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Validation of innovative digital microscopes for the diagnosis of schistosomiasis and other helminthiases

Meulah Tcheubousou, B.

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1.

General introduction

Adapted and extended from: A review on innovative optical devices for the diagnosis of human soil-transmitted helminthiasis and schistosomiasis: From research and development to commercialisation

Brice Meulah, Michel Bengtson, Lisette Van Lieshout, Cornelis Hendrik Hokke, Andrea Kreidenweiss, Jan-Carel Diehl, Ayola Akim Adegnika, and Temitope Ebenezer Agbana.

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Neglected tropical diseases

Neglected tropical diseases (NTDs) are a diverse group of infectious and non-infectious diseases mostly affecting people in tropical and subtropical regions around the world. One feature all NTDs have in common is that, they overwhelmingly affect the poorest and most marginalised communities, most are chronic, slowly developing and becoming progressively worse if undiagnosed on time, some can cause severe life-long disability, and people with NTDs are often stigmatised [1]. However, the impact of NTDs has been overlooked by the Global Health Communities compared to other infectious diseases like HIV/AIDS, tuberculosis and malaria, hence the name “neglected”. The World Health Organization (WHO) has identified a number of NTDs caused by and not limited to a variety of pathogens such as helminths, protozoans, bacteria and viruses and developed a road map to ending the neglect [2, 3]. These pathogens are spread through vectors such as snails, faecal-oral route or contaminated soil, flies and mosquitoes. Timely diagnosis of NTDs, which is often lacking in endemic settings, is crucial for test and treatment, disease control, and prevention of the irreversible life-long disabilities associated with the diseases [4].

Schistosomiasis and soil-transmitted helminth infections

Schistosomiasis and soil-transmitted helminth (STH) infections for example, are two major NTDs that affect approximately 1.5 billion people, predominantly in low- and middle-income countries (LMICs) [5]. Infection with schistosomes occurs when the human skin comes in contact with fresh water contaminated with *Schistosoma* cercariae. The cercariae released from the intermediate snail host penetrates the skin, migrate to the vascular system, and mate as female and male mature worms. Female worms then start producing eggs which can be released in urine or stool into the environment and are the main cause of the disease pathology (Figure 1). The major species in Africa causing urogenital (urine) and intestinal (stool) schistosomiasis in humans are *S. haematobium* and *S. mansoni* respectively. Both species are prevalent in Africa with *S. haematobium* impacting the urogenital system. This leads to symptoms such as hematuria, bladder and kidney failure, along with genital schistosomiasis manifestations like vaginal discharge and postcoital bleeding in women, and hematospermia in men. Chronic infections can lead to risk of miscarriage and infertility, and potentially increase susceptibility to sexually transmitted diseases like HIV [6]. *S. mansoni* infection leads to symptoms such as abdominal pain, diarrhoea as well as blood in stool. When chronic can lead to enlargement of the liver and spleen. The disabilities arising from this disease has a negative effect on the social and economic status of affected individuals in LIMCs with an overall impact on the country’s economic growth.

The transmission of STHs generally follows a common pattern. Adult worms of the STHs residing in the intestines mate, produce eggs which are passed out in human stool and deposited in the environment. Infection occurs through accidental ingestion of eggs (*A. lumbricoides*, *T. trichiura* and to some extent also hookworm) or penetration of the skin (hookworm larvae) which then migrate and develop into adult worms in the intestine (Figure 2). These STH infections have a considerable public health impact when left untreated and can lead to anaemia, malnutrition with opposing effects on both physical and cognitive development in children and

adolescents [7, 8]. The disability caused by STH infections measured as disability adjusted life years has a significant impact on the economy [9].

