Report of the Second Meeting of
the WHO Onchocerciasis Technical Advisory Subgroup

UNAIDS BUILDING, ROOM 46025
Geneva, Switzerland
12-14 February 2018
# Table of Contents

I. Abbreviations v  
II. Executive Summary vi  
III. Report 1-29  
   1. Highlights of the 1st OTS meeting 1  

2. Strategies for implementation of MDA in areas co-endemic for loiasis 2  
   i. Extent of co-endemic mapping gap 2  
   ii. Update on tools 2  
   iii. Risk of adverse events for ivermectin use 3  
   iv. Test and Not Treat protocol 4  
   v. Impact of ivermectin on loiasis 5  
   vi. Mapping of *Loa* – model 6  
   vii. Mapping of *Loa* – Cameroon 7  
   viii. Mapping of *Loa* – Nigeria 7  
   ix. Acceptable risk 8  
   x. Need to determine acceptable risk 9  
   xi. Cost and cost-effectiveness of TnT strategy 10  
   xii. Potential use of LoaScope in hyper- and meso-endemic areas 10  

Discussion of strategies for co-endemic loiasis 11  
   i. Overlap of onchocerciasis and loiasis 11  
   ii. Update on tools 11  
   iii. Risk of adverse events with ivermectin 12  
   iv. TnT strategy and the elimination of onchocerciasis 12  
   v. Settings for the TnT strategy 12  
   vi. Cost of the TnT strategy 14  
   vii. OTS recommendations 14  

3. Post-treatment surveillance – the role of entomology 15  
   i. Review of entomological methods 15  
   ii. Experience with PTS in the Americas 16  
   iii. PTS in the North East Focus of Venezuela (Bolivarian Republic of) 16  
   iv. Uganda experience with entomology for stop-MDA and PTS 17  
   v. Entomology experience in Sudan 17  
   vi. Modelling the risk of recrudescence 18  
   vii. Outstanding questions about PTS 19  
   viii. Update on laboratory capacity 19  

Discussion of PTS and OTS recommendations on post-treatment surveillance – the role of entomology 21  

4. Co-evaluation of onchocerciasis and lymphatic filariasis 23  
   i. Framework for the co-evaluation of onchocerciasis and 23
lymphatic filariasis
ii. Burkina Faso experience with co-evaluation 23
iii. Tanzania experience with co-evaluation 24
iv. Nigeria experience with co-evaluation 25
v. Implications of co-evaluations for (pre) stop-MDA surveys 25
vi. Remaining operational questions for co-assessment of LF and onchocerciasis 27

Discussion of co-evaluation and OTS recommendations 27
Final discussion point 29

IV. Declarations of Interest 30
## I. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ALB</td>
<td>albendazole</td>
</tr>
<tr>
<td>ATP</td>
<td>annual transmission potential</td>
</tr>
<tr>
<td>CAR</td>
<td>Central African Republic</td>
</tr>
<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>DBS</td>
<td>dried blood spots</td>
</tr>
<tr>
<td>DFID</td>
<td>United Kingdom’s Department for International Development</td>
</tr>
<tr>
<td>DRC</td>
<td>Democratic Republic of Congo</td>
</tr>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent Assay</td>
</tr>
<tr>
<td>ESPEN</td>
<td>Expanded Special Project for the Elimination of Neglected Tropical Diseases</td>
</tr>
<tr>
<td>EU</td>
<td>evaluation unit</td>
</tr>
<tr>
<td>FTS</td>
<td>Filariaasis Test Strip</td>
</tr>
<tr>
<td>HRP</td>
<td>horseradish peroxidase</td>
</tr>
<tr>
<td>iTAS</td>
<td>Integrated transmission assessment survey</td>
</tr>
<tr>
<td>IVM</td>
<td>ivermectin</td>
</tr>
<tr>
<td>LF</td>
<td>lymphatic filariasis</td>
</tr>
<tr>
<td>LGA</td>
<td>local government area</td>
</tr>
<tr>
<td>MDA</td>
<td>mass drug administration</td>
</tr>
<tr>
<td>M&amp;E</td>
<td>monitoring and evaluation</td>
</tr>
<tr>
<td>MEC</td>
<td>Mectizan Expert Committee</td>
</tr>
<tr>
<td>Mf</td>
<td>microfilariae</td>
</tr>
<tr>
<td>NIH</td>
<td>United States National Institutes of Health</td>
</tr>
<tr>
<td>NOEC</td>
<td>national onchocerciasis expert committee</td>
</tr>
<tr>
<td>NTD</td>
<td>Neglected Tropical Diseases</td>
</tr>
<tr>
<td>OCP</td>
<td>Onchocerciasis Control Programme</td>
</tr>
<tr>
<td>OEM</td>
<td>Onchocerciasis Elimination Mapping</td>
</tr>
<tr>
<td>OEPA</td>
<td>Onchocerciasis Elimination Program for the Americas</td>
</tr>
<tr>
<td>OTS</td>
<td>Onchocerciasis Technical Advisory Subgroup</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>Pre-TAS</td>
<td>Pre-Transmission Assessment Survey</td>
</tr>
<tr>
<td>PTS</td>
<td>post-treatment surveillance</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>QC</td>
<td>quality control</td>
</tr>
<tr>
<td>RAPLOA</td>
<td>rapid mapping for loiasis</td>
</tr>
<tr>
<td>RDT</td>
<td>rapid diagnostic test</td>
</tr>
<tr>
<td>SAE</td>
<td>severe adverse event</td>
</tr>
<tr>
<td>TAS</td>
<td>Transmission Assessment Survey</td>
</tr>
<tr>
<td>TFGH</td>
<td>Task Force for Global Health</td>
</tr>
<tr>
<td>TnT</td>
<td>Test and Not Treat</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
II. Executive Summary

