



Defining elimination as a public health problem for schistosomiasis control programmes: beyond prevalence of heavy-intensity infections

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WHO's 2021–30 road map for neglected tropical diseases (NTDs) outlines disease-specific and cross-cutting targets for the control, elimination, and eradication of NTDs in affected countries. For schistosomiasis, the criterion for elimination as a public health problem (EHP) is defined as less than 1% prevalence of heavy-intensity infections (ie, ≥ 50 *Schistosoma haematobium* eggs per 10 mL of urine or ≥ 400 *Schistosoma mansoni* eggs per g of stool). However, we believe the evidence supporting this definition of EHP is inadequate and the shifting distribution of schistosomiasis morbidity towards more subtle, rather than severe, morbidity in the face of large-scale control programmes requires guidelines to be adapted. In this Viewpoint, we outline the need for more accurate measures to develop a robust evidence-based monitoring and evaluation framework for schistosomiasis. Such a framework is crucial for achieving the goal of widespread EHP of schistosomiasis and to meet the WHO road map targets. We encourage use of overall prevalence of schistosome infection (instead of the prevalence of heavy-intensity infections), development of species-dependent and age-dependent morbidity markers, and construction of a standardised monitoring and evaluation protocol.

Introduction

The goal for schistosomiasis in the newly released WHO 2021–30 road map for neglected tropical diseases (NTDs) is its elimination as a public health problem (EHP) in 100% of affected countries.¹ Although this goal is an admirable one that should be pursued, the definition of EHP for schistosomiasis stated in the road map could hinder its achievement. The road map uses the same target as the 2013 WHO schistosomiasis guidelines, which defined EHP as less than 1% prevalence of heavy-intensity infections (PHI; ie, ≥ 50 *Schistosoma haematobium* eggs per 10 mL of urine or ≥ 400 *Schistosoma mansoni* eggs per g of stool).² The emphasis on PHI by policy makers in the late 1980s and early 1990s was based on an observed correlation between chronic heavy-intensity infections and severe morbidity (eg, liver or bladder fibrosis) and was determined through expert opinion.^{3,4} Because of the low availability and high cost of praziquantel at that time, the schistosomiasis guidelines focused on a reduction of life-threatening disease through decreasing PHI.⁵

However, for the purposes of the 2021–30 road map, we feel this approach is outdated for several reasons. First, basing the EHP guidelines on measuring and reducing PHI is founded on flawed interpretations of the available data.⁶ The premise that most people with schistosome infections are symptom-free, and that only people with heavy-intensity infections show severe morbidity, is incorrect. The inference was based on the identification of similar proportions of morbidity in lightly infected and uninfected people, especially for *S mansoni* infections.⁴ However, individuals with low intensities of infection can express all forms of the disease, and thus morbidity can be caused by any intensity of schistosome infection.⁷ To draw a conclusion that only high-intensity

infections cause morbidity requires equivalence or non-inferiority testing. Yet, to our knowledge, such analyses were not performed. Second, the issue of not considering morbidity caused by light-intensity infections was compounded by failing to consider the suboptimal sensitivity of the diagnostic tests used to detect parasite eggs. With up to half of *S mansoni* infections being missed in studies using only a single stool sample,^{8,9} individuals with morbidity associated with light-intensity infections would be misclassified as uninfected.⁶ Third, beginning in the mid-2000s, there was recognition that less clinically severe manifestations of schistosomiasis (which can occur even with light infections) have a greater impact on disability-adjusted life-years than the most severe pathologies.⁷ Taken together, focusing EHP targets only on severe pathologies does not address most of the current disease burden.^{6,7} Ultimately, a proxy of severe pathology largely ignores the populations most vulnerable to the effects of schistosome infections, especially paediatric and maternal populations^{10,11} and school-aged children—the primary treatment target group.¹²

