

New Diagnostics for NTDs: Harnessing Advancements to Support Surveillance and Elimination Goals

Session Date & Time:	Tuesday, November 19; 9:00 AM to 12:00 PM
Session Location:	Bellagio Ballroom – Section 2
Session Description:	How could, and how should, the application and refinement of new diagnostics support surveillance and elimination goals?
Session Chair:	Sir Roy Anderson
Session Rapporteur:	Emily Adams, LSTM

KEY DISCUSSION POINTS

This session aimed to review current advances in the development of novel diagnostics for soil-transmitted Helminths (STH) and schistosomiasis, and further to discuss the next steps required to make these tools field-ready and programmatically relevant.

Previous COR-NTD meetings have noted knowledge gaps around diagnostics, in particular the absence of rapid diagnostic tests for mapping the distribution of schistosomiasis in low-prevalence/elimination settings. In COR-NTD 2019, diagnostics was a huge talking point, and we took lessons from session 1G on day one, into our thinking for session 2G on day two.

For design of effective control programs, it is important to determine an accurate estimate of infection levels in a program area. Current diagnostic methods for STH and schistosomiasis (detection of eggs in stool by Kato-Katz) are limited and may be particularly unreliable at low infection intensities, as would be expected after several rounds of treatment or where transmission is low. A particular problem is the high logistical cost and poor compliance to multiple days of Kato-Katz or urine filtration testing, which is required to accurately detect infection at low prevalence. In order to overcome some of the pitfalls of traditional methods, there has been interest in developing more sensitive diagnostic tests.

Anna Phillips spoke about the performance of the point-of-care circulating cathodic antigen (POC-CCA) test for the detection of intestinal schistosomiasis in areas with low parasite burden. This is a test that can detect antigen in the urine and is available commercially in a rapid diagnostic test (RDT) format. POC-CCA can detect pre-patent and patent infection, and remains positive after successful treatment due to antigen persistence. The sensitivity of POC-CCA can be very high, but specificity low. If trace readings are taken as negatives, then the specificity improves, but obviously sensitivity drops. If POC-CCA tests are implemented in programmatic conditions, then the thresholds for MDA campaigns should be changed, although this has not been suggested by the World Health Organization (WHO) as of yet. If thresholds are not changed then the corresponding drug donations would need to significantly increase.

Other highly sensitive diagnostics under development include the molecular diagnostics, quantitative Polymerase Chain Reaction (qPCR) and Real Time Recombinase Polymerase Amplification (RT-RPA). Bonnie Webster and Marina Papaïakovou introduced the developments and complexities of these techniques.

To diagnose STH infections using qPCR, fecal material firstly has to undergo a rigorous DNA extraction procedure which is expensive, laborious and requires additional equipment and time-consuming. qPCR is a very sensitive, DNA- based diagnostics tool but its implementation as a field-based diagnostics tool (as a point-of-need diagnostics or in reference laboratories) is missing. qPCR requires extensive infrastructure, but this is a methodology with high sensitivity/specificity and the power and benefits should not be underestimated.

RPA is an isothermal technique which is quicker than qPCR and does not require a thermocycler. In Bonnie's presentation she showed results of 91% sensitivity and 79% specificity in the elimination setting of Zanzibar for detecting urogenital schistosomiasis. This type of diagnostic is highly tailored to the elimination setting where prevalence (<2%) and intensity (<5 eggs / 10mls) is very low and the sensitivity of current diagnostics tests (filtration) drops by 71%. In this type of setting test and treat scenarios, implemented by highly sensitive and rapid diagnostic tests are needed to test and treat. Bonnie has looked into the diagnosis of female genital schistosomiasis (FGS) using vaginal lavage using the urogenital schistosomiasis RPA assay; results compared to qPCR are also promising, with high sensitivity 98% in a small study. Such a diagnostic could support non-invasive diagnosis of FGS and empower women to seek diagnosis, as could qPCR. The concern for RPA remains the purchase of the kits and high likelihood of small companies being bought out, and so continuity of supply is an issue without substantial investment.

Finally, Joanne Webster spoke about the need for improved diagnostics for animal schistosomiasis in Africa in one-health approach. This is essential due to the potential maintenance of residual transmission by animal reservoirs especially in West African where schistosome genotypes circulating in the rodent population are shared by humans and the snail intermediate hosts, and the high prevalence of hybrids/introgressed schistosomes. Point of care diagnostics have not been evaluated in animals and so sensitivity/specificity is unknown, and Joanne recommended use of statistical techniques to establish accuracy.

