



OPEN LETTER

REVISED **Insights from quantitative analysis and mathematical modelling on the proposed WHO 2030 goals for soil-transmitted helminths [version 2; peer review: 2 approved]**

NTD Modelling Consortium discussion group on soil-transmitted helminths

v2 **First published:** 23 Oct 2019, 3:1632 (<https://doi.org/10.12688/gatesopenres.13077.1>)**Latest published:** 04 Dec 2019, 3:1632 (<https://doi.org/10.12688/gatesopenres.13077.2>)**Abstract**

Soil-transmitted helminths (STHs) are a group of parasitic worms that infect humans, causing a wide spectrum of disease, notably anaemia, growth retardation, and delayed cognitive development. The three main STHs are *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm (*Necator americanus* and *Ancylostoma duodenale*). Approximately 1.5 billion people are infected with STHs worldwide. The World Health Organization goal for 2030 is morbidity control, defined as reaching <2% prevalence of medium-to-high intensity infections in preschool-age children and school-age children (SAC). Treatment guidelines for achieving this goal have been recommended. The Neglected Tropical Diseases Modelling Consortium has developed mathematical and statistical models to quantify, predict, and evaluate the impact of control measures on STHs. These models show that the morbidity target can be achieved following current guidelines in moderate prevalence settings (20-50% in SAC). In high prevalence settings, semi-annual preventive chemotherapy (PC) ideally including adults, or at least women of reproductive age, is required. For *T. trichiura*, dual therapy with albendazole and ivermectin is required. In general, stopping PC is not possible without infection resurgence, unless effective measures for improved access to water, hygiene, and sanitation have been implemented, or elimination of transmission has been achieved. Current diagnostic methods are based on egg counts in stool samples, but these are known to have poor sensitivity at low prevalence levels. A target threshold for novel, more sensitive diagnostics should be defined relative to currently preferred diagnostics (Kato-Katz). Our analyses identify the extent of systematic non-access to treatment and the individual patterns of compliance over multiple rounds of treatment as the biggest unknowns and the main impediment to reaching the target. Moreover, the link between morbidity and infection intensity has not been fully elucidated. By providing more insights on all the above, we aim to inform discussions on the goals and treatment guidelines for STHs.

Keywords

Soil-transmitted helminths, WHO guidelines, morbidity control, NTD Modelling

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REVISED Amendments from Version 1

Minor edits were made to clarify the following issues highlighted by Reviewer 2:

- 1) Achieving 75% community-wide treatment is especially important to reach the morbidity target for hookworm.
- 2) Elimination of transmission can be reached in low-transmission settings. The study on which this insight is based used the basic reproductive number as a measure of transmission intensity, not prevalence.
- 3) All simulation studies have been run for the different STH species (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm species). Insights are, therefore, species-specific.
- 4) The results and conclusion with regard to the importance of WASH are based on simulations for the impact of sanitation and hygiene measures in isolation and in combination.

Any further responses from the reviewers can be found at the end of the article

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Background

Soil-transmitted helminth (STH) infections are caused by several species of parasitic worms that are transmitted by eggs present in human faeces, which contaminate the soil in areas with poor sanitation. STHs cause some of the most common infections, with about 1.5 billion people infected worldwide¹.

The three main STHs are roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and hookworm (*Necator americanus* and *Ancylostoma duodenale*). STHs reduce the nutritional status of infected individuals¹. In particular, infected children can be affected by reduced physical fitness and impaired growth and cognitive development¹. Hookworm infection in women of reproductive age (WRA) can lead to severe anaemia¹. Infections with *A. lumbricoides* and hookworms can be treated effectively with benzimidazole drugs (albendazole, mebendazole). However, benzimidazoles are less effective against *T. trichiura*. Dual treatment with albendazole and ivermectin increases treatment efficacy for *T. trichiura*²⁻⁴. Currently, albendazole and mebendazole are donated to the World Health Organization (WHO) for distribution to affected populations.

