transmitted helminthiasis (Feasey et al., 2010). They often suffer from anaemia, growth stunting, intellectual retardation and cognitive and educational deficits (Bethony et al., 2006; Feasey et al., 2010). The main species are *A. lumbricoides*, *T. trichiura*, *N. americanus* and *A. duodenale*, also called roundworm, whipworm and (the New and Old World) hookworm, repectively (John & Markell, 2006). It is often the case that infected individuals harbour all three species (Bethony et al., 2006). Fig. 1.3 shows the prevalence and distribution of the different STH species.

Life cycle

Hookworm larvae live in the soil and enter the human body by penetrating the skin (often through feet and hands, which are the points of contact with contaminated soil). Traveling through the bloodstream, they reach the heart and later the lung. From there, they are coughed up the air tube and swallowed. Through the esophagus the larvae reach the small intestine, where they mature to worms. In contrast to schistosomes, hookworms are polygamous, which increases the probability of mating. The eggs reach the soil when human faeces are used as fertilizer or in the absence of sanitary facilities (Brooker et al., 2004). The larvae hatch in the soil, closing the

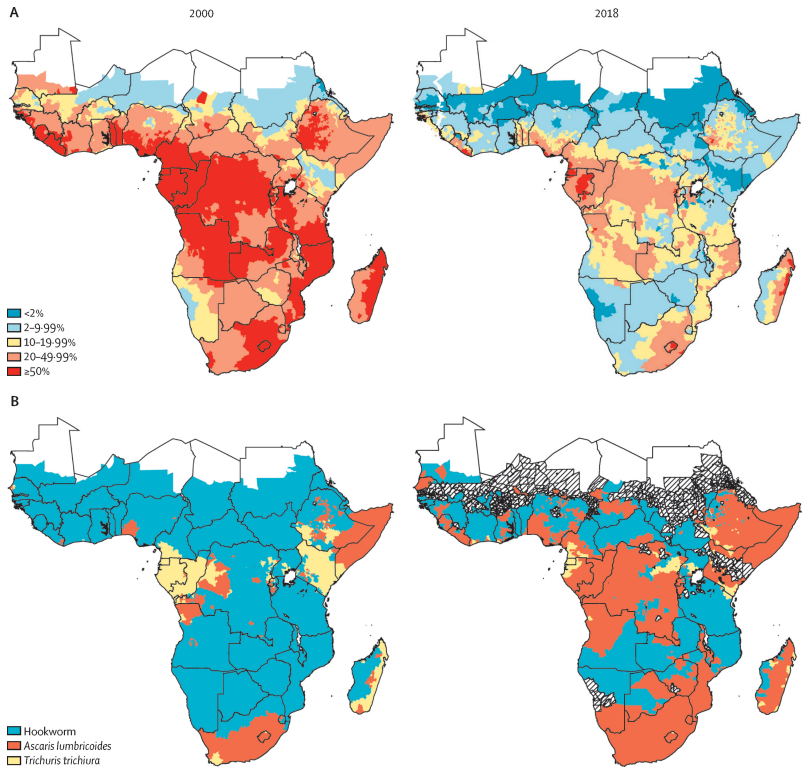

Figure 1.3: Estimated prevalence of soil-transmitted helminth infection (**A**) and distribution of main soil-transmitted helminth species in Africa (**B**), in 2000 (left) and 2018 (right) (source: (Sartorius et al., 2021))

cycle (Fig. 1.4) (Hotez et al., 2004). *A. duodenale* can also infect individuals by oral ingestion (Jourdan et al., 2018).

In the case of *A. lumbricoides*, the larvae pass through three stages while residing in the egg. They enter the body of the human host by oral ingestion, hatch and travel from the intestine to the lungs. They mature and pass through the air tube to be swallowed. In the small intestine, they mature further to worms. An adult female worm releases around 200,000 eggs per day (CDC, 2019a), which are passed through the faeces closing the cycle (Jourdan et al., 2018).

T. trichiura eggs develop in the soil and are first unembryonated, then develop to a 2-cell stage, before they reach the cleavage stage and finally embryonate. The eggs are also ingested orally via food or hands and the eggs hatch in the small intestine, but in contrast to *A. lumbricoides*, they do not travel to the lungs. They mature to adult worms and reside in the caecum or the colon. Finally, the eggs are passed in the stool (CDC, 2019c; Jourdan et al., 2018).

Symptoms and clinical manifestations

The larval migration of hookworms may cause ground itch, cough as well as wakana disease and in the case of *A. lumbricoides* pneumonia. Symptoms due to hookworms are intestinal blood loss, iron-deficiency anaemia and protein malnutrition. Individuals suffering from ascariasis (the disease caused by *A. lumbricoides*) may develop lactose intolerance, vitamin A malabsorption and intestinal obstruction due to the adult worms in the intestine. In the case of *T. trichiura* worms, the clinical features include colitis, rectal prolapse and *Trichuris* dysentary syndrome, which

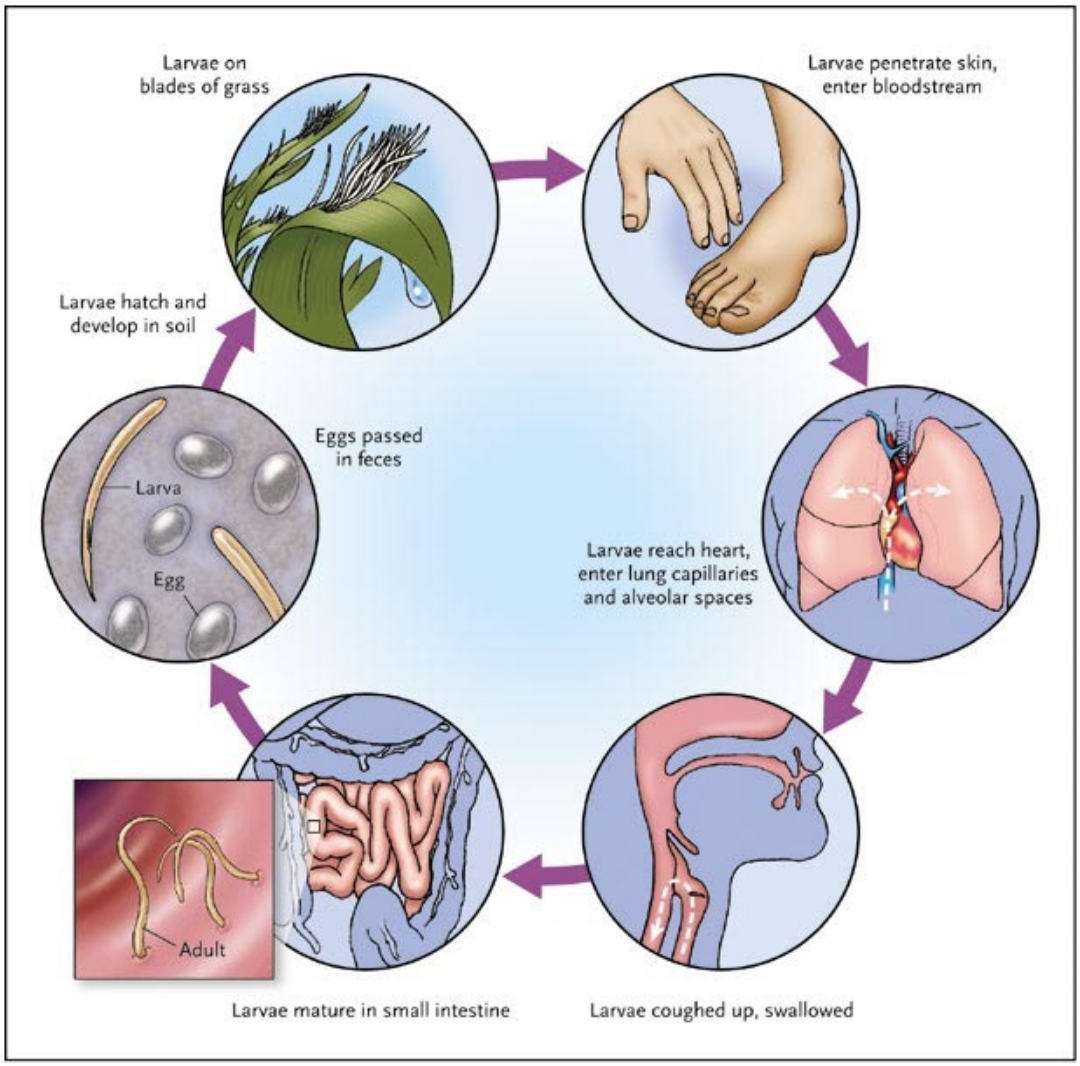

Figure 1.4: Life cycle of *A. duodenale* and *N. americanus* (source: (Hotez et al., 2004))

involves diarrhoea, rectal bleeding, anaemia and finger clubbing (swelling of the tips of the fingers) (Azira, Zeehaida, et al., 2012; Bethony et al., 2006; Rajagopalan & Schwartz, 2022).

1.3 Treatments and their efficacy

To reduce the burden of schistosomiasis and STHs or reach elimination, administration of drug therapies – a strategy termed preventive chemotherapy (PC) – is employed. The three different approaches are mass drug administration (MDA), targeted chemotherapy and selective chemotherapy, i.e. either all individuals in an area or only groups at risk are treated (e.g. school-aged children) or people in an area are tested and only positive individuals treated, respectively (WHO, 2017). Several single-drug and combination therapies are available against schistosomiasis and STHs.

Schistosomiasis

World Health Organization (WHO) recommends praziquantel for treatment of schistosomiasis (WHO, 2018), which works by paralysing the worms (Santos et al., 2020). It is known to be safe and low-cost; no serious adverse events have been observed and in case of re-infection the risk of severe disease is lower (CDC, 2020; Utzinger & Keiser, 2004). Yet, not all patients are cured, as schistosomulae survive this treatment and may further develop in a host. Therefore, administering two doses of praziquantel at few weeks interval has been suggested (Danso-Appiah et al., 2013; Danso-Appiah et al., 2008; Utzinger & Keiser, 2004). Another drug available against schistosomiasis is Oxamniquine, however, it only has an effect against *S. mansoni* (Santos et al., 2020). For both drugs, evidence exists for low efficacy and potential anthelminthic resistance (Santos et al., 2020). For instance, praziquantel shows low efficacy among children, who have been treated repeatedly in MDA campaigns (Crellen et al., 2016). Drug resistance against praziquantel in experiments is low, hence, there is no proof but caution is advised (Colley et al., 2014a). Therefore, new drugs against schistosomiasis are needed.

A global strategy to control morbidity due to schistosomiasis was launched by WHO in 1984, which included PC with praziquantel. Almost 30 years later the recommendation changed towards elimination wherever possible (Colley et al., 2014a). According to the current strategy against schistosomiasis preschool- and school-aged children in endemic areas, adults in endemic areas, adults whose profession involves contact with infested water (e.g. fisher, farmers) and communities in high-endemic areas should be treated (WHO, 2018).

Soil-transmitted helminthiasis

Various drugs are available against STHs; yet their efficacy is low, especially against *T. trichiura*. WHO recommends albendazole (400 mg) and mebendazole (500 mg) for treatment of STH (WHO, 2019a), however these drugs show different levels of efficacy against the different STH species. For instance, albendazole is more efficacious against hookworm than mebendazole, both drugs show high efficacy against *A. lumbricoides* and low efficacy against *T. trichiura*. Pyrantel pamoate

demonstrates high, decent and low efficacy against *A. lumbricoides*, hookworm and *T. trichiura*, respectively. Levamisole is only efficacious against *A. lumbricoides*. In recent years, the efficacy of drug combinations and repurposed drugs developed for veterinary or general anthelmintic use, has been assessed. For instance, tribendimidine was developed to treat humans against various helminths, oxantel pamoate was used in combination with pyrantel pamoate, while ivermectin and moxidectin were developed for the treatment of animals (Moser et al., 2019). The efficacy of these drugs is assessed via cure rates (CRs) and egg reduction rates (ERRs). The CR quantifies the rate of patients with no measurable eggs (cured patients), while the ERR represents the reduction in eggs after treatment. All therapies show high efficacy against *A. lumbricoides* except for oxantel pamoate. For hookworm the highest CR and ERR were achieved with a combination therapy of tribendimidine plus ivermectin, while albendazole plus oxantel pamoate showed the highest efficacy against *T. trichiura*. It is recommended for future campaigns to co-administer ivermectin with albendazole or mebendazole against trichuriasis (the disease caused by *T. trichiura*) for better control or eliminitation of the disease. Furthermore, the efficacy of drug combinations should be further investigated (Freeman et al., 2019; Schulz et al., 2018; Turner et al., 2016).

At present, targeted chemotherapy against STHs is recommended by WHO. The people at risk, who should be treated are preschool- and school-aged children, adolescent girls, women of reproductive age (including pregnant women) and adults working in high-risk professions living in endemic areas (WHO, 2017, 2019a). Due to the COVID-19 pandemic, only 42% of people at risk were treated in 2020 compared to 58% in 2019.

1.4 Diagnostic tools

Unfortunately, many diagnostic tools to detect helminth infections are imperfect, i.e. either positive individuals are wrongly tested negative (false-negative) or non-infected patients show a positive test result (false-positives). The accuracy of a diagnostic technique is characterised by the sensitivity and specificity, which are the rate of sick patients recognized by the test as such and the rate of healthy patients who test negative, respectively (Akobeng, 2007). The following diagnostic tools are available for different Schistosoma species and STHs.

Tools for intenstinal schistosomiasis and STH

For the Kato-Katz technique, a thick smear is prepared using 41.7 mg of stool. A cellophane strip containing glycerin is pressed on top, making the faeces transparent, which enables trained laboratory technicians to count the eggs under a light microscope. Thereby it is imporant to analyse the thick smear as soon as the faeces are clear but before the eggs are over-cleared, which is approximately between 30 min and one hour after preparation (Katz et al., 1972; Martin, Beaver, et al., 1968; Moser, Bärenbold, et al., 2018). McMaster, FLOTAC and mini-FLOTAC are other microscopic egg counting techniques which are used for diagnosis of STHs and the latter two for intestinal schistosomiasis (Utzinger et al., 2015). There is evidence to suggest that FLOTAC may be more sensitive than the Kato-Katz technique for *A. lumbricoides* (Jourdan et al., 2018). The point-of-care urine circulating cathodic

antigen (POC-CCA) detects antigens of the worm in the host urine. It is easy to apply, cost-effective and studies indicate a higher sensitivity than the Kato-Katz technique for *S. mansoni*, particularly in low prevalence settings (Straily et al., 2022). Furthermore, it has been recognized as useful for mapping, but its use for monitoring and control has yet to be analysed.

Tools for urogenital helminths

In case of polycarbonate filters, urine is filled into a syringe and expeled on the filter, which is then placed on a microscope slide. Afterwards a drop of iodine solution is added and the eggs are counted under a microscope (Organization et al., 2013a). Another indication for urogenital schistosomiasis is the detection of blood in urine, called haematuria. This is done either using a reagent strip or by detection of visible blood in urine, called micro- and macro- or gross haematuria, respectively. Dipstick, also called reagent strip, is easy to use, as it only has to be dipped into urine. The strip reacts and changes colour, which can be compared to the manufacturer's chart. The different colours represent categories of blood intensity in urine (Awosolu et al., 2019; King & Bertsch, 2013). For individual diagnosis macrohaematuria has shown higher sensitivity that microhaematuria (Midzi et al., 2020).

Additional tools for helminths

Other diagnostic techniques for schistosomiasis and STH are available such as serological approaches. In the case of schistosomiasis they work by detecting antibodies against the different *Schistosoma* stages as well as proteins linked to them (Hinz et al., 2017). However, a positive test result can arise from previous, current or re-infection, or from an infection with a different parasitic worm. It also might miss an infection of an individual who has low antibody response due to repeated infections. For these reasons serology is mainly employed for patients in non-endemic areas, like travellers (Hinz et al., 2017). A combination of serological tests with existing diagnostic tools should be assessed for schistosomiasis (Hinz et al., 2017). Polymerase chain reaction (PCR) works by detecting parasite DNA. It is a high sensitive tool, but comparatively expensive and therefore not adequate for use in the field (Guegan et al., 2019).

Recommendations

For control and mapping of schistosomiasis the WHO recommends the Kato-Katz technique for detection of eggs in faeces (*S. mansoni, S. japonicum*), as well as polycarbonate (or nylon or paper) filters and dipstick for detection of eggs and blood in urine (*S. haematobium*), repectively (Colley et al., 2014a; Utzinger et al., 2015; WHO, 2018). Nevertheless, these techniques suffer from low sensitivity, mainly in the case of acute infections. WHO has set priorieties regarding diagnostics for control and elimination of schistosomiasis and STH. For schistosomiasis, standardized and sensitive point-of-care diagnostics (easy to use and fast tools), tests for resistance to praziquantel and surveillance should be developed. In the fight against STH, tests for desicion making on when to stop PC, tests to detect resistance to drugs

in the field and standardized diagnostic procedures are needed (Organization et al., 2020b).

1.5 Modelling diagnostic error and transmission mechanism

Diagnostic error

As described above, helminth infections in populations are measured by imperfect diagnostic tools. Hence, the data does not accurately describe the actual situation.

Studies on helminths either provide only one test result per individual or multiple testing of an individual is employed, i.e. multiple samples from one specimen are tested and/or several specimen are collected on different days (generally consecutive days). This is done to get more accurate results as it is known that egg counts vary from day to day and samples from one specimen may differ (Anderson & Schad, 1985; Booth et al., 2003). In most analyses only binary information is used i.e. an individual is either positive (meaning that at least one of the samples contained eggs or blood) or negative (all samples negative). Latent class models are often employed in medical science, where individuals are categorized by disease status. The latent variable generally separates the diseased and non-diseased individuals and the true disease status of an individual is the latent data (Garrett & Zeger, 2000; Tarafder et al., 2010). For instance, these models are used to infer on the accuracy of diagnostics for *Schistosoma* and STH (Booth et al., 2003; Nikolay et al., 2014). Most of these diagnostics suffer from low sensitivity, hence infected individuals are missed, particularly in the case of light infections, leading to an underestimation of disease prevalence (De Vlas & Gryseels, 1992).

If data consist of multiple test results per specimen and day for each individual, they can be used to model the intra-specimen and day-to-day variation, respectively (Bärenbold et al., 2017). This variation in turn enhances the estimation of the 'true' prevalence (De Vlas et al., 1992). Thereby, it is important to comprise that test results for an individual are not independent (Bärenbold et al., 2017). Furthermore, if multiple diagnostic techniques are included in the analysis, the correlation between the tests should be taken into account (Bärenbold et al., 2018).

Transmission mechanism

In most modelling frameworks of helminths it is important to include the transmission mechanism (depending on the objective) as the 'true' infection intensity relies on the worms and not the eggs that are excreted (De Vlas & Gryseels, 1992). This is due to the variation in the measured egg counts for a given worm burden, which is influenced by the variation in egg output on different days, the distribution of eggs within a specimen and inaccuracy that can arise before and while diagnosing (e.g. due to egg decay, improper storage of samples and the ability of the laboratory technicians) (Hall, 1981). By including the transmission mechanism, the number of worms can be estimated, leading to more reliable results. There have been worm expulsion studies as an attempt to relate the measured eggs and the worms. For instance for *A. lumbricoides* it was found that the whole process may take several weeks and it is not clear that all worms are expulsed (Levecke et al., 2018). In most

cases it is not possible to get an estimate of the worm number in a host, except by autopsy (Cheever et al., 1968). Furthermore, there is evidence that STHs and *Schistosoma* worms are highly aggregated in a population, hence, generally a negative binomial distribution is assumed (Bradley & May, 1978; Elkins et al., 1986; Guyatt & Bundy, 1991). This distribution depends on two parameters which represent the mean worm burden and the aggregation in the population. A high degree of aggregation means that only few individuals harbour the majority of the worms (Anderson & May, 1992; J. Truscott et al., 2016).

The transmission mechanism depends on the mating of the parasites, which is determined by the female to male ratio, the number of worms and the parasites being monogamous or polygamous (de Vlas, 1996). In the case of *Schistosoma* the female worm resides in a groove of the abdomen of the male, hence they are monogamous, while STH are believed to be polygamous (Beltran & Boissier, 2008; J. E. Truscott et al., 2019). With increasing number of worms in a host, the egg output per female worm decreases, which is called the density-dependent fecundity (Anderson & May, 1992; J. E. Truscott et al., 2019). Another chracteristic that influences transmission and may be taken into account is the lifespan of worms or the maturation time of a parasite within the host (Anderson & May, 1992). If present also the intermediate host and its lifespan can be included. It depends on the purpose of the analysis which characteristics of the transmission should be taken into account.

To model the age-dependent intensity and prevalence, different approaches have been developed. Holford and Hardy suggested in 1976 an immigration-death model, which can be used to infer on the age-specific prevalence. It includes the entry of the parasite into the host, the parasite mating, egg shedding of the host and death of the parasite in the host (Holford & Hardy, 1976). Anderson and May proposed the 'simplest possible framework' to estimate the worm burden in a host depending on time. It is an immigration-death process, which includes only the infection rate and the worm death rate (Anderson & May, 1992). This modelling approach was extended to infer also on the age-specific worm burden and prevalence (Anderson & May, 1992). More complex models have been elaborated to estimate the age-specific prevalence, however they lack the inclusion of the diagnostic error (Chan et al., 1996; French et al., 2015; J. E. Truscott et al., 2019).

The model used in Chapters 3 and 4, which includes the transmission mechanism, as well as the diagnostic error, is outlined in Fig. 1.5.

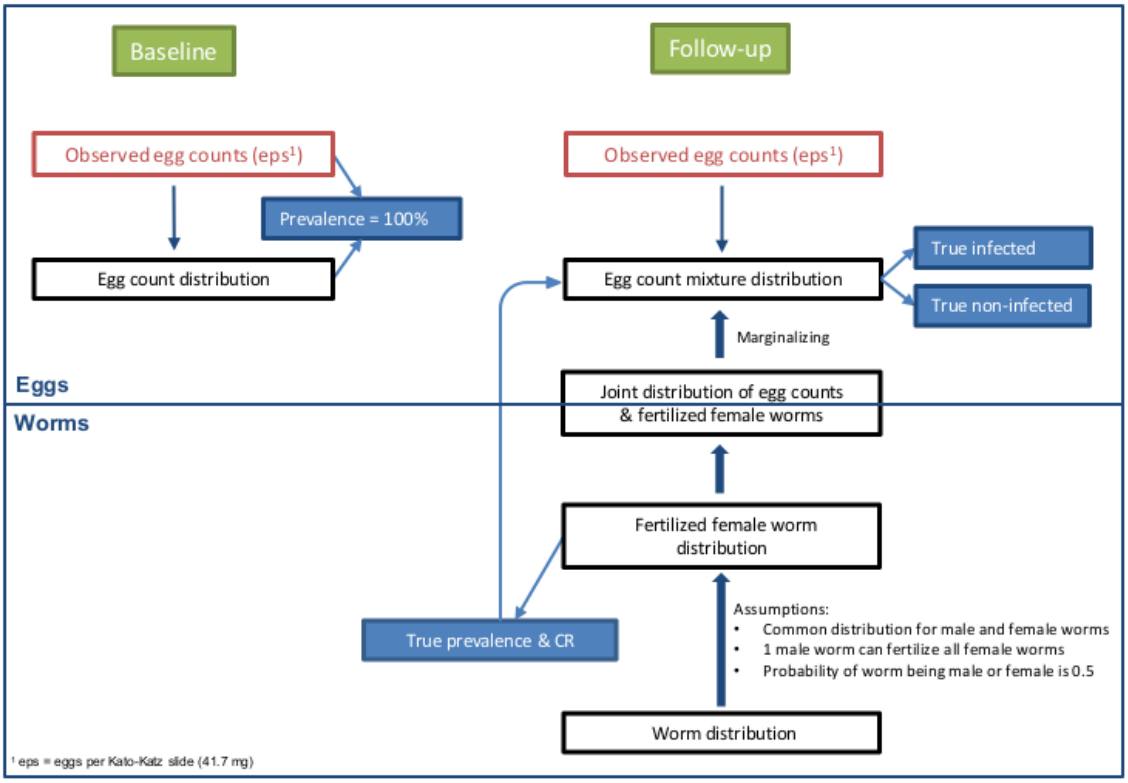

Figure 1.5: Graphical representation of the models used in Chapters 3 and 4 to infer on the cure and egg reduction rates of hookworm and *T. trichiura*.

1.6 Goal and objectives

The overreaching goal of this PhD thesis was to improve the estimation of disease burden caused by schistosome and STH infections, the related accuracy of diagnostic tools and treatment efficacy by further developing and applying Bayesian modelling approaches.

1.6.1 Specific objectives

The thesis pursues the following four interrelated specific objectives:

(i) to evaluate different diagnostic procedures, i.e. reagent strip and urine filtration to translate prevalence thresholds and estimate the intensity-dependent sensitivity of reagent strip and urine filtration for *S. haematobium* (Chapter 2);

(ii) to estimate the 'true' efficacy of different treatments against hookworm and the infection intensity-dependent sensitivity of the Kato-Katz diagnostic technique for hookworm (Chapter 3);

(iii) to estimate the 'true' efficacy of different treatments against *T. trichiura* and the infection intensity-dependent sensitivity of the Kato-Katz diagnostic technique for *T. trichiura* (Chapter 4); and

(iv) to estimate the 'true' age-specific infection intensity and prevalence of *S. mansoni* taking into account diagnostic error and transmission mechanism (Chapter 5).

Chapter 2

Infection intensity-dependent accuracy of reagent strip for the diagnosis of *Schistosoma haematobium* and estimation of treatment prevalence thresholds

Carla M. Grolimund[1,2], Oliver Bärenbold[1,2], Jürg Utzinger[1,2], Penelope Vounatsou[1,2]

1 – Swiss Tropical and Public Health Institute, Basel, Switzerland
2 – University of Basel, Switzerland

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2.1 Abstract

2.1.1 Background

Reagent strip to detect microhematuria as a proxy for *Schistosoma haematobium* infections has been considered an alternative to urine filtration for individual diagnosis and community-based estimates of treatment needs for preventive chemotherapy. However, the diagnostic accuracy of reagent strip needs further investigation, particularly at low infection intensity levels.

2.1.2 Methods

We used existing data from a study conducted in Tanzania that employed urine filtration and reagent strip testing for *S. haematobium* in two villages, including a baseline and six follow-up surveys after praziquantel treatment representing a wide range of infection prevalence. We developed a Bayesian model linking individual *S. haematobium* egg count data based on urine filtration to reagent strip binary test results available on multiple days and estimated the relation between infection intensity and sensitivity of reagent strip. Furthermore, we simulated data from 3,000 hypothetical populations with varying mean infection intensity to infer on the relation between prevalence observed by urine filtration and the interpretation of reagent strip readings.

2.1.3 Principal findings

Reagent strip showed excellent sensitivity even for single measurement reaching 100% at around 15 eggs of *S. haematobium* per 10 ml of urine when traces on reagent strip were considered positive. The corresponding specificity was 97%. When traces were considered negative, the diagnostic accuracy of the reagent strip was equivalent to urine filtration data obtained on a single day. A 10% and 50% urine filtration prevalence based on a single day sampling corresponds to 11.2% and 48.6% prevalence by reagent strip, respectively, when traces were considered negative, and 17.6% and 57.7%, respectively, when traces were considered positive.

2.1.4 Conclusions/significance

Trace results should be included in reagent strip readings when high sensitivity is required, but excluded when high specificity is needed. The observed prevalence of reagent strip results, when traces are considered negative, is a good proxy for prevalence estimates of *S. haematobium* infection by urine filtration on a single day.

2.2 Author summary

Control of schistosomiasis, a parasitic worm infection affecting more than 200 million people worldwide, relies mainly on mass drug administration of praziquantel to school-age children as well as adults in areas where the disease is particularly rampant. The World Health Organization has set thresholds of observed prevalence that require intervention to reach the goal of eliminating schistosomiasis as a public health problem by 2025. Intervention thresholds are defined based on parasitologic methods, which is urine filtration for *Schistosoma haematobium*. There are alternative diagnostic methods to detect *S. haematobium*, such as the detection of blood in urine that is a common symptom of urogenital

schistosomiasis. We determined the diagnostic sensitivity and specificity of a reagent strip to detect microhematuria using data from two villages in Tanzania at multiple time points (once before and several times after treatment with the deworming drug praziquantel) and translate the urine filtration intervention thresholds to reagent strip equivalents. We show that the reagent strip including trace results is almost perfectly sensitive for infections above 15 eggs of *S. haematobium* per 10 ml of urine and that a 10% observed prevalence by urine filtration corresponds to 17.6% observed prevalence by reagent strip including traces.

2.3 Introduction

Schistosoma haematobium is the most prevalent of the schistosome species parasitizing humans, causing urogenital schistosomiasis if left untreated (Colley et al., 2014b; McManus et al., 2018). More than 200 million individuals are infected with any species of *Schistosoma* that, collectively, cause a global burden of 2.1 million disability-adjusted life years (DALYs) (Hotez et al., 2014; James et al., 2018; Kyu et al., 2018). While mortality is relatively low, there is considerable morbidity that might be manifested as anemia, growth stunting, impaired cognition, increased risk for cancer of the bladder, and HIV infections (Abdulamir et al., 2009; Kjetland et al., 2014).

There has been a surge in investment in the control of schistosomiasis as part of the Millennium Development Goals (MDGs) after 2000 and the Sustainable Development Goals (SDGs) from 2015 onwards (Molyneux, 2004; Molyneux et al., 2017). Reduction of disease burden is primarily achieved through preventive chemotherapy with the antischistosomal drug praziquantel (McManus et al., 2018; Organization et al., 2019). Treatment needs are commonly assessed with parasitologic methods (Lai et al., 2015; Montresor et al., 1998; Organization et al., 2002). In 2012, the World Health Organization (WHO) put forward a roadmap for elimination of schistosomiasis as a public health problem (i.e., prevalence of heavy infections under a threshold of 1%) and interruption of transmission in suitable settings by 2025 (Organization et al., 2013b).

The WHO recommended diagnostic method for *S. haematobium* is urine filtration. A midday urine specimen is collected and, after vigorous shaking, 10 ml of urine are filtered and examined under a light microscope by experienced laboratory technicians (Knopp et al., 2018; Montresor et al., 1998). Alternative diagnostic techniques exist, which are often used in parallel on the same individual to increase diagnostic sensitivity. Blood in urine is a common symptom of urogenital schistosomiasis, although it is not fully specific to the disease (Krauth et al., 2015). As blood in urine is relatively easier to detect than *S. haematobium* eggs, three blood-based diagnostic tests are available; namely (i) a simple questionnaire regarding recent history of blood in the urine; (ii) inspection of a urine sample for visible blood; and (iii) a reagent strip for detection of microhematuria (detects visible as well as non-visible blood in urine) (Lengeler et al., 2000; Mafe, 1997). Reagent strip for microhematuria allow for a semi-quantitative assessment of infection-intensity with four grades distinguishing the severity of an infection. Other diagnostic approaches include the detection of a specific antigen in urine and polymerase chain reaction (PCR)-based methods to detect genetic material in urine (Knopp et al., 2015; Shiff, 2015).

In this study, we determined the infection intensity-dependent diagnostic accuracy of reagent strip to detect microhematuria and urine filtration for *S. haematobium* eggs. We considered repeated measurements obtained over consecutive days. Previous studies assessed the sensitivity and specificity of the aforementioned methods, but there is no study that models *S. haematobium* egg counts directly and takes into account day-to-day variation of infection intensity (Knopp et al., 2018; Kosinski et al., 2011; Mafe, 1997;

Midzi et al., 2009; Obeng et al., 2008; Stete et al., 2012). We extended our egg count model for individual-level data, previously developed for the analysis of Kato-Katz thick smears and a point-of-care circulating cathodic antigen (POC-CCA) urine cassette test for the diagnosis of *S. mansoni*. We developed a model to estimate 'true' prevalence and infection intensity-dependent sensitivity for urine filtration and reagent strip testing and determined the specificity of the latter diagnostic test (Bärenbold et al., 2018; Bärenbold et al., 2017). Additionaly, we employed a simulation to translate current WHO urine filtration intervention thresholds to microhematuria analogues based on reagent strip test results.

