OPEN LETTER

REVISED Insights from quantitative and mathematical modelling on the proposed WHO 2030 goal for schistosomiasis [version 2; peer review: 3 approved]

NTD Modelling Consortium Schistosomiasis Group

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Abstract

Schistosomiasis remains one of the neglected tropical diseases (NTDs) impacting millions of people around the world. The World Health Organization (WHO) recently proposed a goal of elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2030. Current WHO treatment guidelines for achieving EPHP focus on targeting school-aged children. The NTD Modelling Consortium has developed mathematical models to study schistosomiasis transmission dynamics and the impact of control measures. Our modelling insights on *Schistosoma mansoni* have shown that EPHP is likely to be attainable in low to moderate prevalence settings using the current guidelines. However, as prevalence rises within high prevalence settings, EPHP is less likely to be achieved unless both school-aged children and adults are treated (with coverage levels increasing with the adult burden of infection). We highlight the challenges that are faced by treatment programmes, such as non-adherence to treatment and resurgence, which can hinder progress towards achieving and maintaining EPHP. Additionally, even though EPHP may be reached, prevalence can still be high due to persisting infections. Therefore, without interruption of transmission, treatment will likely have to continue to maintain EPHP. Further modelling work is being carried out, including extending our results to *S. haematobium*. By providing these modelling insights, we aim to inform discussions on the goals and treatment guidelines for schistosomiasis.

Keywords

Schistosomiasis, WHO guidelines, Elimination as a public health problem, Mass drug administration, NTD Modelling Consortium

This article is included in the 2030 goals for neglected tropical diseases collection.

Open Peer Review

Reviewer Status ✓ ✓ ✓

	Invited Reviewers		
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REVISED **version 2** published 19 Nov 2019		✓ report	
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1 **W. Evan Secor**, Centers for Disease Control and Prevention, Atlanta, USA

2 **Stefanie Knopp**, Swiss Tropical and Public Health Institute, Basel, Switzerland

3 **Darin Evans**, United States Agency for International Development (USAID), Washington, USA

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: NTD Modelling Consortium Schistosomiasis Group (j.toor@imperial.ac.uk)

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REVISED **Amendments from Version 1**

Following helpful reviewer comments, we have revised our letter to improve the clarity of our insights. Specific points added are as follows: uncertainty around how reliable the current WHO definition of EPHP is for estimating a reduction in schistosomiasis-related morbidity; our modelling assumptions on treatment coverage and adherence; input from the Global Schistosomiasis Alliance meeting to show views of its members. More references have also been added where needed.

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

Disclaimer

The views expressed in this article are those of the author(s). The opinions expressed herein are those of the authors and do not necessarily reflect the views of the World Health Organization. Publication in Gates Open Research does not imply endorsement by the Gates Foundation.

Background

Schistosomiasis remains an endemic neglected tropical disease (NTD) affecting approximately 220 million people worldwide[1]. It is an intestinal or urogenital disease caused predominantly by *Schistosoma mansoni* or *S. haematobium*. Individuals become infected when cercariae, released by freshwater snails, penetrate the skin during contact with contaminated water[2]. The disease can result in anaemia, chronic pain, diarrhoea, and malnutrition, causing poor school performance and lower fitness[3]. Donations of the treatment drug, praziquantel, are typically offered in school-based or community-wide mass drug administration (MDA) programmes for schistosomiasis.

The World Health Organization (WHO) has set goals of morbidity control and elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2020 and 2025, respectively[4,5] (defined in Table 1). There are recommended WHO treatment guidelines for achieving these goals based on the prevalence in school-aged children (SAC; aged 5–14 years old) prior to treatment. In low prevalence settings (≤10% SAC prevalence prior to treatment), MDA once every three years is recommended; in moderate prevalence settings (10–50% SAC prevalence prior to treatment), MDA once every two years is recommended; and in high prevalence settings (≥50% SAC prevalence prior to treatment), annual MDA is recommended[4,5]. MDA coverage has mainly focused on reaching 75% of SAC with treatment of adults at risk also recommended[4,5]. The WHO end goal for schistosomiasis is interruption of transmission (IOT) which is achieved once the incidence of infection is reduced to zero[4,5]. In May 2019, following a Global Schistosomiasis Alliance consultation meeting with its members and the WHO, there was support for the IOT goal with an interim and complementary goal of reducing the burden of schistosomiasis[6].

Mathematical models of transmission dynamics and the impact of control interventions have been developed to inform decision makers on the optimal treatment strategies which are required for achieving the WHO goals. The Gates-funded NTD Modelling Consortium brings together multiple institutional groups working on NTDs, including schistosomiasis. Modelling groups based at Imperial College London (ICL) and Case Western Reserve University (CWRU), along with other collaborators have led the recent work for schistosomiasis. A model comparison was carried out for the ICL and CWRU models, and a joint policy paper was also produced[7,8]. Due to knowledge gaps surrounding the epidemiology of schistosomiasis, the models have contrasting underlying assumptions leading to differences in model predictions[8]. Despite these differences, the models generally agree on the treatment strategies required to achieve EPHP for *S. mansoni*, thereby strengthening the evidence for our model recommendations[7].

Moving towards the post-2020 goals, new WHO goals have been proposed for the NTDs to be reached by 2030. Currently, the proposed 2030 goal for schistosomiasis is EPHP. Using the insights that have been gained from recent modelling work on *S. mansoni*, we highlight the practical implications of EPHP (the timelines and feasibility of achieving EPHP) and the risks

Table 1. Summary of modelling insights and challenges for reaching the WHO 2030 goal for *Schistosoma mansoni*.

Current WHO Goal (2020 Goal)	Morbidity control: <5% prevalence of heavy-intensity infections (eggs per gram ≥400) in school-aged children (SAC; 5–14 years old).
Proposed New WHO Goal (2030 Goal)	Elimination as a public health problem (EPHP): <1% prevalence of heavy-intensity infections in SAC. Note that this is the current 2025 goal.
Is the new goal technically feasible under the current disease strategy?	In low to moderate prevalence settings (<50% SAC prevalence prior to treatment), EPHP is likely to be achieved with 75% SAC-only treatment.
If not, what is required to achieve the goal?	As prevalence rises in high prevalence settings (≥50% SAC prevalence prior to treatment), EPHP becomes infeasible unless the disease strategy is scaled-up to treat both SAC and adults. Required coverage levels increase with the adult burden of infection.
Are current tools able to reliably measure the goal?	No; as Kato-Katz has low sensitivity at low prevalence levels, more sensitive diagnostics (able to measure prevalence and intensity of infection) will allow for smaller sample sizes and/or higher prevalence thresholds when measuring the goal.
What are the biggest unknowns?	Prevalence levels and intensity of infections across all age groups (i.e. full age profile of infection); levels of systematic non-adherence and ideal size of implementation unit; modelling insights on *S. haematobium* and other species.
What are the biggest risks?	Stopping treatment after achieving EPHP is highly likely to lead to resurgence of infection. Interruption of transmission (IOT) would alleviate the need for ongoing treatment. Potential risks posed by zoonotic reservoirs and drug resistance.

that need to be mitigated to maintain this goal. There is uncertainty around how reliable the current WHO definition of EPHP is for estimating a reduction in schistosomiasis-related morbidity as lower intensity infections may also be associated with significant morbidity[3]. Further modelling will be required following revision of this goal by WHO as this may impact our recommended treatment strategies.