The WHO has announced morbidity control as the main public health target for STHs to be achieved by 2030. According to the most recent WHO guidelines, morbidity control is defined as <2% prevalence of medium-to-high intensity (M&HI) infections in preschool-age children (preSAC) and school-age children (SAC). WHO treatment guidelines advise preventive chemotherapy (PC) by mass drug administration (MDA) to achieve morbidity control. Previously, WHO recommended school-based PC without including adults. The most recent guidelines recommend PC targeted at preSAC, SAC and WRA. The frequency of PC is based on the prevalence of STH infections in SAC prior to the start of treatment (see decision tree in Figure 1 for WHO guidelines up until 2019). The recommended PC coverage is 75% in all targeted populations.

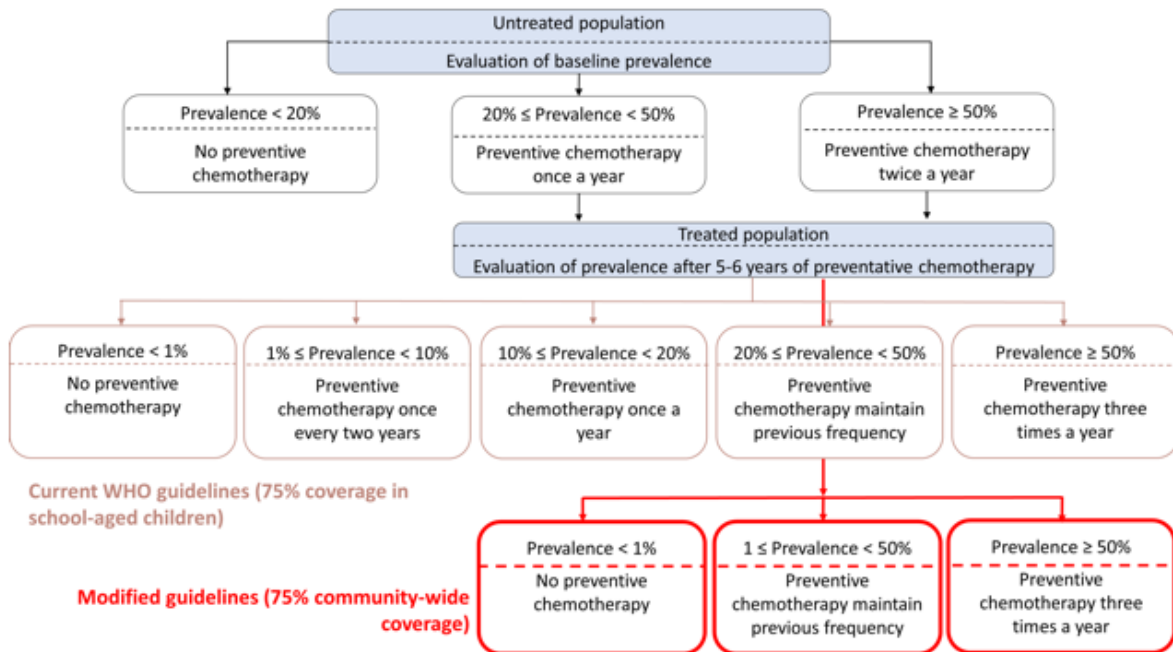


Figure 1. World Health Organization (WHO) decision tree showing the current WHO guidelines to achieve morbidity control in school-aged children (SAC) using 75% coverage in SAC (black and orange boxes). The bright red boxes represent the modified guidelines assuming 75% community-wide coverage (pre-SAC, SAC, and adults) to replace the middle row of boxes that represent the current guidelines. This figure has been adapted from Figure 1 in 5 under a CC-BY 4.0 license.

