A call to strengthen the global strategy for schistosomiasis and soil-transmitted helminthiasis: the time is now

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Summary

In 2001, the World Health Assembly (WHA) passed the landmark WHA 54.19 resolution for global scale up of mass administration of anthelminthic drugs for morbidity control of schistosomiasis and soil-transmitted helminthiasis (STH), which affect over 1.5 billion of the world's poorest people. Since then, over a decade of research and experience has yielded critical new knowledge on the control and elimination of these helminthiases. However, the global strategy has remained largely unchanged since the original 2001 WHA resolution and associated World Health Organization (WHO) guidelines on preventive chemotherapy. Here, we highlight recent advances that, taken together, support a call to revise the global strategy and guidelines for preventive chemotherapy and complementary interventions against schistosomiasis and STH. This includes the development of guidance that is specific to goals of "morbidity control" and "elimination of transmission." We quantify the result of forgoing this opportunity by computing the yearly disease burden, mortality, and lost economic productivity associated with maintaining status quo. Without change, we estimate that the population of sub-Saharan Africa will likely lose 2.3 million disability-adjusted life years and US$3.5 billion of economic productivity every year, which is comparable to recent acute epidemics, including the 2014 Ebola and 2015 Zika epidemics. We propose that the time is now to strengthen the global strategy to address the substantial disease burden of schistosomiasis and STH.

Personal View

Introduction

Over 15 years ago, the World Health Assembly (WHA) passed the landmark WHA 54.19 resolution to address the 1.5 billion people affected by schistosomiasis and soil-transmitted helminthiasis (STH; including ascariasis, hookworm disease, and trichuriasis).[1,2] The WHO subsequently created a Department of Neglected Tropical Diseases (NTDs), and produced guidelines that set a new paradigm for a public health approach against many NTDs, including schistosomiasis and STH, through a strategy of preventive chemotherapy (via 'mass drug administration').[3] This strategy involves large-scale, periodic (e.g., yearly) empiric treatment of entire populations and typically focuses on groups assumed to have the greatest disease morbidity, such as school-aged children (ages 5-15 years) for schistosomiasis and pre-school and school-aged children (ages 1-15 years) for STH.[3,4] These helminthiases are characterized by mostly chronic, often insidious helminth-specific sequelae ranging from mild to severe morbidities. These include anaemia, chronic abdominal pain, and malnutrition, and also more rare and serious complications including bladder cancer, hepatosplenomegaly, and death for schistosomiasis and small bowel obstruction and rectal prolapse for STH.

Today, under the auspices of the WHO Department of NTDs, catalyzed by the 2012 London Declaration for NTDs, and with large-scale support from governments, pharmaceutical companies, and NGOs, preventive chemotherapy programmes have achieved impressive gains. In 2015 alone, these programmes delivered treatment to 65 million people using praziquantel (against schistosomiasis) and 565 million people using albendazole or mebendazole (against STH) throughout Africa, Asia, Latin America, and the Middle East.[5,6] Over this period, there have been corresponding reductions in the number of infections and global disease burden

estimates.[1,2,7] This strategy of "morbidity control" has defined a goal of "eliminating helminths as a public health problem." For STH, this is defined as <1% moderate-to-heavy intensity infection prevalence in at risk populations, as determined by egg counts on microscopic examination, and for schistosomiasis, the goal has been expressed as <1% heavy-intensity infections based on egg counts in stools or urine.

While this commendable morbidity control strategy has certainly led to success, mainly by averting long-term sequelae in school-aged children, the reinfection rate has been high in most settings.[8,9] Unfortunately, even countries that have successfully implemented the recommended preventive chemotherapy strategy for schistosomiasis and STH—i.e., repeated treatment of school-aged children at WHO-recommended ≥75% coverage—have met challenges in achieving optimal morbidity control or the more ambitious goal of transmission elimination.[8,10,11] This finding is consistent with estimates by the Global Burden of Disease (GBD) study and others that have documented how progress has lagged behind for schistosomiasis and STH relative to many other NTDs.[12] To address this challenge, in light of the past decade of data and experience from the field, we re-visit the global strategy for preventive chemotherapy and complementary interventions against schistosomiasis and STH.

