Trends in Parasitology

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Review

Preventive Chemotherapy in the Fight against Soil-Transmitted Helminthiasis: Achievements and Limitations

Jessica D. Schulz,[1,2,3] Wendelin Moser,[1,2,3] Eveline Hürlimann,[1,2] and Jennifer Keiser[1,2,*]

Soil-transmitted helminths (STHs) are endemic in more than half of the world's countries. The World Health Organization has advocated targeted preventive chemotherapy (PC) to control STH infections by distributing albendazole or mebendazole to at-risk populations. While the overall impact and sustainability of this strategy is disputed, a decrease in moderate and heavy STH infections can be largely attributed to a scale-up of drug distribution. Two factors might jeopardise the success of PC programs. First, the benzimidazoles possess unsatisfactory efficacy against *Trichuris trichiura* infections. Second, increased drug distributions might trigger anthelmintic resistance. This review presents an overview of the burden of STH infections, the evolution of PC along with its success and challenges, recent estimates of the efficacy of recommended drugs, and alternative treatment options.

Highlights

For controlling STH infections, millions of single doses of albendazole and mebendazole are distributed yearly in the framework of PC.

Although PC caused a drop in the number of moderate and heavy STH infections, its overall impact is highly disputed.

The STH burden has steadily declined with time but still more than one billion people are infected globally.

Albendazole and mebendazole do not have high efficacy against all STH infections when used in single oral doses – for example, mebendazole lacks efficacy against hookworm; neither drug has high efficacy against *T. trichiura*.

Resistance against both drugs has been observed in the veterinary field but has not yet been confirmed in human medicine.

A few drugs with anthelmintic activity – as well as potential drug combinations with enhanced efficacy profiles – have been identified but they need further evaluation to better treat infections with all STHs.

The Burden of Soil-Transmitted Helminthiasis

Global Epidemiology and Pathology of STH Infections

Soil-transmitted helminthiasis belongs to the neglected tropical diseases (NTDs) and is caused by infections with the roundworm *Ascaris lumbricoides*, hookworms (*Necator americanus*, *Ancylostoma duodenale* and *Ancylostoma ceylanicum*) or the whipworm *T. trichiura*. Helminth eggs or larvae are transmitted through contaminated food or soil, or active skin penetration [1]. Once the hatched larvae reach the intestine they mature into adult worms, which shed eggs that are excreted with the feces. Under optimal conditions (high humidity and warm temperature) eggs embryonate within several days in the environment and develop into the infective stages [2].

Among all NTDs, soil-transmitted helminthiasis affects the largest number of people, with an estimated 1.5 billion infected individuals, and it causes the highest **disease burden** (see Glossary) [3,4]. Although the global STH prevalence has decreased after almost two decades of helminth control activities, there are still more than 100 countries in need of control programs (i.e., infection prevalence >20%) [4,5]. **Morbidity** is particularly related to moderate- and heavy-**intensity** infections causing short-term acute manifestations such as diarrhea, severe dysentery, eosinophilic pneumonia or intestinal, hepatobiliary, or pancreatic obstruction [1,5]. Mid-term consequences triggered by the diseases include chronic inflammation and nutritional impairment (e.g., micronutrient deficiencies) from mechanical damage, blood loss, competition for nutrients, and reduced food intake [1,5]. Untreated STH infections are associated with disabilities such as growth retardation and impaired mental development, decreased functioning of the immune system, and reduced school and work performance [6]. Furthermore, morbidity due to STH infections is species-specific and does not affect all age- or risk-groups equally, which is explained by the different nature of the clinical impairment, the infection

[1]Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Basel, Switzerland
[2]University of Basel, Basel, Switzerland
[3]Equal first authors

*Correspondence:
jennifer.keiser@swisstph.ch (J. Keiser).

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occurrence, and the vulnerability of the respective groups. While hookworm infection and related anemia may be more relevant in pregnant women, young children are more affected by *A. lumbricoides* infection [5,7]. However, many clinical signs are not STH-specific and may be attributed to other comorbidities in burden of disease estimations [8].

This review gives an overview of STH burden estimates and intertwined criticism, and presents the evolvement of **targeted preventive chemotherapy (PC)** guidelines. The controversial discussion about the actual impact of PC and recent estimates on the efficacy of **anthelmintic** drugs are summarized. Finally, alternative treatment options and state-of-the-art reports on **drug resistance** are presented.