Mathematical models of STH transmission dynamics and the impact of interventions have been developed to evaluate optimal treatment strategies for achieving the WHO goals. The Neglected Tropical Diseases Modelling Consortium (NTDmc) funded by the Bill and Melinda Gates Foundation brings together research groups from multiple scientific institutions working on neglected tropical diseases (NTDs), including STHs. Modelling groups based at Erasmus Medical Center (EMC) in Rotterdam and Imperial College London (ICL) have led the recent work on STHs. A model comparison was carried out for the EMC and ICL STH models⁶. Moreover, joint papers evaluating WHO treatment guidelines and monitoring and evaluation strategies have been published^{5,7}. Predictions have been made for each STH species to account for inter-species variability. In these predictions it is important to note that models predict true prevalence while surveillance data make predictions that are sensitive to the diagnostic method employed. The predictions of both models are largely comparable, although the EMC model is more optimistic about the additional impact of community-wide vs. targeted (pre-SAC, SAC and WRA) deworming, which can be readily explained by differences in assumptions about how rates at which individuals contaminate the environment vary with age.

The WHO has proposed new goals for NTDs, including new control targets for STHs in the year 2030. Using insights from recent modelling work we discuss the feasibility of reaching the morbidity target following current guidelines and the risks that need to be mitigated to maintain the target (summary in Table 1).

Insights from modelling: Lessons from the past 10 years for the next 10 years

Our modeling and epidemiological data analyses have shown that the current WHO treatment guidelines are sufficient to

achieve the 2020 morbidity target in settings where the prevalence was moderate (20% to 50% in SAC) prior to the start of PC⁵. For higher prevalence settings, community-wide PC and/or targeting of WRA will be necessary to achieve the morbidity target, especially for hookworm^{5,8}, and/or dual therapy with albendazole and ivermectin for *T. trichiura*^{5,9}. Implementing PC twice-yearly also increases chance to achieve the morbidity target for STH⁵. Scaling down or stopping PC as per WHO treatment guidelines is very likely to lead to resurgence of infection to levels above the morbidity target, unless transmission conditions are addressed with water, sanitation and hygiene (WASH)¹⁰ or elimination of transmission (EOT) is achieved⁵. If this is not feasible, PC needs to be sustained¹⁰. Impact assessments potentially need to be repeated at regular intervals. Accurate measurements of access and compliance to PC remain essential to evaluate and sustain achievement of the targets. It is also important to note the poor sensitivity of Kato-Katz at low prevalence (models predict true prevalence).

Practical implications of the proposed goals

Measuring the target

Geospatial analyses of recent large-scale epidemiological studies of STH prevalence¹¹ show that prevalence heterogeneity is considerable within PC implementation units. Our simulations suggest that to evaluate PC impact, a sufficient number of villages should be sampled in each implementation unit⁷ for an accurate assessment of the prevalence (number of villages depending on geospatial variation).

The indicator for the morbidity target will be measured with Kato-Katz (or any other validated quantitative technique). However, the number of slides/samples used strongly affects the measured prevalence^{12,13}. PCR methods, although expensive at present, are a much more sensitive diagnostic at low prevalence.

Table 1. Summary of modelling insights and challenges for reaching the WHO 2030 goal for soil-transmitted helminths.

Current WHO Goal (2020)	Morbidity control: <1% prevalence of M&HI infections in preSAC and SAC
Proposed new WHO Goal (2030)	Morbidity control: <2% prevalence of M&HI infections in preSAC and SAC
Is the new target technically feasible under the current disease strategy?	Yes, in moderate prevalence settings (20–50% in SAC) in the absence of systematic non-access to treatment. For highly endemic settings (prevalence ≥50%), semi-annual PC, including adults or at least WRA (hookworm), and/or dual PC (<i>Trichuris</i>) are required. A lot depends on the diagnostic used and these targets may have to be revised if the employment of PCR methods reveals much higher levels of infection.
Are current tools able to reliably measure the target?	Yes, although there is a need to test and identify the optimal design for surveys based on Kato-Katz (how many stool samples per person, how many slides per sample) and PCR for the specific purpose of evaluating the target and intermediate markers of progress (which are based on prevalence of any infection instead of M&HI).
What are the biggest unknowns?	Levels of systematic non-access or non-compliance to treatment and its impact on achievement of the target; the link between morbidity and present and past cumulated infection intensity and how the current parasitological target translates to actual morbidity levels; epidemiological situation in settings with pre-control prevalences <20% (meaning no implementation of PC) as PC in other areas continues.
What are the biggest risks?	Systematic non-access and non-compliance to treatment, low coverage and resurgence after reducing treatment frequency, lack of community-wide treatment, especially when hookworm is the dominant infection if the intrinsic transmission potential is high.