The WHO Onchocerciasis Technical Advisory Subgroup (OTS) was established in order to provide advice to WHO in accordance with the terms of reference developed for the subgroup. The objectives of the 2nd meeting were to develop common strategies for mapping and ivermectin treatment in areas co-endemic for onchocerciasis and loiasis, review lessons learned from co-evaluation of onchocerciasis and lymphatic filariasis (LF) and apply them to current strategies, and begin standardization on entomological activities. The key conclusions and recommendations of the OTS are described below. Please note that many of the recommendations are provisional and thus may change over time as new evidence emerges. Evidence that emerges after the meeting will not be reflected in this report. Some lessons will have to be learned while programmes continue to strive to eliminate the transmission of onchocerciasis. Recommendations are based on consensus unless otherwise noted. When consensus could not be reached, operational research questions were defined that should provide the evidence required to obtain a consensus in the future.

1. Strategies for areas co-endemic for onchocerciasis and loiasis. The OTS felt that the current data supported the use of the LoaScope for the measurement of Loa loa microfilarial density in the ranges relevant for identifying individuals at risk for severe adverse events (SAEs) and marked adverse events (AEs), though it would be useful to understand the intra-individual variability as measured by the LoaScope in a field setting. The results of the Test and Not Treat (TnT) study were also encouraging, with more than 37,000 treatment given and no SAEs identified in the high risk study area, though it was not clear how best to implement the TnT strategy in the programmatic context. There is the possibility of using the LoaScope as part of a model-based mapping strategy that would identify communities in areas that are hypoendemic for onchocerciasis that need TnT in order to implement ivermectin mass drug administration (MDA) and those that can proceed with MDA without individual testing. However, a mapping strategy to reduce areas that require TnT requires determination of the acceptable risk for missing an individual who subsequently develops an SAE. Consensus could not be reached on this issue. OTS recommended that WHO convene an ad hoc meeting that would include additional stakeholders where a final recommendation about the acceptable risk could be determined. OTS also recommended operational research be conducted to examine whether the TnT strategy could be used in areas that are poorly performing and meso- or hyper-endemic for onchocerciasis to increase compliance with ivermectin MDA. Additional evidence that using the TnT strategy allows achievement of the coverage required to interrupt transmission of onchocerciasis and that the strategy only needs to be used in ivermectin naive individuals would also be welcome.

2. Post-treatment surveillance and entomology. The deliberations about post-treatment surveillance (PTS) generated a fair number of questions and a few recommendations. It is clear that programmes will need to increase their entomological capacity, particularly at the level of field entomologists or entomology technicians. The identification of new breeding sites, confirmation of the continued productivity of previously identified breeding sites, establishment of biting rates, and determination of transmission seasons should all be considered components of monitoring and
evaluation (M&E) that provide important information to programmes (e.g. information required for identification of 1st-line villages and implementation of stop-MDA surveys) and do not require capacity for molecular testing of blackflies. OTS recommended that the existing entomologic operational manuals be updated with standard approaches to vector monitoring based on the recent experience in Africa and the Americas. The OTS recognized concerns with the length of time required for PTS and looks forward to learning from the experiences of the programmes in Venezuela (Bolivarian Republic of) and Ethiopia, which have plans for addressing challenges not covered in current WHO guidelines. Additionally, the subgroup pointed out that the minimums specified in the WHO guidelines are minimums. If programmes have concerns about particular foci, PTS can be extended for longer time periods or more than 6,000 flies can be evaluated.