Burden Estimates and Dynamics over the Past Two Decades

Disability-adjusted life years (DALYs), the most widely used metric to determine burden figures, estimates disease burden based on **years lived with disability (YLDs)** combined with **healthy years of life lost (YLLs)**, thus taking into account health loss due to both morbidity and mortality [9]. Figure 1 illustrates the soil-transmitted helminthiasis burden changes between 2000 (shortly before the World Health Assembly (WHA54.19) resolution) and 2016 and how dynamics varied by region. Overall, STH infections were estimated to contribute to 3.3 million DALYs lost in 2016, which is significantly lower than the estimated 4.6 million DALYs in 2000 [10]. This decrease is, however, mainly associated with decreasing prevalence in the regions of Southeast Asia, East Asia and Australia (36.0% prevalence in 2000; 22.3% in 2016) [10–13]. This regional decline is related to different country-specific achievements, including high treatment coverage rates within deworming programs (e.g., Bhutan, Cambodia, Lao PDR, Myanmar, Nepal) eventually accompanied by socioeconomic development (e.g., Sri Lanka and Thailand) [14] and integration of **water, sanitation, and hygiene (WASH)** interventions (e.g., China, The Philippines, Timor-Leste) [11]. STH infections rarely lead to death [15], so most of the estimated burden is attributed to YLDs. The majority of STH-related mortality is associated with sub-Saharan Africa whereof a large part may be attributable to intestinal and hepatobiliary obstruction from *A. lumbricoides* in young children [1,5,10,16,17]. While estimated deaths caused by STH infections were cut down by half within the respective period (from ~10 000 to less than 5000, Figure 1), a steady downwards trend is observed for YLDs and the overall DALYs [18].

Debate on the 'True' Burden

Since burden estimates are key information for cost-effectiveness analyses of intervention strategies and are used to set priorities within the health agenda by local, national, and international stakeholders, they are often debated [19,20]. STH infections are more of a chronic nature, and thus their burden refers mainly to morbidity and disability, which is often argued to be underestimated [15,19,21]. Main points of criticism are (i) lack of acknowledgment of economic burden in the context of the affected population [15,22], (ii) not taking into account frequent coinfections and comorbidities that may show potential additive effects on detrimental health outcomes [15,19,22], (iii) biased 'western' determination of disability weights that are used for calculation of DALYs [23], (iv) omission of patient self-reported illness impact and quality of life [19,22], (v) lack of inclusion of less acute sequelae referring to subtle morbidity (e.g., impaired cognitive development due to STH) [17,22] and acknowledgment of long-term outcomes [19]. To address these criticisms, the global burden of disease-assessment tools have been further adapted and refined over the past decades. More infection-related morbidity sequelae were included (e.g., hookworm-related anemia) [17,24], and an attempt was made to evaluate disability-weights by a more culturally diverse sample of respondents [9]. Nevertheless, concerns remain on the accuracy of current burden estimates. Thus, the application of new estimation procedures are warranted to acknowledge the chronic nature and the context

Glossary

Anthelmintic: a drug that can kill or paralyse parasitic worms (helminths). Albendazole and mebendazole are most commonly used to treat soil-transmitted helminth infections.
Community-based treatment: anthelmintic treatment is distributed in regular intervals to the entire community, irrespective of the individual infection status.
Cure rates (CRs): the percentage of patients who are egg-negative after treatment.
Disability-adjusted life years (DALYs): the number of years of healthy life lost attributable to a disease (or group of diseases). It is defined as the sum of healthy years of life lost and years lived with disability. DALYs are used as a measure of disease burden and provide a comparative indication of the relative importance of the disease to public health [5].
Disease burden: the burden of disease is described as the health loss due to disease or condition, and is most often expressed as disability-adjusted life years.
Drug efficacy: a description of how well a drug is able to decrease the worm burden. Efficacy is usually assessed by measuring egg counts before and a few weeks after treatment, and is expressed as cure and egg-reduction rates.
Drug resistance: for anthelmintics, resistance is currently defined as the decrease in ability to reduce the worm burden and clear infections.
Egg-reduction rates (ERRs): the relative reduction in counts of eggs after treatment.
Years of life lost (YLLs): years of healthy life lost due to premature mortality in the population caused by a disease or condition.
Intensity of infection: the number of helminths infecting an individual (also known as the worm burden). It can be measured by counting expelled worms after anthelmintic treatment, or by counting helminth eggs excreted in feces (expressed as eggs per gram). WHO classifies STH infections as light, moderate, and heavy, according to the number of helminth eggs excreted in human feces [5].
Morbidity: the clinical consequences of infections and diseases that

in which STH infections affect populations together with the inclusion of more accurate prevalence estimates from intensified efforts to map NTDs at national levels [12,25].

