HHS Public Access

Author manuscript

Lancet Glob Health. Author manuscript; available in PMC 2023 May 15.

Published in final edited form as:

Lancet Glob Health. 2022 September ; 10(9): e1355–e1359. doi:10.1016/S2214-109X(22)00287-X.

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

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Summary

The World Health Organization's 2021–2030 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 criteria for elimination as a public health problem (EPHP) is defined as <1% prevalence of heavy intensity infections (e.g., 50 or more

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

Declaration of interests

The authors declare that they do not have any commercial or other association that might pose a conflict of interest.

Schistosoma haematobium eggs per 10 ml of urine or 400 or more *S. mansoni* eggs per gram of stool). However, the evidence supporting this definition of EPHP is limited 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 EPHP of schistosomiasis and meeting the road map targets. We encourage using overall prevalence of *Schistosoma* infection instead of the prevalence of heavy intensity infections, developing species- and age-dependent morbidity markers, and constructing a standardized monitoring and evaluation protocol.

Introduction

The goal for schistosomiasis in the newly released World Health Organization (WHO) 2021–2030 road map for neglected tropical diseases (NTDs) is its elimination as a public health problem (EPHP) in 100% of affected countries (1). While this is an admirable goal that should be pursued, the definition of EPHP for schistosomiasis articulated in the road map may hinder its achievement. The road map uses the same target as the 2013 WHO schistosomiasis guidelines, which defined EPHP as <1% prevalence of heavy intensity infections (PHI; e.g., 50 or more *Schistosoma haematobium* eggs per 10 ml of urine or 400 or more *S. mansoni* eggs per gram of stool) (2). The newly released guidelines do not change this target (3, 4). 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 (e.g., liver or bladder fibrosis) and was determined through expert opinion (5, 6). Because of the limited availability and high cost of praziquantel at that time, the schistosomiasis guidelines focused on reduction of life-threatening disease through decreasing PHI (7).

However, for the purposes of the 2021–2030 road map, we feel this approach is outdated based on the following grounds. First, basing the EPHP guidelines on measuring and reducing PHI is founded on flawed interpretations of the available data (8). Notably, the premise that most people with schistosome infections are symptom-free and that only persons with heavy intensity infections demonstrate severe morbidity is incorrect. The inference was based on finding similar proportions of morbidity in lightly infected and uninfected persons, especially for *Schistosoma mansoni* infections (6). However, individuals with low intensities of infection can express all forms of the disease, and thus morbidity caused by *Schistosoma* infection can also be triggered simply by the presence of infection (9). 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. 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 (10, 11), individuals with morbidity associated with light intensity infections would be misclassified as uninfected (8). 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 (DALYs) compared to the most severe pathologies (9). Thus, focusing EPHP targets only on severe pathologies does not address most of the current disease burden (8, 9). Ultimately, a proxy of severe pathology largely ignores the populations most vulnerable to the effects of *Schistosoma* infections, especially paediatric and maternal populations (12, 13) and school-aged children, the primary treatment target group (14).

In addition to more sensitive diagnostic tools (15), other changes needed to improve EPHP of schistosomiasis morbidity include improving decision-thresholds and survey design in the monitoring and evaluation framework. We recently evaluated the associations between morbidity levels and the pre-2022 WHO guideline (2) targets of 1% PHI for EPHP and 5% PHI for control of morbidity and did not find differences in morbidity levels between these targets (16). While there were some associations between PHI-based targets and morbidity levels, there were no consistent differences in morbidity levels between children in schools with <1% PHI and children in 1–5% PHI schools, except when microhaematuria prevalence was compared to *S. haematobium* infection prevalence. The lack of association between the PHI-based targets and morbidity suggest new targets are needed, which is one of the goals of the newly formed WHO Technical Advisory Group on Schistosomiasis and Soil-Transmitted Helminthiasis (TAGSS). Here, 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 instead of the prevalence of heavy-intensity infections

We believe that there is strong rationale to shift the definition of schistosomiasis EPHP targets as a function of prevalence of any *Schistosoma* infection rather than intensity. First, determination of whether a community has achieved EPHP is less predictive when using PHI compared to infection prevalence. Analyses of the associations between school-level microhaematuria prevalence and school-level *S. haematobium* infection levels indicated that prevalence-based targets were more robust and provided greater certainty of eliminating morbidity as a public health problem than PHI-based targets (17). 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 (17).

Furthermore, the treatment strategy for schistosomiasis mass drug administration is determined by the prevalence and does not utilize PHI (3, 4). 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 antigen, antibody, or *Schistosoma* 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 critical implications on the effort, time, and expense for 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 may 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) studies of communities in Kenya and Tanzania with >25% prevalence of *S. mansoni* infections pre-treatment (294 communities), using the PHI thresholds would categorize 58% of 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 (20). By contrast, SCORE studies on childhood morbidity showed treatment-related health benefits in communities that would have been categorized as having controlled schistosomiasis morbidity because they were below the 5% PHI target at baseline (21). The use of the PHI threshold for stopping treatment could result in significant undertreatment of affected communities.