3. Co-evaluation of onchocerciasis and LF. Co-evaluation of the two diseases remains a complex issue, particularly as strategies for a variety of onchocerciasis evaluations are still being developed. None-the-less, programmes should consider integrated or coordinated evaluations whenever one of the two diseases needs to be evaluated, as multiple countries have obtained actionable information from such co-evaluations. Co-evaluations that involved adding an onchocerciasis evaluation to LF transmission assessment surveys (TAS) demonstrated that random evaluations of non-1st-line onchocerciasis villages revealed gaps in programmes’ understanding of transmission in MDA areas. OTS recommended that random surveys be incorporated both into the onchocerciasis elimination mapping (OEM) strategy and stop-MDA surveys. OTS requested that a draft protocol for the random stage of OEM be presented at the next OTS meeting so that it could be finalized for piloting. The data also suggested that pre-stop-MDA-surveys, based primarily on evaluations in 1st-line villages, would be a reasonable approach. Therefore additional operational research is warranted in order to establish thresholds. As LF evaluations are school-based in many circumstances and onchocerciasis evaluations are community-based, comparing the two approaches for onchocerciasis evaluations would help determine if the random component of onchocerciasis evaluations could be school-based and thus integrated with other school-based evaluations. Finally, work is needed to determine the appropriate age group for OEM in areas that have already received ivermectin for LF.
III. Report

Despite the release of the 2016 WHO guidelines for stopping mass drug administration and verification of the elimination of human onchocerciasis, many challenges remain for implementing the guidelines. Additionally, many country programmes are transitioning from disease control to interruption of transmission. In order to augment the guidelines with common strategies for a variety of programme activities needed to achieve elimination and to facilitate the development of the evidence base required for development of new guidelines, OTS was established. The OTS provides advice to WHO in accordance with the terms of reference developed for the subgroup. The objectives of the 2nd meeting were to develop common strategies for mapping and ivermectin treatment in areas co-endemic for onchocerciasis and loiasis, review lessons learned from co-evaluation of onchocerciasis and LF and apply them to current strategies, and begin standardization on entomological activities.

1. Highlights of the 1st OTS Meeting

A brief review of the last meeting was presented. Only highlights will be given in this report because all of the details can be found in the report of the 1st OTS meeting.

- More data are needed for the OTS to make a decision about the preferred Ov-16 enzyme-linked immunosorbent assay (ELISA); programmes using one of the currently available ELISAs need to develop a system of quality assurance (QA)
- The Ov-16 rapid diagnostic test (RDT) cannot be used for stopping decisions, but it may be used for onchocerciasis elimination mapping (OEM) and routine monitoring and evaluation (M&E); dried blood spots (DBS) should be collected for confirmatory testing until the performance of the RDT in low prevalence settings is better defined
- The first steps of OEM include exclusion mapping and purposeful mapping of high risk villages (e.g. known proximity to a breeding site, known black fly nuisance, known proximity to hyper/meso-endemic areas); a mapping protocol that includes a strategy for random sampling is needed for areas that do not identify transmission during purposeful mapping or where first-line villages cannot be readily identified
- The indicator of choice for mapping is Ov-16
- Suggested strategies for M&E were developed; coverage surveys are an important component of M&E and require no laboratory testing
- Entomology is required for identification of first-line villages, however, extensive studies are not needed prior to mapping; as part of M&E, programmes should verify the biting rates and transmission season of the various sites so that this information is available when it is time for a stop-MDA survey
- A suggested strategy for a pre-stop-MDA survey was developed
- Work began on better defining the protocol for stop-MDA surveys; two key recommendations were made:
  o 3,000 children should be sampled for each transmission area evaluated; this number may change as performance of diagnostic tests in low prevalence settings is better defined
  o Children ages 5-9 years old should be evaluated but not children younger than 5 years old
Modeling suggests that the serologic threshold for stopping MDA could be increased to 1% in some settings; research is needed to determine where this threshold might be appropriate.