2.4 Methods

2.4.1 Ethics statement

All data included in this study have been published elsewhere (Hatz et al., 1998). Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.

2.4.2 Data

The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. The study involved 533 school-age children (7-18 years) and included a baseline and six follow-up surveys (at 2, 4, 6, 12, 18, and 24 months) after an initial treatment with praziquantel just after the baseline survey. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany). Urine filtration was performed with samples of 10 ml of urine using Nucleopore membranes with 12 µl pore filters. Readings of the reagent strip were done semi-quantitatively. The results of the reagent strip used here consist of 0 (negative), trace T ($<$ 5 red blood cells (RBC)/µl of urine), 1+ (5-10 RBC/µl of urine), 2+ ($\sim$ 50 RBC/µl of urine), and 3+ ($\sim$ 250 RBC/µl of urine) (Hatz et al., 1998). For each survey, efforts were made to collect urine specimens over five consecutive days (between 10:00 and 14:00 hours). The aim of the study was to characterize the evolution of *S. haematobium* pathology after a single dose of praziquantel (40 mg/kg). However, 52 children were re-treated after 18 months (i.e., 6 months before the last follow-up) because they had heavy infections ($\geq$ 50 eggs/10 ml urine), macrohematuria, or major lesions of the urinary tract. Summary measures of the data, stratified by village at the seven time points, are presented in Table 2.1 and a comparison of prevalence based on test results with reagent strip versus urine filtration for each day at the different time points is given in Fig 2.1.

2.4.3 *S. haematobium* egg count model

We assumed that the *S. haematobium* infection status and intensity of each individual was independent across follow-ups. For each individual, reagent strip (RS) data results were converted into 3 categorical variables with values T when the RS result was at least T (i.e., T/1+/2+/3+), 1 when the RS result was at least 1 (i.e., 1+/2+/3+) and 2 when the RS result was at least 2 (i.e., 2+/3+). The data consist of measurements over 5 consecutive days, and hence, each of the aforementioned variables were split into 5 binary variables corresponding to the z first days, $z = 1$ (i.e., first day of testing), 2 (i.e., first and second day), 3 (i.e., first 3 days), ..., 5 (i.e., all 5 days) leading to 15

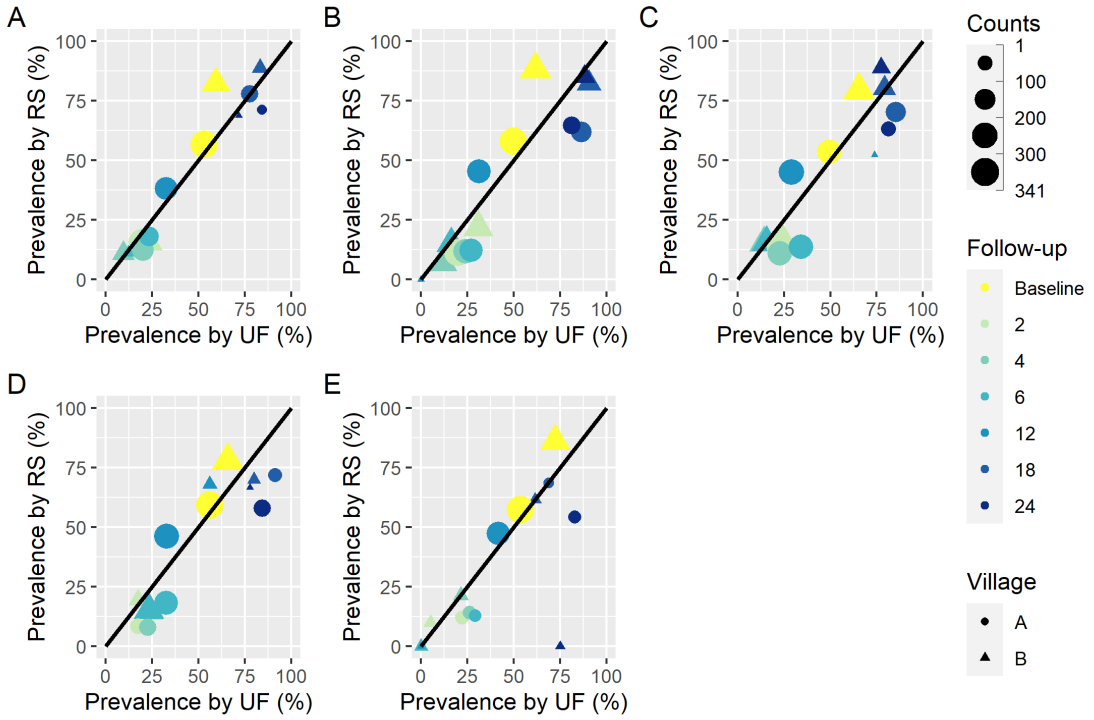

Figure 2.1: Comparison of prevalence by reagent strip (with trace negative) and urine filtration computed from raw data. The dots and triangles represent the prevalence at baseline (before treatment) and follow-up (at 2, 4, 6, 12, 18, and 24 months post-treatment) for each study site and 'Counts' show the number of individuals tested. **A** shows the prevalence computed from individuals with complete data at day 1 regarding reagent strip and urine filtration tests. **B, C, D** and **E** show the same for days 2, 3, 4, and 5, respectively.

binary variables. Data from each cross-sectional time point and village were assumed to arise from a separate, independent population. As we have 7 cross-sectional time surveys corresponding to baseline and 6 follow-up surveys and 2 villages included in the study, we considered 14 independent populations. A joint Bayesian model was fitted separately for each binary RS variable with the corresponding urine filtration (UF) egg count. No diagnostic 'gold' standard was asummed. RS sensitivity for T,1,2 at z was related to infection intensity.

For each individual i in population j, $j = 1, \ldots, 14$, let Y_{jid}^{UF} be the observed egg counts from urine filtration on day d, $d = 1, 2, \ldots, 5$. The results from a semi-quantitative reagent strip for microhematuria were coded into 15 binary variables: $Y_{ji}^{RS,T,z}$ describes all individuals with at least result trace, $Y_{ji}^{RS,1,z}$ with at least result 1+, and $Y_{ji}^{RS,2,z}$ 2+, respectively. The models were fitted separately for each of the 15 binary results $Y_{ji}^{RS,x,z}$, $x = T, 1, 2$, combined with all Y_{jid}^{UF}, where all individuals with both test results at a cross-sectional survey were included, with exception of a few individuals with multiple entries. We inferred on the sensitivity of repeated microhematuria measurements without having to model the correlation structure explicitly.

We assumed that each population consists of a proportion of infected individuals π_j, where each individual had a disease status D_{ji} and infection intensity λ_{ji}. Infected individuals with $D_{ji} = 1$ measurements on consecutive days were modeled as a negative binomial distribution with mean equal to the infection intensity λ_{ji} and dispersion param-

eter depending on it. The infection intesities were assumed to be distributed as a gamma distribution as follows:

$$\begin{aligned} Y_{jid}^{UF} &\sim NB(\lambda_{ji}, k_{ji}), \\ \log(k_{ji}) &= k_0 + \log(\lambda_{ji})k_1, \text{ and} \\ \lambda_{ji} &\sim Gamma(\mu_j^+ \cdot \alpha_j, \alpha_j), \text{ where} \end{aligned} \tag{2.1}$$

k_{ji} is the dispersion parameter of individual i in population j that depends on parameters k_0 and k_1, μ_j^+ is the mean infection intensity of a positive individual in population j, and α_j is the aggregation parameter that describes the aggregation of infection intensities in population j. Individuals with infection status $D_{ji} = 0$ have observations $Y_{jid}^{UF} = 0$, which is equivalent to 100% specificity. The sensitivity of urine filtration s_{jin} for individual i in population j after n days was calculated using the probability of repeated zero measurements under a negative binomial model, that is $s_n(\lambda) = 1 - \left(\frac{k(\lambda)}{\lambda + k(\lambda)}\right)^{n \cdot k(\lambda)}$, where $k(\lambda) = e^{k_0 + \log(\lambda)k_1}$.

Microhematuria measurements were modeled by a Bernoulli distribution,

$$P(Y_{ji}^{RS,x,z} \mid D_{ji}) = \begin{cases} Be(s_{ji}^{RS,x,z}) & \text{, if } D_{ji} = 1 \\ Be(1 - c^{RS,x,z}) & \text{, if } D_{ji} = 0 \end{cases} \tag{2.2}$$

A parametric model was used to relate infection intensity with diagnostic sensitivity, where $s^{RS,x,z}$ is the infection intensity-dependent sensitivity defined by four parameters. a_0 sets the sensitivity for infections approaching to zero intensity, a_1 describes the rate of increase with infection intensity, a_2 changes the shape of the curve, and a_3 limits the maximum sensitivity for very severe infections. $c^{RS,x,z}$ is the specificity of the microhematuria reagent strip, that is the probability of no positive result for an uninfected individual where positive is defined as having at least once a value of x after z observations.

Models were also run with sensitivity and specificity parameters of the reagent strip stratified by sex. The model was formulated using a Bayesian paradigm. We chose a uniform prior for π_j, a gamma distribution with mean 100 and standard deviation (SD) 100 for the mean infection intensity μ_j^+, a gamma distribution with mean 1 and SD 1 for the population variation α_j, a beta distribution with parameters 10 and 1 for c^{RS}, and normal distributions with mean 0 and SD 2 for k_0 and k_1. For a_0 a normal distribution with mean -1 and SD 1.5 was chosen, a gamma distribution with shape and scale parameters 5 and 30 for a_1, a normal distribution with mean 10 and SD 10 for a_2, and a beta distribution with parameters 10 and 1 for a_3 to ensure a non-informative distribution of sensitivity curves in the relevant range of infection intensities. Priors for the sensitivity of the reagent strip were chosen using prior predictive checks to ensure non-informativity (Grinsztajn et al., 2021). Other parameters have semi informative prior distributions over sensible parameter values. Inference was done using Markov chain Monte Carlo (MCMC) simulation. Model fit was carried out in Stan version 1.2.1335 (Stan Development Team; mc-stan.org), running 20 chains for 2,000 iterations of which the first 500 were discarded (Carpenter et al., 2017). There were no divergent transitions, and convergence was assessed using the Gelman-Rubin diagnostics as well as visual inspection of chains (Gelman & Rubin, 1992).

2.4.4 Simulation

To assess the relation between prevalence observed by microhematuria and urine filtration for one, two, three, four, and five days, we run extensive simulations of hypothetical populations in diverse transmission settings. We assumed that worms are negative binomially distributed in the population with worm aggregation parameter w^{agg} and that

a proportion of 30% of the worms are female (Anderson, 1986; R. May & Woolhouse, 1993). The mean number of eggs per 10 ml of urine per female worm was selected from a publication of Truscott et al. who estimated it to be 5.2 (J. Truscott et al., 2017). For the parameters a_0, a_1, a_2, a_3, k_0, and k_1, 100 draws were taken directly from the posterior distribution and thereby correlation between parameters was incorporated in the simulation. The mean number of worms per individual in a population was varied in 40 equal steps on the log-scale from 1 to 200. We used w^{agg} according to a normal distribution with a mean of 0.2 and a SD of 0.03. For each hypothetical population, worm load for 6,000 individuals and corresponding urine filtration and reagent strip results were simulated for all five days.

2.5 Results

2.5.1 Descriptive data analysis

Table 2.1: **Observed prevalence and mean infection intensity by urine filtration and prevalence by microhematuria using reagent strip based on the first sample for all individuals and based on individuals with complete data, stratified by village (Tanzania survey, 1993 (Hatz et al., 1998)).**

		Urine filtration						Reagent strip					
		1 day all			1 day complete			1 day all			1 day complete		
Village	Survey	N	Positive (%)	μ^+	N	Positive (%)	μ^+	N	Positive T+[1] (%)	Positive T-[2] (%)	N	Positive T+[1] (%)	Positive T-[2] (%)
A	Baseline	310	56.5	203.4	152	56.6	187.5	310	59.4	53.2	152	59.2	53.3
	2 months	288	15.3	9.5	17	17.6	2.3	288	24.0	19.4	17	23.5	17.6
	4 months	204	12.3	37.8	20	0	0	204	23.0	20.1	20	20.0	20.0
	6 months	241	40.7	13.6	14	28.6	8.0	241	33.6	25.7	14	21.4	14.3
	12 months	219	37.9	31.1	91	35.2	24.6	219	47.5	32.4	91	49.5	31.9
	18 months	164	70.1	41.0	1	100	5.0	164	100	76.8	1	100	0
	24 months	122	57.4	23.5	0	-	-	122	100	75.4	0	-	-
B	Baseline	178	82.6	189.2	138	86.2	179.4	178	87.6	59.0	138	91.3	62.3
	2 months	163	15.3	14.4	13	7.7	1.0	163	42.3	23.3	13	15.4	7.7
	4 months	129	10.9	6.1	10	0	0	129	17.1	9.3	10	10.0	0
	6 months	172	23.8	10.4	14	0	0	172	25.0	16.3	14	0	0
	12 months	26	46.2	38.7	0	-	-	26	100	61.5	0	-	-
	18 months	103	79.6	153.2	1	100	6.0	103	100	79.6	1	100	100
	24 months	69	69.6	60.3	0	-	-	69	100	71.0	0	-	-

N is the number of individuals tested; μ^+ is the mean number of eggs per 10 ml of urine in the positive individuals.
[1] Trace results are regarded as positive.
[2] Trace results are regarded as negative.

Prevalence by a single urine filtration ranged from 10.9% to 82.6%, while the cumulative prevalence over 5 consecutive days ranged from 20.9% to 98.7%. The mean infection intensity in the study population at the different time points ranged from 0.4 to 107 eggs/10 ml of urine, while the corresponding range in positive individuals was 1.8 to 116.6 eggs/10 ml. Reagent strip prevalence ranged from 17.1% to 100% when traces were considered positive and from 9.3% to 84.2% when traces were considered negative based on observations from a single day. Use of reagent strip over 5 consecutive days increased the observed prevalence from 33.9% to 100% when traces were considered positive and from 22.8% to 89.3% when traces were considered negative.

2.5.2 Sensitivity of urine filtration

Using the egg count model, we estimated the sensitivity of the urine filtration from a single sample to a total of five samples over consecutive days. The posterior medians

for parameters k_0 and k_1, which define the relation between the sensitivity and mean infection intensity and were estimated at -2.3 and 0.4, respectively. The influence of the choice of RS, x, z on estimates of k_0 and k_1 was small (see S1 Text). The aggregation parameter of the negative binomial distribution increased from 0.15 to 0.48 for infection intensity increasing from 0 to 50 eggs/10 ml of urine, which corresponds to a reduction in overdispersion when the infection intensity increases. This is equivalent to a SD of 20 at a density of 10 eggs/10 ml of urine, 73 at a density of 50 eggs/10 ml of urine, and 3.3 at a density of 1 egg/10 ml of urine. The posterior distributions of k_0 and k_1 with the probability for repeated zeros under the negative binomial model enabled us to estimate the sensitivity of urine filtration. In Fig 2.2, we present the estimated sensitivity of urine filtration cumulatively for one to five days (i.e., single versus multiple tests) as a function of infection intensity.

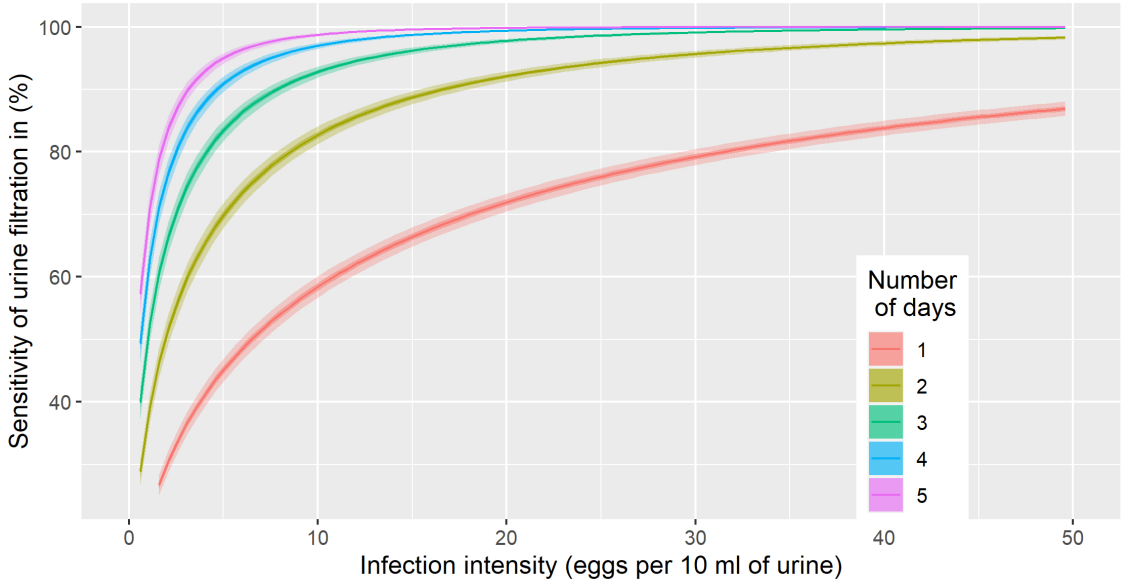

Figure 2.2: Sensitivity estimates of urine filtration (10 ml of urine) from a single to a total of five samples collected over consecutive days. Curves indicate posterior medians, while dark shaded areas provide a 50% and light shaded areas a 95% Bayesian credible interval.

A single urine filtration had a sensitivity of above 85% for heavy infections ($\geq$ 50 eggs/10 ml of urine), while the sensitivity was below 50% at around 7 eggs/10 ml of urine. The sensitivity showed a considerable increase as a function of repeated urine filtration. For example, the sensitivity increased from 50% to 75% when comparing a single with a duplicate urine filtration at a low infection intensity of 7 eggs/10 ml of urine. After five days of urine filtration, an average infection with 1 egg/10 ml of urine showed a probability of around 60% to be detected.

2.5.3 Sensitivity of reagent strip

The model was run for each interpretation of the reagent strip RS, x, z separately, where x is either T for trace, 1, or 2, and z the total number of samples from 1 to 5 (i.e., the test is positive when at least on one of the first z days a value of at least x in the semi-quantitative interpretation of the reagent strip is reported). The parameters a_0, a_1, a_2, a_3, and c fully define the diagnostic accuracy of each RS, x, z. The specificity c for each interpretation is summarized in Table 2.2. The specificity is estimated to basically

100% even after multiple days when only 2+ and 3+ test readings were considered positive while, when trace results were considered positive, the specificity of even a single sample is 97% and only 87% after five days.

Table 2.2: **Specificity of each interpretation of the reagent strip RS, x, z defined as a result of at least x (x being T for trace, 1, or 2), on the first z days. Values are given between 0 and 1, where 1 corresponds to zero probability of a false-positive, values in brackets represent the 95% Bayesian credible interval.**

Reading	RS,x,1	RS,x,2	RS,x,3	RS,x,4	RS,x,5
$x = T$	0.97 (0.92-1.00)	0.93 (0.86-0.99)	0.92 (0.85-0.99)	0.89 (0.82-0.98)	0.87 (0.80-0.96)
$x = 1$	0.99 (0.96-1.00)	0.99 (0.97-1.00)	0.99 (0.96-1.00)	0.98 (0.94-1.00)	0.97 (0.92-1.00)
$x = 2$	1.00 (0.98-1.00)	0.99 (0.98-1.00)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.99 (0.96-1.00)

The parameters a_0, a_1, a_2, and a_3 are reported for all 15 interpretations (S1 Text). Combined with equation 2.2, these parameters estimate the infection intensity-dependent sensitivity of the reagent strip for microhematuria to diagnose *S. haematobium*. Fig 2.3A and 2.3B show the sensitivity of the reagent strip when traces were considered positive or negative, for cumulative results from one, three, and five days. When traces were considered positive, a single reagent strip detected basically all infections with an intensity above 15 eggs/10 ml of urine, and still 40% of infections with only 1 egg/10 ml of urine. Repeating the test over consecutive days increased the sensitivity, for example from 40% to 70% for very light infections after 5 consecutive days, but this increase was modest when compared to urine filtration.

Considering traces as negative resulted in higher specificity of 99% for a single reagent strip and still 97% after five samples. When traces were considered positive, the specificity after five samples was reduced to 87%, however, the sensitivity was higher compared to traces considered negative. A single reagent strip only has a 60% chance to detect an infection of 10 eggs/10 ml of urine and still less than 90% for heavy infections ($\geq$ 50 eggs/10 ml of urine). Repeated sampling over 5 consecutive days increased the sensitivity up to 80% at 10 eggs/10 ml of urine compared to a sensitivity of almost 100% at the same intensity when traces were considered positive. The sensitivity of a single reagent strip when traces were considered negative is similar to a single urine filtration regardless of the level of infection intensity. Stratification by sex did not show any difference in parameter estimates that would indicate an important interaction, for example with menstruation.

The semi-quantitative results of the reagent strip were closely correlated with the infection intensity of an individual. The proportion of trace, 1+, and $>$ 1+ results for infection intensities up to 50 eggs/10 ml of urine are shown in Fig 2.4. The non-monotonic behavior close to an infection intensity of zero is due to increased uncertainty in the sensitivity estimates (not shown in the plot, but visible in Fig 2.3A and 2.3B). At very low infection intensities, there was a considerable probability ($\sim$ 40%) for readings of 2+ or 3+, while at 50 eggs/10 ml of urine almost 80% of tests showed a 2+ or 3+. Trace results, on the other hand, decreased from a proportion of about 30% to around 10% at 50 eggs/10 ml of urine, while the proportion of samples with reading 1+ remained relatively constant.

2.5.4 Relation between the observed prevalence by urine filtration and reagent strip

We conducted extensive simulations of 3,000 hypothetical populations with 6,000 individuals each and generated observations of the two diagnostic tests over 5 consecutive

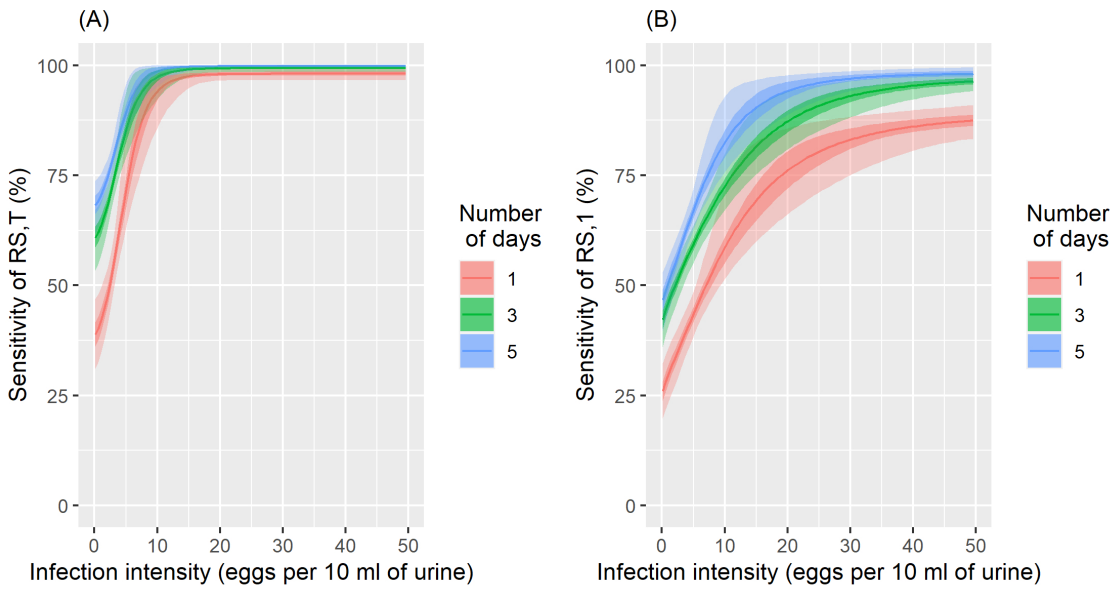

Figure 2.3: Sensitivity of a reagent strip (RS) in relation to infection intensity for measurements from a single to a total of 3 and 5 cumulative tests. Trace results were included in the positives (A) and trace results were included in the negatives (B). Dark shaded areas are the 50% and light shaded areas the 95% Bayesian credible interval.

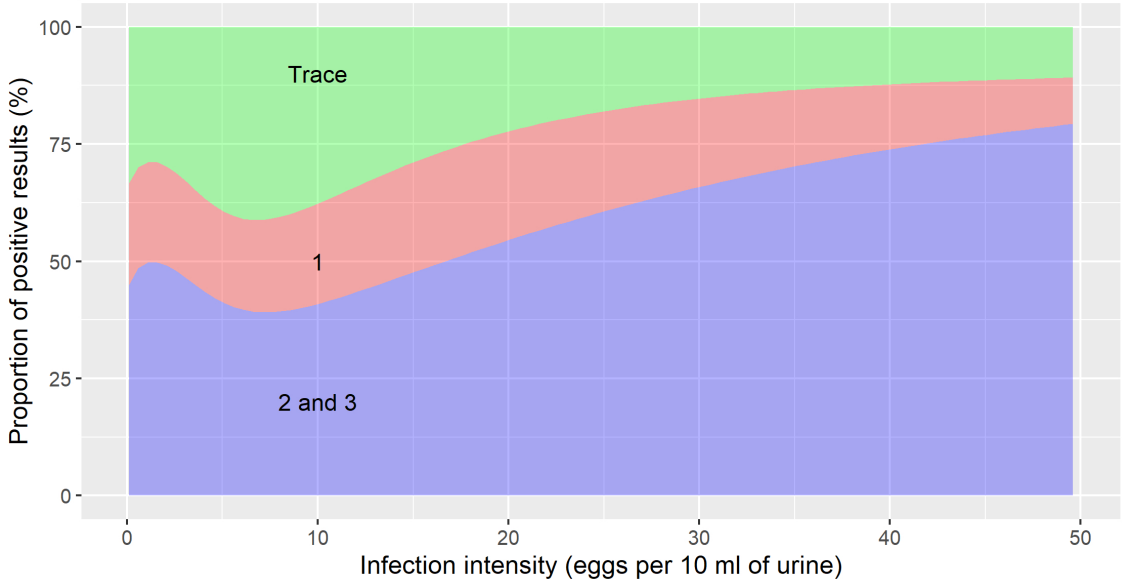

Figure 2.4: Proportion of semi-quantitative results of reagent strip for microhematuria in relation to *S. haematobium* infection intensity. The 2+ and 3+ readings were grouped together.

days based on the individual-level results from the egg count model detailed above. Fig 2.5 depicts the relation between the observed prevalences by reagent strip and urine filtration for up to five samples collected over consecutive days. Traces were treated either as positive or negative. Measurements based on a single reagent strip reading showed equal or higher observed prevalence than urine filtration. When all five samples were considered, the prevalence was higher by urine filtration compared to reagent strip when traces were

considered negative. For the sampling scheme recommended by WHO, i.e., single day sample, and reagent strip without trace results, the observed prevalence by both tests are similar, independent of the setting.

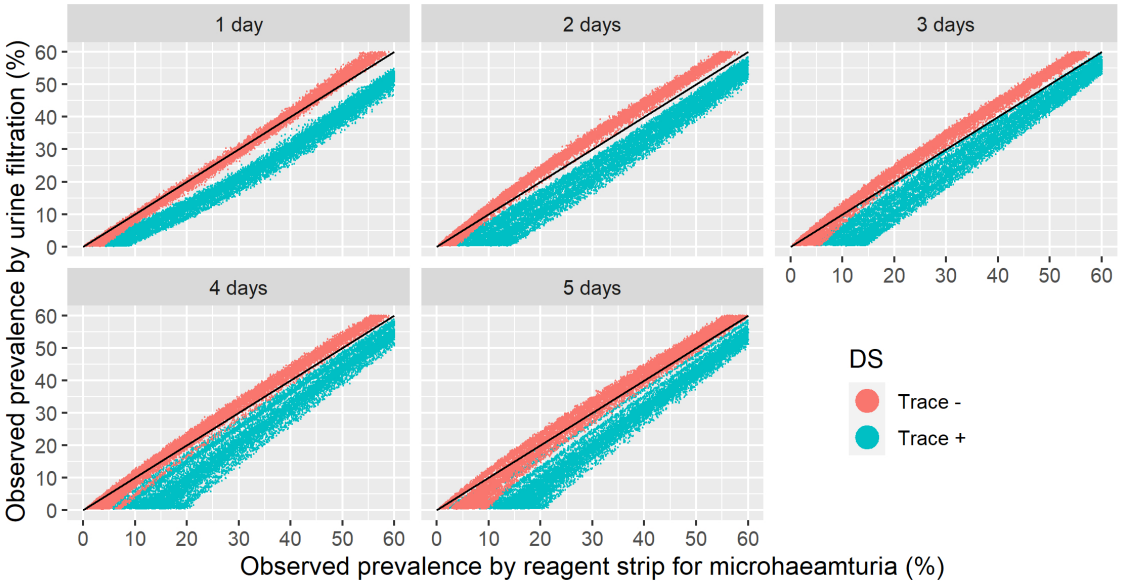

Figure 2.5: Simulated relation between observed prevalence of *S. haematobium* by urine filtration and by reagent strip based on one to five urine samples collected over consecutive days with traces considered either positive or negative. The black line indicates equivalence between urine filtration and reagent strip results.

We translated WHO prevalence thresholds from urine filtration into microhematuria by taking all simulated populations with observed prevalence by urine filtration within a narrow interval of ±0.5% around the threshold and calculating the mean of the observed prevalence by reagent strip and the corresponding Bayesian credible intervals. Table 2.3 shows results for three thresholds of urine filtration, 10%, 25%, and 50%, and the reagent strip when traces were considered positive or negative, for sampling schemes based on a single up to five urine samples over consecutive days. Most relevant for evaluating treatment needs are results for sampling on a single day. When traces were considered negative, the prevalence thresholds for microhematuria were very close to urine filtration thresholds. Including traces in the positive required upwards adjustment of the thresholds, for example a 10% urine filtration corresponds to about 20% prevalence by reagent strip.

Table 2.3: **Translation of prevalence thresholds from urine filtration (UF) into reagent strip (RS) for the diagnosis of *S. haematobium* for sampling schemes varying from one to five urine samples over consecutive days when traces were considered either positive or negative. All numerical values are percentages and the brackets contain 95% percentiles from the simulation.**

RS	UF (%)	1 day	2 days	3 days	4 days	5 days
Traces	10	17.6 (13.4–21.8)	16.5 (10.7–22.3)	19.2 (12.6–25.8)	19.4 (15.9–22.9)	21.4 (14.4–28.4)
+	25	35.0 (31.6–38.5)	31.3 (25.7–36.8)	32.1 (27.8–36.5)	32.9 (29.2–36.6)	34.2 (28.1–40.3)
	50	57.7 (55.2–60.3)	54.8 (51.4–58.3)	54.2 (50.5–57.9)	55.6 (53.3–57.9)	56.2 (51.8–60.5)
Traces	10	11.2 (9.0–13.3)	8.5 (7.2–9.8)	8.9 (6.9–11.0)	9.1 (6.9–11.3)	11.7 (7.7–15.6)
-	25	25.7 (23.1–28.4)	21.5 (19.7–23.3)	21.4 (19.1–23.3)	22.7 (20.1–25.4)	24.0 (19.7–28.3)
	50	48.6 (46.6–50.6)	46.0 (44.4–47.6)	45.8 (449–47.6)	46.9 (44.5–49.3)	48.4 (45.5–51.3)

2.6 Discussion

We determined the diagnostic accuracy of a reagent strip used for detection of microhematuria (a proxy for *S. haematobium* infection) from survey data where participants were subjected simultaneously to urine filtration and reagent strip testing, using a Bayesian egg count model. The study was conducted in the frame of a treatment intervention with a 24-month follow-up post-praziquantel intervention, thus characterized by different infection intensity. The semi-quantitative results of the reagent strip were incorporated into the modeling by determining the sensitivity and specificity profiles, when trace results of the reagent strip were considered either positive or negative, and when only the 2+ and 3+ readings were considered as positive. As the reagent strip results can be influenced by menstruation in females, stratification by sex was also done. Furthermore, we related the observed prevalence by the two tests and translated the urine filtration treatment prevalence thresholds recommended by WHO into thresholds by reagent strip. We analyzed the data cross-sectionally because the longitudinal nature captures the variation in the infection intensity, which is taken into account in the modeling by assuming that the sensitivity parameters of the two tests depend on the infection intensity.