In addition to more sensitive diagnostic tools,¹³ other changes needed to improve the EHP definition of schistosomiasis morbidity include improving decision thresholds and survey design in the monitoring and evaluation framework. We recently evaluated the associations between morbidity prevalence and the pre-2022 WHO guideline² targets of 1% PHI for EHP and 5% PHI for control of morbidity and did not find differences in morbidity prevalence between these targets.¹⁴ Although there were some associations between PHI-based targets and morbidity prevalence, there were no consistent differences in morbidity prevalence between children in schools with less than 1% PHI and

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children in 1–5% PHI schools, except when microhaematuria prevalence was compared with *S haematobium* infection prevalence. The absence of association between the PHI-based targets and morbidity suggests new targets are needed, which is one of the goals of the newly formed WHO Technical Advisory Group on Schistosomiasis and Soil-Transmitted Helminthiases. In this Viewpoint, we present an outline of important considerations and research needs for determining new programme targets for schistosomiasis morbidity control and improving the monitoring and evaluation framework.

Infection prevalence not PHI

We believe that there is a strong rationale to shift the definition of the schistosomiasis EPHP targets to a function of the prevalence of any *Schistosoma* infection rather than its intensity. First, predicting whether a community has achieved EPHP is less accurate when using PHI than infection prevalence. Analyses of the associations between school-level microhaematuria prevalence and school-level *S haematobium* infection prevalence indicated that prevalence-based targets were more robust and provided greater certainty of eliminating morbidity as a public health problem than PHI-based targets.¹⁵ PHI-based targets were highly sensitive to slight variations in egg counts, meaning a small number of missed eggs could alter a community's EPHP status. In addition, prevalence-based targets regularly provided 95% or greater certainty of controlling schistosomiasis-related microhaematuria, whereas PHI-based targets did so only sparingly.¹⁵

Furthermore, WHO's treatment strategy for schistosomiasis mass drug administration is determined by the prevalence and does not use PHI.^{16,17} Collecting intensity data to determine whether a PHI threshold has been reached involves a larger sample to be tested. Intensity determinations also require the counting of eggs and are more prone to measurement error than a binary decision for prevalence. New diagnostic tests based on presence of egg and worm antigens, antibodies, or DNA in an individual would provide a prevalence measure and only a semi-quantitative indication of intensity.¹⁸ Determining PHI based on egg counts has crucial implications on the effort, time, and expense of monitoring by national control programmes. Switching to a prevalence-based threshold, which is already needed for determining treatment strategies, would reduce this burden for national control programmes.

Finally, using PHI cutoffs could result in undertreatment by control programmes due to the often-observed imperfect correlation between intensity of infection and the presence and severity of morbidity.¹⁹ In the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) studies²⁰ of communities in Kenya and Tanzania with more than 25% prevalence of *S mansoni* infections before treatment (294 communities), using the PHI thresholds would

categorise 58% of these communities as having controlled schistosomiasis (<5% PHI) and 28% as having eliminated schistosomiasis as a public health problem (<1% PHI) even before the preventive chemotherapy was delivered. However, SCORE studies²¹ on childhood morbidity showed treatment-related health benefits in communities that would have been categorised as having controlled schistosomiasis morbidity because they were less than the 5% PHI target at baseline. The use of the PHI threshold for stopping treatment could therefore result in considerable undertreatment of affected communities.

Species-dependent and age-dependent morbidity markers

Although it is convenient to have common targets for EPHP across age groups and *Schistosoma* species, the reality is that these factors matter in the expression of disease morbidity, as does host sex (eg, female genital schistosomiasis). Classic manifestations of schistosomiasis (such as hepatosplenic disease in individuals infected with intestinal species, and hydronephrosis and increased risk of bladder cancer in individuals with urogenital schistosomiasis) usually occur in older adolescents or in adults after several years of infection and might not be reversible by praziquantel treatment. By contrast, symptoms that are more common in children (eg, anaemia, exercise intolerance, and haematuria) are less specific for schistosomiasis but tend to be reversible with timely treatment. Thus, it might not be possible to identify markers of morbidity that are consistent across affected populations, especially after multiple rounds of preventive chemotherapy, and achieving EPHP could be harder to define for some age groups than others.