Note that the following sections focus on *S. mansoni* and Kato-Katz (as this is the currently recommended diagnostic technique[9]). Additionally, the current WHO treatment guidelines and EPHP goal have been investigated here but these are currently under revision by WHO. Importantly, our modelling insights remain relevant as we highlight where the current guidelines are sufficient and where programmatic adaptations are needed for achieving the current EPHP goal (refer to Table 1 for a summary).

Insights gained from quantitative and mathematical modelling analyses

Using models developed independently by ICL and CWRU, we investigated whether the currently recommended WHO guidelines (of 75% SAC-only treatment) are sufficient for achieving the EPHP goal for *S. mansoni*. Our modelling and data analyses showed that these guidelines are sufficient for reaching EPHP in low to moderate settings[7,10]. However, as prevalence rises within high settings, an increase and expansion in treatment coverage to include adults, as well as SAC, is required to reach EPHP with coverage levels dependent on the setting[7,10] (Table 2). As the burden of infection (intensity of transmission) in adults relative to SAC increases, the coverage levels needed to achieve EPHP increase (Figure 1)[10]. Coverage levels also increase if EPHP is to be achieved within a shorter amount of time (Figure 1).

Monitoring and evaluation (M&E) programmes are used to collect data to assess the progress of a treatment programme and to determine the appropriate treatment strategy. M&E data are typically collected from SAC as they are relatively easy to sample from. However, as the optimal treatment strategy for *S. mansoni* depends on the burden of infection in SAC and adults, M&E prevalence and infection intensity data need to be collected from a broader age-range[10]. Our work has also shown that despite achieving EPHP, the prevalence may still be high

Table 2. Model recommended treatment strategies for achieving elimination as a public health problem (EPHP) in low to high prevalence settings. SAC refers to school-aged children aged 5–14 years old.

Prevalence in SAC prior to treatment	Model recommended treatment strategy for achieving EPHP
Low (<10%)	75% SAC treatment once every 3 years within 6 years[7].
Moderate (10%–50%)	75% SAC treatment once every 2 years for up to 5 years (this holds for low to high adult burdens of infection)[10].
High (≥50%)	As prevalence rises, SAC and adult annual treatment with coverage levels increasing with the adult burden of infection (coverage also increases as programme duration shortens; shown for 5–10 year programmes in Figure 1)[10].

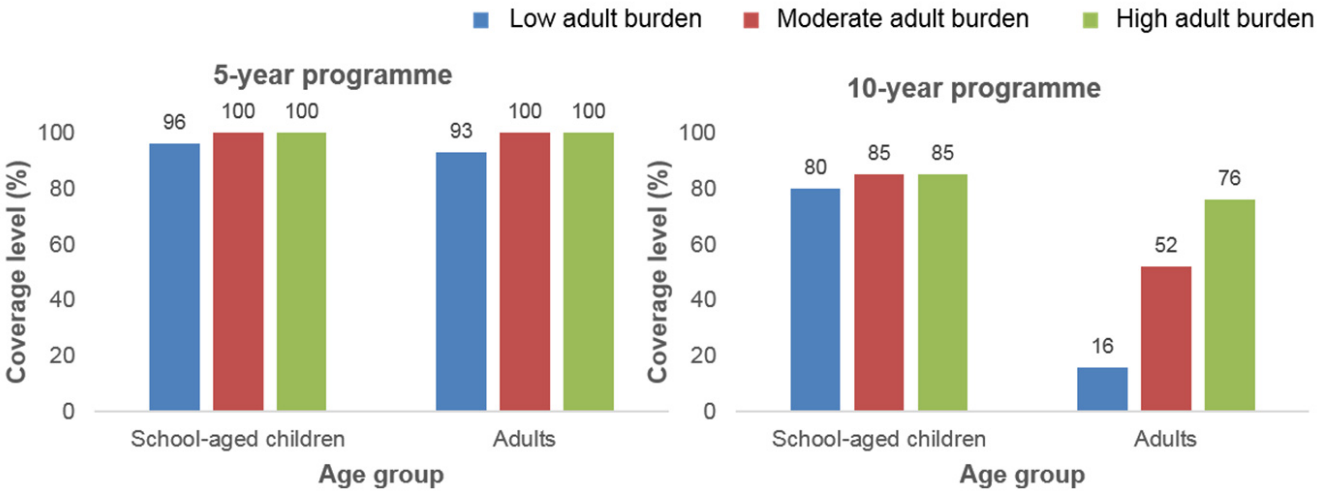

Figure 1. Coverage levels required to reach the WHO goal of elimination as a public health problem (EPHP) in a high prevalence setting (≥50% SAC baseline prevalence) within 5- and 10-year annual treatment programmes (assuming random coverage and no non-adherence). School-aged children (SAC) are 5–14 years old and adults are 15+ years old. This figure has been reproduced from 10 under a Creative Commons Attribution 4.0 International (CC BY 4.0) license.

due to light- to moderate-intensity infections persisting in SAC, in addition to all the infections remaining in pre-SAC and adults[7,10]. Therefore, stopping treatment after reaching EPHP poses a high risk of resurgence.

Practical implications of the elimination as a public health problem goal

Timelines and feasibility of achieving elimination as a public health problem

The treatment strategy required to achieve EPHP is determined by the epidemiological and ecological setting, such as the baseline prevalence/transmission intensity[7,10]. EPHP is technically feasible in all settings within 10 years provided that the appropriate treatment strategy is used. Table 2 shows the model recommended treatment strategies. Achieving and maintaining high coverage, adherence and treatment opportunities over each round of treatment is essential[11]. Here, we have assumed treatment at random with full adherence at each round of MDA. Areas with poor school enrolment may benefit more from community-wide treatment[12].

Measuring the elimination as a public health problem goal

To monitor and assess progress towards the EPHP goal, prevalence and infection intensity data are required from SAC (as the goal is defined by <1% prevalence of heavy-intensity infections in SAC). The goal is typically assessed by averaging the prevalence measured in five schools randomly sampled within a district[13]. This approach does not take into account the high spatial heterogeneity and focality in *Schistosoma* prevalence. Taking implementation decisions at the district level using the currently proposed sampling strategy can lead to under- and over-treatment of SAC. Sampling fewer children in more schools has been shown to improve prevalence estimates, reducing under-treatment[13]. Ongoing work on mapping protocols will allow for more precise targeted treatment.

Kato-Katz is currently the recommended diagnostic test, but there are relatively newer, more sensitive diagnostics available. Due to the reduced sensitivity of diagnostic techniques at low prevalence levels, the true prevalence is likely to be higher than the measured prevalence. Prevalence measured with Kato-Katz will be lower relative to that measured with more sensitive diagnostics, such as point-of-care circulating cathodic antigen (POC-CCA) tests, and this difference has been analysed, although the relationship between the two diagnostics remains unclear[14–16]. Therefore, the diagnostic technique used will impact the sampling strategy, with a more sensitive diagnostic likely facilitating the sampling of fewer people or the use of higher prevalence thresholds when measuring EPHP and furthermore IOT[17].

