Ethics and Algorithms: The Way Forward for Onchocerciasis Elimination in *Loa loa* Endemic Areas

Session Date & Time:	Tuesday, November 19; 9:00 AM – 12:00 PM
Session Location:	MGM Salon B
Session Description:	What further ethical and research questions remain to be resolved in order to implement ivermectin treatment in hypo-endemic onchocerciasis areas co-endemic with loiasis? Session participants will discuss how to prioritize the use of the LoaScope, and which tools to leverage (and how) in areas where loiasis prevalence is less, but its importance is yet to be evaluated.
Session Chairs:	Adrian Hopkins and Joseph Kamgno
Session Rapporteur:	Sarah Sullivan, NTD Support Center

Key Discussion Points

Elimination of onchocerciasis will require expansion of mass drug administration (MDA) of ivermectin or any other treatment tool into areas which are hypo-endemic for the disease and have not yet been treated. Some of these hypo-endemic areas are co-endemic for *Loa loa*, a parasite which, at high levels of microfilaremia, can cause severe adverse events (SAEs) when a person takes ivermectin. New tools and approaches have been developed to assess loiasis prevalence and *Loa loa* microfilarial (mf) load, tests which could inform where and whom we should exclude from MDA. However, ethical and operational questions about the deployment of these strategies remain in view of the costs and scarcity of the LoaScopes and the need to scale up more rapidly if onchocerciasis transmission is to be interrupted. Therefore, the objectives of this breakout session were to elucidate these remaining questions and to suggest operational research questions which would address them.

Through presentations by Drs. Hopkins, Klion, Boussinesq, Kamgno, Biamonte, and Diggle, the available tools, ethical considerations and potential paths forward for onchocerciasis elimination in *Loa loa* co-endemic areas were described. Emphasis was placed on linking tools and strategies to ensure that any proposed OR strategies addressed concerns of safety, cost and feasibility at scale.

Based on feasibility in field settings, discussions about which diagnostics should be used to identify *Loa loa* were quickly narrowed to RAPLOA, the LoaScope and the *Loa loa* antifilarial antibody test (Loa RDT). While previous discussions within the community found that people

were comfortable with the RAPLOA (history of eyeworm) assessment and it has been utilized broadly up to this point in so called meso and hyperendemic foci, its low sensitivity was highlighted as a significant drawback, particularly in low-prevalence or other non-treated areas. In Cameroon, SAEs have occurred in areas that were predicted to be low-risk areas according to maps which were based on RAPLOA assessments and utilized kriging to interpolate in areas where assessments had not taken place, highlighting potential risks of utilizing an insensitive tool.

The LoaScope and Loa RDT tools were highlighted as promising options for assessing mf load and prevalence or just prevalence respectively, though the LoaScope's limited window of application (due to mf periodicity) and the antibody test's inability to distinguish microfilarial load.

The LoaScope is a smartphone-based microscope technology which detects and quantifies the presence and intensity of *Loa loa* mf in the blood. Since SAEs occur in those with high mf load, the LoaScope can be utilized at the point of care to ascertain if an individual's *Loa loa* mf load is too high for them to be safely treated, or if it is low enough (or zero) so that they can be safely treated. This approach, called Test and Not Treat (TaNT) has been deployed in people with no SAEs, and is advocated as a risk-free way of treating with ivermectin in Loa-coendemic areas. However, the cost of the TaNT strategy, which includes the upfront and supplies cost of the LoaScope, as well as extensive social mobilization which accompanies the strategy and a limited window in which tests can be performed (due to parasite diurnal periodicity) have led to questions about the cost and feasibility of large-scale implementation. Additionally, there are not enough LoaScopes currently in production to roll out this strategy everywhere that it is needed. Therefore, interest was registered in alternative strategies to shrink the map of where TaNT is needed.

The Loa RDT is a rapid diagnostic test which detects prior exposure to *Loa loa* infection. While it does not provide a quantitative mf load, on a village level it does indicate areas where *Loa loa* exposure has occurred and can therefore provide valuable information about loiasis history in an area. Additionally, preliminary work shows a relationship between village level antibody prevalence and village-level LoaScope prevalence. Using what we know about the relationship between prevalence and high mf loads as well as the likelihood of SAEs, it could therefore be possible to quantify the risk of an SAE based on RDT prevalence. The RDT is also less expensive than LoaScope testing, and unlike the LoaScope the supply is not currently limited.