2. Strategies for implementation of mass drug administration in areas co-endemic for loiasis

Presentation: Extent of Co-endemic Mapping Gap

The Expanded Special Project for the Elimination of Neglected Tropical Diseases (ESPEN) began the session with a presentation on the potential extent of co-endemicity between loiasis and onchocerciasis. Reports of severe adverse events (SAEs) after MDA in Cameroon and DRC raised initial concerns about treating areas with ivermectin that were co-endemic with *Loa loa*. The rapid mapping for loiasis strategy (RAPLOA) was developed and recommended in all 11 co-endemic countries: Angola, Cameroon, Central African Republic (CAR), Chad, Congo, Democratic Republic of Congo (DRC), Equatorial Guinea, Ethiopia, Gabon, Nigeria, and South Sudan. Areas with prevalence of history of eye worm >40% were considered as high risk for SAEs. However, RAPLOA misclassifies many areas. As OEM will occur in areas that are low risk for blindness and severe skin disease, it was felt that RAPLOA results were insufficient from a safety perspective. To determine areas that need mapping for loiasis in addition to onchocerciasis, districts were classified as RAPLOA = 0%, RAPLOA > 0%, and no data. Only areas with RAPLOA = 0% were felt not to need reassessment of *Loa* endemicity. There are 662 potentially co-endemic districts that are either known to require MDA and not yet treated or that require OEM. 96 districts have RAPLOA = 0% but need OEM. The remaining districts will all require mapping for loiasis unless programmes have data demonstrating why they can be excluded.

Presentation: Update on Tools

The strengths and weaknesses of current *Loa loa* diagnostics are detailed in the table below.

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day time blood smears</td>
<td>1. Can measure 0-&gt;100,000 mf/ml</td>
</tr>
<tr>
<td></td>
<td>2. Have to identify parasite morphologically, requiring expertise</td>
</tr>
<tr>
<td></td>
<td>3. Reading can take many hours + time for slide preparation</td>
</tr>
<tr>
<td></td>
<td>4. The less blood taken, the greater the potential error</td>
</tr>
<tr>
<td></td>
<td>5. Diurnal periodicity needs to be taken into account</td>
</tr>
<tr>
<td></td>
<td>6. Not practical for preventing SAEs in a programmatic setting</td>
</tr>
<tr>
<td>Worm extraction</td>
<td>1.Insensitive but specific</td>
</tr>
<tr>
<td></td>
<td>2. Not practical in the field</td>
</tr>
<tr>
<td></td>
<td>3. Not acceptable as a strategy for preventing SAEs</td>
</tr>
<tr>
<td>PCR</td>
<td>1. DNA primers and PCR equipment needed</td>
</tr>
<tr>
<td></td>
<td>2. More sensitive than blood smear; very specific</td>
</tr>
<tr>
<td></td>
<td>3. Not field friendly; expensive, specialized equipment, time consuming</td>
</tr>
<tr>
<td></td>
<td>4. LAMP Assay – PCR is faster and has a lower limit of detection but</td>
</tr>
<tr>
<td></td>
<td>requires special equipment.</td>
</tr>
<tr>
<td>Antibodies (SXP1)</td>
<td>1. Don’t distinguish between current and previous infection</td>
</tr>
</tbody>
</table>
Specificity and sensitivity have an inverse relationship
Response to recombinant antigen are HLA-restricted, meaning that some infected people will not have an antibody response
Not a quantitative test, so not useful in defining SAE risk at the individual level
RDT in field trials

| **Loa antigen detection** | 1. Antigen detection still elusive
2. Would have advantage of identifying current infection
3. Could be adapted for urine or blood
4. Many antigens in development
5. LOAG_14421 detectable in patients with *Loa*
6. LOAG-16297 based RDT being tested |
| **LoaScope** | 1. Developed for preventing SAEs
2. Requires finger stick for blood
3. Diurnal periodicity needs to be taken into account
4. Gives quantitative results, so can be used to determine SAE risk
5. Testing and presentation of results takes <3 min per test
6. Used in >80,000 people in several settings |

The LoaScope was designed to enable a ‘Test and not Treat’ (TnT) strategy for onchocerciasis. Additional potential uses include the generation of *Loa loa* mapping data that incorporates prevalence and microfilarial (Mf) density for MDA planning and detection of *Loa loa* infected individuals at risk of SAEs from ivermectin treatment for other indications, such as scabies or LF. The costs of LoaScopes and capillaries are $1,500 and $1.50 respectively, but prices could be reduced to $300 and $0.30 once production increases. An estimated 10,000 LoaScopes and 10 million capillary tubes will be needed for TnT and mapping.

**Presentation: Risk of adverse events with ivermectin use**

The Karnofsky performance scale has been used to classify adverse events (AEs) associated with ivermectin use in individuals with *Loa loa* infection. Mild events (Karnofsky ≥ 70) are not associated with functional impairment. Marked events (Karnofsky = 60) are associated with functional impairment requiring several days of assistance in performing some activities of daily living. Serious non-neurologic events (Karnofsky = 40 or 50) are associated with functional impairments that required at least one week of full-time assistance. Serious neurologic SAEs (Karnofsky ≤ 30) are associated with disorders of consciousness and objective neurological deficits that required hospitalization. Although the greatest concern is for neurologic SAEs, marked AEs and serious non-neurologic AEs can have a negative impact on community participation with ivermectin MDA.