WHO, World Health Organization; M&HI, medium-to-high intensity; preSAC, preschool-age children; SAC, school-age children; PC, preventative chemotherapy; WRA, women of reproductive age; PCR, polymerase chain reaction.

The indicator threshold would be more meaningful if linked to a standardized diagnostic procedure, or to the true prevalence of infection from which thresholds for specific diagnostic procedures and sampling designs can be derived.

Current egg counting methods suffer from considerable measurement error, which is compounded by high variation in egg density between and within persons over time^{13–15}, meaning that an observed prevalence of M&HI can be well above the 2% target by chance. This is further compounded by an increase in inter-individual variation in egg counts as infection prevalence goes down during PC (likely due to systematic non-access to PC). Further, modelling suggests that “prevalence of any infection in preSAC and SAC” combined with a higher target threshold is a more informative indicator (higher positive predictive value) for meeting the morbidity target and would require a smaller sample size because of a higher statistical power⁷.

Timeline to achieve the target

The 2030 morbidity target will be achievable in some countries. The frequency and duration of PC and implied resources depend on baseline prevalence and achieved coverage plus patterns of individual compliance to treatment⁵.

Technical feasibility

Treatment guidelines will lead to the achievement of the target in some communities, but not in all⁵. Current WHO guidelines do not call for treatment in low prevalence settings (<20%). However, these areas may still have a prevalence of M&HI >2% in preSAC, SAC and WRA¹⁴. In addition, epidemiological data from the Tumikia study suggest that with lower prevalence, the prevalence of M&HI is relatively higher due to increasing aggregation of parasites as MDA coverage rises, likely due to a small proportion of persistent non-compliers to treatment. A revision of the 20% threshold downwards seems desirable.

WHO guidelines for moderate-prevalence settings suggest annual PC of young children, preSAC, SAC and WRA. This may be sufficient to reach the morbidity target for settings where coverage is sufficiently high (75%) in the absence of systematic non-compliance to treatment.

For high-prevalence settings (>50%), WHO guidelines suggest semiannual treatment. Here the morbidity target is less likely to be achieved following current guidelines, especially for hookworm and *T. trichiura*. As the main burden of hookworm infection lies in adults, the morbidity targets will only be reached when also treating adults as a whole⁵, not just WRA⁸. Control of *T. trichiura* will require community-wide treatment with albendazole³ or dual treatment with ivermectin and a benzimidazole^{3,5}. If systematic non-access to treatment remains high, meeting the target may not be feasible⁸.

Operational feasibility

Reaching the milestone in 2030 will require community-wide coverage and/or targeting of WRA (especially for hookworm),

with low systematic non-access/non-compliance to PC and little coverage heterogeneity within PC implementation units. Modelling suggests that the timeline for achieving the target is expected to be longer if there is re-importation of disease, e.g. by migration for areas with low or no treatment coverage¹⁶. Meeting the target may require coordination of national STH programmes at country borders due to human movement.

Ability to sustain achievement of the goal

After stopping or scaling down treatment (which is an option in the current WHO guidelines, see Figure 1), infection levels are likely to bounce back within one to two years¹⁷. Thus, it may not be possible to decrease the number of required tablets as proposed as a new WHO target^{5,8}. This is further complicated by population growth between now and 2030, which could necessitate a further increase in the number of treatments required for pre-SAC and SAC. See Figure 1 for an alternative decision-tree based on recent modelling.