Considerations of cost

Accurate, representative data on which age groups are infected are required to determine the most cost-effective treatment strategy, for example, only collecting data on high-risk adults can overestimate the benefit of community-wide treatment[12]. The costs of diagnostic techniques also need to be considered. Although the traditional Kato-Katz diagnostic is seen as the cheaper test, given the increased sensitivity of POC-CCA, this may outweigh costs in the long term[18].

Risks faced by treatment programmes

There are risks that need to be mitigated to achieve EPHP. Individuals with no access to treatment or those not taking treatment in any round of MDA (systematic non-adherers) may result in maintained transmission[11,19]. Due to systematic non-adherence, reported coverage may be higher than true coverage[19]. Ideally data on adherence as well as coverage should be collected within M&E programmes as both will impact the outcome of treatment programmes[19].

M&E programmes focus on SAC, and may be biased to those who are treated, making it difficult to promptly identify a failing treatment programme. Therefore, it is vital that the M&E data collected is representative of each age group[10,12]. Manipulation of implementation unit size may mask persistent prevalence of challenging locations, such as hotspots. Guidance on mapping of schistosomiasis prevalence will aid in determining the optimal size of implementation units. Further risks which may reduce the effectiveness of treatment programmes are potential drug resistance (declining praziquantel efficacy following multiple rounds of treatment[20]) and the presence of zoonotic reservoirs[21,22]. More insights are needed on such risks as more intensified treatment strategies than those currently recommended here may be required if they are present.

Following achievement of EPHP, infections may remain present in the population resulting in resurgence if treatment is stopped[7,10]. Pre-SAC can also be infected with schistosomes and a reservoir of infection may remain in this age group following MDA to other age groups. Development of a paediatric formulation of praziquantel for pre-SAC treatment would prevent this[23]. Due to remaining infections, it is highly likely that treatment will still be needed to maintain control after achieving EPHP[24]. Good water, sanitation and hygiene could aid in sustaining EPHP, allowing treatment to be scaled down[25].

Moving towards interruption of transmission

To alleviate the need for ongoing treatment and to prevent resurgence, IOT is required after reaching EPHP[2,7,10]. The transition of treatment programmes from EPHP to IOT will require reassessment of the treatment strategy, with consideration of complementary interventions such as behaviour change and snail control. Once very low prevalence levels have been achieved and a treatment programme is stopped, surveillance is needed to ensure that IOT has been achieved and that resurgence has not occurred. Currently, there is little guidance available for programmes when stopping treatment. Recently, the ICL model determined the post-treatment surveillance criteria for predicting IOT for *S. mansoni*. Results showed that a 1% Kato-Katz prevalence measured 2 years (or later) after stopping treatment across 200 individuals (randomly sampled from all age groups in a population of 500–1000 individuals), means IOT is 90% likely in the absence of re-introduction[17].

Priority questions

Priority issue / question identified in discussion with WHO	How can quantitative and mathematical modelling address this?
Re-run the models with the broad parameters of the new treatment guidelines.	New guidelines can be simulated in the model and followed through to determine if they are sufficient for achieving EPHP (as done previously for current guidelines[5]).
Quantitative assessment of morbidity averted with continued treatment.	Modelling can simulate new guidelines to determine heavy-intensity infection prevalence and overall prevalence cases averted which can be related to morbidity averted.
How do we know when country settings can transition from EPHP to IOT? • What interventions are required? • What criteria are required? • Where possible? • What are the cost implications?	Modelling has been used to show the MDA treatment strategy required to achieve EPHP[7,10]. This can be extended to investigate the interventions required for transitioning to IOT. Modelling can then investigate the feasibility of sustaining EPHP versus moving to IOT. IOT prediction and post-MDA surveillance criteria have been determined for *S. mansoni*[17].

Data availability

No data are associated with this article.

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Members of the NTD Modelling Consortium Schistosomiasis Group:

Jaspreet Toor (j.toor@imperial.ac.uk; corresponding author)[1,2], Claudio Fronterre (c.fronterr@lancaster.ac.uk)[3], Joaquin M Prada (j.prada@surrey.ac.uk)[4], Charles H King (chk@case.edu)[5], T. Déirdre Hollingsworth (deirdre.hollingsworth@bdi.ox.ac.uk)[6], Graham F Medley (graham.medley@lshtm.ac.uk)[7], Roy M Anderson (roy.anderson@imperial.ac.uk)[1,2,8]

[1]London Centre for Neglected Tropical Disease Research, Department of Infectious Disease Epidemiology, St Mary's Campus, Imperial College London, Norfolk Place, London W2 1PG, UK.

[2]MRC Centre for Global Infectious Disease Analysis, Department of Infectious Disease Epidemiology, School of Public Health, Faculty of Medicine, St Mary's Campus, Imperial College London, Norfolk Place, London W2 1PG, UK.

[3]Centre for Health Informatics, Computing and Statistics (CHICAS), Lancaster Medical School, Lancaster University, Lancaster LA1 4YW, UK.

[4]School of Veterinary Medicine, Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7AL, UK.

[5]Center for Global Health and Diseases and Department of Mathematics, Case Western Reserve University, 10900 Euclid Avenue LC: 4983, Cleveland, OH 44106, USA.

[6]Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, Old Road Campus, Headington, Oxford, OX3 7LF, UK.

[7]Centre for Mathematical Modelling of Infectious Disease, London School of Hygiene and Tropical Medicine, 15-17 Tavistock Place, London, WC1H 9SH, UK.

[8]The DeWorm3 Project, The Natural History Museum of London, London SW7 5BD, UK.

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Open Peer Review

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Version 2

Reviewer Report 06 December 2019

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✔ **Stefanie Knopp**
Swiss Tropical and Public Health Institute, Basel, Switzerland

Thanks to the authors for the revisions made to their first version of this open letter. I remain with one comment that pertains to the content of current and future WHO guidelines, recommendations and/or goals, which I feel warrants consideration:

In their letter, the authors refer to two WHO publications and indicate the therein suggested mass treatment recommendations for school-aged children as the basis for their modelling and to check whether elimination as public health problem can be achieved. This is fine. However, I feel it needs to be stated that these WHO recommended treatment strategies are for (morbidity) control of schistosomiasis, but that they are not the WHO recommended strategies to reach elimination as public health problem and interruption of transmission.

I.e., the first document “Helminth control in school-aged children” published in 2011, focuses on schistosomiasis (morbidity) control only. There is no mention of “elimination” at all in this guide.
The second document “Progress report 2001-2011 and strategic plan 2012-2020” published in 2013, distinguishes between treatment approaches for morbidity control (see Section 1.4 “Recommendations for morbidity control” and Table 1.1. in this section) and intervention strategies for elimination as public health problem and interruption of transmission (see Section 3.2 “Progression towards elimination of schistosomiasis” and Table 3.2. in this section). In their letter, the authors seem to refer to the approaches described in Table 1.1.. Again it needs to be clarified that this approach is the one recommended for (morbidity) control, but not for reaching elimination as public health problem.