Strategy for Achieving Global Targets: The Evolution of Preventive Chemotherapy

In 1987, the first report on an expert meeting at the World Health Organization (WHO) 'Prevention and Control of Intestinal Parasitic Infections' was published, becoming the cornerstone for global STH control programs [26]. At this early stage, little scientific information on the treatment of human soil-transmitted helminthiasis was available. Thus, STH prevention and control focused mainly on hygiene and education. However, clearly defined programs and targets did not yet exist [26]. In 1998, the first guideline with information on treatment strategy depending on STH prevalence was reported (Figure 2) [27] and finally, the 54th World Health Assembly (WHA) in 2001 endorsed the reduction of mortality and morbidity caused by STH infections by regular treatment of high-risk groups (school-aged children, SAC) besides promoting access to basic sanitation and safe water (Figure 2) [28]. In more detail, member states were urged to implement regular **PC** (treatment of at-risk populations without prediagnosis) to reach 75% coverage of SAC in endemic areas by 2010. This goal was not achieved, but success stories were reported from countries where persistent treatment and economic development successfully eliminated STH as a public health problem (e.g., Japan, Taiwan, Korea, Caribbean) [29–31]. However, in countries with a lack of sanitary infrastructure and low educational coverage, elimination is not possible due to high reinfection rates [32] so that PC is still the most effective strategy for reducing the burden and prevalence of STH infections. To increase the success of PC, WHO's recommendations on STH treatment have evolved over time (1987–2017) into defined standards for PC programs providing guidance on treatment doses, frequency, and type depending on STH prevalence (key guidelines from 2002, 2006, 2012, and 2017; Figure 2) [5,33,34,35]. The primary focus was set on SAC only, but the strategy broadened in 2012 by including preschool-aged children (PSAC), and since 2017 all populations at (high) risk are considered [5,34,36]. In the latest guideline, periodic single-drug treatment (annual or biannual) of populations at-risk in endemic areas (PSAC, SAC, women of childbearing age, pregnant women) is recommended irrespective of individual infection state. The goal is to achieve a minimum coverage of 75% of the most affected groups, PSAC and SAC, by 2020 (estimated at 836 million in 2016) to eliminate morbidity caused by mainly moderate and heavy STH infections [4,5]. WHO guidelines on PC planning, implementation and monitoring support health care professionals and managers [5,37]. Infants $<$12 months, breastfeeding and pregnant women (first trimester) (Figure 2) are excluded due to a lack of safety evidence [5]. Additionally, men and the elderly are currently not included in PC programs [5]. Besides PC, there has been wide discussion of **community-based treatment** in which entire populations (not only populations at-risk) in endemic areas are treated to diminish the likelihood of reinfection while reducing the worm burden [38]. Most likely, a higher fraction of low or no infections are treated in the framework of community-based treatment, resulting in increasing drug pressure. Thus, this strategy is preferable only in settings with high hookworm endemicity that show main worm burden reservoirs in adulthood or in settings with low prevalence moving towards elimination. Either way, the question is: is it reasonable to treat entire populations, including uninfected people and people with low-infection intensities who would not profit or who would profit minimally? The eligibility of PC is supported by the good safety profile of anthelmintic drugs, and their low cost, which outweighs the advantages of mass prediagnosis and individual treatment [39,40].

School-based PC is currently most commonly performed in addition to treatment as part of health care programs such as prenatal care, or vaccination campaigns to reach SAC, PSAC,

adversely affect human health. Morbidity from STH infections is usually subtle and a result from chronic infection (for example, anemia, malabsorption, stunted growth) rather than presenting acute life-threatening manifestations, and is proportional to the number of worms infecting an individual. The STH infections that cause morbidity are primarily those of moderate or heavy intensity [5].

Targeted preventive chemotherapy (PC): specific risk groups in the population, defined by age, sex, or other social characteristics such as occupation, are given anthelmintic medicines at regular intervals, irrespective of the individual infection status [5].

Water, sanitation, and hygiene (WASH): intervention approach tackling access to, and use of, water and sanitation facilities, often including a health-education aspect aiming at behavior change.

Years lived with disability (YLDs): years lost due to disability for people living with the health condition or disease.

