SOIL-TRANSMITTED HELMINTHS
The business case for new diagnostics

PATH
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Executive summary

Soil-transmitted helminths remain a massive global health problem. Diseases caused by infection with these parasitic worms affect more than 1.5 billion people each year, mostly among impoverished populations. Children bear the greatest burden of disease.

The large roundworm *Ascaris lumbricoides*, the whipworm *Trichuris trichiura*, and the hookworm species *Ancylostoma duodenale* and *Necator americanus* are the most prevalent soil-transmitted helminths (STHs). Strategies to combat disease include mass drug administration (MDA) of the deworming medications mebendazole and albendazole—an effort made possible through large-scale drug donations by Johnson & Johnson and GlaxoSmithKline.

Monitoring the effectiveness of MDA campaigns and other interventions relies on the accuracy of tests to determine the presence and level of infection. The most commonly used tests are laboratory-based methods (Kato-Katz thick smear and mini-FLOTAC) that involve microscopic examination of stool samples for helminth eggs. Although these diagnostic methods are sufficient to inform the early stages of control programs when the prevalence and intensity of infections are moderate to high, the low sensitivity of these tests, particularly with low-intensity infections, reduces the accuracy of population assessments, especially after multiple rounds of MDA have reduced infections to low levels. In addition, the robustness and accuracy of microscopy methods can be affected by the proficiency of the technicians doing the work and by issues with samples, such as the degradation of helminth eggs over time after sample collection and the unequal distribution of eggs within a specimen.

More robust, easier-to-use diagnostic tools with greater sensitivity for detecting infection will improve the ability of control programs to determine whether goals have been achieved and to decide whether and when to reduce or discontinue MDA. Many STH stakeholders have consequently advocated for improving STH diagnostics. Such was the case during a meeting on STH diagnostics convened by the Task Force for Global Health and the Bill & Melinda Gates Foundation and held in Decatur, Georgia, in August 2013.

Based on discussions with STH stakeholders and with support from the Bill & Melinda Gates Foundation, PATH collaborated with academic experts to model the potential impact of new diagnostics on control of disease caused by each type of helminth. The results suggest that new, highly sensitive diagnostics would more accurately determine a community’s true prevalence of infection than is possible with currently used tests.

Project staff then aligned the presumed MDA dose frequency to the true prevalence of disease in each community and assessed the impact of the change in frequency through the use of quantitative simulation programs. In certain epidemiologic settings, increases in MDA frequency would markedly reduce infections and improve the likelihood of reaching control goals in a significantly reduced timeframe. Moreover, simulations suggested that without highly sensitive diagnostics, STH control programs would
likely never reach their programmatic goals. This is because current diagnostics often result in estimates of infection prevalence that are lower than true prevalence rates, leading program managers to use suboptimal MDA frequency.

This document elucidates our findings and contributes toward creating a business case for financing, developing, and deploying new diagnostics for detection of STH infection.
Disease overview

Soil-transmitted helminths (STHs) are parasitic worms that can populate the human intestine. They are transmitted by eggs that are present in human feces and contaminate the soil in areas with poor sanitation. More than 1.5 billion people are affected, particularly in tropical and subtropical countries where poverty prevails and where hygiene behaviors, unsafe water supplies, and deficient sanitation contribute to the problem.\(^1\) The large roundworm *Ascaris lumbricoides*, the whipworm *Trichuris trichiura*, and two hookworm species—*Ancylostoma duodenale* and *Necator americanus*—are the most prevalent STHs. Furthermore, an estimated 30 to 100 million people are infected with *Strongyloides stercoralis*, another STH species with considerable public health impact.\(^3\) Multiple-species infections (i.e., multiple types of STHs in a single individual) are also common.