I have made an attempt to rephrase respective sentences in the revised PDF version of the letter so that they read correctly – please see the file here. The authors may consider to change accordingly. I have also inserted some more specific comments and track changes into the PDF version that the authors may want to address if they agree.

Moreover, I would like the authors to carefully check in the published versions of the two WHO publications mentioned above plus the “proposed WHO goals 2021-2030”, whether at all and for which goal (morbidity control, elimination as public health problem, interruption of transmission) school-aged

children are explicitly mentioned. As far as I can see, this is only the case in the recommendation for morbidity control, but not for elimination in any of the documents, and hence some sentences in the letter might need to be adapted accordingly.

Competing Interests: No competing interests were disclosed.

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.

Version 1

Reviewer Report 22 October 2019

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Darin Evans
United States Agency for International Development (USAID), Washington, DC, USA

In this open letter, Toor and colleagues review the proposed WHO 2030 target for elimination of schistosomiasis as a public health problem (EPHP), defined as <1% heavy intensity (HI) infections, in the context of current WHO guidelines for preventive chemotherapy with praziquantel. Using mathematical models, they predict that, with 10 years of effective coverage of school-aged-children (i.e. 75%), communities with low or moderate prevalence schistosomiasis will be able to achieve the WHO defined threshold but that communities with higher prevalence and greater force of infection will require expanded treatment and greater coverage of adults. Similar findings were shown in a recent publication by Li *et al.* (2019[1]) though in their models expanded interventions, such as vector management, would be required. Importantly, in both cases, the authors recognize that once EPHP is achieved, transmission will continue, prevalence may remain high and treatment must continue. This instinctively draws into question the utility of setting <1% HI infection as a target if it will result in no programmatic change or action. In addition, the 1% HI threshold is an arbitrary one and evidence suggests that low to moderate intensity infections still have significant morbidity (King *et al.*, 2005[2]). The use of intensity of infection is a proxy indicator for morbidity and it relies on the inherently insensitive Kato-katz (KK).

The authors discuss the availability of the more sensitive POC CCA test for *S. mansoni* in the context of comparing it to KK results but these should not be discounted as such tests are likely to become more common. Understanding better the use of such for identifying both transmission and morbidity will be important. Current studies such as the MORBID (Morbidity and Operational Research for Bilharziasis Implementation Decisions) project funded through COR-NTD will help inform better thresholds for programmatic decision making. Regardless of how EPHP is ultimately defined, this publication and others suggest that long-term efforts will be required to achieve and maintain this goal. This was recently highlighted by French *et al.* (2018[3]).

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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?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Preventive chemotherapy/mass drug administration, public health policy, schistosomiasis, onchocerciasis, STH, LF

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 15 Nov 2019

Jaspreet Toor,

We thank Darin for his feedback and agree with the points raised. The following has been added in the background section: “There is uncertainty around how reliable the current WHO definition of EPHP is for estimating a reduction in schistosomiasis-related morbidity as lower intensity infections may also be associated with significant morbidity[3].”

The following has been added to the risks faced by treatment programmes section: “Due to remaining infections, it is highly likely that treatment will still be needed to maintain control after achieving EPHP[20a].”

Competing Interests: No competing interests were disclosed.

Reviewer Report 19 September 2019

https://doi.org/10.21956/gatesopenres.14179.r27700

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Stefanie Knopp
Swiss Tropical and Public Health Institute, Basel, Switzerland

Summary:

- In this Open Letter article the authors reflect on results from quantitative and mathematical modelling that aimed to determine the impact of mass drug administration on the transmission and control of schistosomiasis and the impact of coverage in school-aged and adult populations to achieve elimination as public health problem (defined here as <1% heavy intensity infections in school-aged children) depending on the prevalence level. Challenges that schistosomiasis control programmes might face when they move towards or have achieved elimination as public health problem are presented. With the article, the authors aim to inform discussions on the WHO goals and treatment guidelines for schistosomiasis.

- The modelling results provide important insights into whether, when and how the prevalence of schistosomiasis can be reduced and thus can well contribute to inform WHO guidelines. However, as the article is currently presented, there seems to be confusion of what the currently published (until 17.9.2019) WHO guidelines recommend and for what level of control and elimination. The authors indicate mass drug administration in school-aged children as the intervention recommended by WHO to reach elimination as public health problem. To my understanding, WHO currently recommends to “adjust preventive chemotherapy and to use additional complementary public-health interventions” for reaching elimination as a public health problem (Reference 4 of the article). Also, the Global Schistosomiasis Alliance (GSA) provided invited feedback on the new proposed WHO goals for schistosomiasis post 2020. The goal proposed by WHO on April 10, 2019 was: "Elimination as a public health problem; Criteria to measure the achievement of the goal: Proportion of heavy intensity schistosomiasis infections <1%)". The feedback from GSA on May 2nd, 2019 was "*…the GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease…”.* It would be good if the authors can clarify on the guidelines and their actual content and also refer more to interruption of transmission as the ultimate goal.

- Please also consider my specific comments to the manuscript and peer review form:

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

- The rationale is provided. However, the authors might consider adding some more details. Please see my following comments:

Background:

1. *The authors write:* “The World Health Organization (WHO) has set goals of morbidity control and elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2020 and

2025, respectively[4] (defined in Table 1).“ The authors might consider that the WHO also set a goal for interruption of transmission in selected countries, and present it to provide a complete picture of all goals set for 2020 and 2025.

2. *The authors write:* “There are recommended WHO treatment guidelines for achieving these goals based on the prevalence in school-aged children”. The authors might consider that in their strategic plan 2012-2020, the WHO recommends to “adjust preventive chemotherapy and to use additional complementary public-health interventions” for reaching elimination as a public health problem (World Health Organization, 2013[3]). Hence, in my view, the available guidelines do not focus on targeting school-aged children only. It seems to me that the authors refer to WHO recommendations for achieving morbidity control only, but not the actual guidelines for reaching elimination as public health problem. There are important differences in the approaches, which should be clarified.

3. *The authors write:* “Mathematical models of transmission dynamics and the impact of control interventions have been developed to inform decision makers on the optimal treatment strategies which are required for achieving the WHO goals”. The authors might clarify which goals exactly they write about.

4. *The authors write:* “Currently, the proposed 2030 goal for schistosomiasis is EPHP.” The authors might consider mentioning that WHO invited feedback and strategies for the proposed goals and that in the meantime in line with a consultation meeting, the Global Schistosomiasis Alliance (GSA) challenged that goal to some extent and responded to WHO as follows: “*GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease.....” (https://www.eliminateschisto.org/news-events/news/gsa-consultation-meeting-accelerating-progres).*

5. *The authors write: “*Note that the following sections focus on *S. mansoni* and Kato-Katz (as this is the currently recommended diagnostic technique).” The authors might provide a reference for this recommendation of Kato-Katz.

6. *The authors write: “*Additionally, the current WHO treatment guidelines have been investigated…”. The authors might consider highlighting which guidelines exactly they investigated and for what (i.e. morbidity control or elimination as public health problem) and how, and provide a reference to the guidelines.