There is a clear relationship between pre-treatment Mf density and the risk of AEs in individuals, with the risk of AEs with functional impairment beginning to increase at 8,000 Mf/mL and the risk of neurologic SAEs beginning to increase at 30,000 Mf/mL. From case reports, the lowest known pre-treatment Mf density associated with an SAE was 50,520 Mf/mL. As of 2015, only two studies on the relationship between pre-treatment Mf density and incidence of post-ivermectin AEs have been
performed. In the Lekie division study in Cameroon 24% of the 75 people with ≥50,000 Mf/mL had a neurological (2 events) or non-neurological SAE (16 events) and 2.4% of the 85 people with ≥30,000 Mf/mL but <50,000 Mf/mL had a neurological or non-neurological SAE. Marked AEs occurred in 2.1% of people with ≥8,000 and <30,000 Mf/mL. No SAEs were seen below the 30,000 Mf/mL threshold, and no neurological SAEs were seen below 50,000 Mf/mL. In the East Region study in Cameroon, no neurological SAEs were seen. 17.9% of the 84 people with ≥30,000 Mf/mL had non-neurological SAEs, though 2 occurred in people with ≥15,000 Mf/mL and one in a patient with a density between 5,000 and 8,000 Mf/mL. The conclusion from these data is that when people with ≥30,000 Mf/mL are excluded the risk of neurological SAEs approaches 0 and there is little risk of non-neurological SAEs. When one excludes people with ≥8,000 Mf/mL, 59% of the marked AEs are also avoided.

There is also a relationship between prevalence of Loa loa microfilaremia and risk of SAEs in the community. The predictions based on analysis of the available data suggest the following relationship: At a prevalence of 20%, 5% of the population has >8,000 Mf/mL, 1% of the population has >30,000 Mf/mL, and 2 out of 1,000 people would have an SAE. At a prevalence of 30%, 10% of the population has >8,000 Mf/mL, 3% of the population has >30,000 Mf/mL, and 4.5 out of 1,000 people would have an SAE. At a prevalence of 40%, 15% of the population has >8,000 Mf/mL, 5% of the population has >30,000 Mf/mL, and 7 out of 1,000 people would have an SAE.

**Presentation: Test and Not Treat Protocol**

More than 500 SAEs have been recorded in loiasis endemic areas, and fear of SAEs has resulted in low coverage for onchocerciasis MDA in many areas. Currently treatment cannot be introduced in areas with hypo-endemic transmission of onchocerciasis due to concerns that the risk of SAEs outweighs the benefit of ivermectin treatment in these areas. SAEs related to ivermectin use in co-endemic areas were first reported in 1991, and its incidence and risk factors were described over the course of the next several years. In 1999 and 2003 there were episodes of SAEs in Cameroon and DRC, some of which resulted in MDA being halted. The Mectizan Expert Committee and the Technical Consultative Committee of APOC created guidelines for the use of ivermectin in co-endemic areas that are meso- or hyper-endemic for onchocerciasis. The TnT strategy was developed to determine if a safe strategy for implementing MDA in co-endemic areas that are hypo-endemic for onchocerciasis could be developed. TnT requires the determination of threshold Mf levels in all individuals in a co-endemic area. At present this is done using the LoaScope, which is a device coupled with a smartphone that takes short videos of a blood sample and provides accurate information about Loa Mf density in just 2-3 minutes.

The first TnT study took place in Okola in 2015, after appropriate community sensitization. Okola Health District was an area where MDA was stopped in 1999 due to SAEs (at least 23 cases, including 3 deaths), so it was known to be a high risk area. The LoaScope was used to test everyone ≥ 5 years old who present for treatment and ivermectin was offered to those people with <20,000 Mf/mL. Active surveillance was implemented after treatment to follow the population for SAEs. In this study, 61.5% of the population of 26,430 was tested and 60.4% of the population received ivermectin treatment. Although 737 people were excluded, only 340 (2.1%) were excluded because of high Mf density. No SAEs were identified.
In 2017, TnT was repeated in Okola, with the objectives of determining whether people who were tested in the 1st year required TnT in the second year. Additionally, it was important to determine whether treatment coverage increased during the second round, as the communities began to accept the safety of the strategy. In this study, 71.2% of the population of 29,586 was tested and 70.8% received treatment. Exclusion rates were lower. No SAEs were detected.