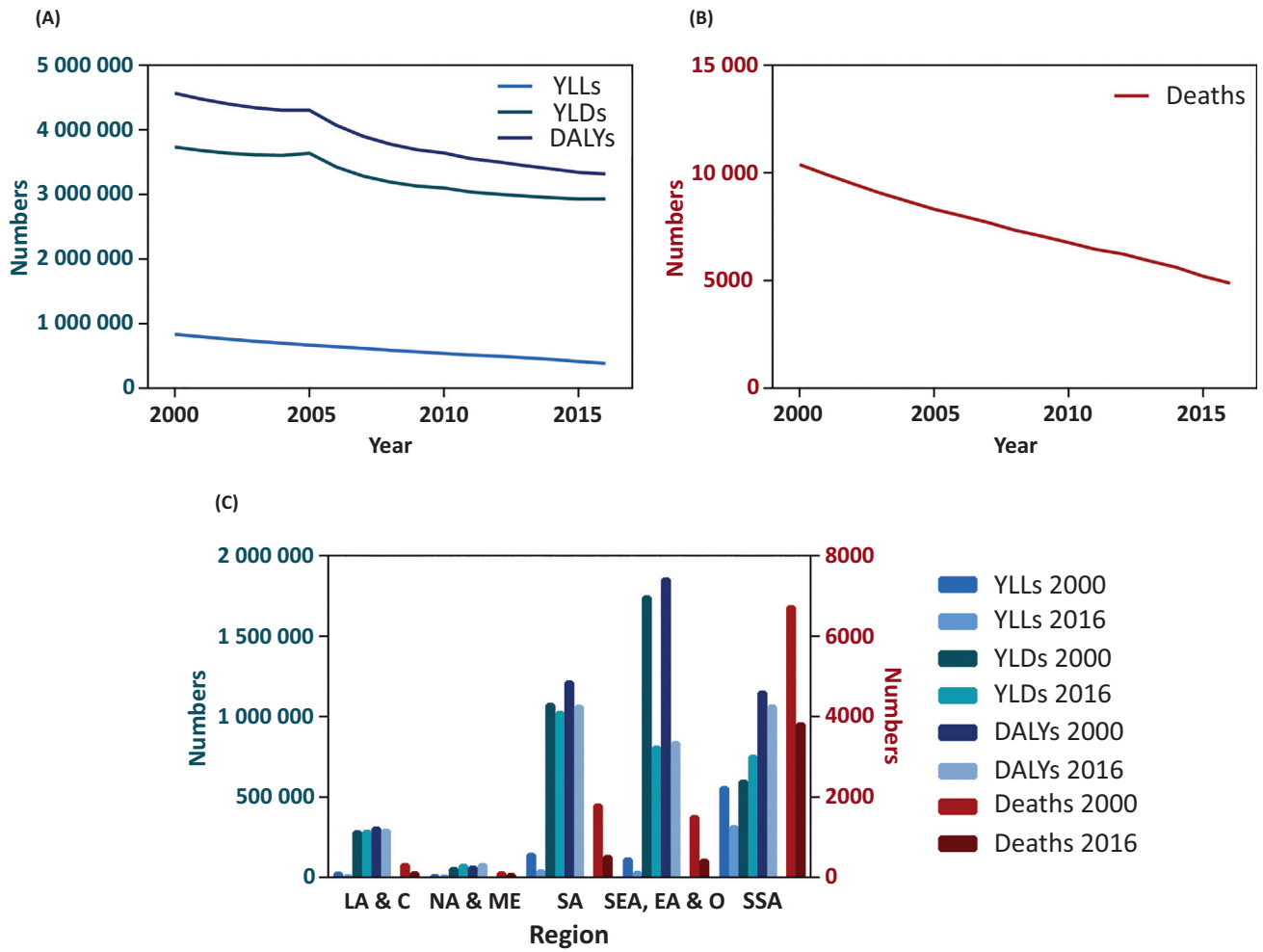


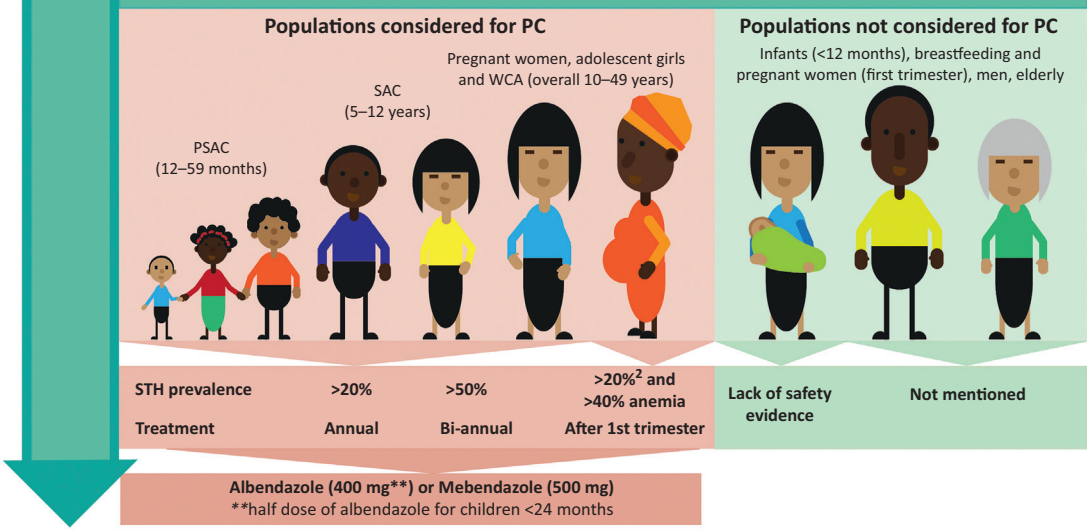
Figure 1. Dynamics of Burden (A) and Mortality (B) due to Soil-Transmitted Helminth (STH) Infections between 2000 and 2016, and by World Region (C) according to the Latest Estimates of the Global Burden of Disease Results Tool [10]. Burden measures: YLLs: years of life lost due to premature mortality; YLDs: years of life lived with any short-term or long-term health loss; DALYs: disability-adjusted life years defined as the sum of YLLs and YLDs. World regions: LA & C, Latin America and Caribbean; NA & ME, North Africa and Middle East; SA, South Asia; SEA, EA & O, Southeast Asia, East Asia, and Oceania, SSA, sub-Saharan Africa.

and women of childbearing age [41]. In 2016, over 50.5 and 68% of affected PSAC and SAC, respectively, were reached with PC, but its continued success strongly depends on the member states' willingness for its implementation in national health programs and by the availability of drugs [4,5]. Systematic realisation of PC was enforced with sustainable drug donations that started in 2006 for STH and increased significantly in 2012 with the London Declaration on NTDs [18,42,43].