7. *The authors write: “…*the currently recommended WHO guidelines (of 75% SAC-only treatment) are sufficient for achieving the EPHP goal for *S. mansoni*.*”* As indicated in my previous comments, the current guidelines indicate that to achieve elimination of schistosomiasis as a public health problem, WHO recommends to “adjust preventive chemotherapy and to use additional complementary public-health interventions” (World Health Organization, 2013[3]). Hence, it remains unclear, why the authors stick to recommendations for morbidity control and not elimination as a public health problem?

8. *The authors write: “*As the burden of infection in adults relative to SAC increases…”. The authors might define burden. Is it measured in intensity, worm numbers, DALYs or something else?

Does the article adequately reference differing views and opinions?

- My feeling is that some background on WHO guidelines for elimination as public health problem and interruption of transmission is missing or confused. Hence, it would be great if the authors can clarify that/why they went for modelling of morbidity control approaches rather than considering what is recommended by WHO to achieve elimination of public health problem as per the strategic plan 2012-2020.

- Moreover, there is a recent trial that underlines that in a mostly low prevalence setting, 5 years of biannual MDA are not sufficient to reach elimination as a public health problem in all sentinel sites and to achieve interruption of transmission (Knopp *et al.*, 2019a[1], Knopp *et al.*, 2019b[2]). Additional operational research studies were published by members of the Schistosomiasis Consortium for Operational Research and Evaluation on controlling morbidity with different MDA approaches. The results and conclusions could be discussed in this letter in relation to the modelling results.

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

- The authors might want to consider the following comments (the one pertaining to the Background was already outlined above):

Abstract:

1. *The authors write:* "The World Health Organization (WHO) recently proposed a goal of elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2030. The authors might consider mentioning that WHO invited feedback and strategies for the proposed goals and that in the meantime in line with a consultation meeting, the Global Schistosomiasis Alliance (GSA) challenged that goal to some extent and responded to WHO as follows: "*GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease." (https://www.eliminateschisto.org/news-events/news/gsa-consultation-meeting-accelerating-progres).* In my view, the advice of the GSA on the proposed WHO goals should also be highlighted somewhere in this article. "Recently" could be replaced by the date so that the reader knows when these new goals were proposed and whether they are still up to date or not.

2. *The authors write: "*Current WHO treatment guidelines for achieving EPHP focus on targeting school-aged children". The authors might consider that in their strategic plan 2012-2020, WHO recommends to "adjust preventive chemotherapy and to use additional complementary public-health interventions" for reaching elimination as a public health problem" (Reference 4 of the article). Hence, the available guidelines do not focus on targeting school-aged children only?

3. *The authors write:* "The NTD Modelling Consortium has developed mathematical models to study schistosomiasis transmission dynamics and the impact of control measures". The authors might consider highlighting which impact was measured (e.g. on prevalence or intensity) and to what control measures they refer (i.e. preventive chemotherapy or also measures such as snail control etc.).

4. *The authors write:* "Our modelling insights on *Schistosoma mansoni* have shown that EPHP is likely to be attainable in low to moderate prevalence settings using the current guidelines". It would be nice if the authors can define how they define low and moderate (i.e. provide a prevalence

range). Moreover, which guidelines do they refer to? As indicated in my 2. comment, the strategic plan 2012-2020 recommends to “adjust preventive chemotherapy and to use additional complementary public-health interventions”. Rather referring to the guidelines (which ones?), the authors might consider referring to their modelling approach on preventive chemotherapy for school-aged children.

5. *The authors write:* “However, as prevalence rises within higher settings…”. The authors might consider defining “higher setting”. The sentence needs revision.

6. *The authors write:* “…(with coverage levels increasing with the adult burden of infection).” It is not clear what the authors mean here. The authors might consider revising the part in brackets for more clarity.

7. *The authors write:* “…hinder progress towards achieving and maintaining EPHP”. The authors might consider that interruption of transmission has been suggested as goal, too (see my 1. Comment).

8. “EPHP” should be defined at the beginning so that the reader better understands the following sentence “Additionally, even though EPHP may be reached, prevalence can still be high”.

9. *The authors write:* “Therefore, without elimination of transmission, treatment will likely have to continue to maintain EPHP.” The authors might consider defining “treatment”. What treatment regimen do they have in mind? MDA?

Background:

1. *The authors write:* “The World Health Organization (WHO) has set goals of morbidity control and elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2020 and 2025, respectively[4] (defined in Table 1).” The authors might consider that the WHO also set goals for interruption of transmission in selected countries, to provide a complete picture of the goals set for 2020 and 2025.

2. *The authors write:* “There are recommended WHO treatment guidelines for achieving these goals based on the prevalence in school-aged children”. The authors might consider that in their strategic plan 2012-2020, the WHO recommends to “adjust preventive chemotherapy and to use additional complementary public-health interventions” for reaching elimination as a public health problem (World Health Organization, 2013[3]). Hence, in my view, the available guidelines do not focus on targeting school-aged children only. It seems to me that the authors refer to WHO recommendations for achieving morbidity control only, but not the actual guidelines for reaching elimination as public health problem. There are important differences in the approaches, which should be clarified.

3. *The authors write:* “Mathematical models of transmission dynamics and the impact of control interventions have been developed to inform decision makers on the optimal treatment strategies which are required for achieving the WHO goals”. The authors might clarify which goals exactly they write about.

4. *The authors write:* “Currently, the proposed 2030 goal for schistosomiasis is EPHP.” The authors might consider mentioning that WHO invited feedback and strategies for the proposed goals and that in the meantime in line with a consultation meeting, the Global Schistosomiasis Alliance (GSA)

challenged that goal to some extent and responded to WHO as follows: "*GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease." (https://www.eliminateschisto.org/news-events/news/gsa-consultation-meeting-accelerating-progres).*

5. *The authors write: "*Note that the following sections focus on *S. mansoni* and Kato-Katz" (as this is the currently recommended diagnostic technique). The authors might provide a reference for this recommendation of Kato-Katz.

6. *The authors write: "*Additionally, the current WHO treatment guidelines have been investigated...". The authors might consider highlighting which guidelines exactly they investigated and for what (i.e. morbidity control or elimination as public health problem) and how, and provide a reference to the guidelines.

7. *The authors write: "…*the currently recommended WHO guidelines (of 75% SAC-only treatment) are sufficient for achieving the EPHP goal for *S. mansoni." As indicated in my previous comments, the current guidelines indicate that to achieve elimination of schistosomiasis as a public health problem,* WHO recommends to "adjust preventive chemotherapy and to use additional complementary public-health interventions" (World Health Organization, 2013[3]). Hence, it remains unclear, why the authors stick to recommendations for morbidity control and not elimination as a public health problem?

8. *The authors write: "*As the burden of infection in adults relative to SAC increases…". The authors might define burden. Is it measured in intensity, worm numbers, DALYs or something else?

Practical implications:

1. *The authors write:* "EPHP is technically feasible in all settings within 10 years provided that the appropriate treatment strategy is used...". A recent study on *S. haematobium* in Zanzibar, a setting targeted for elimination as public health problem and interruption of transmission, showed that despite 5 years of bi-annual MDA in schoolchildren with high coverage and adults with moderate compliance, elimination as public health problem was not reached in all sentinel sites, probably due to heterogeneity in transmission and some remaining pockets with high transmission potential, where people got reinfected rapidly (Knopp *et al.*, 2019a[1], Knopp *et al.*, 2019b[2]). The authors might consider validating their model based on available field data.