Preventive chemotherapy

As the post-2020 agenda for NTDs is considered, there is growing interest in improving the morbidity control strategy, and when appropriate, shifting towards a more ambitious goal of "elimination of transmission," which is defined as interruption of transmission. The critical, policy-relevant question to be asked is how we can leverage new evidence to strengthen current strategies and guidelines for preventive chemotherapy to achieve these goals (see Panel 1). The current strategy of morbidity control emphasises treatment of school-aged children alone (with

extension to preschool-aged children for STH); however, adolescents and adults (15 years and older; including pregnant women) and younger children (<5 years) in the case of schistosomiasis, are often infected and are not rigorously addressed in the current global strategy or in parasitological monitoring.[3,4,13] If left untreated, these groups can serve as a "hidden reservoir" and potential source of reinfection for all age groups. Modelling studies indicate that expanding treatment from school-aged children alone to entire communities could substantially reduce reinfection across all age groups, and avert accumulated morbidity in these populations, especially schistosomiasis-related chronic sequelae in preschool-aged children.[10,13-16] The relative advantage of community-based treatment has been further supported by a recent systematic review and meta-analysis of observational studies.[17] Furthermore, expanded community-wide treatment can be highly cost-effective because of this averted morbidity, even if transmission is not eliminated.[10,18] To achieve community-wide coverage, countries could utilize distribution networks from other community-based health platforms for feasibility and cost-efficiency, including integration with vaccination programmes, Demographic and Health Surveys (DHS), or through continued use of lymphatic filariasis or onchocerciasis drug distributors who have delivered community-wide anthelminthics (e.g., ivermectin, albendazole) at scale.[19,20]

Guidelines currently provide "prevalence thresholds", above which a preventive chemotherapy strategy is recommended, but given recent experience these may be too restrictive to achieve optimal averted disability and cost-effectiveness even under a goal of morbidity control. These prevalence thresholds are based on expert opinion and a historically more limited drug supply, and have remained largely unchanged for over a decade.[3,4] While these thresholds have guided efforts in preventive chemotherapy, analysis of new data suggest they can be

improved by considering transmission dynamics and health economics.[10,18] Notably, a recent study that rigorously assessed these prevalence thresholds found them to often be too restrictive on the basis of morbidity control (measured in disability-adjusted life years (DALYs)) and cost-effectiveness, especially for schistosomiasis.[18] For example, annual school-based treatment of schistosomiasis was cost-effective at 5% prevalence rather than the currently recommended 50% prevalence, and new prevalence thresholds were defined for community-wide coverage for both sets of helminthiases.[18] Importantly, while expanded treatment would have great potential to avert disease morbidity, reduce overall reinfection, and prevent chronic sequelae in young children, the potential emergence of drug resistance from increased treatment pressure is a concern. Therefore, rigorous methods to monitor drug efficacy will be essential, although community-wide treatment at 75% coverage still falls under the best practices according to conservative estimates from veterinary literature.[21] This concern can further be addressed by a longer-term but necessary research and development agenda to create improved drug regimens with greater efficacies against schistosomiasis and STH (particularly trichuriasis), where drug efficacy may be lower than expected, or even anthelminthic vaccines to prevent reinfection.[22-24] New diagnostics for helminths (e.g., point-of-care circulating cathodic antigen urine cassette test for *Schistosoma mansoni*) can also be applied to guide new treatment thresholds.[25]

Re-examination of the preventive chemotherapy strategy should also consider recent evidence from the Cochrane Collaboration and Campbell Collaboration systematic reviews and meta-analyses of trial data that suggests limited benefit of school-based preventive chemotherapy for STH, although should be considered within the limitations of the data and substantial debate surrounding potential methodological challenges (see Appendix).[26-30] For example, studies may be underpowered to detect a meaningful effect and relevant health outcomes may not be realized

within the short timeframe of most trials. Furthermore, children may have high rates of reinfection in school-based programmes that limits improvements to health, but this could be overcome with community-wide treatment strategies.[10,16,17]

The updated global strategy for preventive chemotherapy should increase attention to country-level coordination of integrated programmatic delivery (i.e., giving multiple medicines in the same programme) that would yield substantial cost-savings and biological synergies within the constraints of proven feasibility.[10,18,31,32] While integrated preventive chemotherapy guidelines do exist, improving country-level coordination of these programmes would benefit cost-efficiency.[18,33] The prevalence threshold itself is lower for adding another medicine in addition to an existing treatment programme compared to a standalone programme due to reduced delivery cost, and since the majority of cost is from delivery and not the drugs themselves.[10,31] For example, programmatic delivery of praziquantel should include albendazole or mebendazole, as done by the Schistosomiasis Control Initiative, since STH is most often co-endemic and co-administration is safe.[32] The integration of these programmes should work within the constraints of the drug supply and the relevant ecological zone (e.g., national, sub-national, community) that addresses the focal nature of schistosomiasis, which is in contrast with the more homogenous nature of STH.