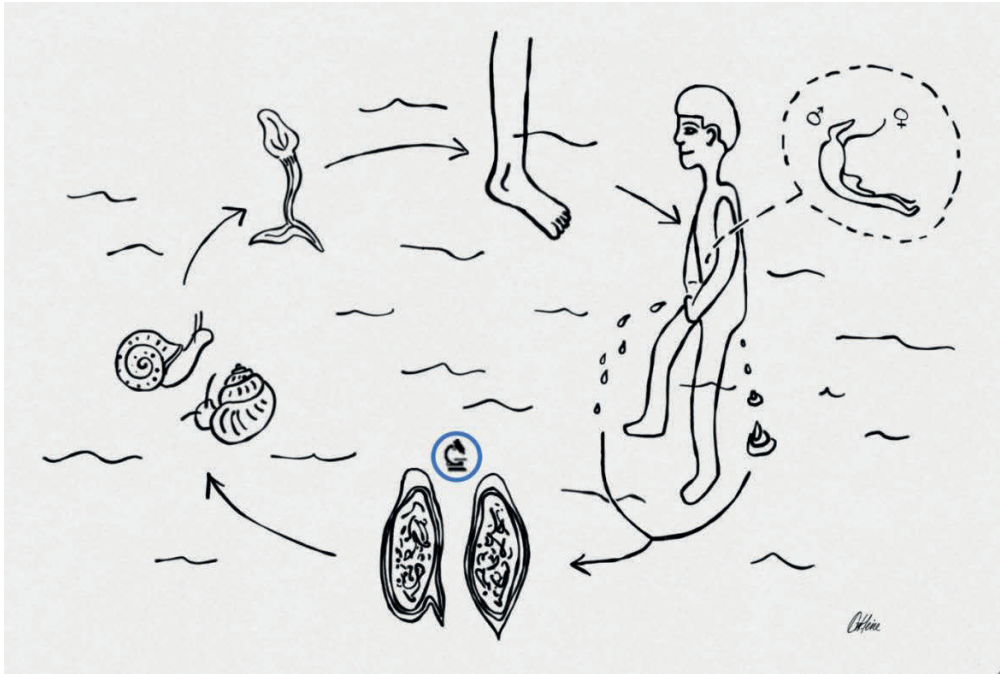


Figure 1: Diagrammatic representation of the lifecycle of *Schistosoma* spp. The stage with the sign  of the parasite and the main focus of this thesis (by C. R. Heine).

Diagnostics methods in field settings

The diagnosis of schistosomiasis and STH infections in LMICs so far relies mainly on conventional microscopy. With this diagnostic technique, parasite-derived products (in particular eggs) in stool and urine can be identified and quantified. This technique applied on urine filtration and Kato-Katz slides for detection and quantification of schistosome and STHs eggs is laborious, requires well-trained personnel as well as infrastructure which is often lacking in resource-limited settings [10, 11]. Alternatives to conventional microscopy for schistosomiasis diagnosis include the urine-based point-of-care test to detect circulating cathodic antigens (POC-CCA) extensively validated in settings endemic for *S. mansoni* infections and endorsed by the WHO [12]. Also, reagent strip tests for detection of microhaematuria as a marker for *S. haematobium* infection have been employed for epidemiological surveys [13-15]. However, this test has a limited specificity [16].

The up-converting particle lateral flow (UCP-LF) assay has been developed to detect circulating anodic antigen (CAA) in urine and serum, which is an antigen produced by all *Schistosoma* spp [17-20]. Nucleic acid amplification tests (NAATs), involve the amplification and detection of parasite's specific nucleic acid sequences, typically through real-time Polymerase Chain Reaction (PCR). The real-time PCRs which have been developed for the diagnosis of

schistosomiasis and STH infections, can be used on clinical samples such as stool, urine and blood and are mainly applied in equipped research laboratory settings in LIMCs or as a laboratory tool for the diagnosis of imported infections in high-income countries [21-25]. The UCP-LF CAA and NAATs, although highly accurate methods, both require well-trained personnel and appropriate laboratory infrastructure, with the UCP-LF CAA being less laborious than NAATs. These two methods are still being validated and standardised for use in daily clinical care and medical research in resource-limited settings [18, 26-29].