For individual-level diagnosis, the reagent strip showed almost perfect sensitivity when infection intensity was above 15 eggs/10 ml of urine, while specificity was high (97%) for a single urine sample when traces were included in the positives. When traces were excluded, a much more similar profile to urine filtration was created across all infection intensities. A key difference between microhematuria and urine filtration is that results are more correlated across samples for microhematuria. This means that for urine filtration, an infection might be missed if tested only once, but captured by an additional urine filtration, whereas for microhematuria repeated tests will more likely reveal the same result leading to less improvement in sensitivity by repeating measurements. It is conceivable that the presence of blood in urine is less variable than the egg excretion by parasitic worms in the case where few worm-pairs are present as the eggs also may remain trapped in the walls of the urinary tract. The reduction in the overdispersion of the negative binomial distribution of egg outputs with increasing infection intensity supports arguments that in the presence of a larger number of worms, the day-to-day variations are low due to averaging. We did not observe a sex difference, which might be explained by the young age of the participants (7-18 years, 58% between 7 and 12 years) although a proportion of the females must have experienced menarche. Yet, the menstruation would have to have occurred at the same time as urine samples were collected and subjected to reagent strip testing to have an influence.

Point estimates of urine filtration and reagent strip sensitivity as well as specificity from other studies are difficult to compare to the results presented here because previous studies did not take into account the relation to infection intensity and they are averaged over the population. Hence, findings are setting specific. Urine filtration is considered the 'gold' standard for *S. haematobium* diagnosis (Stothard et al., 2014). However, results depend on the sampling scheme, as collection of multiple urine sample increases sensitivity. For example, a study conducted by Kosinski et al. (2011) reported a sensitivity of reagent strip using a single urine sample of about 50%, while the corresponding sensitivity for duplicate or triplicate reagent strip were 60% and 70%, respectively. For urine filtration, these estimates were 50%, 80%, and 100%, respectively (Kosinski et al., 2011). Especially in low-endemic settings, a single urine filtration can lead to low sensitivity. Specificity of reagent strip testing decreases from 93% for single, to 88% for two, and 83% for three urine samples. These results are generally in agreement with our estimates, especially considering that those values over-estimate the diagnostic error because of the definition of urine filtration as 'gold' standard. Day-to-day variation in egg output is considerable, rendering a stable

classification of infection intensity into severity classes difficult. Our study revealed that the semi-quantitative results derived from reagent strip testing are correlated with infection intensity, as determined by urine filtration. Variation in microhematuria seems to be lower, indicating that classification based on a reagent strip might be more stable and more insightful.

Our results were derived from the analysis of a study conducted in two villages in Tanzania in 1993 using a reagent strip produced by Boehringer Mannheim (Hatz et al., 1998), a company that was bought and incorporated into Roche in 1997. It is unclear how representative the results are for other reagent strip tests currently on the market. For example, a study carried out in Kenya utilized a reagent strip called Hemastix (Ames, Bie and Bernsten; Copenhagen, Denmark). Mafe (1997) and Kahama et al. (1999), in studies carried out in Nigeria, also used Hemastix (Kahama et al., 1999; Mafe, 1997). More recently Kosinski et al. (2011) evaluated a semi-quantitative reagent strip called U-11 Urinalysis Reagent Strip (Mindray Co. Ltd.; Shenzhen, China). However, this test seems to have been on the market before; indeed, it has been evaluated by Mott et al. in 1985 (Kosinski et al., 2011; Mott et al., 1985). More data should be incorporated to study potential differences between reagent strips from different companies or from the same company over time. Some of the most recent data have been collected in the frame of large-scale preventive chemotherapy programs, which influence microhematuria following repeated praziquantel administration. Hence, this is an important confounder that should be included into future modeling studies.

On the population level, we see a clear relation between the observed prevalence by urine filtration and reagent strip. The size of the 3,000 simulated populations was fixed at 6,000 to be able to observe the influence of uncertainty in diagnostic accuracy, while limiting the influence of sampling error. Important assumptions in the simulation model were primarily the negative binomial distribution of worms in the population and the aggregation parameter that was considered to be independent of infection intensity. The latter may not hold because it has been assessed for hookworm infections, showing that the aggregation parameter increases with infection intensity (J. E. Truscott et al., 2019). In accordance with recommendations put forward by WHO and the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) for estimation of *S. haematobium* prevalence from a single day (King et al., 2020; Organization et al., 2013b), we recommend translating urine filtration thresholds of 10%, 25%, and 50% into 10%, 24%, and 48% when a single reagent strip is employed, considering traces as negative. Trace positive individuals should, however, also be treated with praziquantel, as it might indicate a very light infection with *S. haematobium* that might cause subtle morbidity (King & Bertsch, 2013; King et al., 2006). The reagent strip with traces considered negative serves as a convenient proxy to estimate prevalence almost equivalent to single-day urine filtration. If national control programs would make use of reagent strip instead of urine filtration, the costs could be reduced substantially and proceedings could be accelerated allowing more children to get tested.

Our study has several limitations that are offered for consideration. First, the data stem from a single type of reagent strip from a survey carried out in two villages of Tanzania almost 30 years ago with an age of participants ranging between 7 and 18 years. Importantly though, urine samples were obtained at multiple time points over the course of 24 months after a single oral dose of praziquantel. It is imperative to validate the results with additional data, for example using the Hemastix and U-11 reagent strips, particularly in settings where *S. haematobium* is close to elimination. Second, the simulation depends on the assumption of negative binomial distribution of worms in the population with a constant aggregation parameter, which is likely a good approximation at higher mean worm counts, but cannot be extrapolated to low prevalences below 10% observed urine

filtration prevalence. This is reflected in our results making no recommendations for translation of lower thresholds. Third, it was not uncommon to have individuals where only one diagnostic test was performed on a specific sampling time point, and hence, observed prevalence by reagent strip and urine filtration at the same time point and village are not directly comparable.

Regarding the ethics of the analyzed study the principal investigator emphasized that the children were treated when they were positive upon enrollment and then followed up for 24 months without treatment unless there were important symptoms. All infected children were treated at the end of the study, knowing that their potential or proven morbidity could be cleared with it. Based on previous experience, the study conductors could assume that within the 24 months, no serious morbidity that could not be reversed by treatment will occur, suggesting that such a study is ethically justifiable. The analyzed study was pivotal in defining the intervals possible for treatment and retreatment schemes that otherwise could not have been established for future actions.

2.6.1 Conclusion

Reagent strip testing for microhematuria might be appropiate to test for *S. haematobium* infection, as it showed results with a high sensitivity and a high specificity. Indeed, at infection intensities above 15 eggs/10 ml of urine, sensitivity is close to 100%, while still maintaining a high specificity above 97%. When higher specificity is required, traces can be considered as negative to exclude the majority of false-positives, which lead to a sensitivity almost equal to a single sample urine filtration, therefore enabling direct translation of observed prevalence in the population. Further research is still warranted with additional data, particularly in settings where the prevalence of *S. haematobium* is low and infection intensity below 50 eggs/10 ml of urine.

2.7 Supporting information

2.7.1 S1 Table.

Observed prevalence and mean infection intensity by urine filtration and prevalence by microhematuria using reagent strip on one and five cumulative days, stratified by village (Tanzania survey (Hatz et al., 1998)).

		Urine filtration						Reagent strip					
		Day 1		5 days				Day 1			5 days		
Village	Survey	N	Positive (%)	N	Positive (%)	μ	μ^+	N	Positive T+[1] (%)	Positive T-[2] (%)	N	Positive T+[1] (%)	Positive T-[2] (%)
A	Baseline	310	56.5	357	70.0	52.4	74.8	311	58.8	52.7	357	77.6	63.6
	2 months	288	15.3	328	22.3	0.8	3.5	287	24.0	19.5	328	38.4	27.7
	4 months	205	12.2	249	20.9	1.4	6.9	206	22.8	19.9	248	39.5	31.5
	6 months	241	40.7	244	59.0	5.5	9.4	172	32.0	23.3	244	50.4	39.3
	12 months	219	37.9	288	59.4	13.7	23.0	220	48.2	33.2	288	60.8	48.6
	18 months	202	56.9	237	69.2	22.9	33.1	141	100	77.3	187	100	89.3
	24 months	175	41.7	210	59.0	11.7	19.7	76	100	84.2	139	100	88.5
B	Baseline	178	82.6	207	91.8	107.0	116.6	179	86.6	58.7	207	93.2	81.6
	2 months	163	15.3	197	32.5	1.1	3.5	163	42.3	23.3	196	54.6	40.3
	4 months	129	10.9	171	24.6	0.4	1.8	129	17.1	9.3	171	33.9	22.8
	6 months	173	23.7	177	42.9	2.5	5.9	150	23.3	15.3	176	51.1	26.1
	12 months	67	23.9	76	44.7	4.8	10.8	0	-	-	32	96.9	65.6
	18 months	144	59.7	163	72.4	66.7	92.1	89	100	83.1	117	100	88.9
	24 months	113	44.2	151	50.3	36.8	73.0	68	98.5	70.6	85	98.8	81.2

N is the number of individuals tested; μ is the mean number of eggs per 10 ml of urine in the population after 5 tests on consecutive days; μ^+ is the mean number of eggs per 10 ml of urine in the positive individuals after 5 tests on consecutive days.

[1] Trace results are regarded as positive.

[2] Trace results are regarded as negative.

2.7.2 S1 Text.

Table 2.4: Parameters describing the sensitivity and specificity of a reagent strip test for microhaeamaturia including trace results (T) from one to 5 days of urine testing in a study pertaining to *S. haematobium* morbidity before and up to 2 years after praziquantel treatment.

Number of tests	**1**	**2**	**3**	**4**	**5**
Reagent strip					
c	0.97 (0.92-1.00)	0.93 (0.86-0.99)	0.92 (0.85-0.99)	0.89 (0.82-0.98)	0.87 (0.80-0.96)
a_0	-0.43 (-0.77--0.10	0.09 (-0.24-0.37)	0.46 (0.14-0.73)	0.67 (0.38-0.96)	0.78 (0.49-1.04)
a_1	0.12 (0.04-0.27)	0.10 (0.03-0.23)	0.10 (0.03-0.24)	0.09 (0.03-0.22)	0.09 (0.03-0.21)
a_2	3.60 (1.90-8.29)	3.88 (1.99-9.50)	3.89 (1.94-9.74)	4.02 (2.04-9.27)	4.40 (2.18-10.69)
a_3	0.98 (0.97-0.99)	0.99 (0.99-1.00)	0.99 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Urine filtration					
k_0	-2.34 (-2.47--2.22)	-2.37 (-2.50--2.25)	-2.36 (-2.49--2.24)	-2.36 (-2.48--2.24)	-2.36 (-2.48--2.24)
k_1	0.38 (0.35-0.42)	0.39 (0.36-0.42)	0.39 (0.36-0.42)	0.39 (0.36-0.42)	0.39 (0.35-0.42)

Table 2.5: Parameters describing the sensitivity and specificity of a reagent strip for microhaeamaturia excluding trace results (1) from one to 5 days of urine testing in a study pertaining to *S. haematobium* morbidity before and up to 2 years after praziquantel treatment.

Number of tests	**1**	**2**	**3**	**4**	**5**
Reagent strip					
c	0.99 (0.96-1.00)	0.99 (0.97-1.00)	0.99 (0.96-1.00)	0.98 (0.94-1.00)	0.97 (0.92-1.00)
a_0	-0.93 (-1.31--0.60)	-0.59 (-0.89--0.31)	-0.29 (-0.59--0.04)	-0.16 (-0.47-0.10)	-0.12 (-0.43-0.14)
a_1	0.22 (0.08-0.47)	0.21 (0.09-0.42)	0.18 (0.07-0.37)	0.17 (0.06-0.36)	0.17 (0.06-0.36)
a_2	1.28 (0.73-2.83)	1.15 (0.74-2.14)	1.38 (0.86-2.69)	1.61 (0.91-3.56)	1.75 (0.97-3.94)
a_3	0.89 (0.84-0.95)	0.97 (0.93-1.00)	0.98 (0.95-1.00)	0.98 (0.95-1.00)	0.98 (0.96-1.00)
Urine filtration					
k_0	-2.31 (-2.43--2.19)	-2.30 (-2.43--2.19)	-2.30 (-2.43--2.18)	-2.31 (-2.42--2.19)	-2.31 (-2.43--2.19)
k_1	0.38 (0.34-0.41)	0.37 (0.34-0.41)	0.37 (0.34-0.41)	0.37 (0.34-0.41)	0.37 (0.34-0.41)

Table 2.6: Parameters describing the sensitivity and specificity of a reagent strip for microhaeamaturia excluding trace and 1+ results (2) from one to 5 days of urine testing in a study pertaining to *S. haematobium* morbidity before and up to 2 years after praziquantel treatment.

Number of tests	**1**	**2**	**3**	**4**	**5**
Reagent strip					
c	1.00 (0.98-1.00)	0.99 (0.98-1.00)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	0.99 (0.96-1.00)
a_0	-1.53 (-1.90--1.21)	-1.42 (-1.77--1.13)	-1.18 (-1.52--0.89)	-1.05 (-1.37--0.77)	-0.98 (-1.28--0.70)
a_1	0.28 (0.13-0.51)	0.25 (0.11-0.46)	0.22 (0.09-0.43)	0.21 (0.09-0.41)	0.20 (0.08-0.38)
a_2	0.87 (0.58-1.42)	1.02 (0.70-1.62)	1.14 (0.79-1.84)	1.25 (0.85-2.02)	1.40 (0.94-2.30)
a_3	0.93 (0.86-0.99)	0.98 (0.94-1.00)	0.99 (0.96-1.00)	0.99 (0.96-1.00)	0.99 (0.97-1.00)
Urine filtration					
k_0	-2.31 (-2.43--2.18)	-2.31 (-2.43--2.19)	-2.30 (-2.42--2.18)	-2.30 (-2.41--2.17)	-2.30 (-2.42--2.18)
k_1	0.37 (0.34-0.41)	0.37 (0.34-0.41)	0.37 (0.34-0.40)	0.37 (0.34-0.40)	0.37 (0.34-0.40)

2.7.3 S1 Checklist.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) **Text excerpt:** We developed a Bayesian model linking individual S. haematobium egg count data based on urine filtration to reagent strip binary test results available on multiple days and estimated the relation between infection intensity and sensitivity of reagent strip. (Abstract: Methods)	p. 1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) Methods, Principal findings and conclusions from abstract.	p. 1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test **Text excerpts:** The WHO recommended diagnostic method for S. haematobium is urine filtration. Alternative diagnostic techniques exist, which are often used in parallel on the same individual to increase diagnostic sensitivity. As blood in urine is relatively easier to detect than S. haematobium eggs, three blood-based diagnostic tests are available: (i) a simple questionnaire regarding recent history of visible blood in urine; (ii) inspection of a urine sample for visible blood; and (iii) a reagent strip for detection of microhematuria (detects visible as well as non-visible blood in urine) [1,2]. Reagent strip for microhematuria allow for a semi-quantitative assessment of infection-intensity with four grades distinguishing the severity of an infection. Other diagnostic approaches include the detection of a specific antigen in urine and polymerase chain reaction (PCR)-based methods to detect genetic material in urine [3,4].	p. 2,3
	4	Study objectives and hypotheses **Text excerpts:** In this study, we determined the infection intensity-dependent diagnostic accuracy of reagent strip to detect microhematuria and urine filtration for S. haematobium eggs. We considered repeated measurements obtained over consecutive days. Previous studies assessed the sensitivity and specificity of the aforementioned methods, but there is no study that models S. haematobium egg counts directly and takes into account day-to-day variation of infection intensity [5, 1, 6–9]. We extend our egg count model for individual-level data, previously developed for the analysis of Kato-Katz thick smears and a point-of-care circulating cathodic antigen (POC-CCA) cassette test for diagnosis of S. mansoni. We developed a model to estimate 'true' prevalence and infection intensity-dependent sensitivity for urine filtration and reagent strip testing and determined the specificity of the latter diagnostic test [10, 11]. Finally, we employed a simulation to translate current WHO urine filtration intervention thresholds to microhematuria analogues based on reagent strip test results.	p. 3
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) This is a retrospective study. **Text excerpt:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993.	p. 3
Participants	**6**	Eligibility criteria **Text excerpts:** - The study involved 533 school-aged children (7-18 years) and included a baseline and six follow-up surveys (at 2,4,6, 12, 18 and 24 months) after an initial treatment with praziquantel just after the baseline survey. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany).	p. 3

		-For each survey efforts were made to collect urine specimens over five consecutive days (between 10:00 and 14:00 hours). The aim of the study was to characterize the evolution of S. haematobium pathology after a single dose of praziquantel.	
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) **Text excerpts:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. The study involved 533 school-aged children (7-18 years) and included a baseline and six follow-up surveys (at 2,4,6, 12, 18 and 24 months) after an initial treatment with praziquantel just after the baseline survey.	p. 3
	8	Where and when potentially eligible participants were identified (setting, location and dates) **Text excerpt:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. The study involved 533 school-aged children (7-18 years) and included a baseline and six follow-up surveys (at 2,4,6, 12, 18 and 24 months) after an initial treatment with praziquantel just after the baseline survey. For each survey, efforts were made to collect urine specimens over five consecutive days (between 10:00 and 14:00 hours).	p. 3
	9	Whether participants formed a consecutive, random or convenience series **Text excerpt:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. The study involved 533 school-aged children (7-18 years) and included a baseline and six follow-up surveys (at 2,4,6, 12, 18 and 24 months) after an initial treatment with praziquantel just after the baseline survey.	p. 3
Test methods	**10a**	Index test, in sufficient detail to allow replication **Text excerpts:** The study involved 533 school-age children (7-18 years) and included a baseline and six follow-up surveys (at 2, 4, 6, 12, 18, and 24 months) after an initial treatment with praziquantel just after the baseline survey. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany). Readings of the reagent strip were done semi-quantitatively with values corresponding to 0 (negative), trace T (< 5 red blood cells (RBC)/µl of urine), 1+ (5-10 RBC/µl of urine), 2+ (~50 RBC/µl of urine), and 3+ (~250 RBC/µl of urine) [12].	p. 3
	10b	Reference standard, in sufficient detail to allow replication **Text excerpts:** The study involved 533 school-age children (7-18 years) and included a baseline and six follow-up surveys (at 2, 4, 6, 12, 18, and 24 months) after an initial treatment with praziquantel just after the baseline survey. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany). Urine filtration was performed with samples of 10 ml of urine using Nucleopore membranes with 12 µl pore filters. For each survey, efforts were made to collect urine specimens over five consecutive days (between 10:00 and 14:00 hours).	p. 3
	11	Rationale for choosing the reference standard (if alternatives exist) **Text excerpt:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany).	p. 3
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory **Text excerpt:** Readings of the reagent strip were done semi-quantitatively with values corresponding to 0 (negative), trace (< 5 red blood cells (RBC)/µl of urine), 1+ (5 − 10 RBC/µl of urine), 2+ (~ 50 RBC/µl of urine), and 3+ (~ 250 RBC/µl of urine) [12]. For each individual, reagent strip (RS) data results were converted into 3 categorical variables with values T when the RS result was at least T (i.e. T/1+/2+/3+), 1 when the RS result was at least 1 (i.e. 1+/2+/3+) and 2 when the RS result was at least 2 (i.e. 2+/3+).	p. 3

	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory **Text excerpt:** Urine filtration was performed with samples of 10 ml of urine using Nucleopore membranes with 12 µl pore filters. For each survey, efforts were made to collect urine specimens over five consecutive days (between 10:00 and 14:00 hours).	p. 3
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test **Text excerpt:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany).	p. 3
	13b	Whether clinical information and index test results were available to the assessors of the reference standard **Text excerpt:** The analysis was carried out using a readily available dataset from a study conducted in two villages in Tanzania in 1993. At each survey, urine samples were collected and subjected to urine filtration and reagent strip testing (Boehringer Mannheim; Mannheim, Germany).	p. 3
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy **Text excerpt:** For each individual i in population j, j = 1, . . . , 14 let Yjid be the observed egg counts from urine filtration on day d, d = 1, 2, . . . , 5. The results from a semi-quantitative reagent strip for microhematuria were coded into 15 binary variables: YjiRS,T,z describes all individuals with at least result trace, YjiRS,1,z with at least result 1+ and YjiRS,2,z 2+, repectively. z denotes the first days (z = 1, . . . , 5), i.e. z = 1 refers to the test result of the first day, z = 2 refers to the results of the first two days and so forth. The models were fitted separately for each of UF, where all the 15 binary results YjiRS,x,z , x = T, 1, 2, combined with all Yjid observations were included. We inferred on the sensitivity of repeated microhematuria measurements without having to model the correlation structure explicitly.	p. 4
	15	How indeterminate index test or reference standard results were handled **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
	16	How missing data on the index test and reference standard were handled **Text excerpts:** -The models were fitted separately for each of the 15 binary results Y RS;x;zji , x = T; 1; 2, combined with all Y UFjid , where all individuals with both test results at a cross-sectional survey were included, with exception of a few individuals with multiple entries.	p. 4
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory To assess the relation between prevalence observed by microhematuria and urine filtration for one, two, three, four, and five days, we run extensive simulations of hypothetical populations in diverse transmission settings. We assumed that worms are negative binomially distributed in the population with worm aggregation parameter wagg and that a proportion of 30% of the worms are female [13,14]. The mean number of eggs per 10 ml of urine per female worm was selected from a publication of Truscott et al. who estimated it to be 5.2 [15]. For the parameters a0 , a1 , a2 , a3 , k0 , and k1 100 draws were taken directly from the posterior distribution and thereby correlation between parameters was incorporated in the simulation. The mean number of worms per individual in a population was varied in 30 equal steps on the log-scale from 1 to 400. wagg according to a normal distribution with a mean of 0.2 and a SD of 0.03. For each population worm load for 5000 individuals and corresponding urine filtration and reagent strip results were simulated for all five days.	p. 5
	18	Intended sample size and how it was determined	p. 3

		Text excerpt: All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	
RESULTS			
Participants	**19**	Flow of participants, using a diagram **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
	20	Baseline demographic and clinical characteristics of participants **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
	21a	Distribution of severity of disease in those with the target condition **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
	21b	Distribution of alternative diagnoses in those without the target condition **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
	22	Time interval and any clinical interventions between index test and reference standard **Text excerpt:** The study involved 533 school-aged children (7-18 years) and included a baseline and six follow-up surveys (at 2, 4, 6, 12, 18 and 24 months) after an initial treatment with praziquantel just after the survey.	p. 3
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard Figure 1, Table 1, Table 2	p. 4, 6, 7
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) Table 1, 2 and 3 **Text excerpts:** -A single urine filtration had a sensitivity of above 85% for heavy infections (≥ 50 eggs per 10 ml of urine) while the sensitivity was below 50% at around 7 eggs per 10 ml of urine. The sensitivity showed a substantial increase as a function of repeated urine filtration. For example the sensitivity increased from 50% to 75% when comparing a single with a double urine filtration at a low infection intensity of 7 eggs per 10 ml of urine. After five days of urine filtration, an average infection with a single worm-pair at 1 egg per 10 ml of urine showed a probability of around 60% to be detected. - Considering traces as negative resulted in higher specificity of 99% for a single reagent strip and still 95% after five samples. When traces were considered positive, the specificity after 5 samples was reduced to 85%, however, the sensitivity was higher compared to traces considered negative. A single reagent strip has only a 60% chance to detect an infection of 10 eggs per 10 ml of urine and still less than 90% for heavy infections (≥ 50 eggs per 10 ml of urine). Repeated sampling over five consecutive days increased the sensitivity up to 80% at 10 eggs per 10 ml of urine compared to a sensitivity of almost 100% at the same intensity when traces were considered positive. The sensitivity of a single reagent strip when traces were considered negative is similar to a single urine filtration regardless of the level of infection intensity. Stratification by sex did not show any difference in parameter estimates that would indicate an important interaction for example with menstruation. - The semi-quantitative results of the reagent strip were closely correlated with the infection intensity of an individual. The proportion of trace, 1 and > 1 results for infection intensities up to 50 eggs per 10 ml of urine are shown in Fig 4. The non-monotonic behavior close to an infection intensity of zero is due to increased uncertainty in the sensitivity estimates (not shown in the plot, but visible in Figs 3a	p. 6-9

		and 3b). At very low infection intensities, there was a considerable probability (~ 40%) for readings of 2 or 3, while at 50 eggs per 10 ml of urine almost 80% of tests showed a 2 or 3. Trace results, on the other hand, decreased from a proportion of about 30% to less than 10% at 50 eggs per 10 ml of urine while the proportion of samples with reading 1 remained relatively constant. - We translated the WHO prevalence thresholds from urine filtration into microhematuria by taking all simulated populations with observed prevalence by urine filtration within a narrow interval of ±0.5% around the threshold and calculating the mean of the observed prevalence by reagent strip and the corresponding Bayesian credible intervals. Table 3 shows results for three thresholds of urine filtration, 10%, 25%, and 50%, and the reagent strip when traces were considered positive or negative, for sampling schemes based on a single up to five urine samples over consecutive days. Most relevant for evaluating treatment needs are results for sampling on a single day. When traces were considered negative, the prevalence thresholds for microhematuria were very close to urine filtration thresholds. Including traces in the positive required upwards adjustment of the thresholds, for example a 10% urine filtration corresponds to about 20% prevalence by reagent strip.	
	25	Any adverse events from performing the index test or the reference standard **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability **Text excerpt:** Our study has several limitations that are offered for consideration. First, the data stem from a single type of reagent strip from a survey carried out in only two villages of Tanzania almost 30 years ago with an age of participants ranging between 7 and 18 years. Importantly though, urine samples were obtained at multiple time points over the course of 24 months after a single oral dose of praziquantel. It is imperative to validate the results with additional data, for example using the Hemastix and U-11 reagent strip, particularly in settings where S. haematobium is close to elimination. Second, the simulation depends on the assumption of negative binomial distribution of worms in the population with a constant aggregation parameter, which is likely a good approximation at higher mean worm counts but cannot be extrapolated to low prevalences below 10% observed urine filtration prevalence. This is reflected in our results making no recommendations for translation of lower thresholds. Third, it was not uncommon to have individuals where only one diagnostic test was performed on a specific sampling time point, and hence, observed prevalence by reagent strip and urine filtration at the same time point, and village are not directly comparable.	p. 11
	27	Implications for practice, including the intended use and clinical role of the index test **Text excerpt:** In accordance with recommendations put forward by WHO and the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) for estimation of S. haematobium prevalence from a single day [16,17], we recommend translating urine filtration thresholds of 10%, 25% and 50% into 12%, 26% and 50% when a single reagent strip is employed, considering traces as negative. Trace positive individuals should, however, also be treated with praziquantel, as it might indicate a very light infection with S. haematobium that might cause subtle morbidity [18,19]. The reagent strip with traces considered negative serves as a convenient proxy to estimate prevalence almost equivalent to single-day urine filtration.	p. 10-11
OTHER INFORMATION			
	28	Registration number and name of registry **Text excerpt:** All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	p. 3
	29	Where the full study protocol can be accessed	p. 3

		Text excerpt: All data included in this study have been published elsewhere [12]. Ethics approval and informed consent procedures are given in the aforementioned study from which the data have been extracted.	
	30	Sources of funding and other support; role of funders **Text excerpt:** This study received financial support from the European Research Council (ERC-2012-AdG-323180) and the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.	p. 12

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Chapter 3

Modeling transmission mechanism to infer treatment efficacy of different drugs and combination therapy against *Trichuris trichiura*

Carla M. Grolimund[1,2], Jürg Utzinger[1,2], Jennifer Keiser[1,2], Penelope Vounatsou[1,2]

1 – Swiss Tropical and Public Health Institute, Basel, Switzerland
2 – University of Basel, Switzerland

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Keywords: Hookworm; Ancylostoma duodenale; Necator americanus; diagnostics; Kato-Katz; Bayesian model; diagnostic error; Sensitivity; cure rate; egg reduction rate

3.1 Abstract

3.1.1 Background

Hookworm infections, caused by *Ancylostoma duodenale* and *Necator americanus*, are of considerable public health importance. The World Health Organization recommends preventive chemotherapy as the key strategy for morbidity control. Meta-analyses have been conducted to estimate treatment efficacy of available drugs and drug combinations. However, in most studies, the relation between the diagnostic error and infection intensity have not been considered, resulting in an overestimation of cure rates (CRs).

3.1.2 Methodology

A Bayesian model was developed to compare the 'true' CR and egg reduction rate of different treatment regimens for hookworm infections taking into account the error of the recommended Kato-Katz thick smear diagnostic technique. It was fitted to the observed egg count data which was linked to the distribution of worms, considered the day-to-day variation of hookworm egg excretion and estimated the infection intensity-dependent sensitivity. The CR was obtained by defining the prevalence of infection at follow-up as the probability of having at least one fertilized female worm. The model was applied to individual-level egg count data available from 17 treatments and six clinical trials.

3.1.3 Principal findings

Taking the diagnostic error into account resulted in considerably lower CRs than previously reported. Overall, of all treatments analyzed, mebendazole administered in six dosages of 100 mg each was the most efficacious treatment with a CR of 88% (95% Bayesian credible interval: 79-95%). Furthermore, diagnostic sensitivity varied with the infection intensity and sampling effort. For an infection intensity of 50 eggs per gram of stool, the sensitivity is close to 60%; for two Kato-Katz thick smears it increased to approximately 76%.

3.1.4 Conclusions/significance

Our model-based estimates provide the 'true' efficacy of different treatment regimens against hookworm infection taking into account the diagnostic error of the Kato-Katz method. Estimates of the diagnostic sensitivity for different number of stool samples and thick smears are obtained. To accurately assess efficacy in clinical trials with the Kato-Katz method, at least two stool samples on consecutive days should be collected.

3.2 Author summary

Human hookworm infections are primarily caused by two parasitic worm species, namely *Ancylostoma duodenale* and *Necator americanus*. Already moderate infection intensities can impair cognitive and physical development of children, and reduce fertility in women of reproductive age. The World Health Organization set the global target to eliminate morbidity due to hookworm infections in preschool-age and school-age children by 2030. To reach this goal, different public health interventions are carried out. The most widely used strategy is mass drug administration. To assess the efficacy of treatments,

epidemiologic studies and clinical trials usually employ the Kato-Katz thick smear technique to microscopically examine stool samples of individuals before and after treatment. Of note, this diagnostic test is not 100% accurate such that not all positive individuals are detected. We developed a mathematical model, which takes into account the diagnostic error to compare the 'true' efficacy of different drugs and treatment regimens against hookworm infection. Furthermore, we computed how well the test detects infected individuals in relation to infection intensity. We found that the diagnostic sensitivity of the Kato-Katz thick smear technique increases considerably if two stool specimens from different days are collected and multiple Kato-Katz thick smears are analyzed instead of one.

3.3 Introduction

Human hookworm infections are primarily caused by *Ancylostoma duodenale* and *Necator americanus* (WHO, 2019b). It is estimated that around 450 million people are infected with hookworm and an equivalent of roughly 1.685 million years are lost due to disability annually (Vos et al., 2017). Impaired cognitive and physical development in children, as well as reduced fertility among women of reproductive age due to iron deficiency and anemia are important morbidities caused by moderate or heavy hookworm infection (Loukas et al., 2016). Elimination of morbidity due to hookworm and other soil-transmitted helminth (STH) species in preschool-age and school-age children by 2030 is the global target set forth by the World Health Organization (WHO) (Organization et al., 2020a). To reduce the burden caused by hookworm and other STH species, different control measures are being implemented, such as footwear campaigns, water, sanitation, and hygiene (WASH) interventions, and preventive chemotherapy (PC) that is the periodic administration of anthelmintic drugs without prior diagnosis (Haldeman et al., 2020). PC is the most widely used intervention and has been shown to reduce the burden especially of moderate and heavy STH infection intensities (Haldeman et al., 2020; Montresor et al., 2020; WHO, 2017).