Complementary interventions

The global strategy should include water, sanitation, and hygiene (WASH) interventions, information, education, and communication (IEC) programmes, and focal snail control (for schistosomiasis), especially when elimination of transmission is the goal. Coordinated guidelines are needed that define the conditions (e.g., prevalence threshold, programmatic goals) where each complementary intervention should be implemented alongside preventive chemotherapy

191 within the broad framework of local health needs. While WASH programming, IEC, and snail
192 control are not the focus of current global efforts, growing evidence supports the need for greater
193 inclusion within the updated strategy, especially where disease dynamics are recalcitrant to
194 preventive chemotherapy alone or elimination of transmission is the goal.

195 The implementation of the WHO WASH-NTD global strategy will likely be essential to
196 eliminate transmission.[34] Observational studies have provided evidence for the relationship
197 between various components of WASH (including improved water, sanitation, and hygiene and
198 health behavior) and helminth prevalence and mean intensity.[35-39] However, the experimental
199 evidence from trials is mixed, and studies are ongoing to validate the data from observational
200 studies.[37,39-42] Regardless, these programmes are likely to have substantial spillover benefit by
201 reducing the incidence of other infectious diseases improving country-level cost-effectiveness.[39]

202 The importance of snail control in schistosomiasis control and elimination has been
203 supported by a recent meta-analysis, empirical analyses of historical data and modelling
204 studies.[15,43,44] The inclusion of multiple means of snail control within a coordinated strategy
205 alongside preventive chemotherapy for schistosomiasis is an important step forward in
206 eliminating transmission in low endemicity settings and also controlling disease morbidity in
207 high endemicity settings.

208 *Guidelines for morbidity control versus elimination of transmission*

209 Distinct programmatic guidance is urgently needed that is specific to the different goals of
210 "morbidity control" or "elimination of transmission," and is informed by the setting's local
211 helminthiases epidemiology and health priorities of the country. The decision on strategy should
212 further be made on a sub-national basis with consideration of the focal nature of schistosomiasis.
213 Importantly, disease burden differs considerably among settings, and elimination of transmission

may not be possible in all locations with existing tools and resources. High-burden settings may set a near-term goal of morbidity control, while low-burden settings may target elimination of transmission. In all cases, settings should first aim to achieve effective morbidity control before expanding to a goal of elimination of transmission.

To achieve this, settings targeting STH for morbidity control should focus on ensuring high drug coverage in all risk groups, including preschool-aged children and adults. In contrast, settings with low prevalence may set a goal of eliminating transmission and may prioritise non-drug interventions such as WASH programming, snail control, and intensive surveillance.[45] In all cases, the country's goals and resource constraints will inform this choice, and distinct strategic recommendations should be available to reflect these different scenarios. Importantly, programmatic goals should be established with full country ownership of these programmes, especially in regions with an improving economy and health systems. In developed countries, particular attention should be given to "blue marble health" which recognises the sizable proportion of the global burden of helminthiasis that occurs in the poorer populations of wealthy countries will require distinct strategies and political support structures.[46]

The proposed revision to the global strategy may substantially expand the target population for preventive chemotherapy and resources needed for complementary interventions. In countries that have yet to achieve the 2020 goal of at least 75% drug coverage of all at-risk populations, the development of an updated strategy will serve to clarify resource, drug supply, and programmatic needs to attain the 2020 goal and beyond. In settings that have reached 75% drug coverage targets, strengthened guidance should provide an evidence-based strategy towards a more ambitious and well-defined goal of optimal morbidity control or elimination of transmission without allowing for infection rebound.