Our analyses suggest that uptake of effective WASH is needed to sustain the gains made by PC in the longer term¹⁰. If EOT is not achieved and PC is stopped or scaled down in the absence of effective WASH, the probability of resurgence is very high⁹. In the absence of effective WASH interventions, the sustainability of the morbidity targets is undermined by human population movement unless PC is continued indefinitely¹⁶.

Considerations of cost

Child-targeted treatment for hookworm is cost-effective at reducing morbidity in children, even in high-transmission settings^{18,19}. Community-wide treatment is predicted to be more cost-effective in the longer term with respect to the overall morbidity case-years prevented than child-targeted treatment, as the main hookworm disease burden lies in adults^{18,19}. Annual co-administration of albendazole/mebendazole with ivermectin is predicted to be more cost-effective than semi-annual albendazole/mebendazole treatment for reducing the prevalence of heavy *T. trichiura* infections in SAC⁹. In general, achieving high coverage and good individual compliance in annual treatment rounds may be more cost-effective than treating twice a year with lower coverage.

Risks that need to be mitigated to achieve the stated goals

Population movement can re-import infection into a geographical area that has previously reached morbidity control or EOT. Measures to mitigate this risk include aiming for evenly high coverage across implementation units and co-ordination of programmes across country borders¹⁶.

Systematic non-access and non-compliance to treatment in repeated rounds of MDA and predisposition to heavy infection will create a pool of individuals with high infection burden that can re-infect others^{8,10,20–24}. Increasing access as well as coverage will be important for achieving the 2030 targets^{22,23}.

Reducing frequency of treatment, as proposed in WHO guidelines²⁵ and the new goal for 2030 of reducing the number of tablets required for treating STHs, in the absence of EOT and/or effective WASH measures (including both measures reducing contamination and measures reducing exposure to infection) can lead to rapid resurgence of infection prevalences to pre-treatment levels^{5,10,26–28}. See [Figure 1](#) for an alternative decision-tree based on recent model-based analyses.

Discussion

The morbidity target is defined in terms of the prevalence of M&HI. However, infection intensity does not necessarily reflect morbidity accurately, as light infections can be associated with non-negligible morbidity and the severity of symptoms associated with M&HI is highly variable²⁹. Furthermore, current diagnostic tools have poor sensitivity at low prevalence levels. Defining targets depending on the diagnostic used seems desirable in future policy formulation.

Transmission dynamic models with parameters estimated from cross-sectional and longitudinal epidemiological data show that technically EOT is feasible for STH in some settings. It is predicted that EOT can be achieved in low-transmission settings where *A. lumbricoides* or *T. trichiura* are the dominant parasites by annual treatment of SAC, assuming 80% effective coverage and random compliance at each round of treatment³⁰. Where EOT is feasible, it may be more cost-effective than continuous morbidity control, provided no re-importation occurs¹⁹. In high transmission settings, community-wide treatment is predicted to be more effective (especially for hookworm) and more cost-effective.

Another new WHO goal for 2030 is control of strongyloidiasis. This requires ivermectin treatment, which would particularly benefit areas with high prevalence of *T. trichiura*. Currently, for policy assessments there is only epidemiological data on *Strongyloides stercoralis*^{31,32} but no model-based predictions. As for the other STH, models will provide useful insights for policy formulation.

Future work

Future work that the NTDmc can contribute in support of the design and achievement of the WHO 2030 goals will focus on: 1) an analysis of the value of different diagnostic methods and sampling strategies on M&E of STH morbidity targets and predicting the probability of EOT; 2) understanding the role of spatial heterogeneity in prevalence and coverage and human population movement on STH control programmes; 3) investigating the risk of emergence of drug resistance as well as whether and how monitoring of drug efficacy may help, 4) quantifying the link between infection intensity and morbidity; and 5) assessing the importance of different patterns of individual compliance to treatment to achieving the WHO targets as data becomes available from large-scale epidemiological studies and trials. Other proposed topics for future work include the impact of discontinuation of lymphatic filariasis programmes on STH, infection models encapsulating molecular epidemiology data of who infects whom, defining threshold values for when systematic non-access and non-compliance causes failure to achieve WHO targets, and development of transmission models for *Strongyloides stercoralis*.