Compared to the 23 SAEs that occurred in 1999 after 6000 treatments in Okola district, use of the TnT strategy resulted in 0 SAEs after more than 37,000 treatments. Additionally, participation in TnT increased between the two rounds of the study and coverage increased 10%. All but one individual treated in 2015 and whose results from 2015 and 2017 could be linked had a microfilarial density below 20,000 Mf/mL in 2017 and could be treated (about 5,000 individuals were included in this analysis). About one third of the 642 individuals excluded from treatment returned for complimentary examinations; of these 78% were positive by skin snip and 20% by Ov16 RDT. Only 32 people completed 5 weeks of doxycycline treatment.

There have been concerns about translating TnT into a programmatic activity. For example, 50 people external to the implementing teams were involved in the two studies just described. So the concept of community teams was developed. These teams would include a supervisory nurse at the local health center, a literate community member who would use the LoaScope, a local health person to draw blood, and a community drug distributor (CDD). A study was implemented in Soa district using mobile teams of 3, with the centralized nurse supervisor for support as needed. There was one CDD per 100 people, and one blood drawer and one LoaScopist per 300 people. The 3 people were supervised by one member of the study team and one person from the national onchocerciasis programme. The teams trained for two days before beginning the TnT activities. Each treatment team was supervised by the study team. Surveillance for AEs was performed by two mobile teams of nurses who were supervised by a physician who could be mobilized if needed. There are some very preliminary results from the study. In the first communities in two health areas around 55% of the population received treatment and 1-2.5% of people were excluded because of high microfilarial density. There were some mild and moderate AEs but no SAEs. All AEs were able to be treated easily with medications such as chlorpheniramine, paracetamol, and ibuprofen.

It appears that TnT allows treatment of communities without SAEs. Initial results from Soa are encouraging that with a short training and supervision at the local level, the TnT strategy will be feasible. The limited number of LoaScopes was a major constraint for broader implementation of TnT. The cost of TnT could be greatly reduced if the Soa results continue to be good.

Presentation: Impact of ivermectin on loiasis

Results of a meta-analysis showed that *Loa loa* Mf densities were reduced by 93% the 1st year after IVM treatment. Review of the individual data demonstrated that no individual with <20,000 Mf/mL before treatment had >20,000 Mf/mL one year later. Only one person with >20,000 Mf/mL had a Mf density >20,000 one year later. Among the 5,405 individuals who participated in TnT studies in 2015 and 2017 and who were treated with ivermectin, no individual had >20,000 Mf/mL at follow-up. 45 of the 113 participants who could not be treated in 2015, were able to be treated in 2017. It appears that people who received ivermectin in the past 12 months may not need to have their Mf density re-measured before participating in the next MDA.
Presentation: Mapping of Loa—model

Geospatial modeling provides the opportunity to use Loa prevalence data and parasite load data to predict risk of SAEs in communities. Models can be developed to detect whatever parameters are designated by the NTD community. For the purpose of evaluating and validating the model that is discussed here, the goal was to determine if an evaluated community had >1% of people with >20,000 Mf/mL. The model was initially developed from a database containing microscopy results for 19,128 people from 222 villages in several areas in Central Africa. The data confirmed the relationship between community prevalence and risk of high Mf density infections but revealed variation in this correlation between communities. It was clear that both prevalence and density of microfilaremia provided important information about the risk of high density infections. Mf counts as determined by microscopy and LoaScope were compared and confirmed to highly correlate within the relevant range; however among those which were discordant, when microscopy identified 0 MF, the LoaScope identified from 31-7,261 MF and when LoaScope identified 0 MF, microscopy identified 20 – 19,940 MF. A study was done in Cameroon, more details of which will be described in the next presentation, to validate model predictions. In the investigation phase 100 individuals in each of 30 villages were tested with the LoaScope, and a model projection was generated. In the validation phase larger samples were taken and the results were compared to model predictions. The model decision rule was that if the probability that <1% individuals in a community had >20,000 Mf/mL was >95% then the model would recommend MDA, otherwise it would recommend TnT for all members of the community. For 24 villages, investigation phase model results were compared to validation phase results. In 19, the results of the investigation phase model matched those of the validation phase. In the remaining 5, the investigation phase model results indicated that TnT was needed, but the validation phase found that MDA was acceptable. In no case did the investigation phase model results recommend MDA when the validation phase results indicated TnT was needed. In other words, the model was more conservative in its recommendations for MDA.