WHO recommends single doses of 400 mg albendazole and 500 mg mebendazole in PC campaigns against hookworm and other STH infections (WHO, 2019b). Recent studies and meta-analyses have shown that other regimens and combination treatment are more efficacious. For instance, Palmeirim et al. (2018) found that six dosages of 100 mg mebendazole are more efficacious against hookworm infections than a single dose of 500 mg (Palmeirim, Hürlimann, et al., 2018). Moser et al. (2018) presented data from a trial conducted in Lao People's Democratic Republic (Lao PDR) highlighting high efficacy of a combination of albendazole, pyrantel pamoate plus oxantel pamoate against hookworm infections (Moser, Sayasone, et al., 2018).

Systematic reviews and meta-analyses have been carried out to compare the efficacy of different treatments against hookworm and other STH infections (Clarke et al., 2019; Keiser & Utzinger, 2008; Moser et al., 2019). However, most trials assess the presence of hookworms using the Kato-Katz thick smear technique, which has low sensitivity, and hence, the efficacy of the treatment is overestimated. Meta-analyses using latent class models (LCMs) have been conducted to take into account the diagnostic error (Coulibaly et al., 2016; Nikolay et al., 2014; Tarafder et al., 2010). It must be noted, however, that these models analyze only the positive/negative test result for each individual. In contrast, Bärenbold et al. (2017) developed an individual-level egg count Bayesian model, which takes into account the dependence of sensitivity on the infection intensity and includes the day-to-day variation in helminth egg output (Bärenbold et al., 2017). The model has been succesfully applied to data from a clinical trial on Pemba Island to assess the performance

of FECPAK^{G2} and the Kato-Katz thick smear technique for the diagnosis of STH infection (Moser, Bärenbold, et al., 2018).

In this study, we pursued a Bayesian meta-analysis to compare the 'true' cure rate (CR) and egg reduction rate (ERR) of different treatments against hookworm infection considering the diagnostic error of the Kato-Katz thick smear technique. We fitted a model to the observed egg count data that took into account the distribution of worms and estimated diagnostic sensitivity as a function of the infection intensity. We considered day-to-day variation in the egg counts and correlation of slides from the same stool sample. The CR was estimated by defining the prevalence as the probability of having at least one fertilized female worm. Our analysis includes data from six clinical trials, which comprise 17 unique treatments based on a single drug or a combination of two or three anthelmintic drugs.

3.4 Materials and methods

3.4.1 Ethics statement

The studies from which the data used in this analysis have been obtained have been published elsewhere (Coulibaly et al., 2019; Moser, Coulibaly, et al., 2017; Moser, Sayasone, et al., 2018; Palmeirim, Ame, et al., 2018; Speich et al., 2015; Speich et al., 2014). Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.

3.4.2 Data

We analyzed data from six randomized trials in Côte d'Ivoire, Lao PDR, and Tanzania, which assessed the efficacy and safety of different treatments against STH infection (Coulibaly et al., 2019; Moser, Coulibaly, et al., 2017; Moser, Sayasone, et al., 2018; Palmeirim, Ame, et al., 2018; Speich et al., 2015; Speich et al., 2014). All trials followed the same sampling design and used the Kato-Katz thick smear technique. For each individual, two stool specimens were collected over two consecutive days at baseline and treatment follow-up, usually 14-21 days post-treatment, while two readings were made per specimen. All slides were read within 1 hour after preparation to avoid degeneration of hookworm eggs on microscope slides. At baseline, we only considered hookworm-positive individuals, and hence the prevalence was set at 100%. For trials with a focus on *T. trichiura*, only hookworm-positive individuals were included in the analysis. The observed CRs against hookworm ranged from 11% to 98% and the ERRs from 11% to 100%. A summary of the data, including the treatment arms by trial, is provided in Table 3.1. The confidence intervals (CIs) were calculated in R (version 3.6.1), using the package 'prevalence' for the CRs with Jeffreys method and 'eggCounts' for the ERRs with bootstrapping.

Table 3.1: **Description of trial data: age group included, treatments tested, sample sizes and arithmetic mean of averaged egg counts per gram of stool (EPG) averaged on the four slides at baseline (BL) and follow-up (FU)**

Trial	Country	Age (years)	Treatment	No. of participants with hookworm infection	Mean EPG at BL	Mean EPG at FU
Coulibaly et al. (2017) (Coulibaly et al., 2019)	Côte d'Ivoire	6-13	Tribendimidine 100 mg	33	355	258
			Tribendimidine 200 mg	31	313	130
			Tribendimidine 400 mg	31	215	96
Moser et al. (2016) (Moser, Sayasone, et al., 2018)	Côte d'Ivoire	15-18	Tribendimidine 400 mg	55	421	106
			Tribendimidine 400 mg+ivermectin 200 µg/kg	54	485	27
			Tribendimidine 400 mg+oxantel pamoate 25 mg/kg	53	424	103
			Albendazole 400 mg+oxantel pamoate 25 mg/kg	49	629	113
Moser et al. (2016) (Moser, Sayasone, et al., 2018)	Tanzania	6-14	Tribendimidine 400 mg	96	399	84
			Tribendimidine 400 mg+ivermectin 200 µg/kg	100	377	9
			Tribendimidine 400 mg+oxantel pamoate 25 mg/kg	95	385	57
			Albendazole 400 mg+oxantel pamoate 25 mg/kg	99	459	42
Moser et al. (2017) (Moser, Coulibaly, et al., 2017)	Lao PDR	6-12	Albendazole 400 mg+oxantel pamoate 20 mg/kg	138	1,269	114
			Pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	68	1,317	49
			Albendazole 400 mg+pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	138	1,374	22
			Mebendazole 500 mg+pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	69	1,457	99
Palmeirim et al. (2017) (Palmeirim, Ame, et al., 2018)	Tanzania	6-14	Mebendazole 500 mg	92	443	209
			Mebendazole 6x100 mg	93	465	1
Speich et al. (2012) (Speich et al., 2014)	Tanzania	15-18	Albendazole 400 mg+oxantel pamoate 20 mg/kg[1]	109	434	56
			Oxantel pamoate 20 mg/kg	113	276	238
			Albendazole 400 mg	112	236	57
			Mebendazole 500 mg	108	312	173
Speich et al. (2013) (Speich et al., 2015)	Tanzania	6-15	Albendazole 400 mg+ivermectin 200 µg/kg	42	338	35
			Albendazole 400 mg+mebendazole 500 mg	46	388	106
			Albendazole 400 mg+oxantel pamoate 20 mg/kg	55	222	66
			Mebendazole 500 mg	41	173	153

[1] Administered on 2 consecutive days

3.4.3 Model

Table 3.2: **Description of parameters used in the model**

	Parameter	Description
Eggs	$\mu_{i_{jg}d}^{(t)}$	Daily individual mean egg burden at baseline ($t = 0$) and follow-up ($t = 1$)
	$\mu_{i_{jg}}^{(t)}$	Individual mean egg burden at baseline ($t = 0$) and follow-up ($t = 1$)
	$\mu_{jg}^{(t)}$	Mean egg burden of treatment group g from survey j at baseline ($t = 0$) and follow-up ($t = 1$)
	$k^{(t)}$	Aggregation in infected individuals at baseline ($t = 0$) and follow-up ($t = 1$)
	σ_{jg}^2	Variance of infected individuals of study j and treatment group g
	$v^{(1)}$	Mean egg burden of non-infected individuals
	r	Aggregation in non-infected individuals
	σ_d	Day-to-day variation in egg counts
	π_{jg}	Prevalence of treatment group g of study j
	c_{jg}	Cure rate of treatment group g of study j
	ϕ_{jg}	Egg reduction rate of treatment group g of study j
	α_{jg}, β_{jg}	Parameters of Gamma distribution describing $\mu_{i_{jg}}^{(1)}$
Worms	w_{jg}	Mean worm burden
	k_w	Aggregation of worms
	z	number of eggs per fertilized female worm

We developed a model, fitted to the individual egg count data assuming they arise from a negative binomial distribution at baseline and a mixture of negative binomial distributions at follow-up with mixing proportion equal to the 'true' prevalence of infection in the population. The latter was defined as the probability of having at least one fertilized female worm and derived from a negative binomial distribution of worms, assuming a 1:1 female to male ratio and that one male worm can fertilize all females. We considered conditional independence of the slides given the disease status to take into account the correlation of slides from the same stool sample and took into account day-to-day variation on the individual egg counts. We estimated the 'true' CR from the 'true' prevalence at follow-up. To link the egg counts to the worm burden, we computed the marginal distribution of egg counts from the joint distribution of egg counts and fertilized female worms. The density dependence was not taken into account due to the low infection intensities at follow-up. The ERR was calculated from the treatment group specific mean egg burden at baseline and at follow-up (among the truly infected individuals). The model formulation enabled estimation of the egg intensity-dependent sensitivity of the Kato-Katz method for different number of slides. A mathematical description of the model and a graphical representation are given below and in Fig 3.1, respectively.

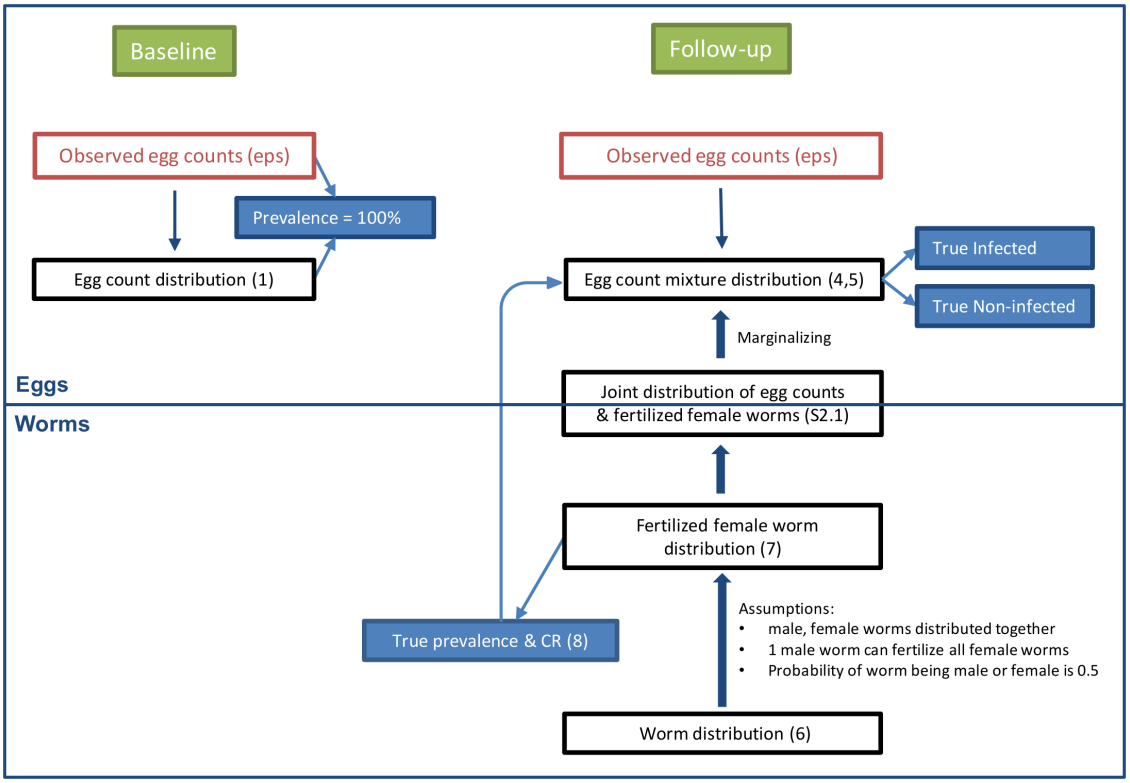


Figure 3.1: **Graphical representation of the model.** Numbers in brackets indicate equation numbers as given in the text below and in S2 Appendix.

Let $Y^{(t)}_{i_{jg}ds}$ be the egg counts (eggs per Kato-Katz slides) for individual i from study j and treatment group g, at measurement day d for sample s at baseline ($t = 0$) or follow-up ($t = 1$). For the baseline data, we assumed a negative binomial distribution with mean $\mu^{(0)}_{i_{jg}d}$ and aggregation parameter $k^{(0)}$:

$$Y^{(0)}_{i_{jg}ds} \sim \mathrm{NB}(\mu^{(0)}_{i_{jg}d}, k^{(0)}). \tag{3.1}$$

For the follow-up data $Y^{(1)}_{i_{jg}ds}$ we chose a mixture model to separate the infected from the non-infected individuals. Let $D_{i_{jg}}$ be the disease status of individual i (from study j and treatment group g) defined as

$$\mathrm{D}_{i_{jg}} = 0, \text{if individual i harbors no fertilized female worms} \tag{3.2}$$
$$\mathrm{D}_{i_{jg}} = 1, \text{if individual i harbors at least one fertilized female worm.} \tag{3.3}$$

We modeled the likelihood of the egg counts at follow-up with a two component mixture, where the 'true' prevalence $\pi_{jg} = \mathrm{P}(\mathrm{D}_{i_{jg}} = 1)$ denotes the mixture component, that is

$$\mathrm{P}(\boldsymbol{Y}^{(1)}_i | \mathrm{D}_{i_{jg}} = 0) \equiv \prod_{d,s} NB(v^{(1)}, r) \tag{3.4}$$
$$\mathrm{P}(\boldsymbol{Y}^{(1)}_i | \mathrm{D}_{i_{jg}} = 1) \equiv \prod_{d,s} NB(\mu^{(1)}_{i_{jg}d}, k^{(1)}), \tag{3.5}$$

with v the mean of the non-infected individuals and r the aggregation in the non-infected individuals. We assume conditional independence of the egg counts from the same individual given the disease status (Bärenbold et al., 2018). $\mu_{i_{jg}d}^{(1)}$ is the daily individual mean of the infected individuals and $k^{(1)}$ is the variation from slide to slide. We took into account the day-to-day variation $(\sigma_d^{(t)})^2$ in the excreted eggs by day-specific random effects for each i and t, as follows $log(\mu_{i_{jg}d}^{(t)}) = log(\mu_{i_{jg}}^{(t)}) + \epsilon_{id}^{(t)}$ where $\epsilon_{id}^{(t)} \sim \mathcal{N}(\frac{-(\sigma_d^{(t)})^2}{2}, (\sigma_d^{(t)})^2)$. The 'true' prevalence π_{jg} was defined as the probability of having at least one fertilized female worm (see equation 3.8) and the CR is therefore given by $c_{jg} = 1 - \pi_{jg}$.

For the mean infection intensities, we assumed a Gamma prior distribution. More specifically, at baseline $\mu_{i_{jg}}^{(0)} \sim \text{Gamma}(\mu_{jg}^{(0)} \cdot \sigma_{jg}^{(0)}, \sigma_{jg}^{(0)})$, where $\mu_{jg}^{(0)}$ and $\sigma_{jg}^{(0)}$ are hyperparameters. At follow-up, the mean and the variance of the gamma distribution $\mu_{i_{jg}}^{(1)} \sim \text{Gamma}(\alpha_{jg}^{(1)}, \beta_{jg}^{(1)})$ are obtained from the distribution of the egg counts which is derived by marginalizing the joint distribution distribution of egg counts and fertilized female worms (see Appendix S2). The joint distribution can be written as the product of the conditional distribution of the egg counts given the feritlized female worms and the distribution of fertilized female worms. The distribution of the fertilized female worms is derived from the distribution of the worms. In particular, we assume that the male and female worms are distributed together (R. M. May, 1977; J. E. Truscott et al., 2019) and that one male worm can fertilize all female worms. Let N_f be the number of female and N_m the number of male worms, w_{jg} the mean worm burden in the population and k_w the aggregation of the worms, then the worm distribution is given below:

$$\text{NB}(N_f, N_m | w_{jg}, k_w) = \frac{\Gamma(N_f + N_m + k_w)}{N_f! N_m! \Gamma(k_w)} \cdot (1-\alpha)^{k_w} \cdot (\alpha p)^{N_f} \cdot (\alpha(1-p))^{N_m}, \tag{3.6}$$

where $\alpha = \frac{w_{jg}}{w_{jg}+k_w}$ and $p = \frac{1}{2}$ is the probability of a worm to be female. It follows that the distribution of fertilized female worms n_f (see S1 Appendix) is

$$P(n_f; w_{jg}, k_w) = \text{NB}(n_f; \frac{w_{jg}}{2}, k_w) - \text{NB}(n_f; w_{jg}, k_w) \cdot \left(\frac{1}{2}\right)^{n_f}, \quad n_f \geq 1. \tag{3.7}$$

We assume that the conditional distribution of the egg counts given the fertilized female worms is a negative binomial distribution with mean $z * n_f$ and aggregation parameter $k^{(1)}$, where z is a parameter describing the net egg output per fertilized female worm. Due to the low infection intensities the density dependence was not taken into account.

The 'true' CR, c_{jg} is computed from the 'true' prevalence that is

$$c_{jg} = P(0, w_{jg}, k_w) = 2\left(\frac{k_w}{w_{jg}/2 + k_w}\right)^{k_w} - \left(\frac{k_w}{w_{jg} + k_w}\right)^{k_w}. \tag{3.8}$$

We defined ϕ_{jg} to be the ERR of treatment g and trial j. By combining the group-specific infection intensity of the population $\mu_{jg}^{(0)}$ at baseline, $\mu_{jg}^{(1)}$ at follow-up, and the prevalence, we were able to compute the ERR ϕ_{jg} as

$$\phi_{jg} = 1 - \frac{\mu_{jg}^{(1)} \cdot \pi_{jg}}{\mu_{jg}^{(0)}}. \tag{3.9}$$

Finally, we calculated the posterior distribution of the treatment-specific ERR ϕ_g and CR c_g, as a weighted average of the trial specific ϕ_{jg} and c_{jg}, respectively, with normalized weights proportional to the sample size. For the hyperparameters, the following priors were chosen: for $\mu_{jg}^{(0)}$ a gamma distribution with mean 50 and variance 1,250; for $\sigma_{jg}^{(0)}$ an

exponential distribution with mean 0.5 and variance 0.25, for $(\sigma_d^{(t)})^2$ a gamma distribution with mean 1 and variance 1; for $1/k^{(0)}$ and $1/k^{(1)}$ normal prior distributions with mean 0 and variance 1; for w_{jg} a gamma distribution with mean 2 and variance 10; for k_w a normal distribution with mean 0.4 and variance 0.5; for r a normal distribution truncated at 0 with mean 0, and variance 1 and for z a normal with mean 0.8 and variance 1. If prior knowledge was scarce or ambiguous, weakly informative priors were chosen, otherwise semi-informative priors were applied according to the biological literature (Levecke et al., 2015). All individuals were included in this analysis as for missing or indeterminate values missing at random (MAR) can be assumed. The model was run in Stan (version 2.19.1) with 10 chains and 10,000 iterations of which the first 5,000 were not included. Convergence was determined with Gelman and Rubin diagnostics (Vats & Knudson, 2021).

Posterior samples of the day-to-day variation in egg excretion $(\sigma_d^{(t)})^2$ and the egg aggregation k were used to obtain the posterior distribution of the sensitivity as a function of infection intensity via the relationship

$$s_{id} = 1 - \prod_{r=1}^{d} NB(0, \mu_{ir}, k)^{s \cdot k} = 1 - \left(\frac{k}{\mu_{i1} + k}\right)^{s \cdot k} \cdot \ldots \cdot \left(\frac{k}{\mu_{id} + k}\right)^{s \cdot k}, \tag{3.10}$$

where k is the posterior mean of the average of $k^{(0)}$ and $k^{(1)}$. We simulated data for mean infection intensities of 0-500 EPG for either one, two, or four Kato-Katz thick smears. For one and two Kato-Katz thick smears it was assumed that the replicate samples were analyzed on the same day, in the case of four Kato-Katz thick smears it was assumed that two samples were analyzed on one day. We considered the above testing regimen as they are the most common ones in clinical trials. Parameter estimates were provided in terms of their posterior median and the 95% Bayesian credible interval (BCI).

3.5 Results

3.5.1 Descriptive data analysis

Table 3.1 shows the mean hookworm infection intensities at baseline in the included studies from Côte d'Ivoire, Lao PDR, and Tanzania. All of the infections were classified as light infections (i.e. <2,000 EPG (Montresor et al., 1998)). The sample sizes were similar for the different treatment arms within the individual studies, with exception of the trial in Lao PDR where approximately twice as many children were assigned to two treatment arms (albendazole plus oxantel and albendazole plus oxantel plus pyrantel) (Moser, Sayasone, et al., 2018). There were slight differences in CRs and ERRs for the same treatments. For instance, there were three trials administering 500 mg mebendazole with CRs of 13%, 18%, and 24% and ERRs of 53%, 45%, and 11%, respectively (Palmeirim, Ame, et al., 2018; Speich et al., 2015; Speich et al., 2014). However for 400 mg tribendimidine, the CRs estimated from three trials were rather similar, i.e. 45%, 55%, and 58%, respectively, whereas the ERRs varied more considerably from 55% to 79%. These results from the descriptive analysis (Table 3.3) are also reflected in the model estimates as they were informed by the data.

Table 3.3: **Estimates of CRs and ERRs among different trials obtained from raw data**

Treatment/dose	CR1	ERR1	CR2	ERR2	CR3	ERR3
Albendazole 400 mg	0.60 (0.51, 0.69)	0.76 (0.54, 0.89)	-	-	-	-
Albendazole 400 mg+ivermectin 200 µg/kg	0.50 (0.35, 0.65)	0.90 (0.69, 0.96)	-	-	-	-
Albendazole 400 mg+mebendazole 500 mg	0.48 (0.34 ,0.62)	0.73 (0.27 ,0.90)	-	-	-	-
Albendazole 400 mg+oxantel pamoate 20 mg/kg	0.53 (0.45, 0.61)	0.91 (0.86, 0.95)	0.45 (0.33, 0.59)	0.71 (0.41, 0.87)	-	-
Albendazole 400 mg+oxantel pamoate 25 mg/kg	0.37 (0.24, 0.51)	0.82 (0.64, 0.91)	0.54 (0.44, 0.63)	0.91 (0.84, 0.95)	-	-
Albendazole 400 mg+pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	0.84 (0.77, 0.89)	0.98 (0.97, 0.99)	-	-	-	-
Albendazole 400 mg+oxantel pamoate 20 mg/kg cons[3]	0.51 (0.42, 0.61)	0.87 (0.68, 0.95)	-	-	-	-
Mebendazole 500 mg	0.18 (0.11, 0.26)	0.45 (0.11, 0.65)	0.24 (0.13, 0.39)	0.11 (-0.76, 0.58)	0.13 (0.07, 0.21)	0.53 (0.29, 0.69)
Mebendazole 500 mg+pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	0.70 (0.58, 0.79)	0.93 (0.79, 0.99)	-	-	-	-
Mebendazole 6x100 mg	0.98 (0.93, 1.00)	1.00 (0.99, 1.00)	-	-	-	-
Oxantel pamoate 20 mg/kg	0.11 (0.06, 0.17)	0.14 (-0.39, 0.47)	-	-	-	-
Pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	0.51 (0.40, 0.63)	0.96 (0.93, 0.98)	-	-	-	-
Tribendimidine 100 mg	0.21 (0.10, 0.37)	0.27 (-0.64, 0.69)	-	-	-	-
Tribendimidine 200 mg	0.39 (0.23, 0.56)	0.58 (-0.14, 0.83)	-	-	-	-
Tribendimidine 400 mg	0.45 (0.33, 0.59)	0.75 (0.46, 0.89)	0.55 (0.38, 0.71)	0.55 (0.03, 0.82)	0.58 (0.48, 0.68)	0.79 (0.52, 0.93)
Tribendimidine 400 mg+ivermectin 200 µg/kg	0.91 (0.81, 0.96)	0.94 (0.86, 0.99)	0.81 (0.72, 0.88)	0.98 (0.95, 0.99)	-	-
Tribendimidine 400 mg+oxantel pamoate 25 mg/kg	0.51 (0.38, 0.64)	0.76 (0.54, 0.90)	0.53 (0.43, 0.62)	0.85 (0.77, 0.91)	-	-

[1] CR = cure rate; CR1, CR2, and CR3 refer to data from individual studies
[2] ERR = egg reduction rate; ERR1, ERR2, and ERR3 refer to data from individual studies
[3] Administered on 2 consecutive days

3.5.2 Model-based estimates

The estimated CRs ranged from 10% to 88% and the ERRs from −26% to 100% (Table 3.4).

Table 3.4: **Posterior estimates (mean, 95% BCI) for CR and ERR**

Treatment	Cure rate (c_g)	Egg reduction rate (ϕ_g)
Albendazole 400 mg	0.44 (0.37,0.51)	0.74 (0.57,0.86)
Albendazole 400 mg+ivermectin 200 µg/kg	0.41 (0.31,0.52)	0.79 (0.55,0.91)
Albendazole 400 mg+mebendazole 500 mg	0.35 (0.25,0.45)	0.68 (0.35,0.86)
Albendazole 400 mg+oxantel pamoate 20 mg/kg	0.38 (0.32,0.43)	0.83 (0.74,0.9)
Albendazole 400 mg+oxantel pamoate 20 mg/kg[1]	0.38 (0.31,0.45)	0.77 (0.63,0.87)
Albendazole 400 mg+oxantel pamoate 25 mg/kg	0.35 (0.3,0.41)	0.82 (0.72,0.88)
Albendazole 400 mg+pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	0.66 (0.59,0.73)	0.98 (0.97,0.99)
Mebendazole 500 mg	0.14 (0.11,0.18)	0.21 (-0.05,0.41)
Mebendazole 500 mg+pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	0.52 (0.43,0.61)	0.96 (0.91,0.98)
Mebendazole 6x100 mg	0.88 (0.79,0.95)	1 (0.98,1)
Oxantel pamoate 20 mg/kg	0.1 (0.07,0.15)	-0.26 (-0.8,0.16)
Pyrantel pamoate 20 mg/kg+oxantel pamoate 20 mg/kg	0.39 (0.3,0.47)	0.94 (0.9,0.97)
Tribendimidine 100 mg	0.18 (0.1,0.28)	0.13 (-0.71,0.62)
Tribendimidine 200 mg	0.27 (0.17,0.39)	0.26 (-0.56,0.71)
Tribendimidine 400 mg	0.39 (0.34,0.45)	0.72 (0.58,0.83)
Tribendimidine 400 mg+ivermectin 200 µg/kg	0.67 (0.6,0.73)	0.95 (0.89,0.98)
Tribendimidine 400 mg+oxantel pamoate 25 mg/kg	0.38 (0.32,0.44)	0.79 (0.67,0.87)

[1] Administered on 2 consecutive days

The treatments that achieved the highest 'true' CRs and ERRs against hookworm infections were mebendazole (6x100 mg) with a CR of 88% (95% BCI 79-95%) and an ERR of 99.6% (95% BCI 98-100%) and the triple combination treatment (albendazole 400 mg plus oxantel pamoate 20 mg/kg plus pyrantel pamoate 20 mg/kg) with a CR of 66% (95% BCI 59-73%) and an ERR of 98% (95% BCI 97-99%). Tribendimidine (400 mg) plus ivermectin (200 µg/kg) resulted in a CR of 67% (95% BCI 60-73%) and an ERR of 95% (95% BCI 89-98%).

The two least efficacious treatments were mebendazole 500 mg and oxantel pamoate (20 mg/kg) with CRs of 14% (95% BCI 11-18%) and 10% (95% BCI 7-15%) and ERRs of 21% (95% BCI -5-41%) and -26% (95% BCI -8-16%), respectively. Fig 3.2 shows a comparison of the model estimates of the CRs and ERRs to the observed ones, where the 'true' estimates of CR were lower than the observed ones. However, 'true' estimates of ERR were similar to the observed ones. The model estimates of the CR, ERR, variation at baseline and aggreagtion at follow-up for every treatment arm and trial and the mean intensities at baseline and follow-up are provided in and , respectively. The estimate of the egg output per fertilized female worm was 1.97 (95% BCI 1.58-2.43).

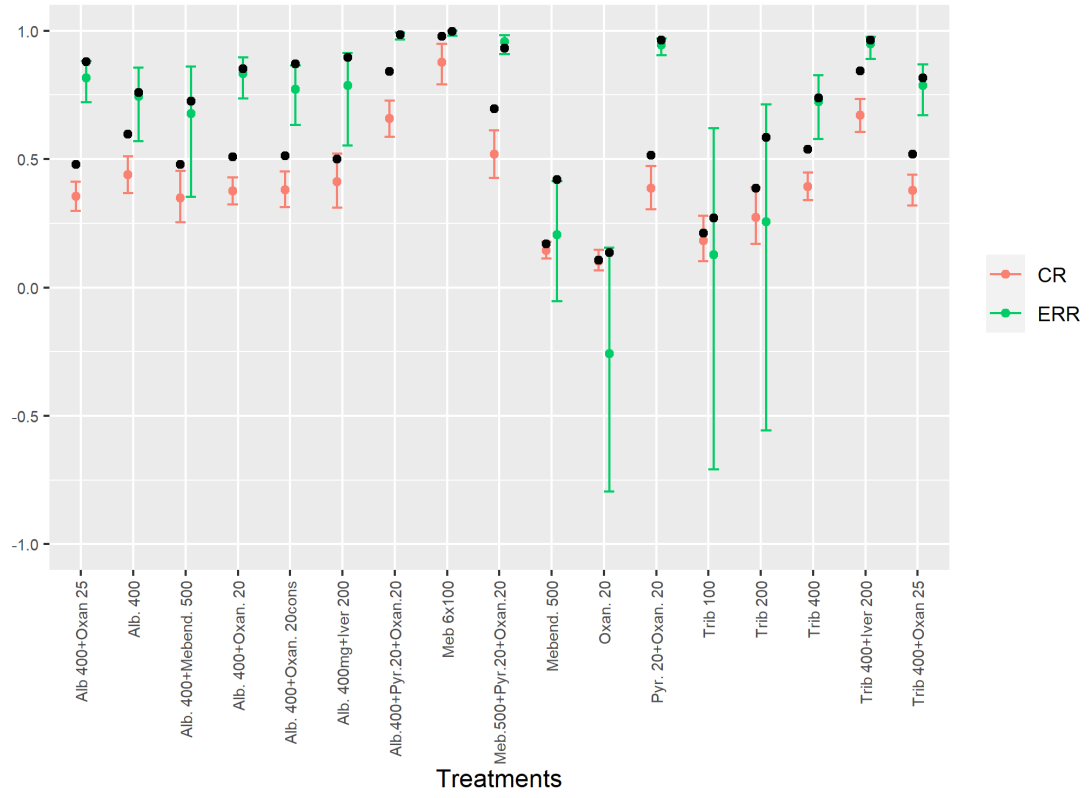


Figure 3.2: **Estimated and observed cure rates (CRs) and egg reduction rates (ERRs).** Posterior mean and 95% Bayesian credible interval of the CR and the ERR (arithmetic mean) for the different treatment arms for hookworm. The black dots show the observed data.

3.5.3 Diagnostic sensitivity

The estimate of the day-to-day variation in egg excretion $(\sigma_d^{(t)})^2$ was 1.19 (95% BCI 1.15-1.25) and of the egg aggregation parameter at baseline $k^{(0)}$ was 9.68 (95% BCI 8.79-10.63) and at follow-up $k^{(1)}$ 11.99 (95% BCI 10.03-14.1). The posterior distribution of the difference has mean 1.95 (95% BCI 0.13-3.63) indicating that the aggregation parameters differ at baseline and follow-up as 0 is not included in BCI. Estimates of the sensitivity of the Kato-Katz thick smear technique are shown in Fig 3.3. For 'true' intensities of an individual with a hookworm infection above 50 EPG, the sensitivity was above 92% for four Kato-Katz thick smears obtained from two stool specimens. For two Kato-Katz thick smears the sensitivity dropped to between 72% and 80% and in the case of only a single Kato-Katz thick smear it ranged between 55% and 65%. For hookworm infection intensities of more than 350 EPG, the sensitivity was above 90% irrespective of the number of Kato-Katz thick smears examined. As the estimated sensitivity from the study of Bärenbold et al. (2017) (Bärenbold et al., 2017) was different to ours, we implemented that model and ran it with the data used in this analysis. We obtained similar results for the sensitivity as in the prior work by Bärenbold et al. (2017) (Bärenbold et al., 2017) (see).

