



Summary of the Thirty-Fourth Meeting of the International Task Force for Disease Eradication (ITFDE) September 19-20, 2022

The 34th meeting of the International Task Force for Disease Eradication (ITFDE) was convened virtually and in person at The Carter Center in Atlanta, Georgia, USA on September 19-20, 2022, to discuss the “World Health Organization's (WHO) New Guidelines on Control and Elimination of Human Schistosomiasis.” The ITFDE previously discussed schistosomiasis in 2001 and 2012, concluding that the disease was not yet eradicable with the available tools, but acknowledged that control of schistosomiasis was possible and could be improved. The ITFDE members are Dr. Kashef Ijaz, The Carter Center (Chair); Dr. Gautam Biswas, WHO; Mr. Simon Bland, Global Institute for Disease Elimination (GLIDE); Dr. Peter Figueroa, The University of the West Indies, Jamaica; Dr. Donald Hopkins, The Carter Center; Dr. Patrick Lammie, The Task Force for Global Health; Dr. Fernando Lavadenz, The World Bank; Dr. Ephrem T. Lemango, United Nations Children’s Fund (UNICEF); Dr. Professor David Molyneux, Liverpool School of Tropical Medicine; Dr. Ana Morice, Independent Consultant; Dr. William Schluter, U.S. Centers for Disease Control and Prevention (CDC); Dr. Laurence Slutsker; Dr. Faisal Sultan, Ministry of National Health Services Regulations and Coordination, Government of Pakistan; Dr. Jordan Tappero, Bill & Melinda Gates Foundation; and Dr. Dyann Wirth, Harvard T.H. Chan School of Public Health.

Presenters included Dr. Amaya L. Bustinduy, London School of Hygiene and Tropical Medicine; Dr. Darin Evans, United States Agency for International Development (USAID); Dr. Amadou Garba Djirmay, WHO; Dr. Deirdre Hollingsworth, University of Oxford; Dr. Charles H. King, Case Western Reserve University; Dr. Stefanie Knopp, Swiss Tropical and Public Health Institute; Dr. Santiago Nicholls, Pan American Health Organization (PAHO); Dr. David Rollinson, Global Schistosomiasis Alliance; Dr. Evan Secor, CDC; Dr. Johannes Waltz, Merck KGaA; Dr. Xiao-Nong Zhou, Chinese Center for Disease Control and Prevention (CCDC).

Overview of Schistosomiasis and New WHO Guidelines

The ITFDE has considered schistosomiasis for potential elimination twice prior to this meeting, first in 2001 and then in 2012, and came to the same conclusion both times: that interrupting transmission was still not yet possible with the available tools in most endemic countries, even though considerable progress had been made in the control of schistosomiasis. The current review looks at what would be required to achieve schistosomiasis elimination considering the new guidelines set forth by WHO in 2022 for schistosomiasis control and elimination.

Schistosomiasis is a parasitic disease caused by *Schistosoma* spp. parasites and has two major forms, intestinal and urogenital schistosomiasis. There are three major species of *Schistosoma* parasites (*S. mansoni*, *S. japonicum*, *S. haematobium*) and three minor species (*S. mekongi*, *S. guineensis*, *S. intercalatum*), which are regionally specific to parts of Africa, Asia, and the Americas. Current WHO estimates show that 78 countries and territories remain endemic for the

disease and that around 240 million people required preventative chemotherapy as of 2020, 91% of whom live in Africa.

Schistosomiasis-associated morbidity is an inflammatory process, which affects individuals from the time of infection and can be found in individuals with current as well as past infections. The inflammatory response is caused by parasitic eggs that become entrapped in the body rather than exiting it to complete the life cycle. Common clinical manifestations include non-specific symptoms such as anemia, fatigue, growth retardation, decreased quality of life, and decreased cognition, which overlap with co-endemic diseases. There are also species-specific chronic clinical manifestations, such as intestinal inflammation, bleeding and periportal fibrosis for intestinal schistosomiasis (caused by *S. mansoni* and *S. japonicum*) and bladder polyps, calcifications, hydronephrosis and bladder cancer for urogenital schistosomiasis (caused by *S. haematobium*). Genital involvement leads to female and male genital schistosomiasis (FGS/MGS) manifesting with sexual and reproductive health disturbances including infertility and pain. The risk of morbidity is partly due to accumulation of parasite exposure, host-related factors, and intensity of infection. However, in all schistosome species, there is an important dissociation between detection of eggs and chronic morbidity, making it challenging to accurately diagnose the extent of the disease and its response to treatment.

