Diagnostic TPP for monitoring and evaluation of soil-transmitted helminth control programs

Soil-transmitted helminths are a group of intestinal worms, including *Ascaris lumbricoides* (giant roundworm), *Trichuris trichiura* (whipworm), *Ancylostoma* spp. *(A. duodenale, A. ceylanicum*) and *Necator americanus* (hookworms). Despite the clear biological differences across the different worm species, their transmission is characterized by the same sequence of events: (i) infected individuals excrete worm eggs through their stool in soil; (ii) under optimal conditions of moisture and temperature the excreted eggs will develop into infectious stages; (iii) finally infection occurs through oral uptake (*Ascaris, Ancylostoma* and *Trichuris*) or skin penetration (*Ancylostoma* and *Necator*) of these infectious stages (embryonated eggs and third stage larvae) that reside in the soil and/or in the environment (referring to their common name).

Epidemiology

It is estimated that 800 million people world-wide are infected with at least one soil-transmitted helminth (STH) species, resulting in global disease burden of more than 3 million disability-adjusted life years (DALYs). Given the route of transmission, infections and the associated disease burden predominantly occur in (sub)tropical countries where optimal climate conditions for egg survival and larval development in the environment, poor socio-economic status, lack of appropriate access to water, sanitation and hygiene all facilitate transmission. STH-attributable morbidity is mainly associated with moderate-to-heavy intensity infections and mainly affects children and women of reproductive age. Effects include impaired growth and cognitive development, malnutrition, anaemia, and school absenteeism in children and malnutrition and anaemia in women.

Public Health Response

In endemic areas, the World Health Organization (WHO) recommends preventive chemotherapy (PC) programs, during which a single tablet of an anthelmintic drug (400 mg albendazole or 500 mg mebendazole) is periodically administered to both pre-school and school age children and other at-risk populations. Both drugs are safe for healthy persons who do not have infections and it is more cost effective to treat all populations at risk than to test and treat each individual. The frequency of large-scale deworming is based on the observed prevalence of any STH species measured by Kato-Katz thick smear on stool samples and whether or not this prevalence exceeds a predefined decision threshold. For example, at the start of the program it is recommended to distribute drugs twice a year when the prevalence is at least 50% and once a year when the prevalence is at least 20%. During the implementation phase, the prevalence of any STH infection is periodically re-evaluated to verify whether objectives are being met, and if necessary, to adjust the frequency of drug administration (observed prevalence ≥50%: 3x PC / year; 50%> observed prevalence ≥20%: maintain PC frequency; 20%> observed prevalence ≥10%: 1x PC / year; 10%> observed prevalence ≥2%: 1x PC / 2 years; observed prevalence <2%: no PC).

However, this is not sufficient to interrupt transmission without additional measures such as increased access to clean water and sanitation, and education and behavioural change, or expanding PC to entire communities. As a result, WHO guidelines for most countries are targeted to reduce the prevalence of moderate-to-heavy intensity infections to less than 2% (in pre-school and school age children), which is the target defined for elimination of STH as a public health problem.

Available Diagnostic Tools

Traditionally, STH infections have been diagnosed by detecting worm specific eggs in stool samples. Since the 1990s, Kato-Katz has been the WHO recommended diagnostic standard for quantifying eggs in stools. During the last decade, a variety of new diagnostic tests have been introduced to the STH-field, including both microscopy-based (e.g., FECPAK^{G2} and (Mini-)FLOTAC), and DNA-based methods (qPCR). Each of these tests have important advantages and disadvantages compared to the Kato-Katz. Important advantages are a clearer microscopic view (FECPAK^{G2} and (Mini-)FLOTAC); a higher clinical sensitivity (= proportion of infected individuals correctly diagnosed as infected (Mini-)FLOTAC, and qPCR); opportunities for automated egg counting and quality control (e.g. FECPAK^{G2}); and the abilities to differentiate hookworm species and to simultaneously detect parasites other than soil-transmitted helminths (qPCR). Chief limitations of these novel tests are the need for well-equipped laboratories with well-trained, skilled technicians (e.g. FLOTAC and qPCR), the higher cost of processing large numbers of samples (FECPAK^{G2}, Mini-FLOTAC and qPCR), and lack of standardized protocols and commercially available kits (qPCR). This is in particular when samples are processed in a laboratory distant from the collection site. Currently, most technologies based on other biomarkers (e.g. antigens, antibodies and metabolites) or other sample matrices (e.g. serum and urine) are either not yet explored, in research phase or only commercialized for certain worm species.

Diagnostic Technical Advisory Group

The WHO Department of Control of Neglected Tropical Diseases (NTD) manages a diverse portfolio of twenty diseases and disease groups, 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 STH that would facilitate monitoring and evaluation of the STH control programs.

Purpose of the TPP

Health ministries currently lack effective tools for monitoring and evaluation of STH 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 lead to development of new diagnostic tools to reliably make program decisions on whether STH programs should start PC, move towards the next phase or ultimately stop PC, based on WHO's decision algorithm.

Brief summary of TPP

The target product is an in vitro/ex vivo laboratory-based (minimum) or point-of-sampling test (ideal) that allows for quantitative detection of analytes specific to soil-transmitted helminths (STHs) in all age groups. For laboratory-based tests, tests can be performed in regional or national diagnostic testing laboratories by trained laboratory technicians (<1-week training) and specific requirements for portability and transport should not exceed those of standard laboratory equipment. For point-of-sampling tests, health personnel and community health 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 test should be specific (Sp) (≥94 %) to each *Ascaris*, *Trichuris* and hookworm and have a sensitivity (Se) of at least 60% for each of the three STHs, though different Se/Sp combinations are possible. The test should allow for a throughput of at least 7 samples per hour and its cost should not exceed 3 US$.

NOTE: Modelling of performance requirements shows different Se/Sp combinations will provide sufficient decision making for this Use Case across six different program decision thresholds that range from 1-50% (i.e, 1, 2, 5, 10, 20 and 50%). It is important to note that these thresholds represent the *true* underlying prevalence and not the observed prevalence. Assuming a true underlying prevalence for program decisions was essential to facilitate comparison across many different sensitivities (Se) and specificities (Sp). The additional program thresholds of 1% and 5% were included because the Sp of the current diagnostic standard (Kato-Katz thick smear) is not 100%, and hence the true underlying prevalence might be overestimated in situations where the true underlying prevalence is approaching zero. Based on this performance modelling, we defined “ideal” and “minimum” combinations of Se/Sp. "Ideal" Se/Sp combinations are those with the least amount of uncertainty around three or more of these thresholds, while “minimum" Se/Sp combinations are those with the least amount of uncertainty around less than three of these thresholds. Note that the specificity requirements shown above were selected on the basis of providing the least uncertainty around a **1%** program threshold, i.e., the thresholds that is driving the diagnostic requirements.