Impact of Preventive Chemotherapy – A Controversy

PC aims to decrease the burden of STH by reducing the number of moderate and heavy infections; consequently seeking improved state of health. Monitoring PC to evaluate its success and pitfalls, both globally and nationally, and defining research needs is essential [44]. In the recent past, several meta-analyses and reviews evaluated the impact of STH PC on weight, height, hemoglobin levels, anemia and other health parameters [45–51]. The conclusions of the

Year	Report (title)	Strategy and aims
1987	Prevention and control of intestinal parasitic infections [26]	Ascariasis: individual medical care, community mass treatment and PC for SAC Hookworm infection: standard case management, community mass treatment No recommendation for trichuriasis
1998	Guidelines for the evaluation of STH and schistosomiasis at community level [27]	>50% STH prevalence, ≥ 10% heavy infections: annual community mass treatment 50% STH prevalence, <10% heavy infections: annual PC for PSAC, SAC and WCA <50% STH prevalence, <10% heavy infections: selective treatment
2001	Schistosomiasis and STH infections WHA54.19 [28]	PC in endemic countries aiming for 75% SAC treated until 2010
2002	Prevention and control of schistosomiasis and STH [33]	≥70% STH prevalence or ≥10% h/m infections: 2–3 PC yearly for SAC and * 50–70% STH prevalence and <10% h/m infections: annual PC od SAC and * <50% STH prevalence and <10% h/m infections: selective treatment *systematic treatment of PSAC and WCA
2006	PC in human helminthiasis [34]	20–50% STH prevalence: annual PC of SAC >50% STH prevalence: bi-annual PC of SAC Treatment of other populations[1] when at high-risk
2008	Monitoring anthelmintic efficacy for STH [44]	
2011	Helminth control in SAC [37]	
2012	Eliminating STH as a public health problem in children [35]	2015: PC for 50% of PSAC and SAC,z affected countries have a plan of action 2020: PC for 75% of PSAC and SAC to reduce prevalence of heavy STH below 1%
2012	London declaration on NTDs [42]	Sustainment/expansion of drug access programs, increase of drug donations 2020: morbidity of STH controlled
2012	Accelerating work to overcome the globe impact of NTDs [6]	
2013	Assessing the efficacy of anthelmintic drugs against schistosomiasis and STH [56]	
2017	PC to control STH infections in at-risk population groups [5]	



STH PC guidelines/documents with detailed information on targeted groups, treatment frequency and specified aims
Guidelines/documents primarily focusing on monitoring, planning and implementing STH PC and/or drug efficacy

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analyses differ, even though the approaches were equivalent or similar – starting a controversial discussion about the actual impact of PC [12]. Overall, data show that PC reduces the prevalence of STH, but the mid- and longer-term impact on health outcomes is either unclear or challenging to assess. It might be worth highlighting that STH infections of low intensity are generally asymptomatic, but that moderate to heavy intensities can lead to, for example, intestinal manifestations, malnutrition, impaired growth and physical development [34]. Moreover, the prevalence of moderate and heavy STH infection is lower than that of light infections and depends on the endemicity [12]. Nevertheless, many clinical trials, especially early ones, did not confirm infection intensities, yet these studies are included in most meta-analyses evaluating the impact of PC on morbidity. Since low STH infection intensities do not cause high morbidity, pooling the results of all individuals – and not distinguishing between infection intensities or even infection status – is misleading and might dilute the real effect of PC [52]. Therefore, meta-analyses evaluating the impact of PC should include clinical studies with identified STH intensities, and following WHO's guidelines: for example, trials in which annual or biannual PC is performed with at-risk populations (defined by the prevalence of STH). Studies that are designed differently (e.g., performed in an area with low STH prevalence where WHO does not recommend PC) should be considered as not eligible for the evaluation of the impact on morbidity measures. Moreover, WHO recommends performing PC for 5 years, aiming for a decrease in heavy infection prevalence below 1% [6]. Although it is possible to observe a benefit of treatment at an earlier time point, it is estimated that the full impact of PC can be fully understood only after 5 years with several successful rounds of PC. Here, the outcome is very complex to assess because trials mostly do not have such long follow-up periods, and it would be unethical to include a placebo group in a trial lasting for so long. Conclusively, the impact of PC on the number of moderate/heavy infection rates in well designed studies, and its correlation to morbidity measures, has not been addressed in most of the reviews so far. Moreover, the impact of PC on health outcomes, such as weight gain or anemia, is, in general, multifactorial, and thus complex to evaluate (e.g., coinfection and nutritional status also play major roles). It might be worth highlighting that Marocco and colleagues developed a more accurate approach which focused on the reduction of STH prevalence taking the infection intensities into account [45]. However, the analysis did not evaluate the impact on morbidity measures. Overall, the conflicting findings of the reviews that evaluated the impact of PC underline that methodological methods differ substantially, and that available data are not sufficient to draw a clear conclusion.