Because morbidity in adults represents the culmination of years of infection and is less likely to quickly reverse, it is important to focus on defining EPHP targets in younger age groups—who are also the primary intervention groups for most national deworming programmes using regular preventive chemotherapy. Furthermore, reducing infection prevalence in children can have a direct benefit of improving children's health later in life²² and an indirect benefit of reducing a community's adult prevalence.²³ The question, however, remains on how to establish targets when the symptoms in children can be caused by other diseases or conditions, such as malaria or malnutrition.

Background morbidity and adjusting morbidity indicators

WHO's 2021–30 roadmap for NTDs includes the goal of reducing schistosomiasis-associated morbidity to a locally acceptable prevalence.¹ One way to define this threshold is by determining the prevalence of a given morbidity in settings where there is little or no schistosomiasis. Once this rate of background morbidity has been established, it is possible to estimate the

likelihood that a prevalence of schistosomiasis is associated with a morbidity prevalence that is greater than the background.

The exploratory analyses that defined *S haematobium* prevalence targets on the basis of the microhaematuria prevalence¹² were possible because of existing knowledge of microhaematuria prevalence not related to schistosomiasis.²⁴ This background proportion of microhaematuria allowed for the use of Bayesian methods to calculate the likelihood that a school with a given infection prevalence would be less than a prespecified microhaematuria prevalence. Other subjectively chosen morbidity prevalence values could be used in analyses, but empirical evidence on the background rate of a morbidity is needed to provide more certainty that an area has eliminated schistosomiasis as a public health problem. To explore potential targets, background rates are needed from areas with different ecological archetypes and for all species that cause human schistosomiasis. Definition of new morbidity indicators is needed, as well as establishment of the background prevalence of morbidity in an area that could be influenced by community factors, such as socioeconomic status and access to health care. Additionally, previous preventive chemotherapy (which might lessen the morbidity caused by reinfection)²⁵ and individual aspects such as age, sex, and coinfections might influence expression of morbidity. Thus, along with developing better morbidity indicators, information will be needed about how background morbidity varies in different settings.

If an appropriate background morbidity prevalence can be established, analytical methods such as those used in microhaematuria analyses can be implemented.¹⁵ Those analyses employed regression models that relate the infection prevalence in the geographical unit to the morbidity indicator prevalence through an errors in variables logistic regression model, which takes into account the uncertainty of both the infection and estimates of the morbidity indicator prevalence. The model then uses the association and uncertainty estimates to calculate the likelihood that a geographical unit with a particular infection prevalence estimate will become less than a previously specified morbidity prevalence. The prevalence estimate from those analyses can then be used as a target for schistosomiasis control programmes in a specific area, and the likelihood of reaching the target can be used to compare different intervention strategies.

Standardised protocols and technology

Detailed templates for the monitoring and evaluation of schistosomiasis are non-existent, inadequate, or in need of updating. A standardised survey design, or designs that can be used across different ecological archetypes which account for the epidemiology of each *Schistosoma* species, is urgently needed. A sentinel site design for

monitoring and evaluation has been used by some control programmes, but other designs might have greater use for assessing progress towards elimination.²⁶ Preventive chemotherapy decreases infection prevalence, or keeps infection prevalence suppressed, in most endemic settings. However, control programmes need clearer guidance on efficient survey designs that are specific to the sample population, sampling design, necessary sample size, measurement of infection or morbidity, and frequency of assessment. A multicountry initiative, the Schistosomiasis Oversampling Study,²⁷ has been designed to capture the expected spatial variation in prevalence across and within ecological archetypes. In each study site, 40–50% of all villages will be sampled. Data will be compiled to generate accurate geospatial layers of prevalence with associated uncertainty representing each setting. These interpolated geospatial layers will then be used to simulate and compare the efficiency and feasibility of a range of sampling strategies intended for use by national programmes to make control decisions at a sub-implementation unit (eg, subdistrict) level.