The historic creation of many aspirational targets in global health, including the "3 by 5" initiative for HIV/AIDS, the Millennium Development Goals (MDGs), and the London Declaration on NTDs illustrates the potential of setting a higher bar to improve human health. The inclusion of NTDs as a specific target within the UN Sustainable Development Goals (SDGs) signifies the role in achieving Universal Health Coverage.[47]

To quantify the potential gains of strengthening the global strategy for schistosomiasis and STH, we compare recent evidence-based strategies for preventive chemotherapy relative to the current global strategy and idealized WHO guidelines. Without change, we estimate that the population of sub-Saharan Africa will likely lose 2.3 million DALYs and US$ 3.5 billion of economic productivity every year, which is comparable to the impact of recent acute epidemics, including the 2014 Ebola and 2015 Zika epidemics combined (see Table 1, Appendix).

Conclusions

With a shared goal of reducing the burden of NTDs on the world's poorest people, and following the leadership of WHO Director-General Dr. Margaret Chan and colleagues around the world in NTDs, we respectfully advocate for revision of the global strategy and associated WHO guidelines for schistosomiasis and STH to incorporate new knowledge and experience gained over the last 15 years. If we miss this opportunity, then we fail to do all we can to help the populations who suffer the greatest burden of helminthiases and other NTDs.

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Panel and Tables

Panel 1: Key steps for strengthening the global strategy for schistosomiasis and STH

Key step	Strength of evidence
Step 1: Update strategy for preventive chemotherapy	
• Expanded treatment across broader age groups (i.e., community-wide treatment)	Modelling and cost-effectiveness studies[10,14,18,48] with support from systematic review and meta-analysis of observational studies[17]
• Lower prevalence thresholds for treatment, especially for schistosomiasis	Modelling and cost-effectiveness studies[18] with support from observational studies
• Formal guidelines for integration of praziquantel and benzimidazole programming	Cost-effectiveness modelling studies with support from feasibility studies[10,18,31,32]
• Validated strategy with trial data	Trials underway
• Rigorous monitoring and evaluation strategies to detect emergence of drug resistance	Statistical models with field validation[49]
Step 2: Incorporate complementary interventions in the global strategy	
• Water, sanitation, and hygiene (WASH) programming (e.g. community-led total sanitation)	Systematic review and meta-analysis with mixed findings including mostly observational studies[34-42]
• Information, education, and communication (EIC) programmes	Trial data[40]
• Snail control (for *Schistosoma* spp).	Systematic review and meta-analysis including mostly observational studies; modeling studies[15,43]
Step 3: Create distinct guidelines based on epidemiology, programmatic goals, and resource constraints	
• Guidelines for a goal of morbidity control *versus* elimination of transmission	Expert opinion

Table 1: Annual disease burden, mortality, and economic burden of current global strategy, idealized WHO preventive chemotherapy guidelines, and cost-effective preventive chemotherapy guidelines for schistosomiasis and STH

Strategy	Disease burden (DALYs)	Mortality (DALYs)	Economic losses[c] (2015 US$, thousands)
No treatment	4,156,306	176,393	6,482,613
Current global strategy[a]	3,957,325	176,392	6,182,450
Idealized WHO guidelines[b]	3,474,731	159,921	5,462,829
Cost-effective guidelines[18]	1,674,551	88,877	2,715,934

Cost-effective guidelines[18] relative to:	Avertable disease burden (DALYs)	Avertable mortality (DALYs)	Avertable economic losses[c] (2015 US$, thousands)
No treatment	2,481,755	87,516	3,766,679
Current global strategy[a]	2,282,774	87,515	3,466,516
Idealized WHO guidelines[b]	1,800,180	71,044	2,746,895

[a]Estimation based on WHO guidelines with current global coverage for preventive chemotherapy.

[b]Estimation based on WHO guidelines with 75% coverage and uses school-based preventive chemotherapy programmes, except for inclusion of preschool-aged children in STH treatment. This reflects the stated priority within guidelines, the current global strategy, and empirical coverage estimated amongst different age groups. However, WHO guidelines do recommend treatment of women of childbearing age for STH, and treatment in entire communities under some circumstances above 50% prevalence for schistosomiasis, although coverage remains minimal in these groups.

[c]Economic losses are estimated as the product of disability (DALYs) and country GDP per capita (see Appendix).

Note: Results are annualized over a 5-year simulation and are intended to give a broad estimate of the magnitude of avertable health and economic loss. Methodological details, limitations, and discussions of uncertainty are provided in the Appendix.

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Contributors:

Mr. Nathan C. Lo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Article conception- NCL

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Contributed intellectual material and approved final draft - All authors

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