Performance of Recommended Treatment

Four drugs are listed on WHO's list of essential medicines to treat STH infections, whereas only two, namely mebendazole and albendazole, are commonly distributed in PC. The remaining two, levamisole and pyrantel pamoate, are less attractive due to lower efficacy, the weight-dependent dosing, and the lack of donation [53]. The efficacy of the two benzimidazoles against STH infections was analysed in three studies in 2017 [5,54,55]. A comparison of the findings is presented in Table 1. Anthelmintic **drug efficacy** is measured qualitatively by **cure rates (CRs)** or quantitatively by **egg-reduction rates** (reduction of egg counts; ERRs). Mrus *et al*. estimated the average ERRs from all as well as only from placebo-controlled studies on mebendazole [54], while WHO calculated the average ERRs of albendazole and mebendazole of epidemiological and clinical studies and in a subgroup, ERRs from studies following the recommended WHO methodology [5,44]. Both studies applied a simple pooling approach to summarise

Figure 2. The Evolution of Preventive Chemotherapy specified by the World Health Organization (WHO) to Control Soil-Transmitted Helminth (STH) Infections. Guidelines of WHO, the World Health Assembly (2001), and the London Declaration (2012) and their treatment targets are illustrated over time. The strategy of 2017 is demonstrated in detail as a cartoon. PC, targeted preventive chemotherapy; STH, soil-transmitted helminths/helminthiasis; SAC, school-aged children; PSAC, preschool-aged children; WCA, women of childbearing age (15–49 years); NTDs, neglected tropical diseases. h/m infections: heavy/moderate infections [1]PSAC, WCA, lactating, pregnant women (after 1st trimester) and adults at high risk (e.g., tea pickers). [2]Accounts only for hookworm and *Trichuris trichiura*.

Table 1. Comparison of Albendazole and Mebendazole Egg-Reduction Rate (ERR) Estimates [%]

	Mrus 2017 [54]		Moser 2017 [55]	WHO 2017 [5]	
	All studies	Placebo- controlled		All studies	WHO methodology
Ascaris lumbricoides					
Albendazole			98.5	98.7	99.9
Mebendazole	97.9	98.1	98.0	98.3	97.6
Hookworm					
Albendazole			89.6	89.8	92.4
Mebendazole	72.0	61.2	61.0	68.2	76.5
Trichuris trichiura					
Albendazole			49.9	60.7	64.4
Mebendazole	72.5	86.8	66.0	69.0	69.3

the ERRs regardless of whether geometric or arithmetic mean was provided without any precision estimates [5,54,56]. On the contrary, Moser *et al*. applied a network meta-analysis, considered the measure of central tendency for estimating the ERRs (i.e., arithmetic, geometric, or unknown) and presented precision estimates for the CRs and ERRs [55].

Similar high ERRs were estimated for mebendazole and albendazole treating *A. lumbricoides* infections (>98%, Table 1) [54–56]. The reported ERRs of mebendazole against hookworm vary (61–77%) and are 7–16% higher in the WHO report, depending on the included studies. On the contrary, ERRs of albendazole treatment against hookworm were estimated similarly (~90%). The opposite trend was observed for *T. trichiura,* where the estimates for mebendazole revealed similar ERRs (~70%), but the efficacy of albendazole varied (50–64%). Here, the WHO analysis reported an almost 10–15% higher efficacy compared to the low ERR of 50% estimated by Moser *et al*. [55]. Regarding the deviation of ERRs, the advanced statistical methods applied by Moser and colleagues might have led to more credible estimates compared to the statistically weaker method used for the analysis by Mrus *et al*. and WHO.

Reference efficacy data for albendazole and mebendazole was published by WHO in 2013 [56]. The reference threshold was identified at >95% ERR for both drugs against *A. lumbricoides*, 90 and 70% ERR for albendazole and mebendazole, respectively, against hookworm, and >50% ERR for both drugs against *T. trichiura* [56–58]. Thus, the conclusion of WHO that ERRs of the drugs are well above the reference threshold [5,56] should be taken with caution; for example the ERRs of albendazole against *T. trichiura* are considerably lower following the more rigorous analysis by Moser *et al*. Moreover, CR estimates are not available from WHO, but mebendazole's CRs were analysed by the remaining two groups with, again, varying results [*A. lumbricoides* (96 and 93%), hookworm (33 and 26%), and *T. trichiura* (42 and 28%)] [54,55].

A single meta-analysis recently evaluated the efficacy of levamisole and pyrantel pamoate on STH [55]. While both drugs show high CRs (>93%) and ERRs (>94%) against *A. lumbricoides*, lower CRs (10 and 50%, respectively) and ERRs (62 and 72%, respectively) were determined for hookworm and *T. trichiura* (CRs <30%, ERRs 28 and 48%, respectively).

Alternative Anthelmintics

Despite the depleted anthelmintic drug pipeline, a few drugs marketed for other diseases have been tested in humans for their anthelmintic activity; this could complement the small drug

armamentarium for STH infections. Ivermectin is a broad-spectrum antiparasitic drug which is marketed for the treatment of onchocerciasis; in combination with albendazole, it is in use against lymphatic filariasis. Several trials evaluated ivermectin's efficacy against STH in children (≥5 years, 200 μg/kg) and reported high CRs (94–100%) and ERRs (94–100%) against *A. lumbricoides*, but only low to moderate CRs (2.4–44%) and ERRs (54–87%) against *T. trichiura* [59–62]. Only one of the trials included hookworm-infected patients; it revealed a CR of 65% [62]. Additionally, a clinical study was performed with pregnant women infected with hookworm, in which ivermectin resulted in a CR of 29% [63]. Wimmersberger *et al*. recently performed a dose-finding study in two populations, SAC and PSAC. Unfortunately, the highest doses tested (600 and 200 μg/kg, respectively) did not lead to attractive efficacy against *T. trichiura* (CRs <21% and ERRs <79%), with results similar to the placebo arms [60]. Additional studies with ivermectin have been performed in STH-infected adults but their results are not discussed here due to the low number of included participants (≤18) [64,65].