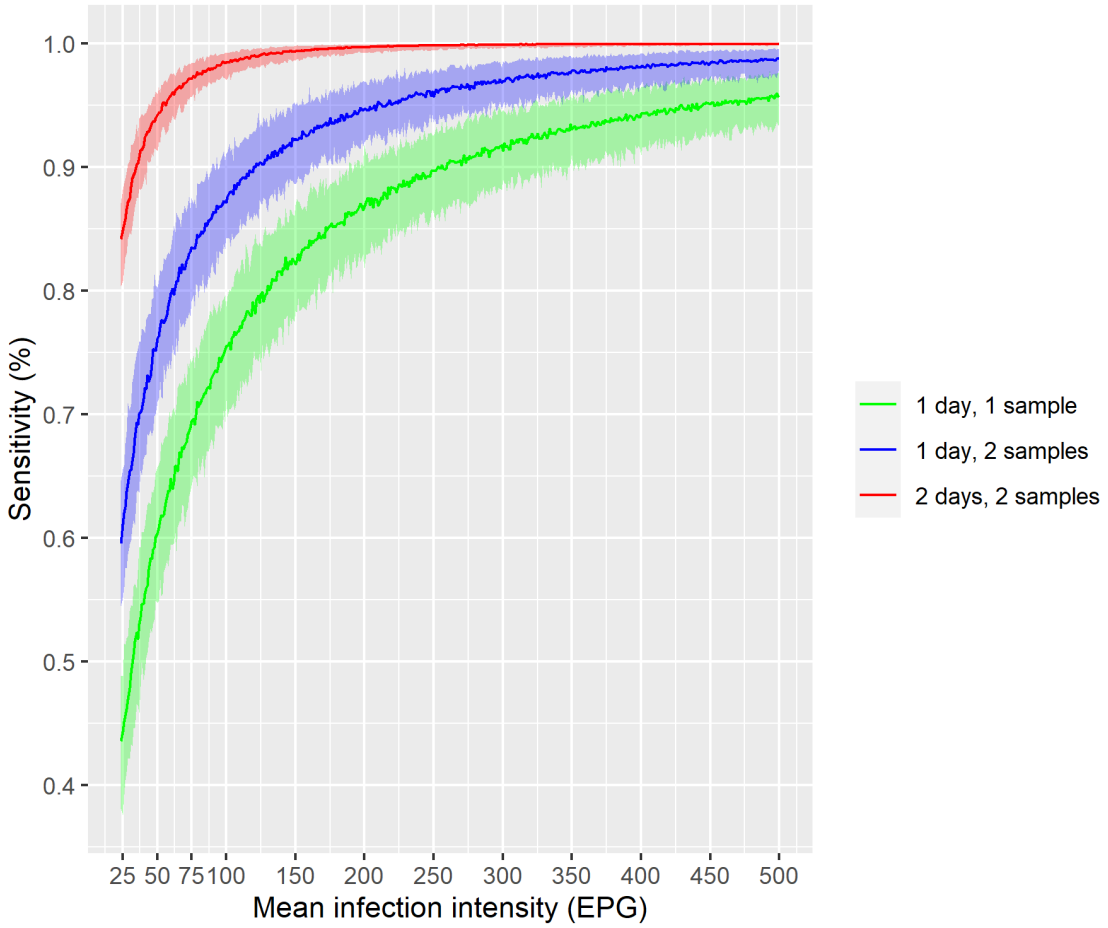


Figure 3.3: Sensitivity of the Kato-Katz thick smear technique for hookworm for one, two, and four Kato-Katz thick smears. The lines show the posterior mean estimate and the shaded areas indicate the 95% Bayesian credible interval.

3.6 Discussion

This is the first model-based meta-analysis of the effects of different drugs and treatment regimen against hookworm infection, which takes into account the diagnostic error of the widely used Kato-Katz thick smear technique. Using Bayesian inferences, we estimated the CR and ERR of 17 different treatments, the infection intensity dependent sensitivity, and the day-to-day variation of the excreted hookworm eggs. All trials included in the meta-analysis were conducted with the same diagnostic procedures and the transmission model was fitted on individual-level egg count data. Our work is in contrast to other analyses based on aggregated data, which suffer from a lack of comparability because of different diagnostic procedures or different summary measures of treatment group intensity. Due to low diagnostic sensitivity of the Kato Katz technique, it is more likely to miss infections of individuals with low intensities, and hence, overestimate CRs (Booth et al., 2003). Our analysis addresses this issue, and hence, our 'true' CR estimates are lower than the observed CRs (Fig 3.2). This is reflected not only in the point estimates, but also in the 95% BCIs of the model-based CRs, which are shifted compared to the confidence intervals of the CRs computed from the raw data. This indicates that the bias due to diagnostic error is quite large. Nevertheless, it is in line with other studies, where Kato-Katz results are compared to polymerase chain reaction (qPCR) results. For

instance, Keller et al. (2020) reported CRs of the combination treatment with ivermectin plus albendazole based on Kato-Katz of 78.3% compared to 52.4% for qPCR (Keller et al., 2020). Barda et al. (2020) report similar CR differences for albendazole, namely 77.8% for Kato-Katz vs 57.1% for qPCR (Barda et al., 2020). In the study of Benjamin-Chung et al. (2020) the participants were also treated with a single dose albendazole and they also observed much higher CRs when derived from Kato-Katz compared to qPCR of 92.5% vs 78.6%, respectively (Benjamin-Chung et al., 2020).

Our results confirm earlier findings that treatments which consist of a combination of drugs or multiple doses are more efficacious than a single-drug treatment (Moser et al., 2019). Mebendazole administered over 3 days in six dosages of 100 mg each is the most efficacious treatment in terms of both CR and ERR (Table 3.4). Eshetu et al. (2020) reported similar CRs and ERRs (Eshetu et al., 2020), as modeled data; however, participants in those included trials were chracterized by slightly higher infection intensities at baseline (1,134 EPG compared to 465 EPG in our case), which were less affected by diagnostic error. The value of 1 for the ERR of aformentioned treatment arm in Table 3.4 (corresponding to 100%) is a rounded value and therefore reliable. Moreover, ERRs close to 100% and low CRs can be observed in the field, as in the data for the combination treatment pyrantel pamoate and oxantel pamoate analyzed here (Moser, Sayasone, et al., 2018). This is the case when many patients have very low egg counts after treatment.

The combination of albendazole, pyrantel pamoate, and oxantel pamoate shows also a very high efficacy in our analysis, as expected. Yet, we obtained a lower CR than reported in a previous meta-analysis (Moser et al., 2019). Tribendimine plus ivermectin showed a slightly lower 'true' CR and a lower, but still high ERR compared to the aforementioned albendazole combination treatment.

On the other hand, our estimates confirm the low efficacy of the WHO recommended drug mebendazole against hookworm infection when used as a single dose. We estimated CRs and ERRs that are similar or lower to those reported in the literature (Moser et al., 2019).

Moser et al. (2018) carried out a Bayesian analysis of a subset of the data of the trials conducted in Tanzania and Côte d'Ivoire (see Table 3.1 trial Moser et al. 2016 (Moser, Sayasone, et al., 2018)), as they only included those individuals who were tested with FECPAK^{G2} (Moser, Bärenbold, et al., 2018). Their estimates for the ERR are similar to ours, however our estimates for the CR are lower, which could be due to improvements in the assumptions of our model.

Our results show that the diagnostic sensitivity increases with the sampling effort. Nevertheless, WHO recommends to collect only one stool sample to be subjected to a single Kato-Katz thick smear, which can have implications, as the CR and ERR are underestimated. Comparing our results to the estimates of Bärenbold et al. (2017) (Bärenbold et al., 2017), we found a higher sensitivity across all levels of infection intensity, indicating that the sensitivity varies among studies because of different day-to-day variation. This in turn can have various reasons, like accuracy of the readings or variation in egg density of different samples from an individual. For example, for 200 EPG, the sensitivity is close to 87% for one Kato-Katz thick smear and 94% for two Kato-Katz thick smears, whereas in aforementioned analysis the estimates are only roughly 51% and 75%, respectively. This finding was not expected and suggests that treatment efficacy estimates may not be comparable even from studies with similar infection intensities and sampling efforts. A first step to clarify this could be to investigate whether the day-to-day variation depends on the mean infection intensity.

Our study has several limitations. First, we addressed uncertainty by linking the mean infection intensity at follow-up with the aggregation of the worms to improve model fitting. The aggregation parameter of the worms in the population is estimated well but

with considerable uncertainty, although we linked the aggregation parameter to the mean infection intensity and the prevalence (Anderson et al., 2013). Furthermore, there were treatment arms where the estimates of the ERR have a rather large uncertainty compared to the estimates of the mean infection intensity at baseline and follow-up. This is the case for low ERRs. Due to the limited number of trials per treatment, we were unable to include a random effect to account for the variation between the trials (Gelman et al., 1995). Moreover, we didn't take into account the density-dependent fecundity of female worms, nevertheless, in this framework this assumption is justified, as only individuals with light infections are analyzed. For settings with higher intensities it should be included.

3.6.1 Conclusion

We developed a Bayesian model including the distribution of the worms which enabled us to directly compare the treatment effect of different drugs and treatment regimen against hookworm taking into account diagnostic error. We also estimated the diagnostic sensitivity of the Kato-Katz thick smear technique. Despite considerably lower CRs obtained by our modeling framework, our results confirm earlier findings that treatments which consist of a combination of drugs or multiple doses are more efficacious than a single-drug treatment. Moreover, we found that diagnostic sensitivity increases considerably if two stool samples are collected on consecutive days instead of only one or if multiple Kato-Katz thick smears are prepared from a single stool sample and examined under a microscope. Hence, we recommend to collect two stool samples on consecutive days. Furthermore, the comparison of our results to a similar work indicates that the diagnostic sensitivity of the Kato-Katz thick smear technique can vary considerably across studies. The modeling framework used here could be adapted for the other helminth species parasitizing humans and animals.

3.7 Supporting information

S1 Appendix.

Derivation of the distribution of fertilized female worms and the corresponding prevalence.

S1 Appendix: Derivation of the marginal distribution of mated female worms

The probability of having N_f female and N_m male worms is according to May and Woolhouse (1993) defined as follows

$$P(N_f, N_m; q, p, w_{jg}, k_w) = (1-\alpha)^{k_w} \frac{\Gamma(N_f + N_m + k_w)}{\Gamma(k_w)} \frac{(\alpha q)^{N_f}}{N_f!} \frac{(\alpha p)^{N_m}}{N_m!}, \quad \alpha = \frac{w_{jg}}{w_{jg} + k_w}$$

where q is the probablity of a worm to be female, p to be male, w_{jg} is the mean worm burden and k_w the aggregation parameter of a negative binomial distribution of the worms in the population. We assume that the probability for a worm to be female is $q = 1/2$ and $p = 1-q = 1/2$ to be male. Moreover, we assume that one male worm can fertilize all female worms.

To derive the marginal distribution of the female worms we sum over the number of male worms

$$\begin{aligned} P(N_f; q, w_{jg}, k_w) &= \frac{(1-\alpha)^{k_w}}{\Gamma(k_w)} \frac{(\frac{\alpha}{2})^{N_f}}{N_f!} \sum_{N_m=1}^{\infty} \frac{\Gamma(N_f + N_m + k_w) \cdot (\frac{\alpha}{2})^{N_m}}{N_m!} \\ &= -\frac{(1-\alpha)^{k_w}}{\Gamma(k_w)} \frac{(\frac{\alpha}{2})^{N_f}}{N_f!} \frac{\Gamma(k_w + N_f + 1) \cdot (1-\frac{\alpha}{2})^{-k_w-N_f} \cdot (-1 + (1-\frac{\alpha}{2})^{-k_w-N_f})}{k_w + N_f} \\ &= \frac{(1-\alpha)^{k_w}}{\Gamma(k_w)} \frac{(\frac{\alpha}{2})^{N_f}}{N_f!} \Gamma(k_w + N_f)(1-\frac{\alpha}{2})^{-k_w-N_f} - \Gamma(k_w + N_f). \end{aligned} \tag{1}$$

Now we use the relations $(1-\alpha) = \frac{k_w}{w_{jg}+k_w}$ and $\left(1-\frac{\alpha}{2}\right)^{-1} = \frac{2(w_{jg}+k_w)}{w_{jg}+2k_w}$ in equation 1:

$$
\begin{aligned}
&\frac{(1-\alpha)^{k_w}(\frac{\alpha}{2})^{N_f}}{\Gamma(k_w)N_f!}\cdot\left[\Gamma(k_w+N_f)\left(1-\frac{\alpha}{2}\right)^{-k_w-N_f}-\Gamma(k_w+N_f)\right]\\
&=\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\frac{2(w_{jg}+k_w)}{w_{jg}+2k_w}\right)^{k_w}\left(\frac{w_{jg}}{2(w_{jg}+k_w)}\frac{2(w_{jg}+k_w)}{w_{jg}+2k_w}\right)^{N_f}\\
&-\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}\left(\frac{w_{jg}}{2(w_{jg}+k_w)}\right)^{N_f}\\
&=\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{2k_w}{w_{jg}+2k_w}\right)^{k_w}\left(\frac{w_{jg}}{w_{jg}+2k_w}\right)^{N_f}-\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}\left(\frac{w_{jg}}{2(w_{jg}+k_w)}\right)^{N_f}\\
&=\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w}\left(\frac{w_{jg}/2}{w_{jg}/2+k_w}\right)^{N_f}\\
&-\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}\left(\frac{w_{jg}}{w_{jg}+k_w}\right)^{N_f}\left(\frac{1}{2}\right)^{N_f}\\
&=\mathrm{NB}(N_f;w_{jg}/2,k_w)-\mathrm{NB}(N_f;w_{jg},k_w)\left(\frac{1}{2}\right)^{N_f}\\
&=\mathrm{P}(N_f;w_{jg},k_w).
\end{aligned}
$$

We consider that all female worms are fertilized when $N_m > 0$ and therefore we replace N_f by n_f.

To compute the prevalence of having at least one fertilized female worm, we need to compute the probability of having no male worms, no female worms and no worms of either sex, which are given in equations 2, 3 and 4, respectively

$$\sum_{N_m=0}^{\infty} P(N_f,0;q=1/2,w_{jg},k_w)=\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w} \tag{2}$$

$$\sum_{N_f=0}^{\infty} P(0,N_m;p=1/2,w_{jg},k_w)=\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w} \tag{3}$$

$$P(0,0;q=1/2,p=1/2,w_{jg},k_w)=\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}. \tag{4}$$

As equations 2 and 3 already contain the probabilty of having no worms, the last term of equation 4 accounts for it in the following definition of the prevalence

$$1-P(0;w_{jg},k_w)=1-2\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w}+\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}.$$

S2 Appendix.

Mean and variance of the distribution of fertilized female worms.

S2 Appendix: Mean and variance of the distribution of egg counts

The marginal distribution of egg counts (i.e. $\boldsymbol{Y}_i^{(1)}$at follow-up) can be computed from the joint distribution of egg counts and fertilized female worms n_f as follows

$$P\left(\boldsymbol{Y}_i^{(1)}\right) = \sum_{n_f=0}^{\infty} P(\boldsymbol{Y}_i^{(1)}, n_f) = \sum_{n_f=0}^{\infty} P\left(\boldsymbol{Y}_i^{(1)}\middle| n_f\right) P(n_{f;} w_{jg}, k_w) \quad \text{(S2.1)}$$

The conditional distribution is $P\left(\boldsymbol{Y}_i^{(1)}\middle| n_f\right) \equiv NB\left(zn_f, k^{(1)}\right)$, where z is the net egg output of fertilized female worms and $k^{(1)}$ is the aggregation of the egg counts at follow-up. $P(n_{f;} w_{jg}, k_w)$ is the distribution of fertilized female worms, where w_{jg} is the mean worm burden and k_w is the aggregation of the worms in the population. The mean and variance of the distribution of the egg counts in (S2.1) are

$$\mu_{jg}^{(1)} = \sum_{n_f=0}^{\infty} z\, n_f\, P(n_f\,; w_{jg}, k_w) = \sum_{n_f=0}^{\infty} z\, n_f \left(NB(n_f; w_{jg}/2, k_w) - NB(n_f; w_{jg}, k_w)\left(\frac{1}{2}\right)^{n_f}\right)$$

$$= \frac{w_{jg}\, z}{2} - 2^{k_w}\, w_{jg} \left(\frac{k_w}{2\, k_w + w_{jg}}\right)^{1+k_w} z$$

$$\sigma_{jg}^2 = \left(1 + \frac{1}{k^{(1)}}\right)\left(\sum_{n_f=0}^{\infty} z^2\, {n_f}^2 \left(NB\left(n_f; \frac{w_{jg}}{2}, k_w\right) - NB\left(n_f; w_{jg}, k_w\right)\left(\frac{1}{2}\right)^{n_f}\right)\right) - \left(\mu_{jg}^{(1)}\right)^2 + \mu_{jg}^{(1)}$$

$$= \left(1 + \frac{1}{k^{(1)}}\right)\left(\frac{\left(\frac{w_{jg}}{2}\right)\left(2k + w_{jg} + k_w w_{jg}\right) z^2}{2k_w} - \frac{k_w w_{jg}\left(\frac{k_w}{k_w + w_{jg}}\right)^{k_w}\left(2k_w + 2w_{jg} + k_w w_{jg}\right)\left(1 - \frac{w_{jg}}{2\left(k_w + w_{jg}\right)}\right)^{-k_w} z^2}{\left(2k_w + w_{jg}\right)^2}\right)$$

$$- \left(\mu_{jg}^{(1)}\right)^2 + \mu_{jg}^{(1)}$$

S3 Appendix.

Posterior distribution.

S3 Appendix: Posterior distribution

In the following the posterior distribution

$$P(\text{model parameters}|\text{data}) \propto P(\text{data}|\text{model parameters}) \cdot P(\text{model parameters})$$
$$\Longleftrightarrow P(\boldsymbol{\theta}|D) \propto P(D|\boldsymbol{\theta}) \cdot P(\boldsymbol{\theta})$$

of the model used in this analysis is presented (see table 2 in the model section of the paper for the definition of the parameters):

$$\begin{aligned}
&P(\mu_{jg}^{(0)}, \sigma_{jg}^{(0)}, k^{(0)}, \sigma_d^{(0)}, w_{jg}, k_w, k^{(1)}, v^{(1)}, r, \pi_{jg}, \sigma_d^{(1)} |\, \boldsymbol{Y}^{(0)}, \boldsymbol{Y}^{(1)}) \\
\propto &\prod_i P(Y_i^{(0)}|\mu_{i_{jg}d}^{(0)}, \mu_{i_{jg}}^{(0)}, \mu_{jg}^{(0)}, \sigma_{jg}^{(0)}, \epsilon_{id}^{(0)}, k^{(0)}) P(\epsilon_{id}^{(0)}|\sigma_d^{(0)}) \\
&P(Y_i^{(1)}|\mu_{i_{jg}d}^{(1)}, \mu_{i_{jg}}^{(1)}, \mu_{jg}^{(1)}, \sigma_{jg}^{(1)}, w_{jg}, k_w, \epsilon_{id}^{(1)}, k^{(1)}, v^{(1)}, r, \pi_{jg}) P(\epsilon_{id}^{(1)}|\sigma_d^{(1)}) \\
&P(\mu_{jg}^{(0)}) P(\sigma_{jg}^{(0)}) P(k^{(0)}) P(\sigma_d^{(0)}) P(w_{jg}) P(k_w) P(k^{(1)}) P(v^{(1)}) P(r) P(\pi_{jg}) P(\sigma_d^{(1)})
\end{aligned}$$

S1 Table.

Parameter estimates for each treatment regimen of all trials for hookworm.

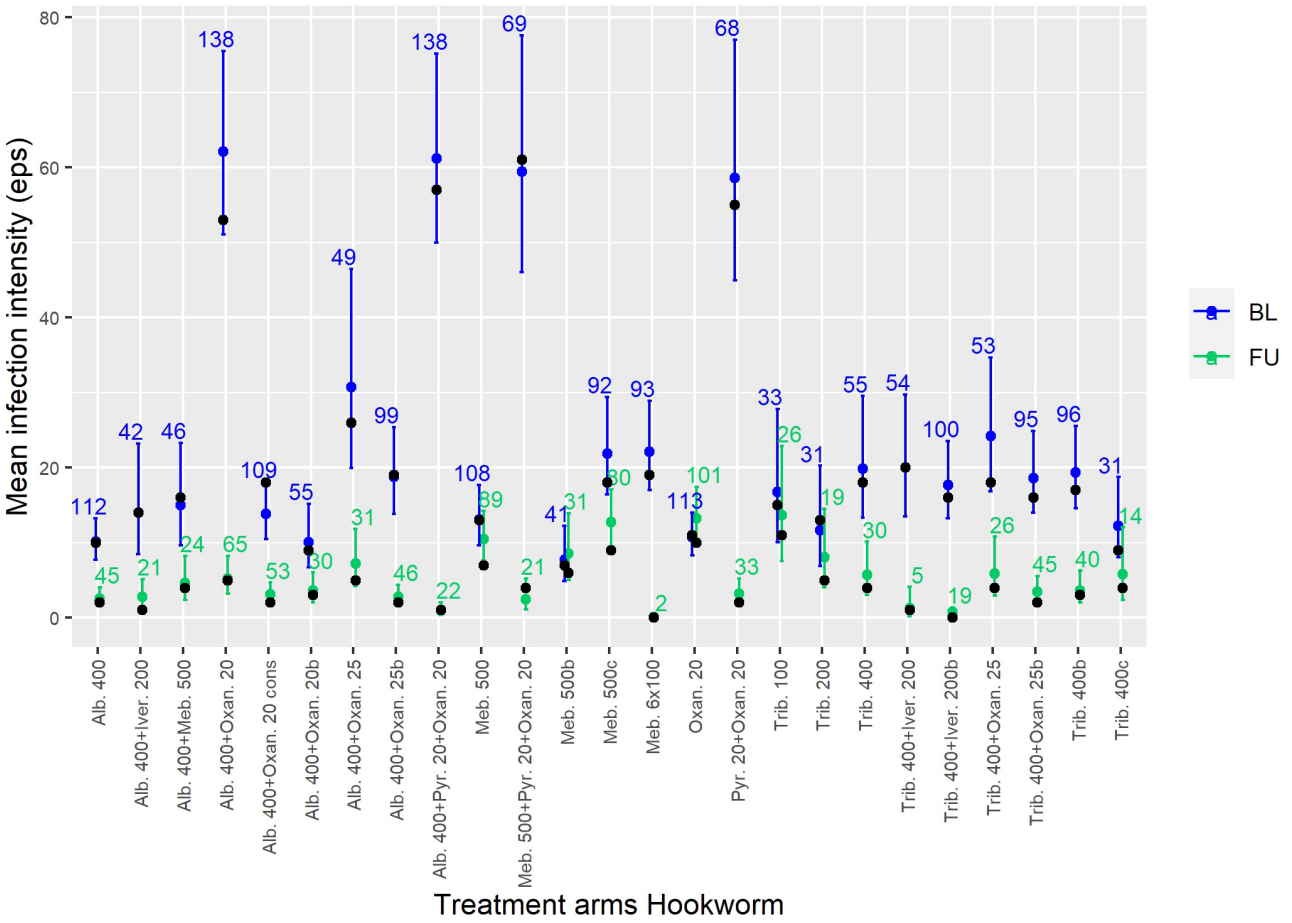
S1 Table. Parameter estimates for each treatment regimen of all trials for Hookworm

Treatment	Cure rate (c_g)	Egg reduction rate (ϕ_g)	Aggregation in group at BL ($\sigma_g^{(0)}$)	Aggregation in group at FU (k_w)
Alb 400+Oxan 25[1]	0.26 (0.18,0.35)	0.75 (0.55,0.88)	0.04 (0.02,0.08)	0.99 (0.58,1.58)
Alb 400+Oxan 25b[6]	0.4 (0.33,0.48)	0.85 (0.74,0.91)	0.07 (0.03,0.12)	1.05 (0.58,1.69)
Alb. 400+Oxan. 20b[5]	0.36 (0.28,0.46)	0.63 (0.31,0.82)	0.15 (0.05,0.35)	1.06 (0.57,1.72)
Alb. 400[4]	0.44 (0.37,0.51)	0.74 (0.57,0.86)	0.16 (0.08,0.31)	0.89 (0.48,1.5)
Alb. 400+Meb. 500[5]	0.35 (0.25,0.45)	0.68 (0.35,0.86)	0.1 (0.03,0.25)	0.88 (0.46,1.5)
Alb. 400+Oxan. 20[3]	0.38 (0.32,0.44)	0.92 (0.86,0.95)	0.08 (0.03,0.29)	0.6 (0.39,0.95)
Alb. 400+Oxan. 20[4]	0.38 (0.31,0.45)	0.77 (0.63,0.87)	0.11 (0.06,0.21)	1.09 (0.63,1.74)
Alb. 400mg+Iver 200[5]	0.41 (0.31,0.52)	0.79 (0.55,0.91)	0.08 (0.03,0.2)	1.03 (0.51,1.74)
Alb.400+Pyr.20+Oxan.20[3]	0.66 (0.59,0.73)	0.98 (0.97,0.99)	0.05 (0.02,0.1)	0.49 (0.18,1.15)
Meb 500c[8]	0.11 (0.07,0.16)	0.41 (0.13,0.62)	0.08 (0.04,0.15)	1.57 (1.11,2.14)
Meb 6x100[8]	0.88 (0.79,0.95)	1 (0.98,1)	0.12 (0.05,0.3)	0.53 (0.04,1.38)
Meb. 500[4]	0.15 (0.11,0.2)	0.18 (-0.23,0.48)	0.08 (0.04,0.14)	1.4 (0.97,1.94)
Meb. 500b[5]	0.21 (0.13,0.3)	-0.17 (-1.14,0.44)	0.25 (0.07,0.73)	1.19 (0.72,1.81)
Meb.500+Pyr.20+Oxan.20[3]	0.52 (0.43,0.61)	0.96 (0.91,0.98)	0.13 (0.02,0.71)	0.54 (0.24,1.13)
Oxan. 20[4]	0.1 (0.07,0.15)	-0.26 (-0.8,0.16)	0.18 (0.09,0.37)	1.61 (1.16,2.16)
Pyr. 20+Oxan. 20[3]	0.39 (0.3,0.47)	0.94 (0.9,0.97)	0.13 (0.02,0.74)	1.03 (0.56,1.7)
Trib 100[2]	0.18 (0.1,0.28)	0.13 (-0.71,0.62)	0.13 (0.03,0.47)	0.94 (0.56,1.47)
Trib 200[2]	0.27 (0.17,0.39)	0.26 (-0.56,0.71)	0.19 (0.04,0.65)	0.85 (0.46,1.43)
Trib 400[1]	0.34 (0.25,0.44)	0.7 (0.42,0.86)	0.07 (0.03,0.17)	0.75 (0.41,1.28)
Trib 400+Iver 200[1]	0.73 (0.62,0.84)	0.93 (0.78,0.99)	0.08 (0.03,0.18)	0.2 (0.06,0.65)
Trib 400+Iver 200b[6]	0.64 (0.56,0.71)	0.96 (0.92,0.98)	0.08 (0.04,0.15)	0.82 (0.31,1.56)
Trib 400+Oxan 25[1]	0.36 (0.27,0.46)	0.75 (0.51,0.89)	0.1 (0.03,0.29)	0.65 (0.36,1.12)
Trib 400+Oxan 25b[6]	0.39 (0.31,0.46)	0.81 (0.67,0.89)	0.08 (0.04,0.16)	0.9 (0.5,1.5)
Trib 400b[6]	0.42 (0.35,0.5)	0.81 (0.65,0.9)	0.09 (0.04,0.18)	0.67 (0.37,1.19)
Trib 400c[2]	0.39 (0.27,0.52)	0.5 (-0.11,0.82)	0.4 (0.07,1.43)	0.58 (0.28,1.09)

[1] CIV (2016)
[2] CIV (2017)
[3] LAO (2017)
[4] TAN (2012)
[5] TAN (2013)
[6] TAN (2016)
[7] TAN (2017a)

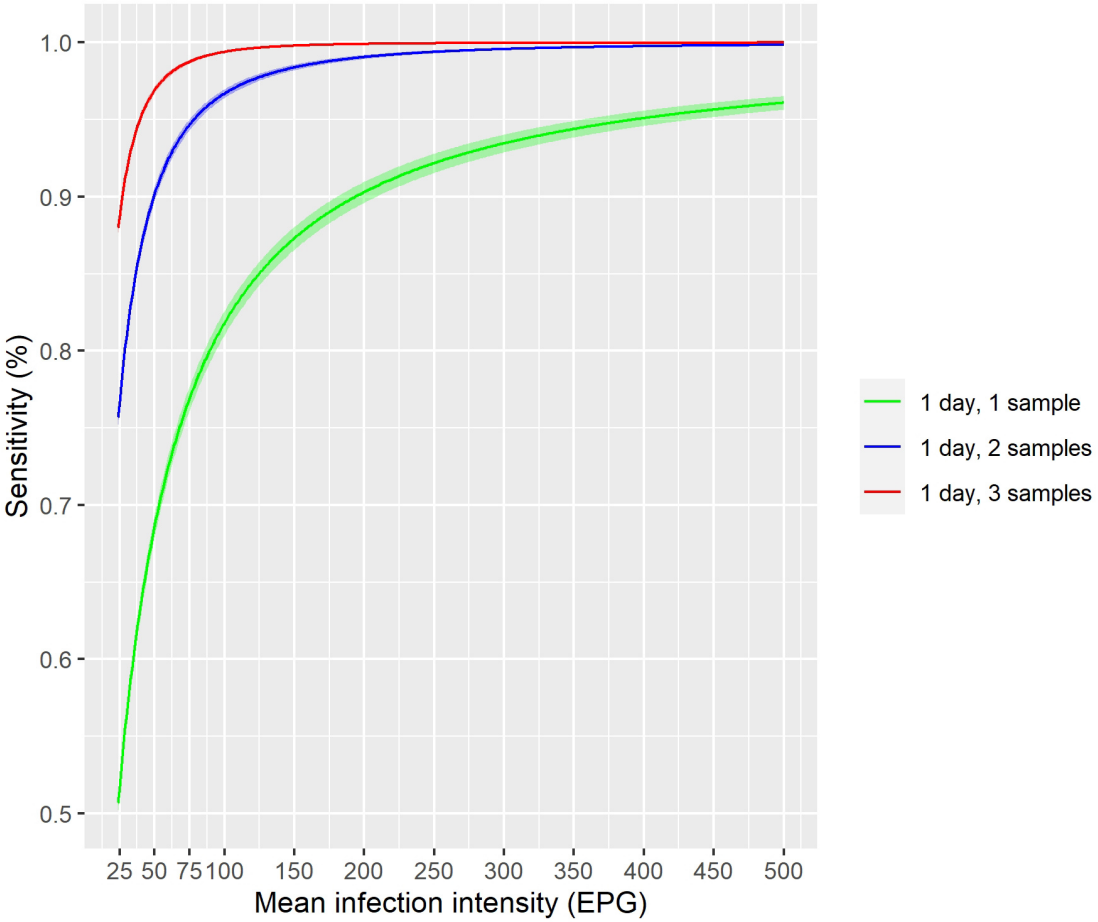
S1 Figure.

The plot shows the estimated mean and 95% Bayesian credible interval for the mean egg intensity at baseline and follow-up for the different treatment arms for hookworm. The black dots show the data.