The model parameters can be set as required by programmes. As the acceptance of risk declines, the closer the model-based strategy will resemble TnT. But it is important to know that zero risk is not attainable. There is no guarantee that there is no risk of SAE below 20,000 Mf/mL, just as having a level >20,000 Mf/mL does not guarantee the occurrence of an SAE. Additionally, little is known about the variation in Mf density in an individual during the 6-hour time period in which the blood may be drawn according to standard criteria. There is also the possibility of extending the results outside the village being evaluated, so that the results in one village could predict the results in some of the nearby villages. The confidence limits around the predictions would grow larger, the farther out one goes, so it would be important to take that into consideration when determining what area one village might be able to represent. This would need to be validated. If successfully validated, geospatial maps could classify areas as requiring TnT, as areas whose results indicate MDA is appropriate, or as areas whose results are uncertain due to the distance from the evaluated village and thus need additional village evaluations. The current model recognizes random variation between villages and between individuals within villages. It might be important to include random variation between blood samples taken from an individual.

In conclusion, the model appears to fit the data from Cameroon well. Variation between villages is spatially correlated and this may allow a mapping strategy that does not require testing every
village. Microscopy and LoaScope results are highly correlated, though the relationship does break down some at high levels of infection. Data from larger geographic areas would strengthen the model-based algorithm and inform the possibility of a mapping strategy that does not require testing in every village.

**Presentation: Mapping of Loa—Cameroon**

A study was designed to use the LoaScope to map loiasis in Cameroon. The study was designed around the hypothesis that ivermectin could be safely distributed in areas where the prevalence of Loa Mf density infections >20,000 Mf/mL was ≤1%. Four districts were selected to map onchocerciasis, loiasis, and LF. In 1 of the 4 districts, a 30-cluster community-based survey was performed. Communities were randomly selected using probability proportional to estimated size methodology. Anyone 10 years old or older was eligible for inclusion in the study. The study was performed in two phases (investigation and validation) as described in the Mapping of Loa—Model presentation. In the investigation phase about 100 individuals were examined to predict the probability of high density infections. In the validation phase, a much larger sample was taken to validate the predictions from the investigation phase. Systematic sampling was used, unless there were <1,000 people in the community, in which case everyone was sampled. Blood was collected for Ov16 RDT, the filarial test strip (FTS), the LoaScope, and dried blood spots (DBS) for ELISA.

For the investigation phase, 3,457 people were tested in 29 clusters. Prevalence of Ov16 was 4.9% (range: 0-20%). Prevalence of loiasis was 8% (range: 0-44%). The mean intensity of infections was 5,690 Mf/mL (range: 107 – 45,978). Nine of the clusters had >1% of the population with >20,000 Mf/mL. For the validation phase, 10,406 people were tested in 28 clusters. Prevalence of loiasis was 8.2% (range: 0-21.4%). The mean intensity of infections was 438 Mf/mL (range: 31 – 29,052). Four of the clusters had >1% of the population with >20,000 Mf/mL. There was a good correlation between Loa prevalence and the number of individuals with high Mf density. Examples of investigation and validation results were given. In general, the investigation sample was more likely to predict the need for TnT than the validation sample. In conclusion: the district has loiasis with some hyper-endemic foci and hypo-endemic transmission of onchocerciasis. The investigation results over-predict the need for TNT but did not miss villages that should receive TnT. It was concerning that some communities with very low prevalence of loiasis had individuals with high density infections.

**Presentation: Mapping of Loa—Nigeria**

RAPLOA was developed to allow the rapid identification of areas at high risk for SAEs. This was defined at 40% prevalence of reported history of eye worm, which correlated with a 20% prevalence of Loa microfilaremia, which correlated with 2% of the population having more than 30,000 Mf/mL. When the RAPLOA validation data from Cross River State, Nigeria, are examined there are no data points with > 40% prevalence of eye worm and no data points with ≥2% high density L. loa infection, even though there are villages with prevalence of eye worm from 20 – 40%. There has been only 1 neurological SAE reported in Nigeria.

A study was implemented in Nigeria to determine the prevalence of high density infections in areas with ≥20% prevalence of history of eye worm. Local government areas (LGAs) bordering areas with active MDA for onchocerciasis were selected. Villages with the highest RAPLOA results within the selected LGAs were then evaluated using the LoaScope. 110 villages were evaluated in the selected
LGAs; 28 had ≥40% prevalence of history of eye worm and 54 had 20-39% prevalence. Fifty adults and 50 children were tested in each village between 10AM and 4PM with the LoaScope. Blood was also collected for performance of the Ov16 RDT. A total of 10,605 people were enrolled. Seroprevalence of Ov16 by RDT was 0.5% and ranged from 0-4.1% in children and was 3.3% and ranged from 0-33.7% in adults. Seroprevalence of loiasis was 4.1% (median 2%) in children and 8.4% (median 5.8%) in adults. There was no correlation between historical RAPLOA prevalence and current LoaScope prevalence. There was also no correlation between historical RAPLOA prevalence and village maximal microfilaremia. The highest Loa count was 11,429 Mf/mL. The highest prevalence of Loa microfilaremia was 26% (for the data shown).