In 2004, tribendimidine was approved for use in human medicine in China for treating STH and *Enterobius vermicularis* infections, and its clinical data were thoroughly reviewed by Xiao *et al*. in 2013 [66]. Tribendimidine is believed to act as a prodrug as it rapidly breaks down into the active deacylated amidantel (dADT), which is further metabolised to acetylated dADT [66]. The review presents high CRs and ERRs against *A. lumbricoides* (>90 and >99%, respectively), moderate efficacy against hookworm (52–89% and >94%, respectively), and variable CRs for *T. trichiura* (24–77%). Only a sole randomised, controlled trial was published to date on the efficacy of tribendimidine outside of Asia. In this study, in two African settings, CRs of 99, 54, and 8%, and ERRs of 99, 97, and 53% were documented for *A. lumbricoides*, hookworm, and *T. trichiura,* respectively [67]. An extensive development program has been initiated to support a successful registration at the Food and Drug Administration (FDA) in the USA.

Oxantel pamoate is an old anthelmintic [68,69] which is not marketed any longer. Recent randomised, controlled trials revealed low CRs (<33%) against *A. lumbricoides* and hookworm, but a comparably moderate CR against *T. trichiura* (26–50%) [70,71]. ERRs ranged from 93 to 98% against *T. trichiura.* A dose-finding study further evaluated 25 mg/kg as the most effective dose for treating *T. trichiura*, and suggested a weight-independent dose of 500 mg for children of the age range 7–14 years [70].

Another veterinary drug that was tested for its anthelmintic activity in humans is moxidectin. A dose of 8 mg was administered to 118 adolescents (12–18 years) in a randomised, controlled trial conducted recently on Pemba island; it yielded CRs of 75, 34, and 14%, and ERRs of 99.9%, 87, and 83% against *A. lumbricoides,* hookworm, and *T. trichiura,* respectively [72]. Moxidectin will soon be registered as a treatment against onchocerciasis and should be further evaluated as a potential treatment for STH.

Obviously, the ideal drug candidate would reveal high activity against all STH species, but remains to be discovered and developed. The anthelmintic drug-discovery pipeline is depleted, with only a handful of compounds currently under investigation (e.g., emodepside, oxfendazole, and CRY5B); however, their efficacy profiles against human STH remain unknown [73–77]. Alternative treatment options include drugs with high activity against hookworm or *A. lumbricoides* but acting with a different mode of action (e.g., tribendimdine). Additionally, drugs with higher efficacy against *T. trichiura* than the available drugs are of high interest as long as they can be safely coadministered with drugs against other STHs. Promising efficacy against *T. trichiura* has been so far only reported for oxantel pamoate, which is no longer produced by the pharmaceutical industry [70,78,79]. Unfortunately, the barriers to introduce or reintroduce

human anthelmintics to the market are high due to high costs and nonprofitability (drugs have to be donated) [80]. Here, strong collaborations between pharmaceutical companies, organizations (WHO and others), research institutions, states, and funding authorities will help to overcome these barriers.

In STH PC guidelines, as described above, so far only single-dose and single-drug administration is considered. On the other hand, in nonendemic countries, individual treatment following diagnosis often includes treatment over several days. However, it is worth stressing that PC in endemic countries currently aims for STH burden reduction, whereas individual treatment targets full cure. Additionally, the single-drug/dose treatment strategy is most feasible regarding costs and logistics in PC programs. Nonetheless, improved treatment regimens – including drug combinations to yield higher drug efficacy – have recently gained importance for treating STH infections. Numerous drug combinations have been tested in clinical settings for treating STH infections [67,71,78,81]. Moreover, in 2017, albendazole–ivermectin was added to the list of essential medicines by WHO for the treatment of STH infections, but this combination has not yet been integrated into PC guidelines [82,83].