Data availability

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The proposed World Health Organization (WHO) 2030 Roadmap goal of morbidity control for soil-transmitted helminths (STH) is defined as reaching <2% prevalence of moderate-to-heavy intensity infections (MHII) in preschool (PSAC) and school age children (SAC). In this manuscript, the NTD Modelling Consortium discussion group on STH provide a summary of insights from mathematical and statistical models into whether this goal is feasible to achieve, and to evaluate the optimal treatment strategies to reach it. In summary, based on two separate but comparable predictive models, the authors determine that the 2030 morbidity target could be achieved using current treatment guidelines in moderate settings (being those with 20-50% prevalence in SAC). Higher prevalence settings are deemed likely to require semi-annual preventive chemotherapy, ideally by including adults (or at least women of reproductive age, WRA), and combined albendazole-ivermectin against *Trichuris trichiura*. To prevent resurgence, preventive chemotherapy needs to be sustained, unless there are effective measures to improve access to water, sanitation and hygiene (WASH), or unless elimination of transmission (EOT) has been achieved. A target threshold for novel, sensitive diagnostic tests is required. The biggest unknowns, and greatest impediments to the target, are deemed to be systematic non-access to treatment and individual compliance over multiple rounds of mass drug administration (MDA). The authors recommend changes to the WHO decision trees, assuming 75% community-wide coverage.

Gaining this level of insight from the NTD Modelling Consortium is very useful and the article itself is well constructed. However, by modelling what would be required to reach the proposed 2030 goal, the authors highlight some key anomalies between the 2030 goal and the current international landscape. The first is that although WRA are not explicitly included in the goal definition, actions to achieve the goal for PSAC and SAC will require treatment of WRA, if not all adults, in certain high prevalence settings. There remains insufficient evidence at this time, particularly on cost-effectiveness, to scale up treatment of the WRA cohort via MDA campaigns. Further, in Figure 1, the authors suggest modified guidelines that assume 75% community-wide coverage. Achieving and sustaining 75% full community coverage would be very hard, and this is neither seen as particularly scalable nor necessary for a morbidity-control goal. WHO guidance is recommended to at-risk (targeted) populations and they stop short of recommending full community treatments. As is known, drug donations and/or implementation advice to reach expanded cohorts are not provided, and examples of programmatic expansion are rare. Is the authors'

recommendation of 75% community-wide coverage applicable to all settings, or has this extended beyond what is required for the current morbidity control goal?

The authors are kindly requested to elucidate further on the statement (Discussion) that “it is predicted that EOT can be achieved in low-transmission settings where *Ascaris lumbricoides* or *T. trichiura* are the dominant parasites by annual treatment of SAC”. If this is the case, but this manuscript has investigated achieving the goal for scenarios above 20%, it seems unlikely that EOT would enter into consideration and thus, preventive chemotherapy would have to continue. The STH morbidity control goal is to eliminate heavy burden of disease, not eliminate a parasite. Whilst, biologically, EOT is feasible, this is not yet considered the best use of sparse resources, and it is an investment with a number of unknown factors that most countries would be inadequately prepared for.

If neither WASH access nor EOT are feasible, then preventive chemotherapy needs to be sustained. This recommendation for indefinite preventive chemotherapy warrants further projections, for example to a second impact assessment, to determine for how long this may need to be the case. Potentially there could be recommendations for a second assessment layer to the decision trees (e.g., hypothetically after 10 years of MDA). For many countries, reaching the point of a second impact assessment will be reached within the 2020-2030 time period.