STH infections have harmful effects on individuals’ health and well-being. The estimated global disease burdens due to hookworm disease, ascariasis, and trichuriasis are 3.2, 1.3, and 0.6 million disability-adjusted life years (DALYs), respectively.\(^4\) For children, STH infections are associated with malnutrition, anemia, abdominal pain, stunted growth, and poor cognitive development. STH infections also reduce the economic productivity of developing countries.\(^5,6\)

Geographic distribution

The prevalence of various types of STH disease varies significantly within and across regions. Table 1 shows years lost to disability (YLD) by region for each type of STH infection.\(^2\) Of the 4.98 million YLDs attributable to STH globally in 2010, 65% were attributable to hookworm, 22% to *A. lumbricoides*, and 13% to *T. trichiura*. Much of the disability due to STH infection occurred in Asia: 35% of YLDs attributable to hookworm and 45% of those attributable to *A. lumbricoides* were among populations in South Asia, and 47% of those attributable to *T. trichiura* were among populations in Southeast Asia. There was considerable variation in distribution of YLDs within regions as well as between regions.

**Table 1. Years lost to disability (YLD) by region for each type of STH infection.**\(^2\)

<table>
<thead>
<tr>
<th>Region</th>
<th>Hookworm</th>
<th><em>Ascaris lumbricoides</em></th>
<th><em>Trichuris trichiura</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YLDs</td>
<td>% total</td>
<td>YLDs</td>
</tr>
<tr>
<td>Asia</td>
<td>2,176,895</td>
<td>67.4%</td>
<td>801,830</td>
</tr>
<tr>
<td>Central</td>
<td>43,086</td>
<td>1.3%</td>
<td>11,986</td>
</tr>
<tr>
<td>East</td>
<td>568,112</td>
<td>17.6%</td>
<td>79,932</td>
</tr>
<tr>
<td>South</td>
<td>1,130,070</td>
<td>35.0%</td>
<td>499,599</td>
</tr>
<tr>
<td>Southeast</td>
<td>435,627</td>
<td>13.5%</td>
<td>210,314</td>
</tr>
<tr>
<td>Latin America</td>
<td>364,962</td>
<td>11.3%</td>
<td>83,776</td>
</tr>
</tbody>
</table>
For hookworm, the highest rates of infection were in southern sub-Saharan Africa (1.14 YLD/1,000 people) and Oceania (2.10 YLD/1,000 people). For *A. lumbricoides*, the highest rates were seen in South and Southeast Asia (0.31–0.34 YLD/1,000 people) and west sub-Saharan Africa (0.29 YLD/1,000 people). Also, most of the estimated 2,824 deaths attributed to infection with *A. lumbricoides* occurred in Asia. For *T. trichiura*, the highest rates were in Southeast Asia (0.49 YLD/1,000 people) and southern sub-Saharan Africa (0.77 YLD/1,000 people). Differences within regions are a consequence of moderate differences in estimated prevalence and the nonlinear relationship between prevalence and intensity of infection (and thus morbidity).

## Control strategy

The current global STH control strategy focuses on reducing morbidity in the most-at-risk populations—such as pre-school-age children, school-age children, and women of reproductive age—through mass drug administration (MDA) of antihelminthic drugs such as mebendazole and albendazole. The recommended treatment schedule depends on the initial prevalence of infection with any STH (*A. lumbricoides, T. trichiura, N. americanus*, and *A. duodenale*) among school-age children (Figure 1). The treatment goal is typically not to eliminate the parasites but to reduce associated morbidity to levels that can be controlled through routine health care or school-based services. This translates to an infection prevalence after treatment of less than 1%.
**Diagnostics to detect STH disease**

**Current diagnostic tools and their shortcomings**

Program decisions for STH control hinge on detecting the presence and load of helminth eggs in stool. The prevalence of infection informs the frequency of MDA for a population, and the intensity of infection (light, moderate, or heavy) helps programs assess the efficacy of MDA and other interventions toward reaching morbidity-reduction goals. Currently, elimination is not the target of global control efforts, due in part to the need for additional concerted effort to improve sanitation to reduce transmission through environmental exposure. However, accurate surveillance is critical to ensure that MDA is not stopped prematurely before morbidity-reduction objectives have been reached. Also, it is important for programs to ascertain whether prevalence has reached levels low enough to reduce the frequency of MDA or even temporarily discontinue MDA to conserve valuable program resources (including donated drugs) and to reduce the likelihood that STHs will develop resistance to drugs used for MDA.