Mean infection intensity (eps)
80
60
40
20
0
112
45
42
21
46
24
138
65
109
53
55
30
49
31
99
46
138
22
108
39
69
21
41
31
92
30
93
2
113
101
68
33
33
26
31
19
55
30
54
5
100
19
53
26
95
45
96
40
31
14
Alb. 400
Alb. 400+Iver. 200
Alb. 400+Meb. 500
Alb. 400+Oxan. 20
Alb. 400+Oxan. 20 cons
Alb. 400+Oxan. 20b
Alb. 400+Oxan. 25
Alb. 400+Oxan. 25b
Alb. 400+Pyr. 20+Oxan. 20
Meb. 500
Meb. 500+Pyr. 20+Oxan. 20
Meb. 500b
Meb. 500c
Meb. 6x100
Oxan. 20
Pyr. 20+Oxan. 20
Trib. 100
Trib. 200
Trib. 400
Trib. 400+Iver. 200
Trib. 400+Iver. 200b
Trib. 400+Oxan. 25
Trib. 400+Oxan. 25b
Trib. 400b
Trib. 400c
Treatment arms Hookworm
BL
FU

S2 Figure.

Sensitivity of the Kato-Katz technique for hookworm for one, two, and three samples. The lines show the mean sensitivity and the shaded areas indicate the 95% BCI.


1.0
0.9
0.8
0.7
0.6
0.5
Sensitivity (%)
25 50 75 100 150 200 250 300 350 400 450 500
Mean infection intensity (EPG)
1 day, 1 sample
1 day, 2 samples
1 day, 3 samples

S1 Checklist.

STARD checklist.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC) **Text excerpts**: -Modeling the effect of different drugs and treatment regimen for hookworm on cure and egg reduction rates taking into account diagnostic error -Furthermore, the model accounted for infection intensity dependent sensitivity and day-to-day variation of hookworm egg excretion.	p. 1,2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts) Methodology, Principal findings and Conclusions from Abstract	p. 1,2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test **Text excerpts**: Systematic reviews and meta-analyses have been carried out to compare the efficacy of different treatments against hookworm and other STH infections [1-3]. However, most trials assess the presence of hookworms using the Kato-Katz thick smear technique, which has low sensitivity, and hence, the efficacy of the treatment is overestimated. - The model has been successfully applied to data from a clinical trial on Pemba island to assess the performance of FECPAKG2 and the Kato-Katz thick smear technique for the diagnosis of STH infection [4].	p. 4,5
	4	Study objectives and hypotheses **Text excerpt**: In this study, we pursued a Bayesian meta-analysis to compare the cure rate (CR) and the egg reduction rate (ERR) of different treatments against hookworm infection considering the diagnostic error of the Kato-Katz thick smear technique. We modeled diagnostic sensitivity as a function of the infection intensity using the basic model formulation of Bärenbold et al. (2017) [5].	p. 5
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study) This is a retrospective study. **Text excerpt**: The studies from which the data used in this analysis have been obtained have been published elsewhere [6, 7-11].	p. 5
Participants	**6**	Eligibility criteria **Text excerpt**: The studies from which the data used in this analysis have been obtained have been published elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry) **Text excerpt**: The studies from which the data used in this analysis have been obtained have been published elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	8	Where and when potentially eligible participants were identified (setting, location and dates) **Text excerpts**: - The studies from which the data used in this analysis have been obtained have been published elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5

		-We analyzed data from six randomized trials in Côte d'Ivoire, Lao People's Democratic Republic, and Tanzania, which assessed the efficacy and safety of different treatments against STH infection [6, 7-11].	
	9	Whether participants formed a consecutive, random or convenience series **Text excerpt**: The studies from which the data used in this analysis have been obtained have beenpublished elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
Test methods	**10a**	Index test, in sufficient detail to allow replication **Text excerpt**: The studies from which the data used in this analysis have been obtained have beenpublished elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	10b	Reference standard, in sufficient detail to allow replication	
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory **Text excerpt**: The studies from which the data used in this analysis have been obtained have beenpublished elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test **Text excerpt**: The studies from which the data used in this analysis have been obtained have beenpublished elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy **Text excerpt**: Posterior samples of sigma_(t)^d)^2 and k were used to obtain the posterior distribution of the sensitivity as a function of infection intensity via the relationship We simulated data for mean infection intensities of 0-500 EPG for either one, two, or four Kato-Katz thick smears. For one and two Kato-Katz thick smears it was assumed that the replicate samples were analyzed on the same day, in the case of four Kato-Katz thick smears it was assumed that two samples were analyzed on one day.	p. 10
	15	How indeterminate index test or reference standard results were handled **Text excerpt**: All individuals were included in this analysis as for missing or indeterminate values missing at random (MAR) can be assumed.	p. 9
	16	How missing data on the index test and reference standard were handled **Text excerpt**: All individuals were included in this analysis as for missing or indeterminate values missing at random (MAR) can be assumed.	p. 9
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory **Text excerpt**: Posterior samples of sigma_(t)^d)^2 and k were used to obtain the posterior distribution of the sensitivity as a function of infection intensity via the relationship We simulated data for mean infection intensities of 0-500 EPG for either one, two, or four Kato-Katz thick smears. For one and two Kato-Katz thick smears it was assumed	p. 10

		that the replicate samples were analyzed on the same day, in the case of four Kato-Katz thick smears it was assumed that two samples were analyzed on one day.	
	18	Intended sample size and how it was determined **Text excerpt**: The studies from which the data used in this analysis have been obtained have beenpublished elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
RESULTS			
Participants	**19**	Flow of participants, using a diagram **Text excerpt**: The studies from which the data used in this analysis have been obtained have beenpublished elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	20	Baseline demographic and clinical characteristics of participants **Text excerpt**: Table 1 shows the mean hookworm infection intensities at baseline in the included studies from Côte d'Ivoire, Lao People's Democratic Republic, and Tanzania. All of the infections were classified as light infections (i.e. <2,000 EPG [12]. The sample were similar for the different treatment arms within the individual studies, with exception of the trial in Lao People's Democratic Republic where approximately twice as many children were assigned to two treatment arms (albendazole plus oxantel and albendazole plus oxantel plus pyrantel) [9]. There were slight differences in CRs and ERRs for the same treatments. For instance, there were three trials administering 500 mg mebendazole with CRs of 13%, 18%, and 24% and ERRs of 53%, 45%, and 11%, respectively [9-11].	p. 10
	21a	Distribution of severity of disease in those with the target condition **Text excerpt**: Table 1 shows the mean hookworm infection intensities at baseline in the included studies from Côte d'Ivoire, Lao People's Democratic Republic, and Tanzania. All of the infections were classified as light infections (i.e. <2,000 EPG [12].	p. 10
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard **Text excerpt**: For each individual, two stool specimens were collected over two consecutive days at baseline and treatment follow-up, usually 14-21 days post-treatment, while two readings were made per specimen. All slides were read within 1 hour after preparation to avoid degeneration of hookworm eggs on microscope slides.	p. 5, 6
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard Table 2 and 3.	p. 11, 12
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals) **Text excerpt**: The estimate of the day-to-day variation in egg excretion was 1.18 (95% BCI 1.14-1.23)and of the egg aggregation parameter was 9.80 (95% BCI 9.00-10.65). Estimates of the sensitivity of the Kato-Katz thick smear technique are shown in Fig 2. For `true' intensities of an individual with a hookworm infection above 50 EPG the sensitivity was above 90% for four Kato-Katz thick smears obtained from two stool specimens. For two Kato-Katz thick smears the sensitivity dropped to between 72% and 82 % and in the case of only a single Kato-Katz thick smear it was as little as between 55% and 67%. For hookworm infection intensities of more than 350 EPG, the sensitivity was above 90% irrespective of the number of Kato-Katz thick smears examined.	p. 13
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability **Text excerpt**: Our study has several limitations. First, we addressed uncertainty by linking the	p. 16

		mean infection intensity at follow-up with the aggregation of the worms to improve model fitting. The aggregation parameter of the worms in the population is estimated well but with considerable uncertainty, although we linked the aggregation parameter to the mean infection intensity and the prevalence [13]. Furthermore, there were treatment arms where the estimates of the ERR have a rather large uncertainty compared to the estimates of the mean infection intensity at baseline and follow-up. This is the case for low ERRs. Due to the limited number of trials per treatment, we were unable to include a random effect to account for the variation between the trials [14].	
	27	Implications for practice, including the intended use and clinical role of the index test **Text excerpt**: Our results show that the diagnostic sensitivity increases with the sampling effort. Nevertheless, WHO recommends to collect only one stool sample to be subjected to a single Kato-Katz thick smear, which can have implications as the CR and ERR are underestimated.	p. 15, 16
OTHER INFORMATION			
	28	Registration number and name of registry **Text excerpt**: The studies from which the data used in this analysis have been obtained have been published elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	29	Where the full study protocol can be accessed **Text excerpt**: The studies from which the data used in this analysis have been obtained have been published elsewhere [6, 7-11]. Details on ethical approvals, trial registration, study design, informed consent procedures, potential risks and benefits are provided in the aforementioned studies.	p. 5
	30	Sources of funding and other support; role of funders	

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Chapter 4

Efficacy of different treatment regimen based on 'true' cure and egg reduction rates for *Trichuris trichiura* taking into account transmission mechanism

Carla M. Grolimund[1,2], Jürg Utzinger[1,2], Jennifer Keiser[1,2], Penelope Vounatsou[1,2]

1 – Swiss Tropical and Public Health Institute, Basel, Switzerland
2 – University of Basel, Switzerland

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4.1 Abstract

Trichuris trichiura is one of four soil-transmitted helminth species that, collectively, are responsible for a considerable public health burden. The World Health Organization (WHO) recommends preventive chemotherapy as the main intervention to eliminate soil-transmitted helminthiasis as a public health problem. Clinical trials assessed the efficacy of different drugs and treatment regimen against *T. trichiura* and other soil-transmitted helminth species, whilst meta-analyses and modeling efforts were conducted to determine the most effective drugs and drug combinations. Of note, the diagnostic error was often neglected, and hence, cure rates (CRs) might be overestimated. We developed a Bayesian model, which estimates drug efficacy against *T. trichiura*, taking into account the transmission mechanism as well as the diagnostic error. The model was fitted to individual-level egg count data from an ensemble of seven trials with 29 treatments. We estimated the 'true' CRs, which were consistently lower than those reported in the literature. In our analysis, the treatment with the highest CR was combination therapy of albendazole plus pyrantel pamoate plus oxantel pamoate with a CR of 79% and an egg reduction rate (ERR) of 91%. Albendazole plus oxantel pamoate showed the highest ERR of 97% and a CR of 69%. Additionally, we were able to estimate the intensity-dependent sensitivity of the Kato-Katz technique. For 24 eggs per gram of stool, the sensitivity was around 50% for a single and increased to almost 70% for duplicate Kato-Katz thick smears.

4.2 Introduction

Trichuris trichiura – also known as whipworm – is an intestinal nematode and one of four soil-transmitted helminth species infecting humans (Else et al., 2020; WHO, 2019b). *T. trichiura* is responsible for a considerable public health burden, particularly in children in low- and middle-income countries. For instance, severe anaemia and inflammation of the colon are distinct consequences of a *T. trichiura* infection (Jourdan et al., 2018). An estimated 450 million people are infected with *T. trichiura*, leading to 337,000 years lost due to disability (Vos et al., 2017). The World Health Organization (WHO) set the target to eliminate morbidity due to soil-transmitted helminthiasis in pre-school-aged children and school-aged children by 2030 (Organization et al., 2020a). To achieve this goal, WHO emphasizes preventive chemotherapy as the main intervention (WHO, 2017). It recommends the use of albendazole (400 mg) and mebendazole (500 mg) in preventive chemotherapy programmes because of simple administration, low cost and community effectiveness. However, it is acknowledged that the efficacy of either treatment against *T. trichiura* is low (Clarke et al., 2019; Keiser & Utzinger, 2008; Moser, Schindler, et al., 2017; Speich et al., 2015). Hence, it is important to investigate treatment efficacy of alternative drugs and combination therapies (Freeman et al., 2019). For instance, Speich et al. (2014) found that combination therapy of oxantel pamoate (20 mg/kg) plus albendazole (400 mg) is more efficacious (higher cure rate (CR) and egg reduction rate (ERR)) against *T. trichiura* than simple-dose albendazole (400 mg) or mebendazole (500 mg) (Speich et al., 2014). Clarke et al. (2019) compared the efficacy of 21 treatment regimens against *T. trichiura* and showed that the combination therapy of albendazole plus ivermectin, albendazole plus oxantel pamoate and multiple-dose mebendazole are more efficacious (regarding relative risk of CR and difference in ERR) than albendazole alone (Clarke et al., 2019). The sensitivity of diagnostics is an important and often discussed topic because of its implications on observed prevalence (Dunn et al., 2020). For instance, WHO highlights the need for more sensitive diagnostic tools for mapping and surveillance (Organization et al., 2020b). Knopp et al. showed that multiple Kato-Katz

thick smears are required to accurately assess prevalences, particularly in low-infection settings (Knopp et al., 2008).

Meta-analyses and systematic reviews as well as analyses with latent class models have been done (Clarke et al., 2019; Moser et al., 2019; Palmeirim, Hürlimann, et al., 2018). However, only the infection status of individuals was included in these analyses. Moreover, the diagnostic error of the Kato-Katz thick smear is not taken into account leading to overestimation of CRs. Bärenbold et al. developed a model, which analysed individual-level egg count data, taking into account the diagnostic error (Bärenbold et al., 2017; Moser, Bärenbold, et al., 2018). Grolimund et al. further developed the model to study efficacy of various drugs against hookworm, including the transmission mechanism of the infection (Grolimund et al., 2022).

In this study, we further adapted the aforementioned model by Grolimund et al. to *T. trichiura* and extended it to include the density-dependent fecundity of worms. Our aim was to determine the CRs and ERRs of different treatment regimes against *T. trichiura* and to estimate the sensitivity of the Kato-Katz technique.

4.3 Materials and methods

4.3.1 Ethics statement

The data used in this analysis have been published elsewhere (Moser et al., 2016; Moser, Coulibaly, et al., 2017; Moser, Sayasone, et al., 2018; Palmeirim, Ame, et al., 2018; Speich et al., 2015; Speich et al., 2014; Wimmersberger et al., 2018). Details on ethical approvals, trial registration, study design, informed consent procedures, drugs and regimens employed, diagnostic approach, potential risks and benefits are provided in the aforementioned studies.

4.3.2 Data

The data used in this analysis consist of seven randomized trials carried out in Côte d'Ivoire, Lao People's Democratic Republic, and Tanzania, which assessed the efficacy of different drugs and combination therapies against soil-transmitted helminth infection using the Kato-Katz thick smear technique (Moser et al., 2016; Moser, Coulibaly, et al., 2017; Moser, Sayasone, et al., 2018; Palmeirim, Ame, et al., 2018; Speich et al., 2015; Speich et al., 2014; Wimmersberger et al., 2018). All trials applied the same diagnostic approach, i.e. two stool specimens were collected from each individual on two consecutive days before and approximately 3 weeks after treatment, with duplicate Kato-Katz thick smears per specimen, analysed under a microscope by experienced laboratory technicians. For the few trials which focused on hookworm, we only included *T. trichiura*-positive individuals at baseline. An overview of the data, including treatment regimen, number of participants and mean infection intensities at baseline and treatment follow-up, is summarised in Table 4.1.

Table 4.1: **Description of trial data used for the current analysis: age group included, treatments tested, sample sizes and arithmetic mean of averaged egg counts per gram of stool (EPG) averaged on the quadruplicate Kato-Katz thick smears at baseline (BL) and follow-up (FU)**

Reference	Country	Age (years)	Drug (dosage)	No. of participants with *T. trichiura* infection	Mean EPG at BL	Mean EPG at FU
Speich et al. (2012) (Speich et al., 2014)	Tanzania	15-18	Albendazole (400 mg)+oxantel pamoate (20 mg/kg)[1]	112	1,358	430
			Oxantel pamoate (20 mg/kg)	114	1,526	507
			Albendazole (400 mg)	115	1,495	1,017
			Mebendazole (500 mg)	109	1,905	1,122
Speich et al. (2015) (Speich et al., 2015)	Tanzania	6-15	Albendazole (400 mg)+ivermectin (200 µg/kg)	108	1,064	155
			Albendazole (400 mg)+mebendazole (500 mg)	106	1,121	763
			Albendazole (400 mg)+oxantel pamoate (20 mg/kg)	108	1,226	338
			Mebendazole (500 mg)	107	1,010	869
Moser et al. (2016) (Moser et al., 2016)	Tanzania	6-14	Oxantel (5 mg/kg)	44	1,014	573
			Oxantel (10 mg/kg)	49	2,288	899
			Oxantel (15 mg/kg)	49	1,320	273
			Oxantel (20 mg/kg)	45	1,508	357
			Oxantel (25 mg/kg)	43	884	302
			Oxantel (30 mg/kg)	46	1,761	499
Palmeirim et al. (2017) (Palmeirim, Ame, et al., 2018)	Tanzania	6-14	Mebendazole (500 mg)	88	1,024	518
			Mebendazole (6x100 mg)	91	1,264	106
Moser et al. (2017) (Moser, Coulibaly, et al., 2017)	Côte d'Ivoire	15-18	Tribendimidine (400 mg)	94	1,883	1,600
			Tribendimidine (400 mg)+ivermectin (200 µg/kg)	100	1,546	176
			Tribendimidine (400 mg)+oxantel pamoate (25 mg/kg)	92	1,726	102
			Albendazole (400 mg)+oxantel pamoate (25 mg/kg)	99	1,844	55
Wimmersberger et al. (2017) (Wimmersberger et al., 2018)	Côte d'Ivoire	2-5	Ivermectin (100 µg/kg)	42	383	382
			Ivermectin (200 µg/kg)	43	527	294
		6-12	Ivermectin (200 µg/kg)	42	892	587
			Ivermectin (400 µg/kg)	41	1,120	560
			Ivermectin (600 µg/kg)	41	896	559
Moser et al. (2018) (Moser, Sayasone, et al., 2018)	Lao PDR	6-12	Albendazole (400 mg)+oxantel pamoate (20 mg/kg)	51	376	0
			Pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	31	210	52
			Albendazole (400 mg)+pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	43	181	10
			Mebendazole (500 mg)+pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	26	160	11

[1] Administered on 2 consecutive days

4.3.3 Model

At baseline, the data consist of egg counts (eggs per Kato-Katz slide) $Y^{(0)}_{i_{jg}ds}$ for individual i, study j, treatment t, testing day d and sample s. They are assumed to follow a negative binomial distribution with a daily individual mean $\mu^{(0)}_{i_{jg}d}$ for each treatment and study and an aggregation parameter $k^{(0)}$:

$$Y^{(0)}_{i_{jg}ds} \sim \text{NB}(\mu^{(0)}_{i_{jg}d}, k^{(0)}). \tag{4.1}$$

The day-to-day variation σ^2_d in the excreted eggs was taken into account by random effects for each day and individual i, as follows $log(\mu^{(0)}_{i_{jg}d}) = log(\mu^{(0)}_{i_{jg}}) + \epsilon^{(0)}_{id}$ where $\epsilon^{(0)}_{id} \sim \mathcal{N}(\frac{-\sigma^2_d}{2}, \sigma^2_d)$. For the individual mean $\mu^{(0)}_{i_{jg}}$ we assumed a gamma distribution, that is $\mu^{(0)}_{i_{jg}} \sim \text{Gamma}(\mu^{(0)}_{jg} \cdot \sigma^{(0)}_{jg}, \sigma^{(0)}_{jg})$, where $\mu^{(0)}_{jg}$ and $\sigma^{(0)}_{jg}$ are hyperparameters.

At follow-up we have egg counts $Y^{(1)}_{i_{jg}ds}$ which are fitted to a mixture distribution which separates the infected and non-infected individuals, that is

$$\boldsymbol{Y}^{(1)}_i \sim \begin{cases} \prod_{d,s} NB(v^{(1)}, r) & \text{non-infected individuals} \quad (4.2a) \\ \prod_{d,s} NB(\mu^{(1)}_{i_{jg}d}, k^{(1)}) & \text{infected individuals,} \quad (4.2b) \end{cases}$$

where $\mu^{(1)}_{i_{jg}d}$ is the daily individual mean and $k^{(1)}$ is the variation from slide to slide of non-infected individuals, while v is the mean and r the aggregation of the non-infected individuals. The mixture component is the 'true' prevalence π_{jg} for each treatment and study and is defined as the probability of harbouring at least one fertilised female worm. We assumed that the male worms N_m and female worms N_f follow a common negative binomial distribution, that is

$$\text{NB}(N_f, N_m | w_{jg}, k_w) = \frac{\Gamma(N_f + N_m + k_w)}{N_f! N_m! \Gamma(k_w)} \cdot (1-\alpha)^{k_w} \cdot (\alpha p)^{N_f} \cdot (\alpha(1-p))^{N_m}, \tag{4.3}$$

where w_{jg} is the mean worm burden, k_w the aggregation of the worms in the population, $\alpha = \frac{w_{jg}}{w_{jg}+k_w}$ and p the probability of a worm to be female. By assuming that the probability of a worm to be of either sex is 0.5 (i.e. p=0.5), that one male worm can fertilise all female worms and summing over the male worms, we derived the following distribution of fertilised female worms n_f (see Supplementary text S1):

$$P(n_f; w_{jg}, k_w) = \text{NB}(n_f; \frac{w_{jg}}{2}, k_w) - \text{NB}(n_f; w_{jg}, k_w) \cdot \left(\frac{1}{2}\right)^{n_f}, \quad n_f \geq 1. \tag{4.4}$$

The distribution of egg counts was computed by marginalizing over the joint distribution of egg counts and fertilized female worms, that is

$$P(Y^{(1)}_i) = \sum_{n_f=0}^{\infty} P(Y^{(1)}_i, n_f) = \sum_{n_f=0}^{\infty} P(Y^{(1)}_i | n_f) P(n_f; w_{jg}, k_w), \tag{4.5}$$

where $P(Y^{(1)}_i | n_f) \equiv NB(cn_f, k^{(1)})$ and c the number of eggs per fertilised female worm. Hence, we were able to compute the mean $\mu^{(1)}_{jg}$ and the variance σ^2_{jg} of the marginal distribution of egg counts (see Supplementary text S2). Finally, from the latter two parameters a gamma distribution was derived for the individual mean infection intensity

at follow-up, that is $\mu_{i_{jg}}^{(1)} \sim \text{Gamma}(\alpha_{jg}, \beta_{jg})$, where $\alpha_{jg} = \frac{\mu_{jg}^{(1)}}{\sigma_{jg}^2}$ and $\beta_{jg} = \frac{(\mu_{jg}^{(1)})^2}{\sigma_{jg}^2}$. The density-dependent fecundity of female worms was included in aforementioned parameters (see Supplementary texts S1 and S2). Therefore, the whole transmission mechanism was taken into account (Grolimund et al., 2022). The day-to-day variation σ_d^2 in the excreted eggs at follow-up was taken into account in the same way as at baseline, that is $log(\mu_{i_{jg}d}^{(1)}) = log(\mu_{i_{jg}}^{(1)}) + \epsilon_{id}^{(1)}$ where $\epsilon_{id}^{(1)} \sim \mathcal{N}(\frac{-\sigma_d^2}{2}, \sigma_d^2)$. The 'true' cure rate was computed as $c_{jg} = 1 - \pi_{jg}$ and the ERR as $\phi_{jg} = 1 - \frac{\mu_{jg}^{(1)} \cdot \pi_{jg}}{\mu_{jg}^{(0)}}$. The sensitivity is estimated from the day-to-day variation σ_d and the aggregation calculated as weighted average from the aggregation at baseline $k^{(0)}$ and follow-up $k^{(1)}$ as follows:

$$s_{id} = 1 - \prod_{r=1}^{d} NB(0, \mu_{ir}, k)^{s \cdot k} = 1 - \left(\frac{k}{\mu_{i1} + k}\right)^{s \cdot k} \cdot \ldots \cdot \left(\frac{k}{\mu_{id} + k}\right)^{s \cdot k}, \tag{4.6}$$

with fixed mean infection intensities μ_{ir} from 24 EPG (corresponds to 1 egg per slide) to 500 EPG. For the hyperparameters, the following priors were chosen: for $\mu_{jg}^{(0)}$ a gamma distribution with mean 50 and variance 1,250; for $\sigma_{jg}^{(0)}$ an exponential distribution with mean 0.5 and variance 0.25, for σ_d^2 a gamma distribution with mean 1 and variance 1; for $1/k^{(0)}$ and $1/k^{(1)}$ normal prior distributions with mean 0 and variance 1; for w_{jg} a gamma distribution with mean 2 and variance 50; for k_w a normal distribution with mean 0.3 and variance 0.5; for r a normal distribution truncated at 0 with mean 0, and variance 1, for c a normal with mean 1 and variance 1 and for d a beta distribution with parameters 10 and 1. Semi-informative priors were used according to the biological literature and weakly informative priors were chosen if prior knowledge was scarce or ambiguous. Semi-informative priors were used according to the biological literature (Else et al., 2020; Levecke et al., 2015) and weakly informative priors were chosen if prior knowledge was scarce or ambiguous. We compared prior and posterior distributions to confirm that inference is driven by the data. The model was run in Stan with 10 chains and 5,000 iterations of which half of them were used for warmup. Convergence was determined via Gelman and Rubin diagnostics.

4.4 Results

4.4.1 Descriptive results

The number of participants and the mean infection intensities at baseline and treatment follow-up of the trials included in this analysis is summarized in Table 4.1. The observed CRs for treatments against *T. trichiura* ranged from 2% to 100%, and the ERRs from 0% to 100%, respectively. The largest difference in CRs between trials was observed for the combination treatment of albendazole (400 mg) plus oxantel pamoate (20 mg/kg). Estimated CRs in the different trials were 31%, 69% and 100%, respectively. The corresponding ERRs were 68%, 72% and 100%. For mebendazole (500 mg), the CRs were similar in the different studies ranging from 8% to 12%. There were larger differences in the ERRs ranging from 14% to 49%. The estimated CRs and ERRs for each treatment arm and trial are shown in Table 4.2.

Table 4.2: **Estimated cure and egg reduction rates of drug therapies against *T. trichiura* in different trials obtained from raw data**

Drug (dose)	CR1	ERR1	CR2	ERR2	CR3	ERR3
Albendazole (400 mg)	0.03 (0.01, 0.08)	0.32 (0.05, 0.51)	-	-	-	-
Albendazole (400 mg)+ivermectin (200 µg/kg)	0.28 (0.20, 0.37)	0.85 (0.78, 0.91)	-	-	-	-
Albendazole (400 mg)+mebendazole (500 mg)	0.08 (0.04, 0.15)	0.32 (-0.16, 0.59)	-	-	-	-
Albendazole (400 mg)+oxantel pamoate (20 mg/kg)	1.00 (0.96, 1.00)	1.00 (1.00, 1.00)	0.31 (0.23, 0.40)	0.68 (0.44, 0.84)	0.69 (0.59, 077)	0.72 (0.31, 0.94)
Albendazole (400 mg)+oxantel pamoate (25 mg/kg)	0.83 (0.75, 0.89)	0.97 (0.94, 0.99)	-	-	-	-
Albendazole (400 mg)+pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	0.93 (0.83, 0.98)	0.95 (0.79, 1.00)	-	-	-	-
Ivermectin (100 µg/kg)	0.12 (0.05, 0.24)	0.00 (-1.59, 0.66)	-	-	-	-
Ivermectin (200 µg/kg)	0.02 (0.00, 0.11)	0.34 (-0.15, 0.62)	0.21 (0.11, 0.35)	0.44 (-0.36, 0.78)	-	-
Ivermectin (400 µg/kg)	0.02 (0.00, 0.11)	0.50 (-0.11, 0.74)	-	-	-	-
Ivermectin (600 µg/kg)	0.12 (0.05, 0.25)	0.38 (-0.25, 0.69)	-	-	-	-
Mebendazole (500 mg)	0.12 (0.07, 0.19)	0.41 (0.01, 0.67)	0.08 (0.04, 0.15)	0.14 (-0.32, 0.46)	0.08 (0.04, 0.15)	0.49 (0.23, 0.67)
Mebendazole (6x100 mg)	0.43 (0.33, 0.53)	0.92 (0.87, 0.95)	-	-	-	-
Mebendazole (500 mg)+pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	0.88 (0.72, 0.97)	0.93 (0.64, 1.00)	-	-	-	-
Oxantel pamoate (5 mg/kg)	0.18 (0.09, 0.31)	0.44 (-0.04, 0.70)	-	-	-	-
Oxantel pamoate (10 mg/kg)	0.22 (0.13, 0.35)	0.61 (-0.14, 0.89)	-	-	-	-
Oxantel pamoate (15 mg/kg)	0.49 (0.35, 0.63)	0.79 (0.57, 0.91)	-	-	-	-
Oxantel pamoate (20 mg/kg)	0.49 (0.35, 0.63)	0.76 (0.31, 0.96)	0.26 (0.19, 0.35)	0.67 (0.49, 0.78)	-	-
Oxantel pamoate (25 mg/kg)	0.60 (0.46, 0.74)	0.66 (0.36, 0.85)	-	-	-	-
Oxantel pamoate (30 mg/kg)	0.59 (0.44, 0.72)	0.72 (0.09, 0.97)	-	-	-	-
Pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	0.74 (0.57, 0.87)	0.75 (0.03, 0.99)	-	-	-	-
Tribendimidine (400 mg)	0.06 (0.03, 0.13)	0.15 (-0.41, 0.50)	-	-	-	-
Tribendimidine (400 mg)+ivermectin (200 µg/kg)	0.32 (0.23, 0.42)	0.89 (0.82, 0.93)	-	-	-	-
Tribendimidine (400 mg)+oxantel pamoate (25 mg/kg)	0.65 (0.55, 0.74)	0.94 (0.90, 0.97)	-	-	-	-

[1] CR = cure rate; CR1, CR2, and CR3 refer to data from individual studies
[2] ERR = egg reduction rate; ERR1, ERR2, and ERR3 refer to data from individual studies

4.4.2 Model-based estimates

The estimates of the 'true' CRs ranged from 1% to 79% and the 'true' ERRs from −76% to 97% (Table 4.3).

The most efficacious treatment against *T. trichiura* in terms of CR was triple therapy (albendazole (400 mg) plus pyrantel pamoate (20 mg/kg) plus oxantel pamoate (20 mg/kg)) with a CR of 79% (95% Bayesian credible interval (BCI) 65-90%) and an ERR of 91% (95% BCI 67-99%). Albendazole (400 mg) plus oxantel pamoate (25 mg/kg) achieved the highest ERR of 97% (95% BCI 94-99%) and a CR of 63% (95% BCI 54-72%). Combination therapy with mebendazole (500 mg) plus pyrantel pamoate (20 mg/kg) plus oxantel pamoate (20 mg/kg) and albendazole (400 mg) plus oxantel pamoate (20 mg/kg) showed high efficacies with CRs of 69% (95% BCI 52-84%) and 63% (95% BCI 56-70%), respectively, and ERRs of 75% (95% BCI 11-97%) and 90% (95% BCI 84-95%), respectively.

The least efficiacious treatments against *T. trichiura* were albendazole (400 mg) with a CR of 1% (95% BCI 0-3%) and an ERR of 2% (95% BCI -4-40%) and tribendimidine (400 mg) with a CR of 2% (95% BCI 0-4%) and an ERR of 40% (95% BCI 18-57%). Mebendazole (500 mg) had a similar CR of 4% (95% BCI 3-7%) and an even lower ERR of 31% (95% BCI 16-45%).

Figure 4.1 shows the estimated 'true' CRs and ERRs with the corresponding 95% BCI. Table S2 shows the estimates of the CRs, ERRs, egg count variation at baseline and aggregation of the worm distribution at follow-up for each treatment arm from every trial. Figure S3 shows the observed and 'true' CRs and ERRs with the corresponding 95% credible interval graphically.