Although WHO reports show that the number of people treated for schistosomiasis has steadily increased since 2006, reaching more than 100 million people in 2019, there was around a 26% decrease in treatment coverage due to the COVID-19 pandemic in 2020. WHO's new guideline outlines several suggestions to continue to improve control and elimination of human schistosomiasis based on use of integrated strategies including preventative chemotherapy (PC), environment management, water, sanitation and hygiene (WASH), and One Health; treatment of all at-risk groups; focal treatment of hotspot areas; a simplified mass drug administration (MDA) threshold of annual PC at 10% or greater infection prevalence; and a framework for verification of transmission interruption through diagnostics of human, snail and animal reservoirs.

Diagnostic Tools for Elimination

WHO has formed a Diagnostic Technical Advisory Group (DTAG) to develop Target Product Profiles (TPPs) for better diagnostic tests for neglected tropical diseases (NTDs) as most existing tests are inadequate. The DTAG subgroup for schistosomiasis developed two TPPs, one for monitoring and evaluation of control programs and one for interruption of transmission and surveillance. Traditionally, schistosomiasis control programs have relied on detection of parasite eggs in stool (*S. mansoni*, *S. japonicum*) or urine (*S. haematobium*) samples to assess prevalence and program status. However, egg detection is not sufficiently reliable due to poor sensitivity in light intensity infections that become more common as control programs progress.

The TPP for monitoring and evaluation is based on a threshold of 10% prevalence following WHO guidelines that recommend MDA in communities above this level. The TPP requires detection of active infections at the point of care with minimal infrastructure requirements. Ideally, testing and decisions for MDA should be made in a single field visit, and the cost of the assessment should be less than the cost of 2-3 rounds of MDA.

Given that antibody responses to antigens used in schistosomiasis immunoassays remain detectable long after treatment, antibodies may not be a good candidate biomarker for monitoring and evaluation tests. However, antibodies may be useful for assessing transmission interruption and for conducting surveillance as communities close to interruption of transmission or undergoing post-transmission surveillance are unlikely to have experienced much recent transmission. The very high specificity requirements for tests used at end stages of the program require a combination of two tests: a screening test that should be conducted at point of care and a confirmatory test for active infection that could be conducted at point of care or in a laboratory setting.

Treatment Strategies for Elimination

Although there is no fully curative treatment for schistosomiasis, praziquantel, given orally at a single dose of 40mg/kg, can prevent and sometimes reverse the clinical damage caused by the disease. In its new guidelines, WHO recommends annual PC in endemic communities with a prevalence of 10% or greater for all age groups, beginning from age 2 years. However, if infection levels remain high, even with adequate coverage of the population, WHO suggests considering biannual treatment. For communities with a prevalence lower than 10%, using one of two strategies is recommended: where populations have received regular PC treatments, annual treatment at the same or reduced dosage should continue, and where they have not, a test-and-treat approach should be used. WHO recommends using praziquantel for morbidity control in all age groups.

Recent large-scale, operational field trials have found wide variability (despite proper drug delivery) in the effectiveness of multi-year schistosomiasis MDA programs. The existence of 'persistent hotspot' communities indicates a significant challenge for current plans to eliminate *Schistosoma* species transmission within targeted districts using drugs alone without any additional complementary interventions.

Certain strategies may improve the impact of drug treatment, such as WHO's recommendations on extending coverage to age groups beyond the usual target population of school-aged children and increasing praziquantel dosage. Other strategies include adding a second drug such as artesunate, oxamniquine, or metrifonate to improve cure; providing a second praziquantel dose 4-6 weeks after initial dosing to eliminate newly maturing worms; and adjusting the timing of MDA to be given 4-6 weeks after the peak transmission period to maximize impact on recently acquired worms. Although controlled trials indicate that these modified approaches may show some modest improvements in the impact of treatment on infection prevalence, they are not guarantees of complete elimination of transmission.