Currently, microscopic examination to determine the number of helminth eggs per gram of stool for each of the four STH species is the “gold standard” method for informing control-program decisions regarding
MDA. The Kato-Katz thick smear is the most common copromicroscopy (stool microscopy) method used for analysis. Another copromicroscopy method, known as mini-FLOTAC, has also recently been recommended for use in STH surveillance by the World Health Organization (WHO). Compared with the Kato-Katz thick smear, mini-FLOTAC may improve specimen preservation and the ease of slide reading, albeit with added cost and complexity, including the need for specialized test materials for sample collection and analysis.

Both copromicroscopy methods have significant limitations, however. For example, they lack the sensitivity to detect low-intensity infections, especially among populations that have previously received multiple rounds of MDA in accordance with WHO recommendations. In addition, although the presence of eggs in stool is a good proxy for morbidity at high worm burdens, it is a fallible proxy for future transmission risk with lower worm burdens. Thus, there is increasing recognition within the international stakeholder community that diagnostic tools with improved performance compared to current methods are needed to support late-stage control program decisions, such as when to stop or reduce the frequency of MDA, even though current methods may be adequate for use in the early stages of control programs.

Another shortcoming of existing tests is their reliance on use of a stool sample, which is currently the only validated sample matrix for STH diagnosis. Programs would prefer to use blood or urine samples for diagnostic testing, although the use of these types of specimens will require further research to identify and assess the feasibility of alternative indicators, such as antibodies. Furthermore, if stool remains the only feasible sample for diagnosis for the foreseeable future, additional research is needed to improve specimen collection, handling, and more importantly, processing techniques.

Prioritized uses for new, improved diagnostics

Prioritized uses for new STH diagnostic tools are to inform reduction of MDA interventions and to monitor the post-MDA reduction phase, where better tools are needed to accurately assess STH control program progress (Figure 2). Additionally, new diagnostic tools that improve detection of low-intensity infections will also meet surveillance needs as programs transition to elimination goals and low-prevalence areas must be monitored. Finally, although more sensitive diagnostic tools may enable early recognition of drug resistance as indicated by the reduced efficacy of MDA, confirmation of drug resistance is an additional diagnostic need for which use cases still need to be addressed. Diagnostics to confirm drug resistance were beyond the focus of the current landscape analysis.
Figure 2. Uses for which current diagnostics are adequate or deficient.

Diagnostic gaps in STH control programs

- Mapping prevalence: Establishing baseline disease prevalence to target MDA.
- Monitoring impact of MDA: Measuring prevalence during MDA program.
- Reducing or stopping MDA: Determining when morbidity targets have been achieved.
- Post elimination surveillance: Detecting potential re-emergence of disease.

Diagnostics considered adequate
- Reference standard microscopy (Kato-Katz method) is sufficient for now, but as prevalence decreases, the method’s poor sensitivity may become an issue.

Diagnostic gaps exist
- Microscopy is relatively poor at detection of lower-intensity infections, and greatly underestimate prevalence in many communities.
- The establishment of a reference assay for STH with improved performance remains a critical gap.
- The collection, testing, and processing of a high-quality sample is critical, regardless of the downstream analytical tool used in testing.

Research priorities

Any new diagnostics need to have appropriate cost and user characteristics to enable broad access, uptake, and routine use by STH control programs. To advance the development of new STH diagnostic tests, further research is needed to identify, characterize, and/or validate candidate biomarkers; develop these biomarkers into robust tests, including selection of an appropriate diagnostic platform; and then demonstrate their field use, including their impact on the accuracy of decision-making by control programs.

Stakeholders surveyed by PATH have indicated that a sensitive rapid diagnostic test (RDT) for detecting parasite antigens would be the preferred alternative to current field-based microscopy methods.\(^{21-24}\) To date, however, there are limited data validating STH antigens for use in such tests, particularly a complete set of biomarkers that would enable detection of all four major STH species, either alone or in concert.\(^{25,26}\)

Species-specific excretory/secretory (ES) antigens may allow for antigen detection in the stool and have shown promise in early research, primarily in the detection of specific helminth species in animal infections.\(^{27}\) Further research is needed to characterize the use of these and other STH antigens for
diagnosis of human disease, including evaluating their performance with clinical samples from STH-endemic human populations. For instance, it will be critical to ensure that new antigen markers offer adequate specificity and do not cross-react with analogous proteins in other related helminth species that are found within the same environment in endemic settings.