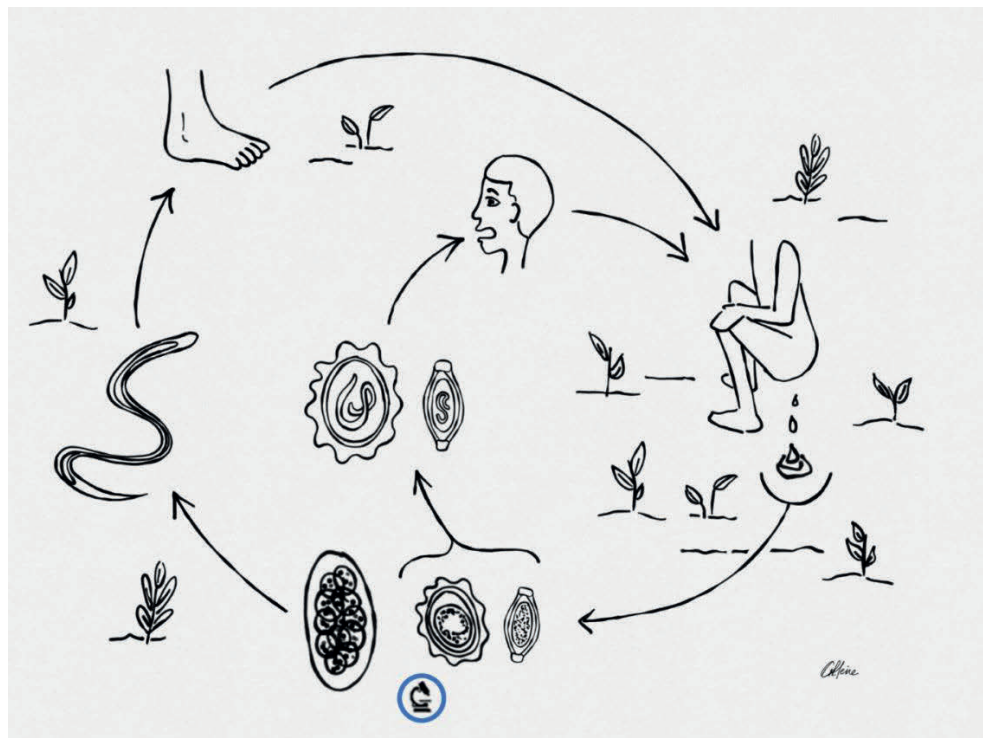


Figure 2: Diagrammatic representation of the life cycle of *Ascaris*, *Trichuris* and hookworm. The stage with the sign  is a diagnostic stage of the parasites and the main focus of this thesis (by C. R. Heine).

Approach to control and challenges

In order to accelerate control of schistosomiasis and STH infections, focus is placed mainly on mass drug administration (MDA) of praziquantel to all persons above the age of 2 years and albendazole or mebendazole to school age children, respectively. In addition, approaches such as increased access to clean water and sanitation, snail control (for schistosomiasis only), education and behavioural changes are adopted, together with a multi-diagnostic approach to support monitoring and evaluation these programs [30]. Detecting and quantifying schistosome and STHs eggs with conventional microscopy has been the primary approach to determining the level of ongoing transmission, serving as a crucial tool in assessing

the effectiveness of control programs in endemic setting. Although conventional microscopy remains the most commonly used diagnostic method, it confronts challenges, particularly the need for trained personnel to meet the overwhelming diagnostic demands of control programs and test and treat in clinical settings. Novel diagnostics are needed and automating conventional microscopy could offer a viable solution to this challenge. The development of automated, easy to use digital microscopes for the detection of parasite eggs in faeces or urines, and based on low-cost platforms may provide a matching solution. The WHO has postulated a target product profile (TPP) to guide development of novel diagnostics to reliably measure the effectiveness of control programs in endemic settings [31-33] and advance towards elimination as well as for case management.

Digital optical diagnostic devices

Innovative digital optical diagnostic devices (DODDs), designed to (semi-) automatically detect helminth eggs in clinical samples have been built based on technical modifications of the optical train of a smartphone [34, 35] or mounting off the-shelf optical components [36, 37]. The integrated sensors on smartphones are commonly used for image acquisitions [38, 39]. The processing power of smartphones as well as simple computer units (e.g. Raspberry Pi, Jetson nano) have equally been exploited for the development and running of artificial intelligence (AI) algorithms. The AI algorithms are developed for analysis of registered image data. Such devices have been reported to possess the potential for (semi-) automated medical diagnosis in endemic settings [36-38, 40-42].

Over the last years, several investigators have reported the use of multiple digital devices to detect schistosomiasis and STH infections. While these devices show promise for diagnosing these diseases, they are currently underrepresented in LIMCs. The nine-level technology readiness level (TRL) scale developed by National Aeronautics and Space Administration (NASA) has been used by engineers to qualify readiness for technology applications [43]. However, the TRL scale does not consider extensive medical and design outcomes including the WHO TPP. Using an adapted version (Figure 3) of the TRL scale including the WHO TPP and context specific needs to qualify the readiness of DODDs for field applications in LIMCs, revealed that a majority (85%) are not ready [44]. Meeting the WHO TPP for the majority of these devices in field validation stage (TRL 5,6 and 7) was found to be a major bottle neck, followed by non-continuous validation after the demonstration of proof of concept, despite promising outcomes.