2. *The authors write:* "To monitor and assess progress towards the EPHP goal, prevalence and infection intensity data are required from SAC (as the goal is defined by <1% prevalence of heavy-intensity infections in SAC)." The authors might consider adding a reference. When checking the proposed goals published by WHO at https://www.who.int/neglected_diseases/news/NTD-Roadmap-targets-2021-2030.pdf?ua=1, I did not see any mention of "SAC". The current guidelines define elimination as public health problem as "<1% heavy infection intensities in all sentinel sites" (World Health Organization, 2013[3]).

3. *The authors write:* "The goal is currently assessed by averaging the prevalence measured in five schools randomly sampled within a district." Is measuring prevalence in 5 schools related to the

modelling approach of the authors or is it a recommendation by WHO to? If the latter, the authors might consider providing a reference.

4. *The authors write:* "Pre-SAC can also be infected with schistosomiasis…". The authors might consider that a patient is not infected with a disease but with the disease-causing agent, in this case schistosomes.

5. *The authors write:* "Development of a paediatric formulation of praziquantel for pre-SAC treatment would prevent this". The authors might consider that not only the development but finally only the large-scale application of the paediatric praziquantel would reduce a potential reservoir in PSAC.

6. *The authors write:* "Due to remaining infections, it is highly likely that treatment will still be needed after achieving EPHP". Again, it would be nice if the authors can clarify what is meant with "treatment".

7. *The authors write:* "To alleviate the need for ongoing treatment and to prevent resurgence, EOT is required after reaching EPHP." The authors might consider indicating that this is/was one of the goals of WHO for selected countries until 2025 and that also "*GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries".*

8. *The authors write:* "The transition of treatment programmes from EPHP to EOT will require reassessment of the treatment strategy." The authors might consider clarifying if they indeed refer to treatment strategies only, or broader intervention strategies, i.e. including also snail control, WASH, behaviour change, surveillance-response, etc.

Table 1:

1. *The authors write:* "Elimination as a public health problem (EPHP): <1% prevalence of heavy-intensity infections in SAC". Note that this is the current 2025 goal. To my knowledge, the current goal is not referring to SAC but sentinel sites?

2. *The authors write:* "In low to moderate prevalence settings (<50% SAC prevalence prior to treatment), EPHP is likely to be achieved with 75% SAC-only treatment." For how many years is SAC needed to be treated?

Priority questions:

- Validation of the models with real data from different prevalence and intensity settings could be one additional aim.

Is the Open Letter written in accessible language?

- Some sentences need to be carefully revised, but generally fine.

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

- Yes.

References

1. Knopp S, Ame SM, Person B, Hattendorf J, Rabone M, Juma S, Muhsin J, Khamis IS, Hollenberg E, Mohammed KA, Kabole F, Ali SM, Rollinson D: A 5-Year intervention study on elimination of urogenital schistosomiasis in Zanzibar: Parasitological results of annual cross-sectional surveys.*PLoS Negl Trop Dis*

. 2019; **13** (5): e0007268 PubMed Abstract | Publisher Full Text
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3. World Health Organization: Schistosomiasis: progress report 2001-2011, strategic plan 2012-2020. *World Health Organization*. 2013. Reference Source

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

Does the article adequately reference differing views and opinions?
Partly

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

Is the Open Letter written in accessible language?
Partly

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

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology and control of helminth infections; elimination research

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, however I have significant reservations, as outlined above.

Author Response 15 Nov 2019

Jaspreet Toor,

We thank Stefanie for her comments and have responded to them in more detail below.

Summary:
In this Open Letter article the authors reflect on results from quantitative and mathematical modelling that aimed to determine the impact of mass drug administration on the transmission and control of schistosomiasis and the impact of coverage in school-aged and adult populations to achieve elimination as public health problem (defined here as <1% heavy intensity infections in school-aged children) depending on the prevalence level. Challenges that schistosomiasis control programmes might face when they move towards or have achieved elimination as public health problem are presented. With the article, the authors aim to inform discussions on the WHO goals and treatment guidelines for schistosomiasis.

The modelling results provide important insights into whether, when and how the prevalence of

schistosomiasis can be reduced and thus can well contribute to inform WHO guidelines. However, as the article is currently presented, there seems to be confusion of what the currently published (until 17.9.2019) WHO guidelines recommend and for what level of control and elimination. The authors indicate mass drug administration in school-aged children as the intervention recommended by WHO to reach elimination as public health problem. To my understanding, WHO currently recommends to “adjust preventive chemotherapy and to use additional complementary public-health interventions” for reaching elimination as a public health problem (Reference 4 of the article). Also, the Global Schistosomiasis Alliance (GSA) provided invited feedback on the new proposed WHO goals for schistosomiasis post 2020. The goal proposed by WHO on April 10, 2019 was: "Elimination as a public health problem; Criteria to measure the achievement of the goal: Proportion of heavy intensity schistosomiasis infections <1%)". The feedback from GSA on May 2nd, 2019 was "…the GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease…”. It would be good if the authors can clarify on the guidelines and their actual content and also refer more to interruption of transmission as the ultimate goal.

Please also consider my specific comments to the manuscript and peer review form.

*In the background section, the end goal of interruption of transmission has been stated more clearly (had previously been referred to as elimination of transmission throughout the letter). The last paragraph of the background section has been edited to make clearer that we have investigated current WHO guidelines in relation to the current EPHP goal. We have also noted in this paragraph that the current WHO goals and guidelines are under revision. Also see response * to comment below.*

Is the rationale for the Open Letter provided in sufficient detail?
The rationale is provided. However, the authors might consider adding some more details. Please see my following comments.

Does the article adequately reference differing views and opinions?
-My feeling is that some background on WHO guidelines for elimination as public health problem and interruption of transmission is missing or confused. Hence, it would be great if the authors can clarify that/why they went for modelling of morbidity control approaches rather than considering what is recommended by WHO to achieve elimination of public health problem as per the strategic plan 2012-2020.
** As stated in the background section for morbidity control and EPHP, the WHO currently recommends 75% SAC treatment with treatment of adults at risk also being recommended. However, reported coverage shows that typically SAC are treated (ref 1); country programme managers have also said that they typically only have praziquantel available for SAC and not adults. Hence, we have followed treating 75% of SAC at the recommended MDA frequency (as detailed in background section; Table 1.1 recommended treatment strategy for schistosomiasis in WHO reference 4 of paper which is for morbidity control and EPHP). WHO reference 4a has also been added which states that the WHO target is to reach at least 75% SAC.*

-Moreover, there is a recent trial that underlines that in a mostly low prevalence setting, 5 years of biannual MDA are not sufficient to reach elimination as a public health problem in all sentinel sites and to achieve interruption of transmission (Knopp et al., 2019a[1], Knopp et al., 2019b[2]). Additional operational research studies were published by members of the Schistosomiasis Consortium for Operational Research and Evaluation on controlling morbidity with different MDA approaches. The

results and conclusions could be discussed in this letter in relation to the modelling results.
*** We are presenting these results as modelling insights and are aware of the risks faced by treatment programmes which will mean that our model recommendations are too optimistic if such risks are faced.*
We have clarified the model assumptions on coverage and adherence in the timelines section: "Here, we have assumed treatment at random with full adherence at each round of MDA". We have added "More insights are needed on such risks as more intensified treatment strategies than those currently recommended here may be required if they are present" to the risks faced by treatment programmes section (also within our biggest unknowns and risks in Table 1).