Most investigations related to morbidity and its control have been conducted in different ecological settings and measured different symptoms in populations that might have different distributions of age and infection prevalence. These geographical and sampling differences have hindered the development of evidence-based guidelines owing to the challenges of reaching a consensus on which morbidities to measure, and appropriate targets for these morbidities. A way to overcome this obstacle would be to follow the example of the SCORE project,^{20,28} which brought together researchers, disease control programme managers, and policy makers to develop harmonised protocols before the start of the research studies in different countries. Although this approach did not work perfectly, it allowed for the combination and analysis of data across sites, resulting in increased statistical power.²⁹ Morbidity data across age groups from the Morbidity Operational Research for Bilharziasis Implementation Decisions pilot studies in Kenya (where *S mansoni* is prevalent) and Malawi (where *S haematobium* is prevalent) could be combined with other previously published research to develop coordinated investigations using harmonised protocols to better define EPHP targets.³⁰

Another factor that could facilitate more accurate measurement of schistosomiasis morbidity and delineation of EPHP targets is the development of a tablet-based ultrasound system that allows for collection of pathology measurements in the field.³¹ Ultrasound has long been the standard for measuring schistosomiasis fibrosis and organomegaly, but the size and expense of available machines has previously constrained the practicality of field-based ultrasonic evaluation for research studies.³² Newer technology now allows combination of a transducer with standard electronic tablets to collect and electronically store ultrasound

images and videos economically. Demonstrations of the tablet-based ultrasound's utility, updated measurement standards, the creation of an updated ultrasound protocol with a focus on less severe morbidity, and the development of ethical guidelines are required before ultrasound evaluations can become more accessible and comparable.

Conclusions

WHO's 2021–30 roadmap for NTDs aims to increase the number of schistosomiasis-endemic countries validated for EPHP from 26 in 2020 to 49 in 2023, 69 in 2025, and all 78 in 2030.¹ To achieve these ambitious goals, a robust monitoring and evaluation framework is needed to measure progress and validate whether geographical areas indeed have eliminated schistosomiasis as a public health problem. Calls to develop specific programmatic guidance on how to achieve and maintain EPHP^{6,33} have yet to be heeded.^{16,17}

Unfortunately, we believe an outdated framework for EPHP remains in place and a large disconnect remains between existing practice and recent findings. A move away from PHI-based targets is needed to align with current knowledge of morbidity. Developing prevalence of infection targets on the basis of morbidity that might differ by *Schistosoma* species, age, sex, and other factors can provide a more accurate assessment of whether an area has eliminated schistosomiasis as a public health problem. Importantly, though, estimates of the background morbidity are needed to develop such targets. Finally, a standardised protocol should be developed that harmonises the sampling population, sampling design, infection and pathology measurements, and assessment frequency. The methods of this protocol should be clearly defined and broadly validated in different archetypal settings, thus allowing for standardised analyses that can better define EPHP targets.

Contributors

REW wrote this manuscript as a chapter for his PhD thesis, for which PV and JU were first and second advisers. REW and WES edited the dissertation chapter into manuscript format and all authors revised and approved the report.

Declaration of interests

CHK served on the Data Safety Monitoring Board, Praziquantel for Children Under Age Four Years Trial, National Institutes of Health; WHO Expert Advisory Panel on Parasitic Diseases (Schistosomiasis); WHO Guidelines Development Group on the implementation of control and elimination of schistosomiasis and the verification of elimination; WHO technical working group on protocols for remapping and impact assessment of schistosomiasis; and expert panel, praziquantel trial assessment, Pediatric Praziquantel Consortium. All other authors declare no competing interests.

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