This clearly highlights the need for more research and development of DODDs alongside preclinical and in field validation studies in different endemic settings with diverse conditions to meet the desired TPPs.

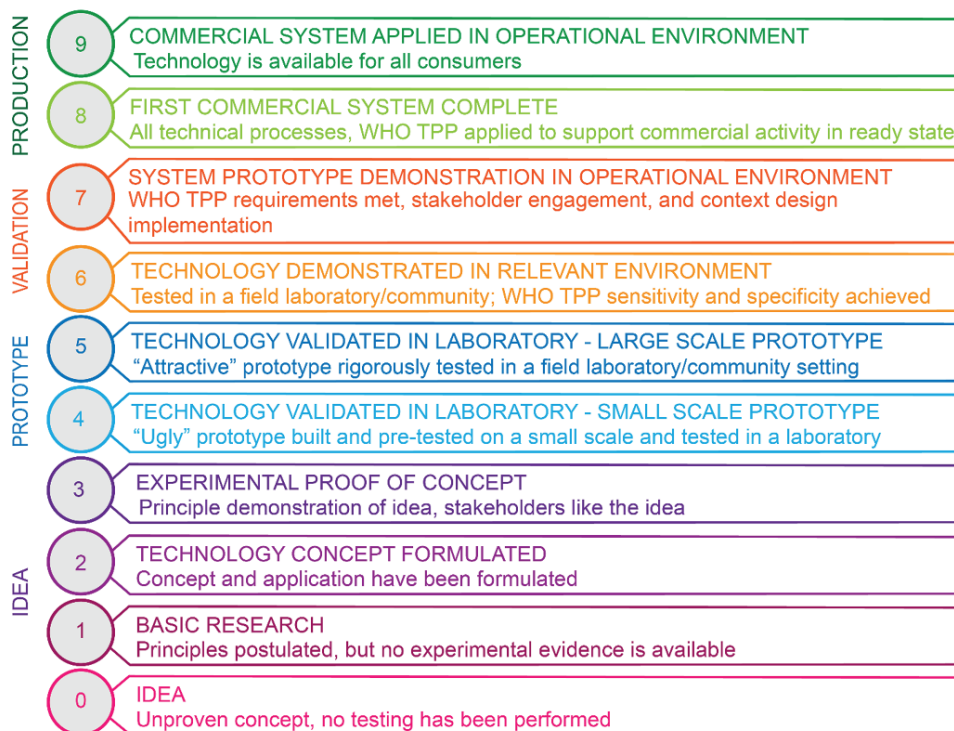
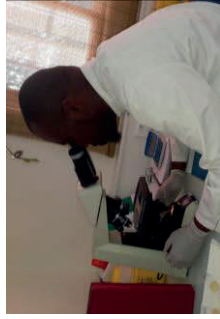


Figure 3. The nine-scale TRL classification chart. Image adapted from (43). TPP= Target product profile

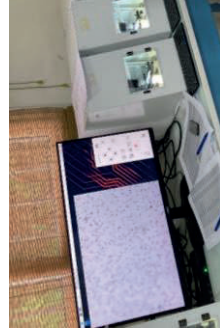
The Schistoscope [36] and AiDx Assist devices are AI-powered automated slide-scanner digital microscopes developed for the diagnosis of schistosomiasis, STHs and other parasitic infections. They are both composed of a custom-designed optical bright-field illumination, x, y, x-axis movement and a condenser controlled by a custom printed circuit board but differ in their electronic and computing modules including the AI framework used. The Schistoscope consist of a Raspberry Pi 4B computer connected to a Raspberry Pi HQ camera that has a pixel size of $1.55 \mu\text{m}$ and an image resolution of 2028×1520 pixels. The AiDx Assist consists of a Jetson Nano computer connected to a Sony IMX 178 CMOS camera sensor with a pixel size of $2.40 \mu\text{m}$ and an image resolution of 3088×2076 pixels. The Schistoscope and AiDx Assist digital microscopes have a $4\times$ objective sufficient to resolve *Schistosoma* spp, STHs eggs and microfilaria. The Schistoscope has been developed as a standalone AI-based device for diagnosing these infections, with the AI analysis result serving as the conclusive test outcome (Figure 4). In contrast, for the AiDx Assist, the AI results undergo additional verification by the operator before a final test outcome is reported. These devices have gone through multiple iterations in their development.