In the long term, parasite antigens may serve as good biomarkers for the development of new antibody tests for STH as an adjunct to tests directly assessing the presence and intensity of current infection, particularly as programs move toward elimination and post-elimination use cases. While an antibody-negative result could be used as an excellent proxy for a true negative, which makes it a good confirmatory test in low-prevalence, low-burden situations, antibody tests offer only indirect measures of infection and are, in general, poor at distinguishing past exposure from current infection. Assuming appropriate biomarkers for each STH species can be identified, further development of antibody tests as a useful tool for STH surveillance will require generation of more evidence to better understand their performance characteristics within different endemic populations and how they can be used as an effective measure to monitor progress of control programs.

Preferred product characteristics and promising solutions

Ideally, a new STH test will enable multiplex detection and/or discrimination of all four major STH species from a single sample. This will ensure the test warrants consideration as a comprehensive diagnostic alternative to Kato-Katz. Although lab-based platforms including enzyme-linked immunosorbent assays (ELISAs) could likely accommodate multiplex immunoassays if suitable biomarkers are identified, stakeholders expressed a preference for ultimately having a multiplex test that is more field-deployable.\textsuperscript{21-24} Emerging point-of-care (POC) immunoassay platforms may be able to accommodate the high degree of multiplexing needed for pan-STH detection, including some newer RDT formats that may not require the use of a separate reader. These new formats include emerging RDT technologies from developers such as NG Biotech (http://www.ngbiotech.com/). However, further use of these tests will require verification of manufacturer claims, including assessing how these tests perform under field conditions, their compatibility with stool samples, and their performance when a high level of multiplexing is applied. A minimum of four separate markers plus process controls will be required for a test to provide complete coverage of the high-priority STH species.

For the development of near-term solutions, members of the STH research community have prioritized molecular-based tests for detection of helminth nucleic acid, given the current availability of characterized genomic biomarkers and the more advanced stage of verification of current laboratory-developed assays for all four high-priority STH species.

However, further evaluation is needed to advance lab-based nucleic acid amplification tests (NAATs) from their current early-stage research assays to mature commercialized products. In addition, full characterization and verification of the performance characteristics of current polymerase chain reaction
(PCR)-based assays, including extensive evaluation with samples from different endemic settings, is still required. If the parasite DNA targets currently under consideration are used, then further research may also be required to understand the rate of degradation of parasite DNA in host samples, the correlation of DNA levels to numbers of live worms and/or eggs, and the impact that DNA from nonviable worms may have on assay interpretation, including prevalence and intensity estimates. From an assay design standpoint, further research is needed to ensure assays can provide robust, reliable quantification of STH genomic targets and to determine how quantitative NAAT results will be developed into guidelines as an alternative indicator to eggs counts for assessing infection intensity. Once STH molecular assays have been further verified, current protocols will likely require further modifications to adapt lab-developed methods for use in commercial tests, including those intended for use with field-deployable molecular platforms that may be needed to ensure access for all STH programs.

**Potential markets for improved diagnostic tools**

To estimate the total number of new tests needed worldwide, STH prevalence for each country should be established or at least reliably estimated. Because STH prevalence data were not available for most countries, and in an effort to create a standard method to estimate prevalence, the project team accessed the WHO STH data repository and compared the number of school-age children (SAC) requiring preventive chemotherapy for STH with the estimated total population. The result gave a ratio or estimated prevalence number for each of the 128 countries with various levels of STH prevalence. Four countries were subsequently excluded from additional consideration because WHO identified them as not requiring further preventive therapy. Another 19 countries were excluded because less than 5% of their SAC required preventive chemotherapy for STH.