Species- and age-dependent morbidity markers

While it is convenient to have common targets for EPHP across age groups and schistosome species, the reality is that these factors matter in the expression of disease morbidity, as does host sex (e.g., 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 following several years of infection and may not be reversible by praziquantel treatment. By contrast, symptoms that are more common in children (e.g., anaemia, exercise intolerance, and haematuria), are less specific for schistosomiasis but tend to be reversible with timely treatment. Thus, it may not be possible to identify markers of morbidity that are consistent across affected populations, especially after multiple rounds of preventive chemotherapy, and achieving EPHP may 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 cogent to focus on defining EPHP targets in younger age groups that are also the primary intervention groups for most national deworming programmes using regular preventive chemotherapy. Furthermore, reducing infection levels in children can have a direct benefit of improving children's health later in life (22) 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

The 2021–2030 NTD roadmap includes the goal of reducing schistosomiasis-associated morbidity to a locally-acceptable level (1). One way to define this level is by determining the prevalence of a given morbidity in settings where there is little or no schistosomiasis. Once this level 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 defining *S. haematobium* prevalence targets based on the microhaematuria prevalence [14] were possible because of existing knowledge of microhaematuria prevalence not related to schistosomiasis (24). This background proportion of microhematuria allowed for the use of Bayesian methods to calculate the likelihood that a school with an infection prevalence would fall below a certain microhaematuria prevalence. Other subjectively chosen morbidity prevalence values could be utilized in analyses, but empirical evidence on the background proportion 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 levels 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 defining the background prevalence of morbidity in an area that may be influenced by community factors such as socioeconomic status and access to health care. Additionally, prior preventive chemotherapy, which may lessen the morbidity due to reinfection (25), and individual aspects such as age, sex, and coinfections may 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, analytic methods like those used in microhaematuria analyses can be implemented (17). Those analyses employed regression models that relate the infection prevalence in the geographic unit to the morbidity indicator prevalence through an errors in variables logistic regression model, which takes into account the uncertainty for both the infection and morbidity indicator prevalence estimates. The model then uses the association and uncertainty estimates to calculate the likelihood that a geographic unit with a certain infection prevalence estimate will fall below an *a priori* specified morbidity level. The prevalence estimate from those analyses can then be used as a target for schistosomiasis control programmes in a specific area and the efficacy of reaching the target can be used to compare different intervention strategies.

Standardized monitoring and evaluation protocols and technology

Detailed templates for the monitoring and evaluation of schistosomiasis are lacking, inadequate, or in need of updating. A standardized survey design or designs that can be utilized 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 recent research has found other designs may have greater utility 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 on the population to sample, the sampling design, necessary sample size, measurement of infection or morbidity, and frequency of assessment. A multi-country 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 prevalence geospatial layers 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 to be used to by national programmes to make control decisions at a sub-implementation unit (e.g., sub-district) level.

Most investigations pertaining to morbidity and its control have been conducted in different ecological settings and measured different symptoms in populations that may have different age and infection prevalence distributions. These geographic and sampling differences have hindered the development of evidence-based guidelines due to the challenges of reaching a consensus on which morbidities to measure and appropriate targets for those morbidities. A way to overcome this obstacle would be to follow the example of the SCORE project that brought together researchers, disease control programme managers, and policymakers to develop harmonized protocols prior to the initiation of the research studies in different countries. While this approach did not work perfectly, it allowed for the combination and analysis of data across sites, resulting in increased statistical power (28). Morbidity data across age groups from the Morbidity Operational Research for Bilharziasis Implementation Decisions (MORBID) pilot studies in Kenya (*S. mansoni*) and Malawi (*S. haematobium*) could be combined with other previously published research to develop coordinated investigations using harmonized protocols to better define EPHP targets (29).

Another factor that may facilitate more accurate measurement of schistosomiasis morbidity and delineation of EPHP targets is development of a tablet-based ultrasound system that allows for collection of pathology measurements in the field (30). Ultrasound has long been the standard for measuring schistosomiasis fibrosis and organomegaly, but the size and expense of available machines has limited the practicality of field-based ultrasonic evaluation to research studies (31). Newer technology now allows combining a transducer with standard electronic tablets to collect and electronically store ultrasound images and videos more 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 2021–2030 NTD roadmap targets the number of countries validated for EPHP to increase from 26 in 2020 to 49 in 2023, 69 in 2025, and include all 78 schistosomiasis endemic countries in 2030 (1). To achieve these goals, a robust monitoring and evaluation framework is needed to measure progress and validate whether geographic areas indeed have eliminated schistosomiasis as a public health problem. Calls to develop specific programmatic guidance on how to achieve and maintain EPHP (8, 32) have yet to be heeded (3, 4).

Unfortunately, an antiquated framework for EPHP remains in place and a large disconnect remains between existing practice and recent research. Moving away from PHI-based targets is needed to align with current knowledge of morbidity. Developing prevalence of infection targets based on morbidity that may differ by 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 standardized protocol should be developed that harmonizes 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 standardized analyses that can better define EPHP targets.

Acknowledgements

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention (CDC).

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