Conventional microscopy



Manual sample analysis

Schistoscope



Automated image capture



Image analysis by expert

Semi-automated Schistoscope

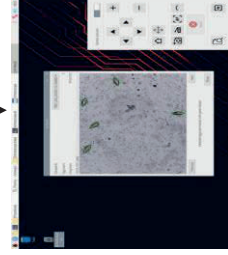


Image analysis by AI

Fully-automated Schistoscope

AiDx Assist



Automated image capture

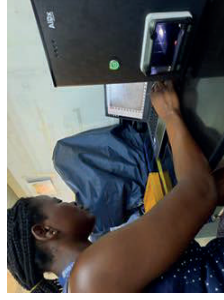
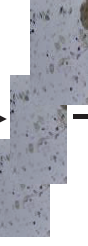


Image analysis by expert

Semi-automated AiDx

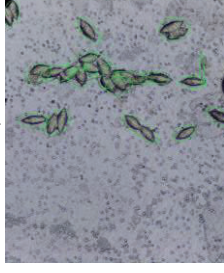
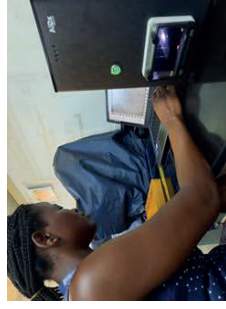


Image analysis by AI



AI result confirmed by expert

Fully-automated AiDx

Figure 4: Comprehensive flow chart showing the use case scenario of conventional microscopy, Schistoscope and AiDx Assist for disease diagnosis

In this thesis we conducted preclinical and in-field validations of the Schistoscope and AiDx Assist at different iterations of their research and development. These devices underwent validation procedures throughout their development, beginning with preclinical validation in a technical laboratory setting using phosphate buffer saline or human biological samples spiked with parasitic worm eggs. Based on the preclinical outcomes, we proceeded to an in-field validation with the objective to achieve the WHO diagnostic TPP (with a focus on sensitivity and specificity) for the Schistoscope and AiDx Assist and to further explore their performance in comparison to conventional microscopy.

Scope and outline of this thesis

The main objective of the work described in this thesis is to validate the diagnostic performance of the Schistoscope and AiDx Assist as egg-based detection methods for schistosomiasis and the STHs through their research and development. The validation was performed through preclinical and in-field studies based on collected clinical samples of potentially infected individuals, in different endemic settings. In **Chapter 1** we present an overview of this thesis and highlight the main challenges faced with the research and development to commercialisation of DODDs as egg-based detection methods. In **chapter 2** we demonstrate context specific needs with regards to different diagnostics methods by highlighting the limitation of POC-CCA and haematuria rapid test as field friendly alternatives of conventional microscopy. In addition, we determined the need for egg-based detection (microscopy) methods in accessing the current prevalence of schistosomiasis in a particular setting in Tanzania, endemic for *S. haematobium* and *S. mansoni* infections. In **chapter 3** the Schistoscope was evaluated as a semi-automated and fully automated (with AI algorithm) microscope, compared to conventional microscopy for the detection and quantification of *S. haematobium* eggs in urine in Nigeria. In **chapter 4** we carried out improvements of the AI algorithm of the Schistoscope through a two-stage automated diagnosis framework for *S. haematobium* eggs detection and quantification with pre-clinical validation on microscopy images obtained from endemic settings. In **chapter 5** we performed a follow up validation of the Schistoscope in Lambaréné, Gabon. The detection and quantification of *S. haematobium* eggs in urine by the Schistoscope was compared to conventional microscopy and to a more sensitive composite reference standard, including real-time PCR and UCPLF-CAA data. In **chapter 6** we evaluated the AiDx Assist digital microscope as a tool for diagnosing *S. haematobium* in urine and *S. mansoni* and other STHs in stool under field conditions in Nigeria. The results are summarised and discussed in **chapter 7** highlighting the progress made in the development of DODDs, looking beyond diagnostic performance including some additional field experience with the devices, discussing the context specific diagnostic needs and the prospects of DODDs for schistosomiasis and other helminthiasis in endemic settings.

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