Each of the remaining 105 countries was divided into districts of 200,000 population. Based on WHO guidelines for Kato-Katz testing, the project team assumed that countries would conduct testing in either five or ten schools per district and would sample 50 students per school. Given that STH is not focal and can occur across geographic areas and environments, the project team assumed that countries would conduct sampling and testing across the entire population and that they would follow MDA and monitoring guidelines in accordance to WHO guidelines (see Figure 1). It was further assumed that Brazil, China, and India should be analyzed separately because of their large populations and significant disease burdens.

Excluding Brazil, China, and India, we calculated that sampling in five schools per district across 102 countries would lead to demand for 2.96 million tests. Increasing sampling to ten schools per district would double demand to 5.92 million tests.

Including Brazil, China, and India in the calculations dramatically affects the projections for potential market demand. Sampling in five schools per district would lead to a global demand of 6.47 million tests,
and increasing sampling to 10 schools would double demand to 12.95 million tests. This assumes, however, that STH infection would be widespread over these countries, and that is likely not the case.

Some countries had both high prevalence (>25% of SAC) and high potential test demand (>100,000 tests in both scenarios). These countries include Bangladesh, Brazil, Ethiopia, India, Indonesia, Nigeria, Pakistan, and the Philippines. This suggests an opportunity for robust demand for diagnostic tests from some large, developing countries, many in Southeast Asia.

Projected health and economic impacts of new diagnostics

Health impact modeling was based on methods used in the Global Burden of Disease Study and provided outcomes in terms of disability-adjusted life years (DALYs) for each scenario along with estimated benefit in terms of DALYs averted (see Figure 3). Overall, development and use of new, more sensitive diagnostics was projected to help increase DALYs averted by 70%, with more than 80% of these averted DALYs coming from school-age or pre-school-age children. These findings suggest that new STH diagnostics could contribute substantially to improved health outcomes among this vulnerable population.

![Figure 3: Projected disability-adjusted life years (DALYs) averted with new STH diagnostics (Dx).](image)

Importantly, modeling showed that control programs will likely fail to reach programmatic goals unless they use more sensitive diagnostics, which are needed to optimize MDA frequency (see Figure 4).
Figure 4. Projected trends in STH prevalence with or without use of new diagnostics.

Without new diagnostics, control efforts could extend past 20 years

Modeling simulations demonstrated that highly sensitive diagnostics will assess a community’s true prevalence of infection more accurately than less sensitive diagnostics. In modeling simulations of 1,400 communities, the difference between the true prevalence of infection as detected by sensitive diagnostics and the apparent prevalence as indicated by less sensitive diagnostics was significant for more than 650 communities. The higher level of sensitivity is achieved largely by detecting infections of lower to moderately lower intensity.

The new prevalence estimates obtained with more sensitive diagnostics increased the frequency of MDA in most cases because WHO guidelines determine the frequency of MDA based on the prevalence of infection. Although MDA frequency would initially increase, it would eventually decrease as programmatic goals are reached.

In some modeling scenarios, the use of more sensitive tests results in an earlier decision to stop MDA. In other cases, modeling suggests more frequent MDA. In either case, resources are more efficiently deployed, and health impact is improved.

Effects depend on initial community prevalence

The ultimate health effect of using more sensitive diagnostics is principally determined by the prevalence of infection in the community when the new diagnostic tool is introduced, relative to WHO thresholds (see Figure 5). Use of more sensitive diagnostic may result in faster elimination of disease and an increase in DALYs averted, but the impact may be determined by which age groups are targeted and the frequency of MDA. Overall, improved administration of MDA can be highly cost-effective in terms of DALYs averted per additional dose administered. The highest degree of benefit is for treatment of *Ascaris*, with
lower levels of benefit for treatment of hookworm. Even these lower-level benefits, however, improve general health and are within the confines of the WHO guidelines, which allow for only one course of MDA every three years in areas of lower prevalence. Infection and re-infection rates are high, and this affects the ability to reach control goals. A summary of species-specific outcomes are included in Appendix A.

Figure 5. Effect on initial prevalence on health impact from use of better diagnostics.