KNOWLEDGE GAPS IDENTIFIED

In this session we focused on the knowledge gaps identified from the point where new diagnostics have been developed, and now need to be implemented.

- **Disease Requirements**

The laboratory needs will be different for each disease due to the fact that the diagnostic needs and target product profiles (TPPs) are different for each disease. For example, a mobile diagnostic clinic for Trachoma is much more feasible than that needed for molecular diagnostics for STH, mainly due to the DNA extraction requirement. Therefore, the laboratory and technology needs should be tailored to the disease and what the operational research question is: For example, for monitoring control interventions of schistosomiasis basic microscopy is

sufficient and no technology transfer maybe needed but, for the elimination of schistosomiasis highly sensitive diagnostics are needed and the more advanced methodologies need to be transferred. **The diagnostic and technology will be different for different diseases.** For example, for STH, presence absence in the general community maybe sufficient but for schistosomiasis each individual infected needs to be identified and treated. This relates to the biology of the pathogens, and this should not be over-simplified.

- **Engagement with Policy**

The diagnostics that are currently being developed are frequently more sensitive due to the need to detect low level infection in an elimination setting. This needs to be taken into account when determining thresholds for elimination. Will these need to be changed to take into account the rise in infection once new tests introduced. This could affect drug donations, and national targets.

- **Lack of standards for commercially developed tests:**

Both commercial companies that have developed the lymphatic filariasis (LF) antigen test and POC-CCA, do not want to produce a quality control test. This should be a part of test development and needs to be included in Target Product Profiles to include standards. In this case, two academic groups have independently developed a control. For LF this standard is provided to WHO, who then provide this to endemic countries. For POC-CCA the standard is provided to those who ask. It is unclear if this mechanism is widely used.

- **Evaluation of diagnostics is difficult for commercial companies:**

Companies can not access clinical samples and data, and there is currently no central source or repository of samples. This may not be possible centrally due to restrictions in sample movement. However, a virtual biobank or list of resources, where ethics are in place to use samples is worthwhile. Groups storing samples should be incentivised or recompensed in some way for provision, storage, expertise and reference test results. Further involving groups by knowledge transfer or capacity building would be best.

- **Training gaps:**

The ESPEN Onchocerciasis lab was mentioned as a good example where technology transfer and knowledge exchange are successfully being implemented. This is a high-level reference lab, and we need to think about the implementation of diagnostics at all levels in the system:

- Very basic (very little or no infrastructure) – no trained staff available
- Basic laboratories (infrastructure in place but needs development)– capacity for training staff
- Working laboratories (currently working but will need continued support and training) – staff members available but need training
- Advanced laboratories (up and running and well maintained - trained staff available

RECOMMENDED NEXT STEPS

Standardization and external quality assessment (EQA): Need to develop standards for quality assurance and build capacity in laboratories for implementation.

- Requires an expert team to come up with standardised protocols for collection and storage of samples
Incorporating ethical considerations for long term storage and use in initial ethics applications
- Need to combine a number of laboratories in Africa (ESPEN has started this process) and beyond.
- POC-CCA are now undergoing quality control by industrial partners. Proficiency testing kits need to be developed for countries that re-package the test kits such as Brazil.

Virtual Biobank: Equivalent Open Access for data in papers.

- Requires a team to decide what information would need to be stored
- How to incentivize groups to contribute, especially considering that many countries will not allow samples to be sent out.
- How to ensure that these samples are good quality, and standardize data collection processes.

Reference Laboratory(ies):

- ESPEN Oncho lab has been developed (funded by USAID) whereby a subset of the samples is quality control checked. As the network is created LF antigen test and POC-CCA, both commercial companies that make this test do not want to produce a quality control test. However, two academic groups have independently developed a control. For LF this standard is provided to WHO who then provide this to endemic countries. For POC-CCA the standard is provided to those who ask.

Training Gaps:

- The example of microscopy detecting eggs was brought up and how quality control has shown that training is needed to maintain high standards. i.e. it is not only new diagnostics that need access to standards, but also we must maintain expertise in traditional areas of diagnostics.
- Can we produce training materials for all levels of laboratory and staff in order that we retain knowledge and importantly quality of testing.

Funding: Who will fund these activities?

- Ideally for sustainability multiple funding sources such as USAID, CDC. Walter Reed already run reference laboratories around the world, perhaps they could be asked to help either contribute knowledge and know-how.
- If labs can put budgets and requests together then funders will be interested in this. ESPEN is currently setting up this laboratory network for this standardisation purpose.