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
-The authors might want to consider the following comments:

Abstract:
1. The authors write: "The World Health Organization (WHO) recently proposed a goal of elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2030. The authors might consider mentioning that WHO invited feedback and strategies for the proposed goals and that in the meantime in line with a consultation meeting, the Global Schistosomiasis Alliance (GSA) challenged that goal to some extent and responded to WHO as follows: "GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease."
(https://www.eliminateschisto.org/news-events/news/gsa-consultation-meeting-accelerating-progress-
In my view, the advice of the GSA on the proposed WHO goals should also be highlighted somewhere in this article. "Recently" could be replaced by the date so that the reader knows when these new goals were proposed and whether they are still up to date or not.
^ *The following has been added to the background: "In May 2019, following a Global Schistosomiasis Alliance consultation meeting with its members and the WHO, there was support for the IOT goal with an interim and complementary goal of reducing the burden of schistosomiasis [4b]." Many of the abstract comments have been addressed throughout the text due to the word limit for the abstract.*

2. The authors write: "Current WHO treatment guidelines for achieving EPHP focus on targeting school-aged children". The authors might consider that in their strategic plan 2012-2020, WHO recommends to "adjust preventive chemotherapy and to use additional complementary public-health interventions" for reaching elimination as a public health problem" (Reference 4 of the article). Hence, the available guidelines do not focus on targeting school-aged children only?
*This is explained in the background section: "MDA coverage has mainly focused on reaching 75% of SAC with treatment of adults at risk also recommended." We are using the WHO recommended treatment strategy shown in Table 1.1 and 2.2 in reference 4 and 4a of paper, respectively. This refers to treatment of SAC and adults at risk. To maintain clarity of which WHO guidelines we have analysed we are keeping the focus on targeting of SAC. Also see response * to comment above.*

3. The authors write: "The NTD Modelling Consortium has developed mathematical models to study schistosomiasis transmission dynamics and the impact of control measures". The authors might consider highlighting which impact was measured (e.g. on prevalence or intensity) and to what control measures they refer (i.e. preventive chemotherapy or also measures such as snail control etc.).

Control measures investigated vary within the consortium. ICL looks at MDA, whereas, CWRU looks at MDA and snail control. We look at both prevalence and intensity. We feel this is too detailed to add to the abstract and have made it clear throughout the letter that we are focussing on MDA-only here. Further model details are available in the cited references, e.g. reference 6 in letter.

4. The authors write: "Our modelling insights on Schistosoma mansoni have shown that EPHP is likely to be attainable in low to moderate prevalence settings using the current guidelines". It would be nice if the authors can define how they define low and moderate (i.e. provide a prevalence range). Moreover, which guidelines do they refer to? As indicated in my 2. comment, the strategic plan 2012-2020 recommends to "adjust preventive chemotherapy and to use additional complementary public-health interventions". Rather referring to the guidelines (which ones?), the authors might consider referring to their modelling approach on preventive chemotherapy for school-aged children.
Using current WHO guidelines as stated. We use WHO definitions for low, moderate and high prevalence settings which are explained in the background section and tables 1-2.

5. The authors write: "However, as prevalence rises within higher settings…". The authors might consider defining "higher setting". The sentence needs revision.
Edited to "as prevalence rises within high prevalence settings…" Using WHO definition for high prevalence settings which is defined in background section and tables 1-2.

6. The authors write: "…(with coverage levels increasing with the adult burden of infection)." It is not clear what the authors mean here. The authors might consider revising the part in brackets for more clarity.
This is explained in the insights gained from quantitative and mathematical modelling analyses section and shown in figure 1.

7. The authors write: "…hinder progress towards achieving and maintaining EPHP". The authors might consider that interruption of transmission has been suggested as goal, too (see my 1. Comment).
IOT has been mentioned in the background: "The WHO end goal for schistosomiasis is interruption of transmission (IOT) which is achieved once the incidence of infection is reduced to zero[4, 4a]."

8. "EPHP" should be defined at the beginning so that the reader better understands the following sentence "Additionally, even though EPHP may be reached, prevalence can still be high".
EPHP has been defined in Table 1 at its first mention in the letter.

9. The authors write: "Therefore, without elimination of transmission, treatment will likely have to continue to maintain EPHP." The authors might consider defining "treatment". What treatment regimen do they have in mind? MDA?
Treatment has been left broad here as it does not mean only MDA necessarily, e.g. could include WASH as mentioned in the risks faced by treatment programmes section.

Background:
1. The authors write: "The World Health Organization (WHO) has set goals of morbidity control and elimination as a public health problem (EPHP) for schistosomiasis to be reached by 2020 and 2025, respectively[4] (defined in Table 1)." The authors might consider that the WHO also set goals for interruption of transmission in selected countries, to provide a complete picture of the goals set

for 2020 and 2025.
This has been mentioned in the background: "The WHO end goal for schistosomiasis is interruption of transmission (IOT) which is achieved once the incidence of infection is reduced to zero[4, 4a]."

2. The authors write: "There are recommended WHO treatment guidelines for achieving these goals based on the prevalence in school-aged children". The authors might consider that in their strategic plan 2012-2020, the WHO recommends to "adjust preventive chemotherapy and to use additional complementary public-health interventions" for reaching elimination as a public health problem (World Health Organization, 2013[3]). Hence, in my view, the available guidelines do not focus on targeting school-aged children only. It seems to me that the authors refer to WHO recommendations for achieving morbidity control only, but not the actual guidelines for reaching elimination as public health problem. There are important differences in the approaches, which should be clarified.
*See responses to abstract comment 2 and comment *.*

3. The authors write: "Mathematical models of transmission dynamics and the impact of control interventions have been developed to inform decision makers on the optimal treatment strategies which are required for achieving the WHO goals". The authors might clarify which goals exactly they write about.
The last paragraph of the background section has been edited to make clearer that we have investigated current WHO guidelines in relation to the current EPHP goal.

4. The authors write: "Currently, the proposed 2030 goal for schistosomiasis is EPHP." The authors might consider mentioning that WHO invited feedback and strategies for the proposed goals and that in the meantime in line with a consultation meeting, the Global Schistosomiasis Alliance (GSA) challenged that goal to some extent and responded to WHO as follows: "GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries and an interim and complementary goal of reducing the global burden of schistosomiasis disease." (https://www.eliminateschisto.org/news-events/news/gsa-consultation-meeting-accelerating-progress-f
).
See response ^.

5. The authors write: "Note that the following sections focus on S. mansoni and Kato-Katz" (as this is the currently recommended diagnostic technique). The authors might provide a reference for this recommendation of Kato-Katz.
Reference 6a has been added for this.

