Diagnostic TPP for schistosomiasis transmission interruption and subsequent surveillance

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 if the prevalence is beyond a certain threshold. 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.

The eventual goal of control programs is to bring infection levels down to a point where interruption of transmission could be envisaged. If successful, countries stop praziquantel MDA and can reallocate the resources that had gone to schistosomiasis control into other programs. However, even when elimination of transmission has been achieved, there is a need for continued surveillance for schistosomiasis over a period of time to ensure that recrudescence does not occur. The prevalence at which MDA can be stopped and the length of time over which surveillance should be conducted remain undefined as interruption of transmission is within reach for only a few countries. However, countries with good coverage of clean water and sanitation, successful snail control

programs, and/or strong behavioural compliance to avoid transmission, can provide the necessary evidence to inform when interruption of transmission has occurred and how long subsequent surveillance is necessary.

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 implementation 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. Its level in the urine 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 measure 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.

Current schistosome-specific antibody detection tests are not useful in ongoing control programs because they are unable to distinguish active from former infections. However, as prevalence approaches 0% they can be useful for both deciding when to stop MDA and conducting surveillance because there are fewer "former" infections, especially in younger age groups. Antibody detection is highly sensitive and can have high throughput on a variety of platforms at a modest cost. It is also easily multiplexed with other serologic assays such that serum or plasma collected for a different purpose can be used to provide information about potential schistosome infections, thus reducing survey costs.

Although current antibody tests are not useful for monitoring and evaluation programs because the antibodies to the currently used antigens remain long after successful treatment, there may be certain antigens to which antibodies, especially those of a certain isotype subclass (e.g., IgG4) disappear more rapidly.

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 determining if transmission had been interrupted and then conducting surveillance in a post-MDA program phase.

Purpose of the TPP

Ministries of Health currently lack effective tools for conducting surveillance and for determining when schistosomiasis transmission has been interrupted. Traditional egg detection methods have the high specificity necessary for elimination program success but lack sensitivity, especially for low the intensity infections most likely encounters in interruption of transmission scenarios.

The purpose of this TPP proposed by WHO NTD is to guide development of new diagnostic tools to reliably detect 3% infection prevalence. While this cut-off may seem relatively high, it is what can realistically be achieved by using an economical lot quality assurance sampling (LQAS) approach. Using this approach, any confirmed positive would trigger additional intervention measures. Even using the 3% cut-off, a combined, 2-step test approach will be necessary to achieve the required survey testing specificity. By this approach, an initial (lower cost) screening test with higher sensitivity would be coupled with a secondary test with higher specificity that might be more expensive, but would be utilized with a more limited sample size (and would have the option of being centralized). To attain the required survey specificity, a positive result in both tests would be needed to confirm an active infection.

In a limited prevalence or ‘post-elimination’ surveillance situation, tests otherwise unable to distinguish active from former infections (e.g., current antibody tests) could be used in children younger than the number of years transmission is thought to have been interrupted, as all such individuals should be negative. Antibody responses that linger after treatment could also be used for initial screening purposes in older individuals if followed by a test confirming if there is an active infection. Antibodies to antigens that clear following treatment could be used for all age groups.