The authors recommend co-administered albendazole-ivermectin against *T. trichiura*, and also community-wide treatment when hookworm is the dominant infection. This differentiation of some of the STH is welcomed, but WHO guidelines are for undifferentiated STH. Can the authors please advise what level of *T. trichiura* prevalence/intensity would be the recommended ‘trigger’ for co-administration? What level of hookworm prevalence/intensity would be the trigger for risk mitigation activities such as expanding treatments to additional cohorts? Were helminth-specific cutpoints considered in the modelling to arrive at the optimum treatment requirements? If not, is there intent to research this further, with the aim of providing additional advice for implementation considerations? Similarly, can the authors please indicate what aspects of “effective WASH” were modelled – was this access to a latrine, access to a water source, combined interventions, etc?

What is concerning is that the insights from the NTD Modelling Consortium highlight that this new Roadmap goal will require more investment, and more drugs, for STH, but donations for both are likely to decrease. The clarion call from this manuscript is that unless there is careful long-term sustainability and alternative delivery planning, it could well be that the 2030 STH goal will be too ambitious for many settings.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Yes

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Soil-transmitted helminth and schistosomiasis epidemiology, global health policy, public health policy and implementation.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 02 Dec 2019

Luc Edgar Coffeng,

Reviewer 2: Is the authors' recommendation of 75% community-wide coverage applicable to all settings, or has this extended beyond what is required for the current morbidity control goal?

Answer: As mentioned in the paper, community-wide coverage of 75% is especially important for settings where hookworm is the dominant STH. This is because of the age-prevalence profile of hookworm where adults bear the main burden of infection. In settings where *A. lumbricoides* or *T. trichiura* are the dominant species 75% coverage in adults is probably not strictly necessary provided that the coverage in pre-SAC and SAC is sufficiently high, because the age-prevalence profile peaks in children. We have not run simulations to determine the minimum PC coverage of adults required to reach the morbidity target in settings where *A. lumbricoides* or *T. trichiura* are the dominant species, given that 75% coverage of preSAC and SAC is achieved. The minimum PC coverage of adults required in these settings will depend on the baseline prevalence and transmission intensity.

Reviewer 2: The authors are kindly requested to elucidate further on the statement (Discussion) that "it is predicted that EOT can be achieved in low-transmission settings where *Ascaris lumbricoides* or *T. trichiura* are the dominant parasites by annual treatment of SAC". If this is the case, but this manuscript has investigated achieving the goal for scenarios above 20%, it seems unlikely that EOT would enter into consideration and thus, preventive chemotherapy would have to continue.

Answer: The conclusion that EOT can be reached in low-transmission settings comes from earlier simulation studies that classified transmission settings using the basic reproductive number R_0 , rather than baseline prevalence (1). Any given value of R_0 does not directly translate into a particular prevalence of infection, because the prevalence also depends on other model parameters, such as the aggregation parameter k (describes the tendency that a few individuals will be infected by many worms while most individuals will have low-intensity infections) and the density-dependence of female worm fecundity. However, in general, low-prevalence settings will also have low transmission intensities (low R_0) values. Therefore, one can predict that EOT can be achieved in low-transmission/low-prevalence settings. Moreover, it is possible that some moderate-prevalence settings also have low-transmission intensity as measured by R_0 . This needs to be estimated on a case-by-case basis. In these settings, EOT can also be achieved. It is true that in settings where EOT cannot be achieved using current MDA strategies (all high-prevalence settings and some moderate-prevalence settings) and WASH facilities are not

improved to the degree that transmission ceases, MDA would have to be continued indefinitely.

Reviewer 2: If neither WASH access nor EOT are feasible, then preventive chemotherapy needs to be sustained. This recommendation for indefinite preventive chemotherapy warrants further projections, for example to a second impact assessment, to determine for how long this may need to be the case. Potentially there could be recommendations for a second assessment layer to the decision trees (e.g., hypothetically after 10 years of MDA).