There is also concern about the potential impact on praziquantel demand due to the new guidelines, particularly for adult treatment. The Merck Schistosomiasis Elimination Program, established by pharmaceutical company Merck KGaA, provides up to 250 million tablets of praziquantel annually. Since 2007 the company, in partnership with WHO, has delivered a total of more than 1.5 billion tablets of praziquantel to more than 45 countries, primarily in sub-Saharan Africa. WHO states that "...some 236 million people required [preventive chemotherapy] in 2019," which would

translate into 500 million¹ tablets of praziquantel annually, vastly exceeding current global praziquantel production capacities. While it is unlikely that demand at this level can be met in the foreseeable future, endemic countries will increasingly seek to follow treatment guidelines by escalating their respective praziquantel demand. Together with WHO, Merck is creating decision-making criteria to allocate some of its praziquantel for adult treatment, which will cover some of the expected increased demand, and will continue to provide up to 250 million tablets of praziquantel per annum. Additionally, three sources of praziquantel are now available in WHO's list of prequalified manufacturers to ensure quality of praziquantel tablets procured outside of Merck's donation.

Modeling the Feasibility of Elimination

Currently, most efforts to model the feasibility of schistosomiasis elimination use individual-based models, which look at each individual in an endemic community who may act as a host for a number of worms, leading to excretion of a certain number of eggs. Their history of infection, as well as their current infection, may also be tracked, allowing the potential for modeling morbidity. The wide variability in non-human animal hosts and environmental factors in different settings is a significant hurdle in modeling feasibility of elimination. Uncertainties in snail dynamics mean that different modeling assumptions can result in starkly different rates of bounce-back in infection following treatment, and variable predictions on the impact of snail control. Moreover, many models do not consider factors such as hybridization (i.e., interbreeding between two species) or zoonotic transmission (i.e., transmission of disease from animals to humans or vice versa), systematic lack of access or non-compliance with treatment regimen, and each round of MDA may be reaching and overlooking the same groups.

The degree of aggregation of eggs amongst hosts (the fact that some people have many eggs and others have very few) is critical in understanding the dynamics of transmission, especially for persistent hotspots. Communities with the same level of prevalence can have different degrees of egg aggregation, which can have a profound impact on which control strategies will be most effective. For example, highly aggregated populations where worms are concentrated in a small number of people can maintain transmission, despite generally good coverage of control and treatment interventions. Mass treatment may be ineffective in such cases, as these smaller groups may be harder to reach and overlooked.

Taking into consideration these uncertainties, modeling suggests that MDA alone may achieve elimination in communities with low to medium prevalence, if there is high coverage of the population, including treatment for adults. Even so, while MDA can reduce heavy infections in the population quickly, it takes longer to reduce prevalence with the risk of bounce-back in infection. A vaccine against schistosomiasis would likely be the best strategy, however, that would be dependent on the effectiveness and duration of protection and whether pre-exposed people could be vaccinated, and even if available would still take considerable time to achieve elimination.

¹ This number is based on WHO estimates. However, estimates presented by Dr. Johannes Waltz from Merck put this number at 700 million tablets annually.

Country Perspectives

1. *The Americas*

Schistosomiasis has been historically endemic in 11 countries in the Americas: Antigua and Barbuda, Guadeloupe, Martinique, Montserrat, Saint Lucia, Saint Kitts, and Nevis, Saint Martin, Dominican Republic, Puerto Rico, Brazil, and Venezuela. Schistosomiasis transmission has likely been eliminated in most countries and territories in the Caribbean, but persists in Brazil, mainly in the Atlantic coast in the states of Alagoas, Bahia, Minas Gerais, Pernambuco, and Sergipe, and in Venezuela, in the states of Aragua, Carabobo, and Guarico. However, the average prevalence in Brazil and Venezuela is below 10%. The total estimated population at risk in the Americas Region is 1.6 million people, most of them in Brazil.

Evidence suggests that some countries that seem to have interrupted transmission, such as Dominican Republic, Puerto Rico, and St. Lucia, have been aided in decreasing prevalence due to economic development, urbanization, improvement in water and sanitation, and growth in tourism.