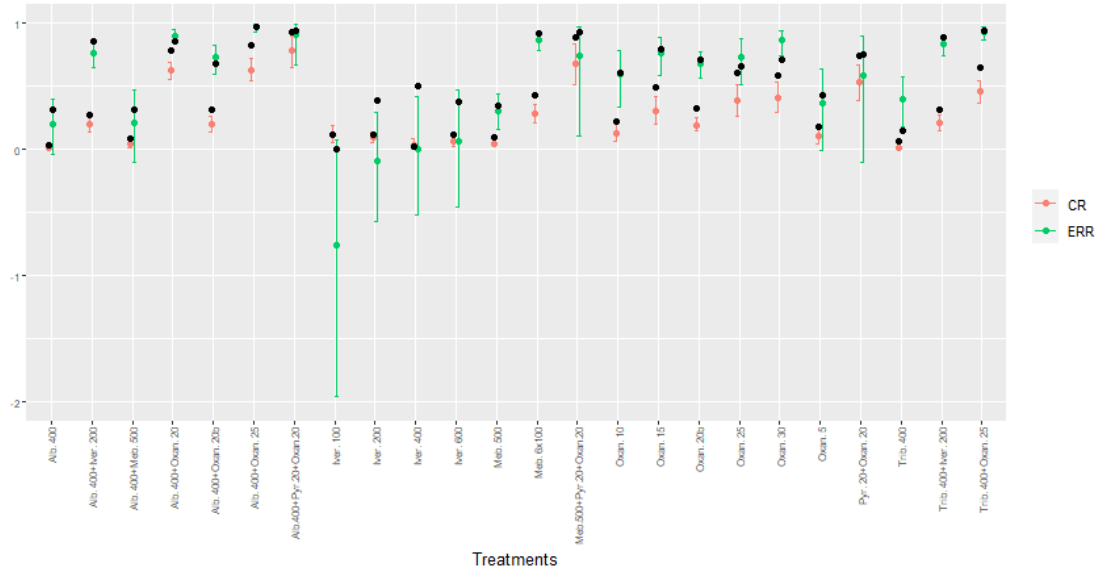

Figure 4.1: **Estimated and observed cure rates (CRs) and egg reduction rates (ERRs) of drug therapies against *T. trichiura*.** Posterior mean and 95% Bayesian credible interval of the CR and the ERR (arithmetic mean) for the different treatment arms for *T. trichiura*. The black dots show the observed data.

4.4.3 Diagnostic sensitivity

The estimated day-to-day variation $(\sigma_d^{(t)})^2$ was 0.94 (95% BCI 0.91-0.97) and the variation in egg counts at baseline ($k^{(0)}$) was 0.08 (95% BCI 0.07-0.09) and 0.11 (95% BCI 0.1-0.12) at follow-up ($k^{(1)}$). Figure 4.2 shows the estimated sensitivity with 95% BCI of

Table 4.3: **Posterior estimates (mean, 95%BCI[1]) for cure rate (CR) and egg reduction rate (ERR) against *T. trichiura***

Drug (dose)	CR (c_g)	ERR (ϕ_g)
Albendazole (400 mg)	0.01 (0.00, 0.03)	0.20 (-0.04, 0.40)
Albendazole (400 mg)+ivermectin (200 µg/kg)	0.20 (0.14, 0.26)	0.77 (0.65, 0.85)
Albendazole (400 mg)+mebendazole (500 mg)	0.04 (0.02, 0.08)	0.21 (-0.10, 0.47)
Albendazole (400 mg)+oxantel pamoate (20 mg/kg)	0.63 (0.56, 0.70)	0.90 (0.84, 0.95)
Albendazole (400 mg)+oxantel pamoate (20 mg/kg)[2]	0.20 (0.14, 0.26)	0.73 (0.60, 0.83)
Albendazole (400 mg)+oxantel pamoate (25 mg/kg)	0.63 (0.54, 0.72)	0.97 (0.94, 0.99)
Albendazole (400 mg)+pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	0.79 (0.65, 0.90)	0.91 (0.67, 0.99)
Ivermectin (100 µg/kg)	0.11 (0.05, 0.20)	-0.76 (-1.95, 0.07)
Ivermectin (200 µg/kg)	0.09 (0.05, 0.14)	-0.09 (-0.57, 0.30)
Ivermectin (400 µg/kg)	0.04 (0.01, 0.08)	0.00 (-0.52, 0.42)
Ivermectin (600 µg/kg)	0.07 (0.02, 0.13)	0.06 (-0.45, 0.47)
Mebendazole (500 mg)	0.04 (0.03, 0.07)	0.31 (0.16, 0.45)
Mebendazole (6x100 mg)	0.29 (0.21, 0.36)	0.87 (0.79, 0.92)
Mebendazole (500 mg)+pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	0.69 (0.52, 0.84)	0.75 (0.11, 0.97)
Oxantel pamoate (5 mg/kg)	0.11 (0.05, 0.18)	0.37 (0.00, 0.64)
Oxantel pamoate (10 mg/kg)	0.13 (0.07, 0.21)	0.59 (0.33, 0.79)
Oxantel pamoate (15 mg/kg)	0.31 (0.21, 0.42)	0.77 (0.59, 0.89)
Oxantel pamoate (20 mg/kg)	0.20 (0.15, 0.25)	0.68 (0.57, 0.78)
Oxantel pamoate (25 mg/kg)	0.39 (0.27, 0.51)	0.73 (0.51, 0.88)
Oxantel pamoate (30 mg/kg)	0.41 (0.29, 0.53)	0.87 (0.75, 0.94)
Pyrantel pamoate (20 mg/kg)+oxantel pamoate (20 mg/kg)	0.53 (0.39, 0.67)	0.59 (-0.10, 0.90)
Tribendimidine (400 mg)	0.02 (0.00, 0.04)	0.40 (0.18, 0.57)
Tribendimidine (400 mg)+ivermectin (200 µg/kg)	0.21 (0.15, 0.28)	0.84 (0.75, 0.90)
Tribendimidine (400 mg)+oxantel pamoate (25 mg/kg)	0.46 (0.37, 0.55)	0.93 (0.87, 0.97)

[1] BCI=Bayesian credible interval
[2] Administered on 2 consecutive days

the Kato-Katz technique for *T. trichiura*. For a 'true' infection intensity of 24 eggs per gram of stool (EPG), which corresponds to the minimal infection intensity of one egg per slide using standard 41.7 mg templates, the sensitivity for a single Kato-Katz thick smear is between 44% and 53%; for duplicate Kato-Katz thick smears it is between 65% and 71%; and for quadruplicate Kato-Katz thick smears, obtained from two stool samples, it ranges from 88% to 92%. The sensitivity is above 90% for 'true' infection intensities above 300 EPG for the aforementioned sampling schemes.

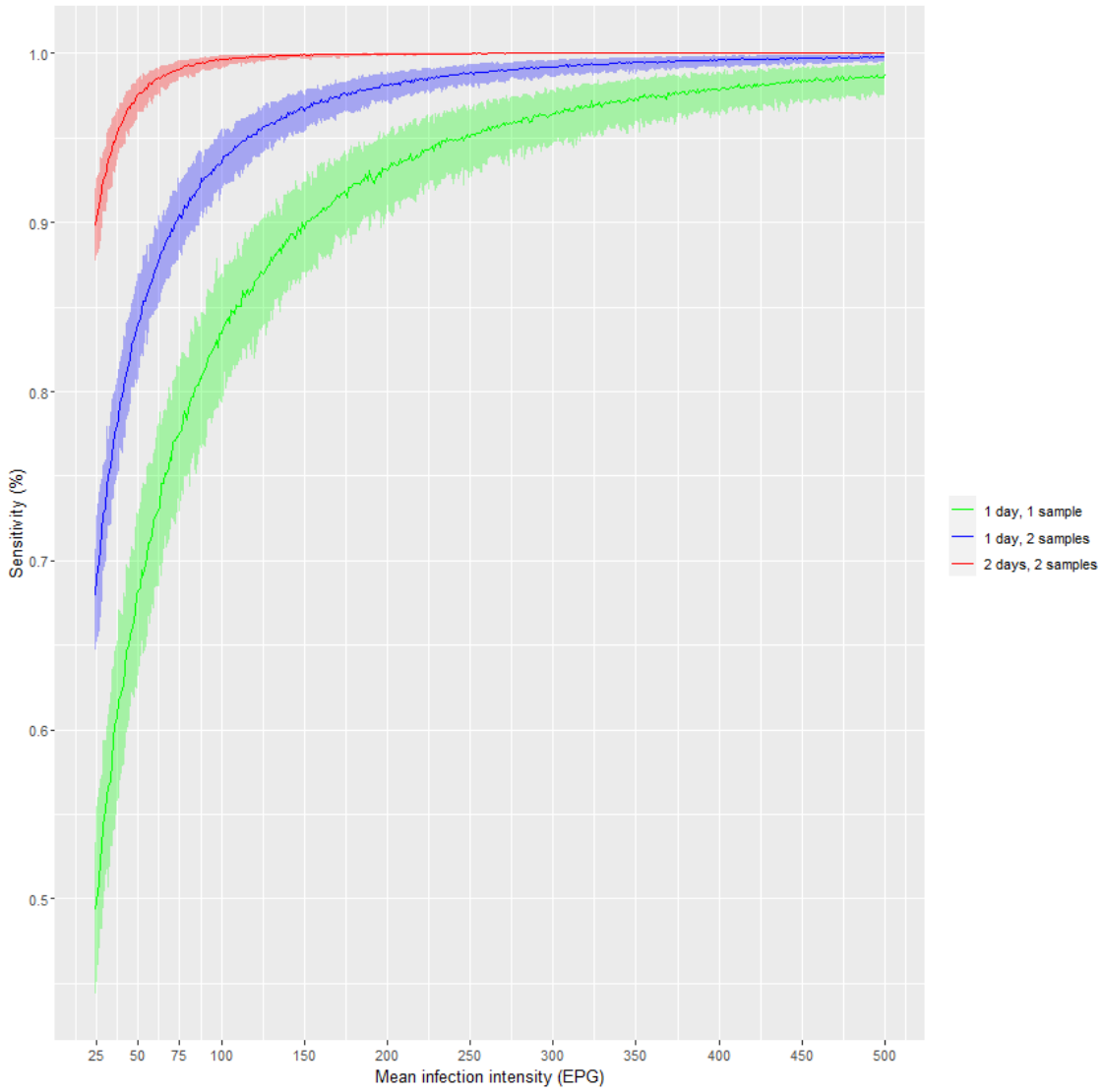

Figure 4.2: Sensitivity of the Kato-Katz thick smear technique for *T. trichiura* for one, two, and four Kato-Katz thick smears. The lines show the posterior mean estimate and the shaded areas indicate the 95% Bayesian credible interval.

4.5 Discussion

The Bayesian model used in this analysis takes into account diagnostic error, and hence, enabled us to infer on the 'true' efficacy of a large number of different drugs and treatment regimen against *T. trichiura*. We not only estimated the 'true' CRs and ERRs of 29 different treatments separately, but also the weighted 'true' CRs and ERRs of those treatments, where data were collected in several of the analysed trials. Apart from that, we provide the first intensity-dependent sensitivity estimation of the Kato-Katz technique for *T. trichiura* for different sampling schemes.

The data analysed in this study were collected by the same research group using the same sampling procedures, which enhances comparability between studies and treatments. Moreover, our estimates are infered from individual-level egg count data, which lead to better comparability to other studies and enabled us to estimate day-to-day variation. Since we take into account the diagnostic error, we account for individuals with low infec-

tion intensities, which are likely to be missed with the Kato-Katz thick smear technique. Hence, our estimates of the prevalence for the different treatments were higher than the observed ones, leading to lower CRs compared to those reported in the literature. These differences were also observed in studies which estimated CRs with the Kato-Katz technique and a quantitative real-time polymerase chain reaction (qPCR). For instance, Barda et al. (2020) observed CRs for combination therapy of albendazole plus oxantel pamoate of 82% for duplicate Kato-Katz thick smears from two days, compared to 79% with qPCR (Barda et al., 2020). In our study, the observed CR was 78% compared to our model-based estimate of 63%. For albendazole plus ivermectin, Keller et al. (2020) found CRs of 47% compared to 23% for the Kato-Katz technique and qPCR (Keller et al., 2020), respectively, which is similar to our estimates.
Our results, which showed that combination therapy have a higher efficacy against *T. trichiura* in terms of CR and ERR compared to single-drug treatments, are in line with earlier findings (Moser et al., 2019). The triple combination treatment with albendazole (400 mg), pyrantel pamoate (20 mg/kg) and oxantel pamoate (20 mg/kg) showed the highest efficacy in terms of CR. In a meta-analysis by Moser et al., the estimated CR and ERR of the aforementioned treatment were 84% and 92% (Moser et al., 2019), repectively, which is similar to our results. The highest ERR was estimated for albendazole plus oxantel pamoate. The CR is comparable to the higher CR in aforementioned meta-analysis, as the difference arises because of taking into account diagnostic error. WHO recommends single-dose albendazole and mebendazole for the treatment of soil-transmitted helminth infection; yet, the low efficacy of those treatments reported by others was confirmed by our results (Clarke et al., 2019; Keiser & Utzinger, 2008; Moser, Schindler, et al., 2017).

In comparison to the model developed by Grolimund et al. (2022), we include the density-dependent fecundity of egg production. Hence, all transmission mechanisms are taken into account and the model can be applied for high transmission settings. Although the distribution and administration of combination therapies is more difficult than single-drug therapies, their high efficacy could be crucial in the fight against soil-transmitted helminthiasis. We were able to confirm that the sensitivity of the Kato-Katz technique increases substantially if multiple slides are read instead of a single one (Liu et al., 2017; Moser, Bärenbold, et al., 2018). This insight could be useful for control measures, as at present, the recommended sampling scheme by WHO is to collect only one Kato-Katz thick smear. If financial resources are not an issue and qPCR is not available, quadruplicate Kato-Katz thick smear should be employed for diagnosis. The intensity-dependent sensitivity curves developed in this analysis (for different numbers of Kato-Katz thick smears) can be consulted, particularly for low intensity settings, to decide how many thick smears should be analysed per individual depending on how accurate the results should be.

Our study has several shortcomings that are offered for discussion. First, the estimates of the ERR have a rather large uncertainty. Second, the mean egg burden of the positives at follow-up is difficult to estimate for a treatment where no individual is positive. Nevertheless, the CR and ERR for such a treatment are estimated well as they are also informed by the priors and the non-infected individuals. In the future our model could be extended to include factors such as age and sex. Large datasets would be required to undertake these analyses.

Our model can be adapted for other helminth species. For polygamous species only transmission priors would have to be changed, while for the monogamous case, also the mean and variance of the fertilized female worm distribution would have to be derived.

4.5.1 Conclusion

We developed a Bayesian model, which takes into account the transmission mechanism as well as the diagnostic error, which enabled us to directly compare the 'true' efficacy of 24 different treatment regimen against *T. trichiura*. We found that combination therapy is more efficacious, than single-drug treatment, which is in line with earlier findings. Furthermore, we estimated the infection intensity-dependent sensitivity of the Kato-Katz technique for different sampling schemes. Duplicate Kato-Katz thick smears increase the sensitivity considerably compared to a single thick smear. The administration of combination therapies against soil-transmitted helminthiasis and the evaluation of infection intensity in low transmission settings via multiple Kato-Katz thick smears is recommended. This recommendation should be validated by cost-benefit analysis for interventions in different settings.

4.6 Supporting information

Supplementary text S1: Derivation of the marginal distribution of mated female worms

The probability of having N_f female and N_m male worms is according to May and Woolhouse [1] defined as follows

$$P(N_f, N_m; q, p, w_{jg}, k_w) = (1-\alpha)^{k_w} \frac{\Gamma(N_f + N_m + k_w)}{\Gamma(k_w)} \frac{(\alpha q)^{N_f}}{N_f!} \frac{(\alpha p)^{N_m}}{N_m!}, \quad \alpha = \frac{w_{jg}}{w_{jg} + k_w}$$

where q is the probablity of a worm to be female, p to be male, w_{jg} is the mean worm burden and k_w the aggregation parameter of a negative binomial distribution of the worms in the population. We assume that the probability for a worm to be female is $q = 1/2$ and $p = 1-q = 1/2$ to be male. Moreover, we assume that one male worm can fertilize all female worms.

To derive the marginal distribution of the female worms we sum over the number of male worms

$$\begin{aligned} P(N_f; q, w_{jg}, k_w) &= \frac{(1-\alpha)^{k_w}}{\Gamma(k_w)} \frac{(\frac{\alpha}{2})^{N_f}}{N_f!} \sum_{N_m=1}^{\infty} \frac{\Gamma(N_f + N_m + k_w) \cdot (\frac{\alpha}{2})^{N_m}}{N_m!} \\ &= -\frac{(1-\alpha)^{k_w}}{\Gamma(k_w)} \frac{(\frac{\alpha}{2})^{N_f}}{N_f!} \frac{\Gamma(k_w + N_f + 1) \cdot (1-\frac{\alpha}{2})^{-k_w - N_f} \cdot (-1 + (1-\frac{\alpha}{2})^{-k_w - N_f})}{k_w + N_f} \\ &= \frac{(1-\alpha)^{k_w}}{\Gamma(k_w)} \frac{(\frac{\alpha}{2})^{N_f}}{N_f!} \Gamma(k_w + N_f)(1 - \frac{\alpha}{2})^{-k_w - N_f} - \Gamma(k_w + N_f). \end{aligned} \tag{1}$$

Now we use the relations $(1-\alpha) = \frac{k_w}{w_{jg}+k_w}$ and $\left(1-\frac{\alpha}{2}\right)^{-1} = \frac{2(w_{jg}+k_w)}{w_{jg}+2k_w}$ in equation 1:

$$
\begin{aligned}
&\frac{(1-\alpha)^{k_w}(\frac{\alpha}{2})^{N_f}}{\Gamma(k_w)N_f!}\cdot\left[\Gamma(k_w+N_f)\left(1-\frac{\alpha}{2}\right)^{-k_w-N_f}-\Gamma(k_w+N_f)\right]\\
&=\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\frac{2(w_{jg}+k_w)}{w_{jg}+2k_w}\right)^{k_w}\left(\frac{w_{jg}}{2(w_{jg}+k_w)}\frac{2(w_{jg}+k_w)}{w_{jg}+2k_w}\right)^{N_f}\\
&-\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}\left(\frac{w_{jg}}{2(w_{jg}+k_w)}\right)^{N_f}\\
&=\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{2k_w}{w_{jg}+2k_w}\right)^{k_w}\left(\frac{w_{jg}}{w_{jg}+2k_w}\right)^{N_f}-\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}\left(\frac{w_{jg}}{2(w_{jg}+k_w)}\right)^{N_f}\\
&=\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w}\left(\frac{w_{jg}/2}{w_{jg}/2+k_w}\right)^{N_f}\\
&-\frac{\Gamma(k_w+N_f)}{\Gamma(k_w)N_f!}\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}\left(\frac{w_{jg}}{w_{jg}+k_w}\right)^{N_f}\left(\frac{1}{2}\right)^{N_f}\\
&=\mathrm{NB}(N_f;w_{jg}/2,k_w)-\mathrm{NB}(N_f;w_{jg},k_w)\left(\frac{1}{2}\right)^{N_f}\\
&=\mathrm{P}(N_f;w_{jg},k_w).
\end{aligned}
$$

We consider that all female worms are fertilized when $N_m > 0$ and therefore we replace N_f by n_f.

To compute the prevalence of having at least one fertilized female worm, we need to compute the probability of having no male worms, no female worms and no worms of either sex, which are given in equations 2, 3 and 4, respectively

$$\sum_{N_m=0}^{\infty} P(N_f,0;q=1/2,w_{jg},k_w)=\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w} \tag{2}$$

$$\sum_{N_f=0}^{\infty} P(0,N_m;p=1/2,w_{jg},k_w)=\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w} \tag{3}$$

$$P(0,0;q=1/2,p=1/2,w_{jg},k_w)=\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}. \tag{4}$$

As equations 2 and 3 already contain the probabilty of having no worms, the last term of equation 4 accounts for it in the following definition of the prevalence

$$1-P(0;w_{jg},k_w)=1-2\left(\frac{k_w}{w_{jg}/2+k_w}\right)^{k_w}+\left(\frac{k_w}{w_{jg}+k_w}\right)^{k_w}.$$

References

[1] May, R. M., & Woolhouse, M. E. J. Biased sex ratios and parasite mating probabilities. Parasitology. 1993; 107(3), 287-295.

Supplementary text S2: Mean and variance of the distribution of egg counts

The marginal distribution of egg counts (i.e. $\boldsymbol{Y}_i^{(1)}$at follow-up) can be computed from the joint distribution of egg counts and fertilized female worms n_f as follows

$$P\left(\boldsymbol{Y}_i^{(1)}\right) = \sum_{n_f=0}^{\infty} P(\boldsymbol{Y}_i^{(1)}, n_f) = \sum_{n_f=0}^{\infty} P\left(\boldsymbol{Y}_i^{(1)}\middle| n_f\right) P(n_{f;} w_{jg}, k_w) \qquad \text{(S1.1)}$$

The conditional distribution is $P\left(\boldsymbol{Y}_i^{(1)}\middle| n_f\right) \equiv NB\left(cn_f, k^{(1)}\right)$, where c is the net egg output of fertilized female worms and $k^{(1)}$ is the aggregation of the egg counts at follow-up. $P(n_{f;} w_{jg}, k_w)$ is the distribution of fertilized female worms, where w_{jg} is the mean worm burden and k_w is the aggregation of the worms in the population. The mean and variance of the distribution of the egg counts in (S1.1) are

$$\mu_{jg}^{(1)} = \sum_{n_f=0}^{\infty} cd^{n_f} n_f \, P(n_f\,; w_{jg}, k_w) = \sum_{n_f=0}^{\infty} cd^{n_f} n_f \left(NB\left(n_f; \frac{w_{jg}}{2}, k_w\right) - NB\left(n_f; w_{jg}, k_w\right)\left(\frac{1}{2}\right)^{n_f}\right)$$

$$= 2^k d w_{jg} c \left(\frac{1}{\left(2 + w_{jg}(1-d)/k_w\right)^{k_w+1}} - \frac{1}{\left(2 + w_{jg}(2-d)/k_w\right)^{k_w+1}}\right)$$

$$\sigma_{jg}^2 = \sum_{n_f=0}^{\infty} c^2 d^{2n_f} {n_f}^2 \left(NB\left(n_f; \frac{w_{jg}}{2}, k_w\right) - NB\left(n_f; w_{jg}, k_w\right)\left(\frac{1}{2}\right)^{n_f}\right)$$

$$= \left(1 + \frac{1}{k^{(1)}}\right)\left(k_w c^2 w_{jg} d^2 \left(-\frac{\left(\frac{k_w}{k_w + w_{jg}}\right)^{k_w}\left(2\left(k_w + w_{jg}\right) + k_w w_{jg} d^2\right)\left(1 - \frac{w_{jg} d^2}{2\left(k_w + w_{jg}\right)}\right)^{-k_w}}{\left(-2\left(k + w_{jg}\right) + w_{jg} c^2\right)^2}\right.\right.$$

$$\left.\left. + \frac{\left(\frac{k_w}{k_w + \frac{w_{jg}}{2}}\right)^{k_w}\left(2k_w + w_{jg} + k_w w_{jg} d^2\right)\left(1 - \frac{w_{jg} d^2}{2k_w + w_{jg}}\right)^{-k_w}}{\left(2k_w + w_{jg} - w_{jg} d^2\right)^2}\right)\right) - \left(\mu_{jg}^{(1)}\right)^2 + \mu_{jg}^{(1)}$$

$$= \left(1 + \frac{1}{k^{(1)}}\right)\left(k_w^{k_w+1} c^2 w_{jg} d^2 2^{k_w} \left(\left(2\left(k_w + w_{jg}\right) + k_w w_{jg} d^2\right)\left(2\left(k_w + w_{jg}\right) - w_{jg} d^2\right)^{-(k_w+2)}\right.\right.$$

$$\left.\left. + \left(2k_w + w_{jg} + k_w w_{jg} d^2\right)\left(2k_w + w_{jg} - w_{jg} d^2\right)^{-(k_w+2)}\right)\right) - \left(\mu_{jg}^{(1)}\right)^2 + \mu_{jg}^{(1)}$$

Supplementary table S2: Parameter estimates for each treatment regimen of all trials for T. trichiura

Treatment	Cure rate (c_g)	Egg reduction rate (ϕ_g)	Aggregation in group at BL ($\sigma_g^{(0)}$)	Aggregation in group at FU (k_w)
Alb. 400	0.01 (0,0.03)	0.2 (-0.04,0.4)	0.03 (0.02,0.05)	1.63 (1.14,2.23)
Alb. 400+Iver. 200	0.2 (0.14,0.26)	0.77 (0.65,0.85)	0.03 (0.02,0.04)	1.58 (1.04,2.23)
Alb. 400+Meb. 500	0.04 (0.02,0.08)	0.21 (-0.1,0.47)	0.02 (0.01,0.03)	1.29 (0.82,1.9)
Alb. 400+Oxan. 20	0.91 (0.77,0.99)	0.99 (0.93,1)	0.11 (0.04,0.21)	0.48 (0.02,1.32)
Alb. 400+Oxan. 20b	0.2 (0.14,0.26)	0.73 (0.6,0.83)	0.03 (0.02,0.04)	0.82 (0.43,1.31)
Alb. 400+Oxan. 20c	0.49 (0.41,0.58)	0.86 (0.78,0.93)	0.02 (0.01,0.03)	0.26 (0.14,0.5)
Alb. 400+Oxan. 25	0.63 (0.54,0.72)	0.97 (0.94,0.99)	0.01 (0.01,0.01)	0.31 (0.09,0.78)
Alb.400+Pyr.20+Oxan.20	0.79 (0.65,0.9)	0.91 (0.67,0.99)	0.15 (0.06,0.31)	0.41 (0.04,1.19)
Iver. 100	0.11 (0.05,0.2)	-0.76 (-1.95,0.07)	0.37 (0.1,1.08)	1.18 (0.63,1.86)
Iver. 200	0.04 (0.01,0.09)	0 (-0.52,0.41)	0.07 (0.02,0.17)	1.3 (0.79,1.96)
Iver. 200b	0.14 (0.07,0.23)	-0.17 (-1,0.41)	0.19 (0.06,0.52)	1.15 (0.58,1.83)
Iver. 400	0.04 (0.01,0.08)	0 (-0.52,0.42)	0.05 (0.02,0.12)	1.35 (0.82,2.02)
Iver. 600	0.07 (0.02,0.13)	0.06 (-0.45,0.47)	0.06 (0.02,0.15)	1.1 (0.64,1.72)
Meb. 500	0.05 (0.02,0.09)	0.52 (0.35,0.66)	0.01 (0.01,0.02)	1.07 (0.73,1.56)
Meb. 500b	0.04 (0.02,0.08)	0.12 (-0.21,0.39)	0.03 (0.02,0.05)	1.25 (0.8,1.83)
Meb. 500c	0.04 (0.02,0.08)	0.29 (0,0.53)	0.07 (0.03,0.14)	1.51 (0.93,2.19)
Meb. 6x100	0.29 (0.21,0.36)	0.87 (0.79,0.92)	0.03 (0.02,0.06)	1.27 (0.73,1.92)
Meb.500+Pyr.20+Oxan.20	0.69 (0.52,0.84)	0.75 (0.11,0.97)	0.24 (0.06,0.6)	0.57 (0.09,1.35)
Oxan. 10	0.13 (0.07,0.21)	0.59 (0.33,0.79)	0.02 (0.01,0.03)	0.89 (0.48,1.48)
Oxan. 15	0.31 (0.21,0.42)	0.77 (0.59,0.89)	0.02 (0.01,0.03)	0.53 (0.25,1.01)
Oxan. 20	0.33 (0.22,0.44)	0.77 (0.57,0.9)	0.02 (0.01,0.04)	0.6 (0.24,1.17)
Oxan. 20b	0.14 (0.09,0.2)	0.65 (0.51,0.77)	0.02 (0.02,0.04)	0.8 (0.47,1.26)
Oxan. 25	0.39 (0.27,0.51)	0.73 (0.51,0.88)	0.03 (0.01,0.07)	0.35 (0.18,0.68)
Oxan. 30	0.41 (0.29,0.53)	0.87 (0.75,0.94)	0.01 (0.01,0.02)	0.39 (0.17,0.79)
Oxan. 5	0.11 (0.05,0.18)	0.37 (0,0.64)	0.04 (0.02,0.08)	0.94 (0.52,1.52)
Pyr. 20+Oxan. 20	0.53 (0.39,0.67)	0.59 (-0.1,0.9)	0.14 (0.05,0.33)	0.65 (0.16,1.38)
Trib. 400	0.02 (0,0.04)	0.4 (0.18,0.57)	0.01 (0.01,0.02)	1.37 (0.94,1.91)
Trib. 400+Iver. 200	0.21 (0.15,0.28)	0.84 (0.75,0.9)	0.02 (0.01,0.03)	1.29 (0.77,1.92)
Trib. 400+Oxan. 25	0.46 (0.37,0.55)	0.93 (0.87,0.97)	0.01 (0.01,0.02)	0.54 (0.2,1.07)

[1] CIV (2016)
[2] CIV (2017)
[3] LAO (2017)
[4] TAN (2012)
[5] TAN (2013)
[6] TAN (2016)
[7] TAN (2017a)

Chapter 5

The extension of a modeling framework for Schistosomiasis taking into account diagnostic error

Carla M. Grolimund[1,2], Jürg Utzinger[1,2], Penelope Vounatsou[1,2]

1 – Swiss Tropical and Public Health Institute, Basel, Switzerland
2 – University of Basel, Switzerland

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5.1 Introduction

Schisotosomiasis is a disease caused by parasitic worms which belong to the genus of blood flukes. According to the latest global burden estimates, 140 million people were infected in 2019, leading to 1.64 million disabillity adjusted life years (DALYs) (Vos et al., 2020). The parasite studied here, *Schistosoma mansoni*, is one of the main five Schistosoma species. It lives in the blood vessels of the intestine and causes fever, blood in stool, anemia and in more serious cases convulsions or even liver failure among others (van der Werf et al., 2002).
Therefore, control efforts are of utmost importance, also to approach the long-term aim of elimination (Colley et al., 2014b; Tchuenté et al., 2017). They consist of preventive chemotherapy (PC), water, sanition and hygiene interventions (WASH), education and snail control. The World Health Organization (WHO) recommends treatment of people in high endemic areas and groups at high risk of morbidity for control and elimination of schistosomiasis (WHO, 2017). Furthermore, the need of knowledge about the burden and prevalence in adults, to plan further interventions, has been highlighted (Toor et al., 2018). Different appoaches to study the relation between age and prevalence have been done in the last decades, as PC campaigns need to be informed if targeted or community-wide treatment is necessary. Gryseels et al. studied 41 localities in Burundi to find that without exception the highest prevalence was in the groups of 15-20 years of age and that age-prevalence curves vary depening on the area (Gryseels & Nkulikyinka, 1988). Also numerous modeling efforts have been done. In 1976 Holford and Hardy proposed an immigration-death model to estimate age-prevalence curves for schistosomiasis (Holford & Hardy, 1976). Several modeling approaches have been developed based on the transmission models introduced by Anderson and May, which allow to estimate age-specific burden, prevalence and transmission parameters (Anderson & May, 1982, 1992; Chan & Bundy, 1997; Chan et al., 1996). The first Bayesian model was implemented by Raso et al. on the basis of the aforementioned formulation to achieve more accurate estimates of the age-specific prevalence (Raso et al., 2007). Bärenbold et al. also used a Bayesian framework and introduced the diagnostic error but didn't include the transmission mechanism (Bärenbold et al., 2017).

In this work we use a Bayesian modeling approach to infer on the age-specific mean worm burden and prevalence extending aformentioned formulations and taking into account the diagnostic error (Anderson, 1986; Bärenbold et al., 2017; De Vlas & Gryseels, 1992). This enables us to esimate the 'true' prevalence and therefore 'true' age-prevalence curves. Furthermore, we are able to predict the prevalence in adults from the prevalence of school-aged children (SAC).