6. The authors write: "Additionally, the current WHO treatment guidelines have been investigated...". The authors might consider highlighting which guidelines exactly they investigated and for what (i.e. morbidity control or elimination as public health problem) and how, and provide a reference to the guidelines.
*See response to comment 3 above, comment 2 in abstract and *.*

7. The authors write: "…the currently recommended WHO guidelines (of 75% SAC-only treatment) are sufficient for achieving the EPHP goal for S. mansoni." As indicated in my previous comments, the current guidelines indicate that to achieve elimination of schistosomiasis as a public health problem, WHO recommends to "adjust preventive chemotherapy and to use additional complementary public-health interventions" (World Health Organization, 2013[3]). Hence, it remains

unclear, why the authors stick to recommendations for morbidity control and not elimination as a public health problem?
*See response to comment 2 in abstract and *.*

8. The authors write: “As the burden of infection in adults relative to SAC increases…”. The authors might define burden. Is it measured in intensity, worm numbers, DALYs or something else?
The burden relates to the transmission intensity - The age-specific contact rates, i.e. transmission intensities by age group, were varied such that the adults have a low or high burden of infection relative to SAC. This has been clarified in the sentence referred to: “As the burden of infection (intensity of transmission) in adults relative to SAC increases…”

Practical implications:
1. The authors write: “EPHP is technically feasible in all settings within 10 years provided that the appropriate treatment strategy is used...”. A recent study on S. haematobium in Zanzibar, a setting targeted for elimination as public health problem and interruption of transmission, showed that despite 5 years of bi-annual MDA in schoolchildren with high coverage and adults with moderate compliance, elimination as public health problem was not reached in all sentinel sites, probably due to heterogeneity in transmission and some remaining pockets with high transmission potential, where people got reinfected rapidly (Knopp et al., 2019a[1], Knopp et al., 2019b[2]). The authors might consider validating their model based on available field data.
*Agree, we are planning to do this. Our modelling insights here are assuming 100% adherence and coverage at random at each round of MDA (see response ** above).*

2. The authors write: “To monitor and assess progress towards the EPHP goal, prevalence and infection intensity data are required from SAC (as the goal is defined by <1% prevalence of heavy-intensity infections in SAC).” The authors might consider adding a reference. When checking the proposed goals published by WHO at https://www.who.int/neglected_diseases/news/NTD-Roadmap-targets-2021-2030.pdf?ua=1, I did not see any mention of “SAC“. The current guidelines define elimination as public health problem as “<1% heavy infection intensities in all sentinel sites” (World Health Organization, 2013[3]).
**** We are referring to the current EPHP goal here as stated at the end of the background section. Defined in table 4.4 in reference 4a (reference has been added to letter) as heavy-intensity infections are measured in SAC.*

3. The authors write: “The goal is currently assessed by averaging the prevalence measured in five schools randomly sampled within a district.” Is measuring prevalence in 5 schools related to the modelling approach of the authors or is it a recommendation by WHO to? If the latter, the authors might consider providing a reference.
5 schools per district are frequently surveyed for mapping schistosomiasis. This has been edited to: “The goal is currently typically assessed by averaging the prevalence measured in five schools randomly sampled within a district[10].”

4. The authors write: “Pre-SAC can also be infected with schistosomiasis…”. The authors might consider that a patient is not infected with a disease but with the disease-causing agent, in this case schistosomes.
Corrected to schistosomes.

5. The authors write: “Development of a paediatric formulation of praziquantel for pre-SAC

treatment would prevent this". The authors might consider that not only the development but finally only the large-scale application of the paediatric praziquantel would reduce a potential reservoir in PSAC.
We have not used our modelling analyses to determine the coverage at which paediatric praziquantel would need to be given in order to have an impact. Hence, we do not mention the scale of this.

6. The authors write: "Due to remaining infections, it is highly likely that treatment will still be needed after achieving EPHP". Again, it would be nice if the authors can clarify what is meant with "treatment".
See response to abstract comment 9.

7. The authors write: "To alleviate the need for ongoing treatment and to prevent resurgence, EOT is required after reaching EPHP." The authors might consider indicating that this is/was one of the goals of WHO for selected countries until 2025 and that also "GSA strongly supports the proposal of the ambitious goal of interruption of transmission in selected countries".
In the background we state that IOT is the WHO end goal for schistosomiasis. Also see response ^.

8. The authors write: "The transition of treatment programmes from EPHP to EOT will require reassessment of the treatment strategy." The authors might consider clarifying if they indeed refer to treatment strategies only, or broader intervention strategies, i.e. including also snail control, WASH, behaviour change, surveillance-response, etc.
We are referring to MDA and broader intervention strategies. The following has been added to the sentence to clarify: "with consideration of additional interventions such as behaviour change and snail control."

Table 1:

1. The authors write: "Elimination as a public health problem (EPHP): <1% prevalence of heavy-intensity infections in SAC". Note that this is the current 2025 goal. To my knowledge, the current goal is not referring to SAC but sentinel sites?
*See response ***.*

2. The authors write: "In low to moderate prevalence settings (<50% SAC prevalence prior to treatment), EPHP is likely to be achieved with 75% SAC-only treatment." For how many years is SAC needed to be treated?
Timelines to achieve EPHP are shown in Table 2.

Priority questions:

- Validation of the models with real data from different prevalence and intensity settings could be one additional aim.

We agree and this is part of our ongoing work. However, the priority questions listed here are those which have been identified in discussions with WHO.

Competing Interests: No competing interests were disclosed.

Reviewer Report 04 September 2019

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W. Evan Secor
Parasitic Diseases Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, GA, USA

The Schistosomiasis Group of the NTD Modelling Consortium reports the projected coverage levels necessary to achieve the WHO-defined elimination of schistosomiasis as a public health problem (EPHP, <1% prevalence of heavy-intensity infections). The modelling results demonstrate that this definition of EPHP may be possible (at least under a 10 year program) if sufficient levels of MDA coverage are attained. The challenge comes from how reliable this definition of EPHP is in terms of true elimination of schistosomiasis-associated morbidity. It has never been clearly demonstrated that morbidity is eliminated when there are fewer than 1% heavy infections. This is not the responsibility or intent of the authors but it would be valuable for them to mention the limitations of EPHP as currently defined and that the model requirements for length and minimum coverage of MDA may well need revising once an evidence-based definition of schistosomiasis morbidity elimination has been established.

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?
Partly

Is the Open Letter written in accessible language?
Yes

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

Competing Interests: No competing interests were disclosed.

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 15 Nov 2019

Jaspreet Toor,

We thank Evan for his feedback and agree with the concerns raised regarding the current WHO definition of EPHP. We have added more about how this current definition is limited in terms of its

relationship to the reduction of schistosomiasis-associated morbidity. Further modelling will be done following revision of the goal as this may impact our recommended treatment strategies.

The following has been added in the background section: “There is uncertainty around how reliable the current WHO definition of EPHP is for estimating a reduction in schistosomiasis-related morbidity as lower intensity infections may also be associated with significant morbidity [3]. Further modelling will be required following revision of this goal by WHO as this may impact our recommended treatment strategies.”

Competing Interests: No competing interests were disclosed.