Geostatistical modeling is an additional tool which can be used to map *Loa loa* utilizing several different inputs. Utilizing environmental covariates, as well as existing data from both gold-standard tests, other less ideal but more feasible tests, it is possible to model predicted prevalances and predicted risk as well as the uncertainty of those predictions. Further adaptive sampling can then be performed in areas with high uncertainty using a balance of tests which give the best indication of risk but are currently limited in availability (i.e. LoaScope), and those which provide less sensitive or specific information but are more feasible and/or cheaper (ie RAPLOA or Loa RDT).

Bearing in mind the diagnostic and statistical tools at our disposal, it is important not to lose sight of the ethical implications of this work. While onchocerciasis elimination is an important

goal, the risk of SAEs cannot be forgotten. Especially given that ivermectin MDA in areas hypo-endemic for onchocerciasis may provide a group benefit at the expense of an individual risk, we cannot allow eagerness to eliminate onchocerciasis make us move too fast and potentially cause SAEs. By waiting for onchocerciasis elimination mapping to be completed and prioritizing use of LoaScopes for TaNT activities we could mitigate these risks substantially, however this strategy could take a long time.

Knowledge Gaps and Recommended Next Steps

The breakout session split into two groups. The first discussed what operational research (OR) questions need to be answered to ensure that TaNT can be applied in a programmatic setting, and the second discussed how we shrink the map to determine where TaNT needs to be performed. OR questions which need to be answered to ensure that TaNT can be applied programmatically include:

- What is the best approach to identify people in need of testing year after year?
    - Options suggested: Tablet-based, paper-based, biometrics
- Effect of forecasting LoaScopes on the efficiency of TaNT
    - What is the ideal number of LoaScopes?
    - What is the impact of incoming children, migration and systematic non-compliers?
    - When deploying Loa TaNT, should onchocerciasis also be tested for using the RDT (or dried blood spots), and could community teams do this, so that patients negative for onchocerciasis are not treated?
    - Is there a need to re-map in districts that are partially treated?
- Coverage and Compliance
    - What is the impact of previous SAEs on coverage in a district?
    - How does the LoaScope allow for increased coverage?
    - How do we optimize coverage in hypo-endemic areas?
        - What is the impact of social mobilization?
        - Does integration with other diseases/programs increase coverage?
    - What are the current barriers to high coverage in co-endemic areas and how can we increase acceptance?
    - How does TaNT affect compliance in areas which are highly endemic for *Loa loa*?
    - What is the desired coverage of TaNT to hit desired elimination goals?
- Cost:
    - What are the costs of TaNT s and how would they change over time?
    - What is the cost/benefit to the overall onchocerciasis elimination program of not doing TANT?
        - Do hypo-endemic onchocerciasis areas go away?
        - Do they worsen (become meso-endemic)?
        - Do they re-infect neighboring meso-endemic areas?
    - What adjunctive strategies could be used and what are their costs (i.e. doxycycline)?

The proposed strategy for "shrinking the map" is to combine existing knowledge, geostatistical inference, adaptive mapping, and new sampling using the LoaScope and Loa RDT to exclude areas where *Loa loa* is not endemic and therefore TaNT is not needed and ivermectin MDA can be performed. The key OR questions which this approach seeks to address are:

- What is the relationship between Loa RDT village-level prevalence and the presence of high mf individuals in those communities as measured by the LoaScope?
- How can we combine information from the RDT and LoaScope to find a cost- and resource- efficient way to map for loiasis non-endemic areas where people feel comfortable treating?

The exclusionary mapping strategy proposed is, for a country with *Loa loa*:

1. Exclude areas where *Loa loa* transmission is not possible:
    a. Map the vector (*Chrysops*) to determine which areas could not have *Loa loa* based on environmental covariates and can therefore be excluded
2. Exclude areas where *Loa loa* is not endemic:
    a. Utilize existing data from across diagnostics to create a map that determines in which areas ivermectin MDA would be safe, unsafe and of unknown safety
    b. Adaptively sample in areas of unknown safety: Sample using 200 villages in a country and test all of them with RDT, as well as testing a subset of those with LoaScopes (at a rate limited by their availability)
3. Exclude areas where oncho is not endemic:
    a. Include ongoing data from onchocerciasis elimination mapping
    b. Potentially add an onchocerciasis testing component to determine if onchocerciasis is truly endemic in the areas thought to be hypo-endemic and therefore being targeted.

Note: Selection of the country in which to test this strategy should keep in mind that as an exclusionary strategy, it needs to have non- and low- endemic areas.