Diagnostic TPP for monitoring and evaluation of schistosomiasis control programs

Schistosomiasis is a parasitic disease of 240 million people globally. Infection occurs when people come into contact with contaminated water populated with the appropriate intermediate host snail. Larval parasites penetrate the skin and enter the body where they mature into adult male and female worms, mate, and produce eggs. Some eggs released by adult females exit the body to continue the parasite's life cycle, but other eggs become trapped in host tissues where they stimulate immunologic responses that cause the morbidity associated with schistosomiasis.

Epidemiology

In humans, schistosomiasis, also known as Bilharzia or snail fever, is caused by 5 species of trematodes in the genus *Schistosoma.* Approximately 90% of infections and the vast majority of morbidity occur in sub-Saharan Africa, where the 2 primary species that cause human disease are *S. mansoni* and *S. haematobium.* Adult *S. mansoni* worms live in the mesenteric veins surrounding the intestines. To complete the life cycle, eggs must make their way to the lumen of the gut where they are excreted in host feces. However, many eggs are washed by the portal circulation to the liver where they become trapped and stimulate granulomatous responses. Over time, untreated schistosomiasis can stimulate fibrosis of the liver and increased portal pressure, resulting in liver and spleen enlargement. In the most severe cases, ascites and esophageal varices develop and can lead to hematemesis and death. *S. haematobium* adult worms live in the blood vessels surrounding the bladder and eggs are excreted in the urine. This results in hematuria, which can be microscopic or visual. Chronic infection can result in bladder fibrosis with obstructive uropathy and is associated with increased risk of squamous cell carcinoma of the bladder. Worms in the venous plexus can also result in egg deposition in genital tissues, causing female and male genital schistosomiasis, which is associated with greater risk of HIV transmission. The severe morbidities described above tend to affect older individuals who have been infected for several years. However, the bulk of the more than 3.3 million Disability Adjusted Life Years (DALYs) caused by schistosomiasis worldwide affect children, who have the highest prevalence and intensity of infections. Morbidities in children include anemia, delays in physical and cognitive development, and reduced exercise tolerance.

Public Health Response

Because prevalence and intensity of infection peaks between the ages of 7 and 15, the main strategy for schistosomiasis control focuses on mass drug administration (MDA) of the drug praziquantel in priority to primary school age children. Praziquantel is safe for persons who do not have infections and it is more cost effective to treat all school age children in a community above a certain prevalence threshold than to test and treat each individual. MDA is typically administered by control programs in endemic areas once each year. However, this is not enough to interrupt transmission without additional measures such as increased access to clean water and sanitation, control of intermediate host snails, or education and behaviour change. As a result, WHO guidelines for most countries are targeted to control, and then eliminate morbidity.

In general, higher intensities of infection are associated with higher levels of morbidity but these relationships are poorly defined, and most control programs only monitor prevalence of infection and not intensity. Research is underway to better define the relationship between prevalence, intensity of infection, and various manifestations of morbidity but for the time being, the working guidance for control programs is that communities with ≥ 10% prevalence among primary school age children should receive annual MDA. Because distribution of schistosomiasis is highly focal, implementation decisions are applied at the subdistrict level. Additional operational research is

needed to determine the frequency of prevalence reassessment and the characteristics of communities that respond well to MDA compared to those where prevalence remains persistently high despite good treatment coverage.

Available Diagnostic Tools

Traditionally, schistosomiasis has been diagnosed by detecting parasite eggs in host stool (*S. mansoni S. mekongi, S. japonicum*) or urine (*S. haematobium*). These methods have the advantage of providing information on both prevalence and intensity of infection and in theory can distinguish active infection from successful cure and/or subsequent reinfection. However, it is sometimes hard to obtain samples for egg detection methods, their sensitivity for low intensity infections is poor, and they require access to both microscopes and trained personnel. Usually, samples are processed in a laboratory distant from the site.

Circulating Cathodic Antigen (CCA) is regurgitated from the blind gut of schistosomes, cleared by the patient's kidneys, and excreted in the urine. Like eggs, urine CCA disappears after successful cure and resumes after reinfection. It also provides a relative intensity of infection and is considered much more sensitive than egg detection. A point-of-care (POC) CCA test is commercially available. Unfortunately, current formulations of the test are only reliable in high prevalence areas and the false positivity rate is too high to accurately determine prevalence below 10%. Furthermore, recent manufacturing issues have resulted in product lots that have had variable performance and very high false positive rates. Even when working well, the POC-CCA is much more effective at detecting *S. mansoni* infections than *S. haematobium* infections.

Like CCA, Circulating Anodic Antigen (CAA) can also be detected in an infected host's blood or urine, is a marker for active infection, provides information on relative intensity of infection, and has the added advantage of being produced in detectable amounts by both *S. mansoni* and *S. haematobium*. However, it is not available as a commercial test and current developmental tests require laboratory equipment for sample concentration and final test readout. PCR to detect parasite DNA in stool or urine is anticipated to be more sensitive than egg detection methods but similarly requires laboratory equipment and relatively expensive reagents to perform and is not available as a commercial test. Some commercial tests for schistosome-specific antibody detection do exist but are not useful in ongoing control programs because they are unable to distinguish active from former infections. The magnitude of antibody response is less reflective of intensity of infection than other methods.

Diagnostic Technical Advisory Group

The WHO Department of Control of Neglected Tropical Diseases (NTD) manages a diverse portfolio of twenty diseases, each with its own unique epidemiological and diagnostic challenges. The Strategic and Technical Advisory Group (STAG), the principal advisory group to WHO for the control of NTDs, decided that a single WHO working group would help ensure that a unified approach could be used to identify and prioritize diagnostic needs, and to inform WHO strategies and guidance on the subject.

Thus, the Diagnostic Technical Advisory Group (DTAG) was formed as an advisory group to the Department of Control of Neglected Tropical Diseases. The first meeting of the DTAG was held in Geneva, Switzerland, on 30 and 31 October 2019.

DTAG members discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of the WHO NTD portfolio. Recommendations

were made, based on the understanding that they would be reviewed at the next meeting, as it had been made clear that all NTDs had diagnostic needs which would have to be addressed in due course.

One of the recommendations was that TPPs for diagnostics were needed for *S. mansoni* and *S. haematobium* that would facilitate monitoring and evaluation of schistosomiasis control programs.

Purpose of the TPP

Ministries of Health currently lack effective tools for monitoring and evaluation of schistosomiasis control programs. Egg detection can be used but the cost, challenges of obtaining samples, and the need for trained personnel and equipment limit frequency of monitoring. The purpose of this TPP proposed by WHO NTD is to guide development of new diagnostic tools to reliably measure when prevalence is above or below a cut-off of 10% in school age children. Communities remaining above 10% require annual MDA while communities below 10% can reduce MDA frequency as long as < 10% prevalence can be maintained. However, the lack of a reliable test has hindered the development of maintenance strategies. The test is also needed to track changes of prevalence above 10% to ensure that annual MDA is reducing overall prevalence. In some areas with very high force of transmission, annual MDA is not sufficient to reduce baseline prevalence and more frequent MDA or additional interventions should be employed. But again, lack of a cost-effective test has hindered the development of what strategies are effective in high transmission areas.

Use of the test in a survey should be less expensive that 2-3 rounds of MDA, the number of treatments expected to demonstrate a meaningful difference in prevalence or the lack thereof. Field workers should be able to perform and interpret the test with only a single day of training and any equipment used for reading the test should be highly portable and battery powered if it needs electricity at all. The amount of time it takes to collect samples, perform the test, interpret the data, and make a treatment decision should be less than one work day so that only a single field visit would be required for each community.