Resistance

Anthelmintic drug resistance is of major concern in human medicine since its wide occurrence in the veterinary field [84–87]. Resistance can develop due to a variety of circumstances such as the use of single-drug regimens, under-dosing, or mass treatment within the context of small refugia. Indeed, the upscaling of PC for STH infections, and the availability of few drugs, raises the likelihood that drug resistance will develop. So far, well established resistance markers for human STH infections do not exist, as, to date, no phenotypic benzimidazole-resistant human STH strain has been identified. In veterinary medicine, benzimidazole resistance in *Haemonchus contortus* was associated with a single nucleotide polymorphism (SNP) in the β-tubulin gene at each of three positions (i.e., codons 200, 167, and 198) [88]. Studies investigating the same SNPs in human STHs reported the finding of a single SNP in each STH species [89,90]. After treatment with albendazole an increased frequency of codon 200 SNPs in *T. trichiura* was observed, but no association with reduced efficacy could be confirmed [91]. In-depth studies have to be launched using next-generation sequencing technologies to reliably identify resistance – which might be multifactorial rather than caused by only a single SNP. Therefore, currently, only the change in efficacy (ERRs) can help to estimate the development of drug resistance. As mentioned earlier, reference ERRs for the benzimidazoles were published by WHO in 2013; these were based on two multicountry studies, and are presented in Table 2 [55–58,87]. The comparison of efficacy estimates (ERRs) for 1995 and 2015, put forth by the meta-analysis of Moser *et al.*, illustrate that neither albendazole nor mebendazole have changed significantly and are almost equal, or above, the reference level for treating *A. lumbricoides* (Table 2) [55]. The ERRs against hookworm indicated a significant decrease over time (albendazole: 95–77%, mebendazole: 69–52%) and are now below WHO's reference value (90 and 70%, respectively). For *T. trichiura*, the albendazole estimates dropped from 73 to 43%, and are thus below the reference threshold of ≥50%, while mebendazole decreased from 91 to 55%.

This analysis gives an overview of the drugs' efficacy development over time, but accounts for only their overall efficacy and not individual impact, which could differ depending on location and population. Generally, results need to be interpreted with caution as study design and quality, baseline infection intensity, or length of follow-up period differ between trials, possibly leading to confounded results. Thus, the change in ERRs cannot serve as an absolute indicator

Table 2. Development of Efficacy of Albendazole and Mebendazole over Time, Showing Egg-Reduction Rate (ERR) and 95%-CI

	Albendazole		Mebendazole	
	ERR [%]	95%-CI [%]	ERR [%]	95%-CI [%]
A. lumbricoides				
WHO reference efficacy[a]		≥ 95		≥95
1995[b]	99.5	94.7–100	99.7	93.3–100
2015[b]	95.4	88.2–100	94.8	87.3–100
Hookworm				
WHO reference efficacy[a]		≥90		≥70
1995[b]	95.6	85.3–100	69.4	54.3–84.6
2015[b]	77.1	62.5–91.7	51.8	35.3–68.2
Trichuris trichiura				
WHO reference efficacy[a]		≥50		≥50
1995[b]	72.6	53.7–91.5	91.4	72.9–100
2015[b]	43.4	23.5–63.3	54.7	34.6–74.8

[a][56].
[b][55].

for drug resistance, but new tools need to be developed for this purpose. However, WHO might consider a refinement of their reference ERRs.

Concluding Remarks

Global burden estimates of STH infections steadily decreased due to the upscaling of helminth-control efforts – particularly through PC in combination with WASH and educational interventions. The importance of PC programs is greatest in countries with low hygiene and unsatisfactory educational coverage. Monitoring PC is essential, but its impact should be evaluated primarily by the decrease in moderate and heavy infections, which cause the highest disease burden (see Outstanding Questions). In addition, it is important to assess the effect of PC on health outcomes – such as weight gain or improved physical and cognitive development – but here, multiple confounding factors must be considered, such as coinfections and poor dietary intake. Control programs are limited by the number of available drugs. Only four drugs are recommended for STH infections, of which only two are widely used, resulting in high drug pressure. These drugs are characterised by insufficient efficacy, particularly against *T. trichiura.* Therefore, drug-screening efforts should be strengthened to identify alternative broad-spectrum anthelmintic drug candidates. In parallel, a review of oxantel pamoate's dossier and subsequent preclinical and clinical studies should be launched with the ultimate goal of approving the drug by a stringent authority as the drug exhibits by far the highest efficacy against *T. trichiura*. In the meantime, drug combinations should be further evaluated for potentially enhanced efficacy. Finally, in-depth research on the mode of action of existing drugs and pharmacokinetic/pharmacodynamic relationships in humans, as well as on their resistance mechanism, is necessary to fill knowledge gaps helping to fight STH infections.

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Outstanding Questions

Are the available anthelmintic drugs, albendazole and mebendazole, able to reduce moderate and heavy STH infections to a level below 1% by 2020 and ultimately achieve elimination? Or do we need alternative anthelmintics or drug combinations?

Is PC sufficient to reach this goal by 2020, or is its combination with alternative strategies (e.g., improved sanitation, hygiene, health education) the only way to eliminate STH infections as a public health problem? If the goal is reached, how can we proceed to eliminate STH infections?

What are the correct indicators to measure the impact of PC? How can we appropriately assess the short- or long-term morbidity associated with STH infections? How can STH-related morbidity be adequately evaluated to correctly estimate the disability-adjusted life years?

How can we foster research and development on novel anthelmintic drugs? How can the development and approval of oxantel pamoate at a stringent regulatory authority be promoted so that the drug can be used widely in PC programs? Is the combination of two or more drugs – with different efficacy profiles and modes of action – the most efficient option for treating STH infections?

Anthelmintic drug resistance is a well known problem in veterinary medicine; will it also become an issue for human STH control? What is benzimidazole's mode of action in human STH infections, and how does anthelmintic drug resistance develop? Are SNPs responsible for resistance, or is resistance rather multifactorial? Which resistance markers could be used to prove the existence of, and monitor, anthelmintic drug resistance?

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