Following WHO's recently published new guidelines, PAHO is supporting countries and territories in the Caribbean to carry out studies in school-age children, adults, and snails to assess the status of transmission and verify whether transmission has been interrupted. Verification of interruption of transmission seems feasible in the Caribbean by 2030 at the latest. To further reduce disease burden and transmission, recommendations for Brazil and Venezuela include implementing a test-and-treat approach, WASH and environmental interventions (including snail control), and behavioral interventions.

2. *Zanzibar*

Urogenital schistosomiasis has been a major public health problem in Zanzibar over the past century. Since the early 2000s, the Zanzibar Ministry of Health, together with implementation partners, conducted regular rounds of MDA with praziquantel. By 2017, the overall prevalence had been reduced to less than 2% and heavy intensity infections were found in less than 1% of the surveyed population. Hence, Zanzibar has successfully eliminated schistosomiasis as a public health problem and is now committed to progress towards interruption of transmission. Challenges to achieving this goal in Zanzibar include (i) the heterogeneity of transmission, with many low-prevalence areas and few remaining pockets of high transmission (hotspots); (ii) the rapid bounce-back in hotspots when PC is paused; and (iii) the low sensitivity of standard diagnostic tests and the unavailability of point of care diagnostic tests for *S. haematobium* detection.

The "SchistoBreak" operational research project, funded by the Swiss National Science Foundation, is being implemented in the North of Pemba Island from 2020 to 2024 and aims to provide evidence for the feasibility of interrupting urogenital schistosomiasis transmission by micro-targeting interventions at the sub-district level. Based on pre-defined prevalence thresholds, communities and schools located in hotspot areas receive at least annual PC by the Ministry of Health, plus complementary behavior change measures in schools and communities, and snail control in water bodies. In low-prevalence areas, no MDA is provided, but a surveillance-response

strategy is implemented, which consists of active surveillance in schools, reactive surveillance in households of positive children, reactive surveillance at water bodies that are used by positive children, reactive snail control in water bodies used by positive children where the intermediate host snail is found, passive surveillance in health facilities, and treatment of positive individuals. For surveillance, where several thousands of individuals are tested, in addition to the standard tests, new diagnostic approaches are assessed for their performance and suitability at the point of care.

3. *China*

Due to infections with *S. japonicum*, schistosomiasis has been prevalent in China for more than 2,100 years. Based on data from a national survey conducted in the 1950s, 11.6 million human cases were detected with approximately 100 million people at risk of infection, and 1.2 million infected livestock, with a total of 14.3 billion square meters of snail-infested areas found.

Various control strategies and interventions have been administered at different stages by China's national schistosomiasis control and elimination program. For example, (i) a national survey was carried out in the preparation stage from 1950 to 1955 to understand the endemic status, treat schistosomiasis cases, and establish institutions with facilities in endemic areas; (ii) a mass campaign with a primary focus on snail control was executed from 1956 to 1980; (iii) the morbidity control program using chemotherapy was piloted in 1980, followed by scaling up from 1992 to 2003; (iv) the integrated control stage emphasized control of infectious sources and was implemented in all endemic areas from 2004 to 2014, with assistance in rebuilding lavatory or biogas pools, replacing bovines for agricultural cultivation with machines for agricultural work, isolating marshland and prohibiting grazing or rearing of domestic animals, and providing containers to boat- or fisher-men. As of 2014, about 98.9% of endemic counties (449/454) had achieved the criteria of transmission interruption or transmission control.

Highly integrated approaches, such as multi-sectoral cooperation among ministries of health, agriculture, and education, among others, and strengthened surveillance and response systems for control, have been key in achieving this progress. The One Health approach targeted endemic areas to meet the target of transmission interruption by 2025. A variety of surveillance activities have been systematically implemented, including routine passive surveillance, community-based active surveillance, and risk active surveillance. Surveillance data show that the number of cases in 2021 was 29,041, reflecting a reduction of 92.97% compared to 2008. Most cases were advanced schistosomiasis and thus were not involved in transmission of the disease.