5.2 Data

We analysed data collected by SCI, Imperial College London, and the Uganda MoH in Uganda. From 2014-2016 one survey was carried out each year. In the first two years two stool specimen were collected for each individual on two days, while in 2016 three specimen were taken. All specimen were analysed with duplicate Kato-Katz thick smears. To have the same sampling scheme for all individuals, the third stool specimen from the survey in 2016 was not included in this analysis. Data was collected approximately one month prior to the mass drug administration. The age-specific prevalence is shown in Figure 5.2.

5.3 Model

A transmission model was developed to estimate the age-specific mean worm burden in the population taking into account the diagnostic error of the Kato-Katz technique. Therefore we separated the zero counts to get the proportion of infected and non-infected individuals. By adding the variation in egg-output of individuals, as well as the variation in the testing procedure and aggregation of the eggs in the population we obtained the age-dependent 'true' prevalence as well as the sensitivity of the Kato-Katz technique.

5.3.1 Modeling egg counts

Let $X_{ijs}^{(a)}$ be the eggs per slide (eps) for individual i on day $j = (1, \ldots, d)$ and sample $s = (1, \ldots, n)$, n the number of samples per individual and d the number of measurement days, then $\mathbf{X}_i^{(a)} = (X_{i11}^{(a)}, \ldots, X_{idn}^{(a)})$ are all samples for individual i. Furthermore let D_i be the disease status ($1 =$ positive, $0 =$ negative) and a be the age, then we get the following due to the law of total probability:

$$\mathrm{P}(\boldsymbol{X}_i^{(a)}) = \mathrm{P}(\boldsymbol{X}_i^{(a)} | D_i = 1) \cdot \pi_a + \mathrm{P}(\boldsymbol{X}_i^{(a)} | D_i = 0) \cdot (1 - \pi_a), \tag{5.1}$$

where $\pi_a = P(D_i = 1)$ and $\boldsymbol{X_i} = 0$ means that the Kato-Katz samples from individual i were all negative and $\boldsymbol{X_i} = 1$ means that at least one sample was positive. Hence, we defined a mixture model which separates the infected from the non-infected individuals swhich enabled us to take into account the diagnostic error. The mixture component was defined as π_a, the age-dependent 'true' prevalence. To take into account the diagnostic error and the transmission model the following distributions were assumed:

$$\mathrm{P}(\boldsymbol{X}_i^{(a)} | \mathrm{D}_i = 0) \equiv NB(v, \xi) \tag{5.2}$$

$$\mathrm{P}(\boldsymbol{X}_i^{(a)} | \mathrm{D}_i = 1) \equiv \prod_j NB(\mu_{ij}^{(a)}, \phi). \tag{5.3}$$

The negative binomial distribution above is parametrized as follows:

$$NB(x|\mu, r) = \binom{x + r - 1}{x} \cdot \left(\frac{\mu}{\mu + r}\right)^x \cdot \left(\frac{r}{\mu + r}\right)^r, \tag{5.4}$$

where μ denotes the mean, $\mu + \frac{\mu^2}{r}$ the variance and r the aggregation parameter of the eggs. The parameter v is the mean of the non-infected individuals and ξ describes how the eggs are aggregated in the false positive individuals. Equation (5.3) on the other hand is the distribution of the counts for the infected individuals. $\mu_i^{(a)}$ is the age-dependent mean egg burden and ϕ the aggregation of the eggs of the positive individuals. We took into account the day-to-day variation σ_d^2 in the excreted egg counts by day-specific random effects for each individual, as follows $log(\mu_{ij}^{(a)}) = log(\mu_i^{(a)}) + \epsilon_{ij}$ where $\epsilon_{ij} \sim \mathcal{N}(\frac{-\sigma_d^2}{2}, \sigma_d^2)$.

To estimate the mean worm burden a transmisson model was used, which is explained in Chapter 5.3.2 in detail.

5.3.2 Estimating worm burden

Let W_a denote the worm burden, $M(a)$ the mean worm burden at age a and k the aggregation of the worms in the population. As commonly assumed a negative binomial distribution was chosen for the worm burden, that is:

$$W_a \sim \mathrm{NB}(M(a), k). \tag{5.5}$$

To model the mean worm burden $M(a)$, we defined the infection intensity and the density-dependent establishment functionas follows. The age-dependent rate of exposure $\lambda(a)$ is given by

$$\lambda(a) = A \cdot \exp(-(Ba)^2) + C. \tag{5.6}$$

The parameter A stretches and shrinks the curve and therefore changes the range of the overall intensity. B influences the peak intensity and C the infection intensity in adults. For the density-dependent establishment function $f(M(a))$ we chose the same function as Anderson and May (Anderson & May, 1992)

$$f(M(a)) = \left(1 + \frac{M(a)}{k} \cdot (1 - e^{-\gamma})\right)^{-(k+1)}. \tag{5.7}$$

The term $e^{-\gamma}$ describes at which extent the density influences the worm fecundity. Because of computational reasons, $e^(- \gamma)$ was estimated as one parameter instead γ . All in all we have the following transmission model describing the distribution of worm burden with age (Chan et al., 1996):

$$\frac{dM(a)}{da} = \lambda(a) \cdot f(M(a)) - \mu \cdot M(a). \tag{5.8}$$

where μ denotes the death rate of the worms. By solving this differential equation we were able to estimate the mean worm burden $M(a)$. To separate the infected individuals from the non-infected ones we truncated the negative binomial distribution of the worms at zero (Geyer, 2007). The mean of the positives is then

$$\eta_a = (M(a) + \frac{1}{p_a \cdot (1 + \delta)}) \cdot z \tag{5.9}$$

where $p_a = \frac{k}{k+M(a)}$, $\delta = \frac{P(W_a>1)}{P(W_a=1)}$ and z the number of eps per worm. The 'true' prevalence of disease for agegroup a is given by $\pi_a = 1 - p_a^k$. The variance of the truncated distribution is described as:

$$\sigma_a = (k \cdot \frac{1 - p_a}{p_a^2} - \frac{1}{p_a^2 \cdot (1 + \delta)} \cdot \left[-(1 - p_a) + \frac{(1 + k)(1 - p_a)}{1 + \delta} + [k - p_a \cdot (1 + k)] \cdot \frac{\delta}{1 + \delta}\right]) \cdot z^2. \tag{5.10}$$

Equation 5.10 can be simplified (Shonkwiler, 2016) to:

$$\sigma_a = (\eta_a + \eta_a \cdot M(a) \cdot (1 + 1/k) - \eta_a^2) \cdot z^2 \tag{5.11}$$

For the mean egg intensity of positive individuals $\mu_i^{(a)}$, we assumed a Gamma distribution as follows:

$$\mu_i^{(a)} \sim \text{Gamma}(\delta_{1a}, \delta_{2a}). \tag{5.12}$$

The parameters δ_{1a} and δ_{2a} were computed with the definition of the mean and variance of the gamma distribution from η_a and σ_a:

$$\delta_{1a} = \frac{\eta_a^2}{\sigma_a} \tag{5.13}$$

$$\delta_{2a} = \frac{\eta_a}{\sigma_a}. \tag{5.14}$$

For the hyperparameters the following priors were chosen: for A and C a gamma distribution with mean 1 and variance 1, for B and k a gamma distribution with mean 0.1 and variance 0.1, for $e^{-\gamma}$ a beta distribution with mean 1 ond variance close to 0, for μ a gamma distribution with mean 0.25 and variance 0.25, a normal distribution with mean 1 and variance 1 for z, for σ_d^2 a gamma distribution with mean 1 and variance 1 and a normal distribution for the inverse of ϕ. Where information was scarce weekly informative priors were used, otherwise semi-informative priors were employed according to the literature.

Table 5.1: Posterior estimates (mean, 95% BCI [1]) of transmission parameter for *S. mansoni*

Parameter	Description	Estimates
A	range of overall intensity	1.34 (1.18, 1.53)
B	peak intensity	0.08 (0.07, 0.09)
C	infection level in adults	0.14 (0.05, 0.25)
k	worm aggregation	0.12 (0.12, 0.13)
$e^{-\gamma}$	γ = density-dependent fecundity	1.00 (0.998, 1.00)
μ	death rate of worms	0.07 (0.05, 0.10)
$conv$	conversion factor from worms to eggs per slide	1.26 (1.19, 1.33)
σ_d^2	day-to-day variation	0.66 (0.63, 0.68)
ϕ	egg aggregation	22.83 (20.99, 24.83)

[1] BCI=Bayesian credible interval

5.3.3 Sensitivity of Kato-Katz

Let μ_i be mean egg intensities between 0 and 500 eps and μ_{ij} the corresponding daily mean egg intensities. The sensitivity s_{id} of the test was computed using posterior samples of the day-to-day variation σ_d^2 and the aggregation in the egg counts ϕ:

$$s_{id} = 1 - \prod_{j=1}^{d} \mathrm{NB}(\mathbf{X}_i = 0 | \mu_{ij}, \phi)^{s \cdot \phi} = 1 - \left(\frac{\phi}{\mu_{i1} + \phi}\right)^{s \cdot \phi} \cdot \ldots \cdot \left(\frac{\phi}{\mu_{id} + \phi}\right)^{s \cdot \phi}. \quad (5.15)$$

5.4 Results

The parameter estimates of the transmission parameters are presented in Table 5.1. The converion factor z which relates worms to eggs per slide (eps) of the positives corresponds to roughly 30 eggs per gram (EPG) per worm. The worm lifespan was estimated to be $1/\mu \approx 14$ days.

Figure 5.1 depicts the mean infection intensity of the positives in eps, while figure 5.2 shows the age-dependent 'true' infection prevalence for *S. mansoni*. The largest mean infection intensity in the positives and the prevalence estimates were found for the age range of 10-16. The difference in prevalence estimates estimated from the model compared to observed data is roughly 20%.

The infection intensity-dependent sensitivity for different sampling schemes, which is shown in Figure 5.3, was computed from the mean posterior estimates of the day-to-day variation σ_d^2 and egg aggregation ϕ (see Table 5.1). For 24 eggs per gram of stool (EPG), which corresponds to 1 egg per slide and is the minimum infection intensity, the sensitivity was estmated to be 55%, 77% and 99% for simple, duplicate and quadruplicate Kato-Katz thick smear.

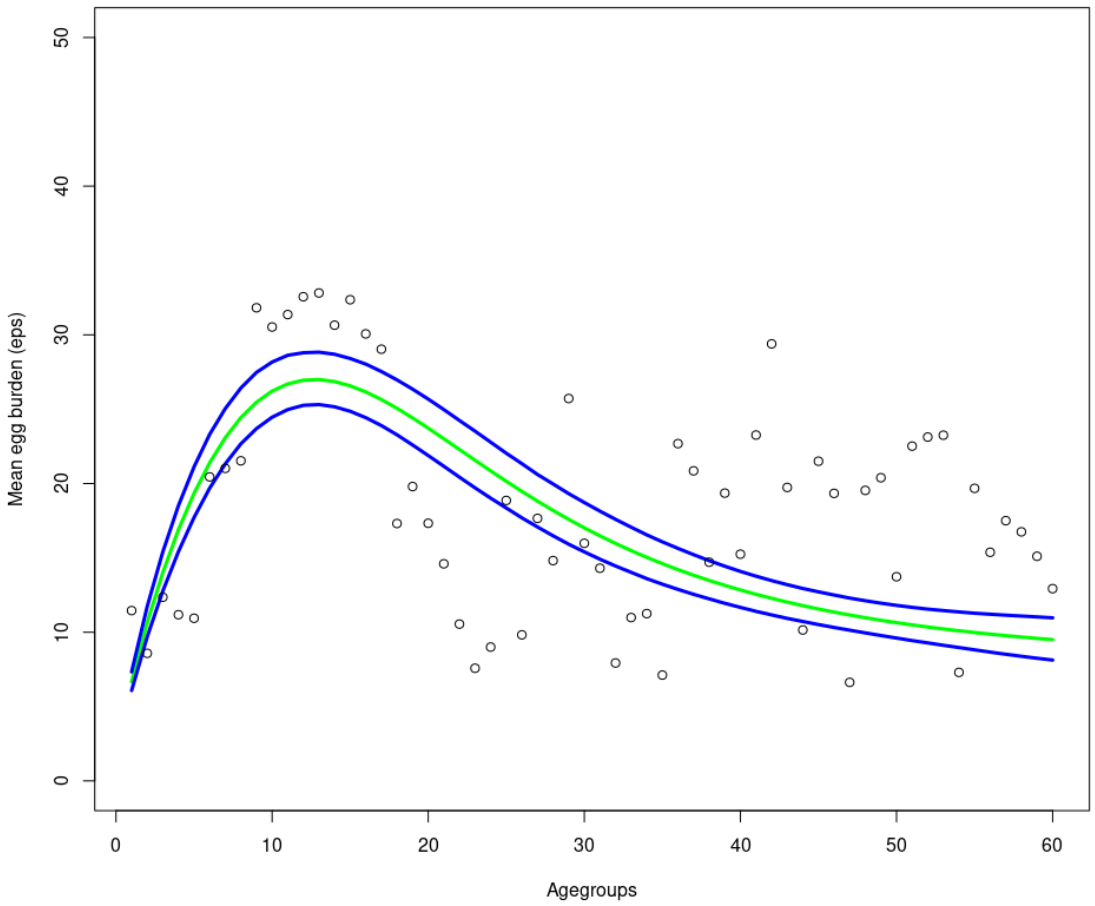

Figure 5.1: Estimated age-specific mean number of eggs per slide of positive individuals (green and blue curves show the posterior mean and 95% BCI, repectively) and the corresponding mean of the observed data (shown as circles) for *S. mansoni*.

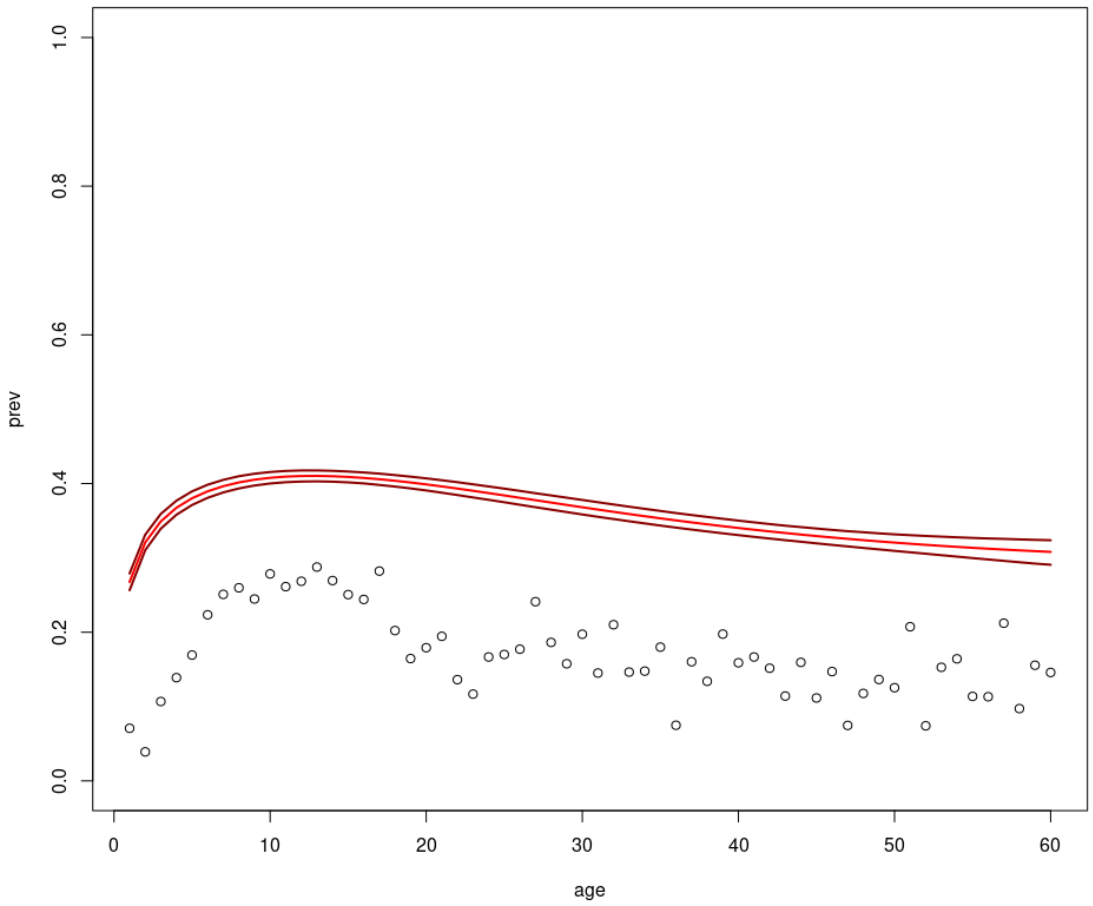

Figure 5.2: Estimated posterior mean (red curve) and 95% BCI (brown curve) of the age-specific prevalence and the mean prevalence from the observed data (dots) for *S. mansoni*.

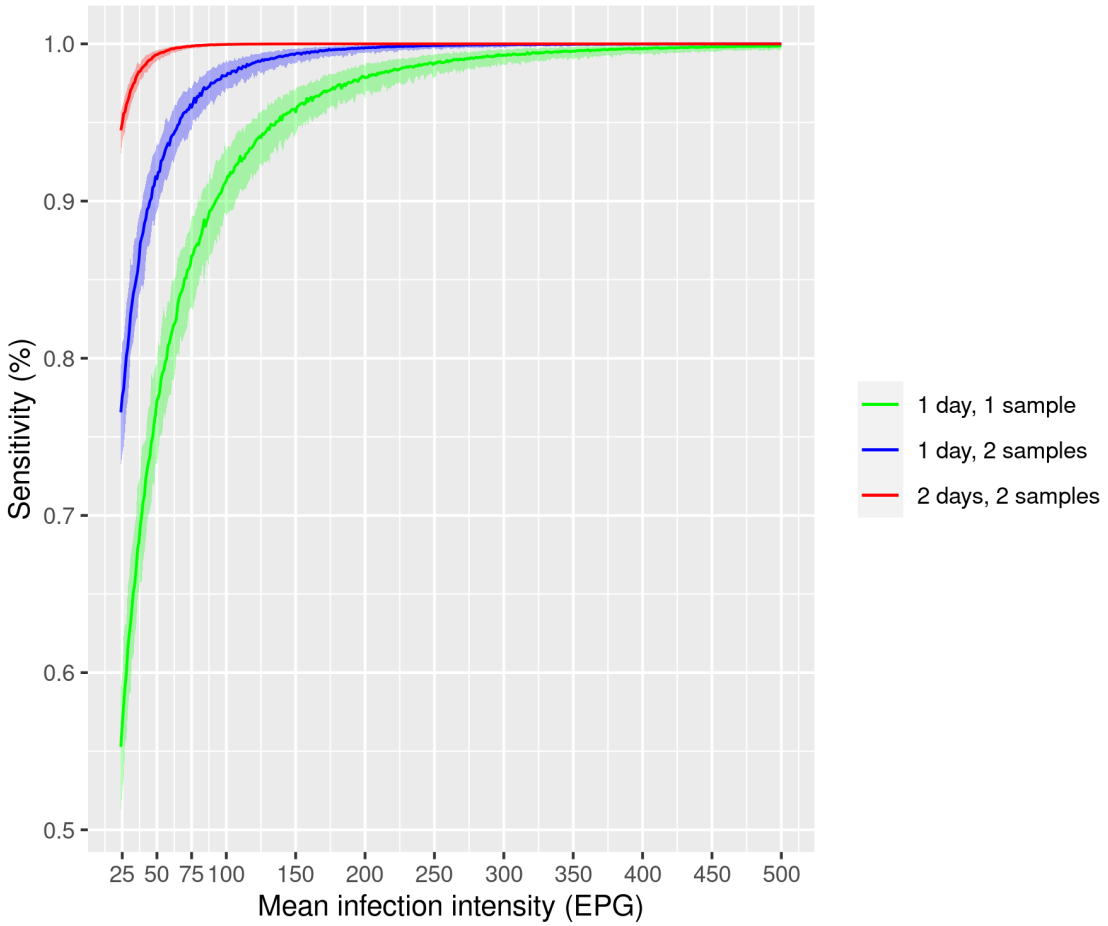

Figure 5.3: Infection intensitiy-dependent sensitivity of the Kato-Katz diagnostic technique for *S. mansoni*.

5.5 Discussion

To our knowledge, this is the first analysis which estimates age-specific egg infection-intensity and prevalence taking into account day-to-day variation, egg aggregation and transmission mechanism. Hence, the diagnostic error was taken into account, which resulted in considerably larger model estimates of the prevalence compared to estimates computed from observed data. The largest prevalences were found for the age range of 10-16, which is in line with the literature.

We found a worm lifespan of roughly 14 years which is higher as reported by others (Chan et al., 1996; French et al., 2010).The function used here for the rate of exposure is different to the literature, for instance, Chan et al. (1996) and French et al. (2010) multiply the exponential function by age. We argue that our function is more flexible, as our parameter A may capture the effect of the additional multiplication by age. Yet, different definitions of the rate of exposure should be compared in future work.

Taking into account diagnostic error enabled the estimation of the infection-intensity sensitivity for various sampling schemes. Compared to Bärenbold et al. (2017), who took into account day-to-day variation and egg aggregation but no transmission, our sensitivity estimates are slightly higher but similar for one sample and almost the same for two samples (Bärenbold et al., 2017).

Our analysis has several limitations. First, the model was developed only for data

consisting of a specific number of specimen per individual. Yet, a new model which can be applied for different sampling schemes has been developed but not yet applied. Furthermore, the uncertainty of the estimates is small, which can be due to the rather informative priors or the definition of the variance of the mean egg intensity or both. We only analysed data of individuals up to age 60 because of the smaller number of individuals for the other years of age. The data show more than one peak for the mean infecion intensity and the prevalence in adults. Unfortunately, our model is not able to capture more than one peak due to its formulation.

The underestimation of the prevalence, due to the low sensitivity of the Kato-Katz diagnostic technique, should be taken into account for interventions regarding control and elimination of *S. mansoni*. As multiple peaks in infection intensity and prevalance of adults have also been reported by others, it should be taken into account in future models (Raso et al., 2007).

Chapter 6

Discussion

The main contribution of this PhD thesis to the field of mathematical modelling in public health is the development or extension of modelling frameworks to accurately compare the performance of diagnostics, assess their sensitivity, estimate treatment efficacy and age-specific prevalence for parasitic worm infections. More specifically, the thesis contributes to (i) a comparison of reagent strip and urine filtration for the diagnosis of *S. haematobium*; (ii) an assessment of the intensity-dependent sensitivity for different sampling schemes for hookworm and *T. trichiura*; (iii) an assessment of the efficacy of different treatments against hookworm and *T. trichiura*; (iv) determination of age-specific prevalence of *S. mansoni*; and (v) prediction of the prevalence in adults from the prevalence in school-aged children for *S. mansoni*. The higher accuracy compared to existing studies was achieved by taking into account diagnostic error and disease transmission mechanism.

Chapters 2 through 5 each include a comprehensive discussion and conclusions. In this chapter the key findings, strengths and limitations, and potential extensions of the presented work are discussed.

6.1 Significance of the work

6.1.1 Modelling diagnostic error

In most studies, which use latent class models, only aggregated data were analysed (Coulibaly et al., 2016; Nikolay et al., 2014; Tarafder et al., 2010), although the variation of microscope egg counting techniques for an individual contains valuable information regarding the performance of such diagnostics. Moreover, comparability suffers if different summary measures and sampling schemes are applied. The models developed in this work include this variation and hence, the diagnostic error, which results in more accurate estimates than reported before. De Vlas and Gryseels were the first to realize the connection between incorporating the variation in egg counts and estimation of 'true' prevalence (De Vlas & Gryseels, 1992). We developed another approach, by taking into account day-to-day and slide-to-slide variation, thereby extending the work of Bärenbold and colleagues (Bärenbold et al., 2017). Mixture models were used in Chapters 2 through 5 to separate infected and non-infected individuals. The mixing proportion, which corresponds to the prevalence, is defined depending on the disease, i.e. as harbouring at least one female worm for polygamous species and one worm for monogamous species.

In Chapter 2, the data analysed comprised five urine samples per individual taken on consecutive days for baseline and each treatment follow-up. By including the day-to-day variation, we were able to estimate the 'true' prevalence, and hence, the performance of urine filtration. Additionally, by running extensive simulations of hypothetical populations in diverse transmission settings, we related prevalence thresholds from urine filtration into reagent strip. This enabled us to formulate recommendations put forward by WHO and the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) for estimation of *S. haematobium* prevalence observed from a single day (King et al., 2020; Organization et al., 2013b).

In Chapters 3 and 4, the data consisted of an ensemble of clinical trials which assessed the efficacy of different drugs and combination therapies against soil-transmitted helminths (STHs) using the Kato-Katz technique. We developed the first model which takes into account diagnostic error by including the egg count variation from day-to-day and slide-to-slide to estimate the 'true' efficacy of different drugs and combination therapies. In Chapter 5 the diagnostic error was also included, which enabled us to estimate the 'true' age-specific prevalence of *S. mansoni*. In Chapters 2 through 5 we estimated the infection intensity-dependent sensitivity for different sampling schemes for Kato-Katz, reagent strip

and urine filtration.

6.1.2 Modelling transmission mechanism

Individuals infected with STHs or *Schistosoma*, harbour a specific number of worms but the number of eggs that are shed depends on several factors like diet or distribution of parasite eggs in faeces. Moreover, differences in egg counts often arise because of the inaccuracy of diagnostic techniques. Therefore, the infection intensity and prevalence should be estimated from the underlying worms instead of egg counts to improve accuracy. Another important advantage of using a transmission model is that the prevalence can be linked to the mean infection intensity, which improves statistical power. We included the transmission mechanism to relate the measured egg counts to the worm burden and the prevalence.

In Chapters 3 and 4, we derived the distribution of fertilized female worms from the worm distribution and the prevalence of infection was defined as the probability of having at least one fertilized female worm. This enabled us to have more accurate estimates of cure rate (CR) and egg reduction rate (ERR) estimates. In contrast, in Chapter 5, the prevalence of infection was defined as harbouring at least one worm, which is an approximation, as we could not use the definition of having at least one fertilized female worm for a monogamous species. A model developed by Anderson and May and extended by Chan et al., which contains the transmission mechanism, was used to calculate the mean worm burden. It was extended with a truncated negative binomial distribution for the infected individuals to finally fit to the observed egg counts. By taking into account these transmission mechanisms, we achieved more accurate age-specific prevalence estimates. To our knowledge, this is the first attempt which takes into account diagnostic error and transmission mechanism for the estimation of treatment efficacy and age-specific prevalence.

6.1.3 Estimation of efficacy via model-based meta-analyses

In Chapters 3 and 4 the first model-based meta-analyses, including dianostic error and transmission mechanism, were developed to assess the efficacy of different drug therapies against hookworm and *T. trichiura*. By linking the prevalence to the mean infection intensity, statistical power was achieved. Moreover, compared to other meta-analyses or reviews, the data were collected by the same research group using the same sampling design, which ensures excellent comparability. Yet, there is a risk of leaving out evidence and of not having the complete picture compared to a systematic review. Our results are comparable to quantitative polymerase chain reaction (qPCR) test results, which confirm the validity of our estimates. Furthermore, WHO recommends single-dose albendazole and mebendazole for the treatment of STH infection; yet, the low efficacy of those treatments reported by others was confirmed by our results. Our estimates also show that multiple drug therapies are more efficacious than single drug treatments.

6.1.4 Bayesian inference

In the past decades, Bayesian inference has become popular for analysis in various fields of research because the required computational power is now available. Lately, the advantages of Bayesian methods for analysis in the field of epidemiology have been pointed out (Kokaliaris et al., 2022; Martinez & Achcar, 2014). In this work, Bayesian inference was used in Chapters 2 through 5. Compared to frequentist approaches, this enabled us to include prior knowledge from the literature particularly for transmission parameters, which

improved estimation. In latent class models conditional dependence can be introduced by adding a normally distributed random effect, but in this work we took inspiration from the biological process.

Because of the complexity of the models, the computation takes a large amount of time (from hours to days) even on powerful computers. Yet, we utilised Stan, which is faster than other widely used Bayesian modelling software, because the model is compiled to C++ code. Stan makes use of Markov chain Monte Carlo (MCMC), which has the benefit, that it incrementally improves the approximate distributions, eventually converging to the posterior distribution (Gelman et al., 1995).

6.1.5 Implications for public health

If reagent strip instead of urine filtration would be employed in control programmes, the costs could be substantially reduced and proceedings would be more efficient allowing more children to get tested. Moreover, the treatment efficacy estimates for different sampling schemes may be considered in aforementioned programmes to make decisions about suitable drug therapies.

The infection intensity-dependent sensitivity curves for Kato-Katz, reagent strip and urine filtration could be consulted to inform decision makers to propose guidelines about the best suitable sampling scheme for control programmes or clinical trials, particularly for low intensity settings. This in turn depends on how much accuracy is needed taking the costs into account.

For control measures, the administration of combination therapies generally implies more efforts and financial resources; nevertheless, a cost-benefit analysis is recommended.

6.2 Strengths, limitations and extensions

There are few limitations of the work that are offered for discussion. Generally, it is difficult to verify some of the assumptions of mathematical transmission models because of the lack of worm count data. Moreover, it is also difficult to confirm prevalences as no 'gold' standard exists to compare it against. Yet, the qPCR technique is a good proxy for a 'gold' standard diagnostic technique.

6.2.1 Data

It is essential to confirm the findings of Chapter 2 using other types of reagent strips for detection of *S. haematobium*, especially in settings with prevalences below 10%. Moreover, it was not uncommon that individuals only had one diagnostic test run at a particular sampling time point; as a result, the observed prevalence by reagent strip and urine filtration at the same time point and village are not directly comparable. Yet, we were interested in the overall change in prevalence, which can be estimated by our modelling approach despite this inconsistency. In Chapters 3 and 4 the data represent only low intensity settings. In particular, the model from Chapter 4, which includes the density-dependent fecundity, should be validated for moderate and high intensity settings.

6.2.2 Modelling

The main limitation in Chapters 3 and 4 is that CRs and ERRs are difficult to estimate if all patients are cured, because no data are available to estimate the mean infection intensity of infected individuals and the results are sensitive to the the prior distributions.

Yet, the prevalences and hence, the CRs of the different drug therapies were approximated well because of the mixture which depends also on data for the non-infected individuals. The ERR have a rather large uncertainty as we did not limit it to be between zero and one. The reason was that we also included drug therapies for *T. trichiura* in the analysis for hookworm and vice versa, which we knew could result in a negative ERR. To reduce uncertainty, the model could be changed to include aforementioned limit. The female worm fecundity is not taken into account in Chapter 3, as we can assume a linear relation of the number of eggs per worm for low intensity settings. For higher infection intensities it is important to include the female worm fecundity following the described approach in Chapter 4. We were not able to include a random effect to take into account the variation between the trials due to the small number of trials per treatment. For future work, if enough data are available, including the aforementioned random effect is straightforward.

The results in Chapter 5 show narrow credible intervals for the infection intensity and the prevalence. Informative priors had to be used as otherwise the model showed unidentifiability for some parameters. The prevalence defined as harbouring at least one worm is a good approximation, but could be more accurate by defining it as having at least one worm pair. The data analysed in Chapter 5 shows more than one peak for the mean infecion intensity and the prevalence in adults. Unfortunately, our model is not able to capture more than one peak due to its formulation. As multiple peaks have also been reported by others, it should be taken into account in future models (Raso et al., 2007). The models from Chapters 3 and 4 can be adapted for other helminth species. For polygamous species only transmission priors would have to be changed. For the monogamous case, the mean and variance of the fertilised female worm distribution, which then should be redefined as the worm pair distribution, would have to be derived.

We found a higher sensitivity across all levels of infection intensity, while comparing our results to the estimates of Bärenbold et al. (2017), indicating that the sensitivity varies among studies because of different day-to-day variations. This can have various reasons, like varying accuracy of the readings or variation in egg density of different samples from an individual. It is possible that treatment efficacy estimates may not be comparable even from studies with similar infection intensities and sampling efforts. A first step to clarify this assumption could be to investigate whether the day-to-day variation depends on the mean infection intensity.

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