More sensitive diagnostics identify communities where changes to MDA have greatest impact

<table>
<thead>
<tr>
<th>Initial Prevalence</th>
<th>Probability of Control</th>
<th>Time to Control</th>
<th>Doses</th>
<th>DALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Intermediate</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Investment and value proposition

Soil-transmitted helminths affect more than 1.5 billion people worldwide, mostly in impoverished communities in tropical and subtropical countries. Infection with these worms leads to sickness, disability, pain, and suffering, and often individuals are infected with more than one species at the same time. The harmful effects on health and development compound to keep the world’s most vulnerable people trapped in a cycle of illness and poverty.

PATH is developing new diagnostics to detect STH infection. Based on input from experts and modeling simulations, we believe that new diagnostics with greater sensitivity than previously used tests can substantially improve programmatic control and monitoring efforts. Although our modeling revealed that highly sensitive diagnostics will not always lead to substantial improvements in disease control and
reductions in disability in every community, there are many communities where highly sensitive
diagnostics can dramatically improve control efforts by identifying lower intensity infections and thus the
true prevalence of infection. Knowing the true prevalence, especially after repeated rounds of mass drug
administration, will enable better decision-making on the appropriate MDA strategy (frequency of
treatment) and thus more optimal use of scarce resources.
Appendix A. Modeling results for each type of helminth

Conclusions related to *Ascaris* infections

Communities at low true prevalence (< 30%) and high true prevalence (> 70%) will not benefit substantially from improved diagnostics in terms of infection reduction or averted disability-adjusted life years (DALYs). Communities at intermediate prevalence will benefit greatly from increased chemotherapy application and thus will be the key initial focus areas for deployment of diagnostics.

Communities at low prevalence will not benefit greatly because treatment frequency, even with poor diagnostics, results in elimination, provided the diagnostics are sensitive enough to detect a meaningful amount of disease prevalence. In any case, communities with low prevalence suffer relatively little DALY loss, so any benefit of more sensitive diagnostics is marginal, if we are using reduction of DALYs as the measure of success (which is controversial in the soil-transmitted helminth [STH] community). At the same time, communities at high prevalence do not benefit greatly because treatment frequency, even with poor diagnostics, is maximal yet is insufficient to eliminate disease. This scenario reveals why use of new diagnostics alone, without changes to World Health Organization treatment algorithms, will have difficulty in achieving more control.

Most DALY loss related to *Ascaris* infection is among pre-school-age children, and *Ascaris* accounts for much more DALY loss than do infections with *Trichuris* and hookworm species. Use of a more sensitive diagnostic will lead to less extra treatment for *Ascaris* than for other STHs but will result in more cost-effective intervention: approximately 3 DALYs gained per 1,000 additional doses of chemotherapy administered.

Conclusions specific to *Trichuris*

DALY losses from *Trichuris* infection are an order of magnitude lower than those from *Ascaris*, so the impact of additional chemotherapy is lower. Communities at low true prevalence (< 35%) and intermediate true prevalence show a marginal benefit from additional chemotherapy, but communities with high true prevalence (> 60%) do not. Infection in communities with low or intermediate prevalence is eliminated faster or controlled, but the DALY losses in these communities are too small to be meaningful. By contrast, communities at high prevalence do not benefit greatly because treatment frequency, even with poor diagnostics, is maximal yet is insufficient to eliminate disease. As with *Ascaris*, pre-school-age children have higher DALY losses.
Conclusions specific to hookworm

DALY losses attributable to hookworm fall between those for *Ascaris* and *Trichuris*, and the impact of additional chemotherapy is similarly scaled. DALY losses are relatively skewed toward adults because of their higher worm burdens. Elimination of hookworm is far rarer than for *Ascaris*. Treatment of school-age children results in elimination only among the lowest-burden communities because adults contribute the most to transmission. This is similar to the situation with *Ascaris*, where infections among adults in the highest prevalence communities can prevent elimination. With hookworm, however, this pattern is observed in communities at all prevalence levels. In terms of the impact of more sensitive diagnostics, communities can be classified as either low (in which case additional chemotherapy has little effect because elimination is achieved with any diagnostic) or high (in which case chemotherapy has some effect, but elimination is not possible if only school-age children are targeted).
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