Partner and Donor Perspectives

The Global Schistosomiasis Alliance (GSA) is a multi-stakeholder platform consisting of public and private sector partners across the globe contributing to the elimination of schistosomiasis as a public health problem, with the goal of sustained interruption of transmission. The Alliance has grown in strength and activity in recent years and consists of various Working Groups and Work Streams populated by experts exploring issues relating to praziquantel coordination, diagnostics, snail control, behavior change, monitoring and evaluation, and engineering. The GSA promotes the wider integration of control and elimination activities between NTD programs and is a strong

advocate for forming productive links with organizations outside the NTD sector. Examples of the need for better and wider integration extend to education, social sciences, engineering, One Health, and reproductive health services. The GSA also coordinates a genital schistosomiasis community of practice and has an active group of GSA Ambassadors across Africa who exchange information and explore topics relating to schistosomiasis control and elimination in line with their country's experiences.

Elimination, whether as a public health problem or interruption of transmission, is generally appealing to donors and they seem to be aligned with WHO's overall NTD elimination agenda. However, current schistosomiasis funding is not nearly enough to achieve WHO NTD Roadmap 2030 targeted goals. Part of the challenge is the disease itself – schistosomiasis is a complex disease that is difficult to eliminate due to several factors. Although some countries have achieved elimination, it is not feasible everywhere with current tools and resources. More attention is needed to contextual factors including consideration of morbidity associated with light-intensity infections as they contribute to most of the disease burden and encompass the majority of the affected population.

Conclusions and Recommendations

1. The ITFDE believes that for schistosomiasis elimination to be possible, inter-sectoral cooperation is vital. Given that the challenges for schistosomiasis elimination are diverse, including animal reservoirs, farming and irrigational practices, development of dams and lack of sanitation, coordinated action and partnership is needed across the health, water, agriculture, animal, and education sectors. The establishment of intersectoral committees could help sustain cooperation. There is also need for better integration of schistosomiasis diagnosis and treatment into primary and reproductive health care programs.
2. Further research and development are needed into more effective diagnostics and point of care tests, treatment (including both a human and a livestock schistosomiasis vaccine), and surveillance methods. Attention is also needed to how environmental changes will affect vector-borne and parasitic diseases such as schistosomiasis.
3. Schistosomiasis programs are encouraged to follow WHO guidelines for targeted use of praziquantel. However, the strengths and limitations of praziquantel and the possibility for praziquantel resistance should be considered and monitored. There is progress in development of new drug treatments for schistosomiasis. There have also been promising advancements in the development of a schistosomiasis vaccine for both *S. mansoni* (Calpain – Sm-p80/GLA-SE) and *S. haematobium* (Glutathione S-transferases – Sh28GST). The ITFDE encourages further innovation in this area as a vaccine may be crucial to eliminate schistosomiasis as a public health problem.
4. The ITFDE does not believe that preventative chemotherapy alone can eliminate schistosomiasis. Interventions complementary to preventative chemotherapy such as snail control, WASH, behavioral change, One Health approaches, and health education must be reinforced. Interventions should be tailored to the specific ecological and epidemiological

context, given the wide variability of the disease depending on the type of parasite, various non-human animal hosts, and environmental factors. Although implementation of integrated interventions can be a challenge, strategies such as cross-training of drug distributors, coordination with other NTD programs, working directly with communities, establishing a platform for intervention delivery, and providing MDA at the community level may aid in promoting effective interventions.

5. Given the new recommendations for treatment, WHO estimates that the amount of praziquantel needed to achieve elimination will increase to around 500 million praziquantel tablets annually. As praziquantel demand is expected to soar with the implementation of new WHO guidelines, more attention needs to be directed toward increasing praziquantel supplies. The development of eligibility and allocation criteria for praziquantel by Merck in partnership with WHO is a positive step in this direction. However, the inevitable need for increased manufacturing should be addressed. The ITFDE also commends Merck for continuing its commitment to donating 250 million tablets of praziquantel annually until the elimination of schistosomiasis as a public health problem is achieved.
6. With funding for NTDs on the decline for the past four years and significant budgetary cuts made by the United Kingdom's FCDO (Foreign Commonwealth Development Office) for NTD elimination efforts, donors need to be engaged now more than ever. Donor fatigue is a challenge in this area that merits attention. Highlighting the link between FGS/MGS and sexual and reproductive health issues such as HIV, sexually transmitted infections and cervical cancer may help to attract additional interest, support, and funding.
7. Countries should be encouraged to take ownership of schistosomiasis control and elimination efforts and promote sustainability of programs at the national level. This requires countries to carry out robust active and passive surveillance, especially to combat and prevent reinfections.