Answer: We agree with Reviewer 2 that repeated impact assessments are necessary where EOT cannot be achieved by MDA and/or WASH measures.

Reviewer 2: The authors recommend co-administered albendazole-ivermectin against *T. trichiura*, and also community-wide treatment when hookworm is the dominant infection. This differentiation of some of the STH is welcomed, but WHO guidelines are for undifferentiated STH. Can the authors please advise what level of *T. trichiura* prevalence/intensity would be the recommended 'trigger' for co-administration? What level of hookworm prevalence/intensity would be the trigger for risk mitigation activities such as expanding treatments to additional cohorts? Were helminth-specific cutpoints considered in the modelling to arrive at the optimum treatment requirements?

Answer: In the simulation models, cut-off points were investigated for each helminth species separately. We did not investigate settings where several STH species are present simultaneously. However, we would expect that cut-off values for one species would still be valid, regardless for the presence of other STH species. It follows that co-administration of albendazole-ivermectin in the case of *T. trichiura* or community-wide treatment in the case of hookworm are recommended when the prevalence of either species is above 20%. We have not investigated if intensified PC strategies are necessary where species-specific prevalences are lower.

Reviewer 2: Similarly, can the authors please indicate what aspects of "effective WASH" were modelled – was this access to a latrine, access to a water source, combined interventions, etc?

Answer: The WASH simulation study (2) distinguished two WASH modalities: sanitation, which reduces individuals' contributions to environmental contamination, for example, access to latrines; and hygiene, which reduces individuals' exposure to infection, for example hand washing, access to clean water sources. Both sanitation and hygiene measures in isolation and in combination were investigated. One interesting finding was that the impact of hygiene is determined more by the effectiveness of the intervention than its overall uptake, whereas the impact of sanitation depends more directly on the product of uptake and the effectiveness.

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Competing Interests: The author declare no competing interests.

Reviewer Report 05 November 2019

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Rubina Imtiaz 

Children Without Worms, The Task Force for Global Health, Decatur, GA, USA

This is a very well written Open Letter which clearly presents the background on Soil Transmitted Helminths, their health effects on risk populations, the WHO goals and treatment guidelines. The authors then state the proposed new, 2030 goals for STH "morbidity control" defined by <2% prevalence of medium- to high-intensity infections in pre-school age and school age children.

Two mathematical models were used to assess the feasibility and relative efficiency of WHO-proposed end goals, in light of current diagnostic and program-decisional thresholds. Good news is that these models are largely comparable. Key outcomes and recommendations from the models are nicely summarized in Table 1. Both models predict that the new target is feasible in moderate prevalence settings (20-50% in SAC) in the absence of systematic non-access to PC. For highly endemic settings (prevalence \geq 50%), they recommend semi-annual PC including adults, and dual PC for Trichuris. Shortcomings of the current diagnostic of choice (Kato Katz) are well discussed with options for newer, more sensitive diagnostics open (e.g. PCR methods in low prevalence settings).

It's very good to see the recommendation to have the flexibility in current indicator thresholds by WHO to accommodate future, more sensitive tests (link indicator threshold to standardized diagnostic procedure or to the true infection prevalence from which specific diagnostic procedures and sampling designs can be derived).

An additional consideration that may strengthen the model and recommendations for advanced programs, is to consider modeling for specific worms within the STH group: STH comprises 3 discrete parasites, each with its own different drug responsiveness and life cycle (e.g. hookworms have a shorter environmental life cycle, so more prone to "elimination" if adult worm reservoir is effectively reduced through sustained, high-level treatment cycles). So, the baseline data on species-specific burden of STH in an area, and appropriate treatment would be ideal.

In the absence of large scale quality data on STH morbidity, this article addresses the current issues very competently with some feasible recommended actions.

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Yes

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Is the Open Letter written in accessible language?

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Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious disease epidemiology, public health program implementation and global health policy

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