In conclusion, no high density Loa infections were identified. This may explain the lack of neurologic SAEs observed in Nigeria. Nigeria may be an exception to the RAPLOA prevalence-intensity relationship used by WHO. It may not be necessary for Nigeria to use the TnT strategy in co-endemic areas. Additionally, Ov16 RDTs may be useful for OEM, though comparisons with ELISA are needed. Ivermectin will be needed for treatment in hypo-endemic areas with positive results. Nigeria requested MDP to approve ivermectin for MDA despite prior RAPLOA results, whose use has been approved for the states in which the study took place. Nigeria is also requesting that all other areas in the country be excepted from further evaluation of Loa.

Presentation: Acceptable risk

The question of acceptable risk originated from a discussion at the Mectizan Expert Committee (MEC) Loa Sub-working Group in 2016, during which it was stated that a community with 0% of the population with ≥ 30,000 Mf/mL would be one in which it was safe to implement MDA. However, as it is not possible to measure 0% without testing the entire population, would it be acceptable if <0.5% or <1% of the community has high microfilarial density? District level surveys involving 30 clusters of 100 people per cluster selected were proposed as a method by which a district could be evaluated. The tool would be the LoaScope, which allows one to determine the prevalence of infection in the community as well as the Mf counts in individuals. If all communities were below the prevalence threshold, the entire district would be cleared for treatment. If any community had prevalence above the threshold, community level assessments would be required. Community level surveys would involve random selection of 100 people per community. If the results were less than the threshold, MDA could proceed. Otherwise all individuals would need to be tested before treatment. The sub-working group recommended that 20,000 Mf/mL be used as the individual safety threshold and that the model be tested in programmatic settings.

A mapping strategy, instead of TnT for everyone, forces one to ask the question whether it is ethically acceptable to introduce any risk into targeted communities when the communities do not suffer the symptoms of disease. In theory, TnT should avoid introduction of risk into these communities. The main argument for introducing risk appears to be cost-effectiveness. Does this argument outweigh the ethical concerns? If OTS or MEC was to move forward with this strategy, it would be important to consider what to do if an individual were found to have >20,000 Mf/mL during community mapping; should TnT be required in that community even if the community-level risk was below the agreed upon threshold? As the mapping strategy at the community level is dependent on random sampling, consideration needs to be given to refusals and how they might
impact estimates of risk. Additionally, there may be people in the communities who want to be tested even though they are not selected. More importantly, recently it has been demonstrated that there is a familial, probably genetic in origin, predisposition to hypermicrofilaria. This results in clustering of people with high Mf density infections and may explain some of the inter-community variability in the relationship between community prevalence and proportion of high density infection. This clustering will need to be taken into account for any mapping strategy to be feasible. In some areas, 30 cluster surveys may not reduce costs much. For example, there is an average of 69 villages per health district in Cameroon. It seems that one might be able to get information from all villages without a huge increase in effort, rather than mapping 50% of the villages. Consideration should also be given to where to implement a mapping strategy. Areas that are highly endemic for loiasis, probably should just have TnT implemented, as it is unlikely that health districts in those areas would qualify for MDA without TnT. Operational research in mosaic-savanna regions will be important, as the forested areas should be at higher risk. It would be best to start in the most forested locations and then move into the savanna locations.

Finally, it should be recognized that a neurological SAE or other SAE may impact more than just the MDA, such SAEs have real and lasting effects on the affected individuals. (An image of an individual with a facial droop 11 years after his SAE was shown).

Presentation: Need to determine acceptable risk

In order to eliminate onchocerciasis a strategy that allows MDA for onchocerciasis in hypo-endemic areas that are co-endemic for loiasis is needed to prevent reintroduction into bordering areas where MDA has been stopped. In areas that were hyper- and meso-endemic for onchocerciasis, this could result in reoccurrence of severe skin disease or blindness or the need to restart MDA. Currently, TnT, which requires testing of everyone before treatment with ivermectin, is the most conservative approach for delivering treatment. This may entail testing large numbers of people. Currently it is estimated that 10 million people live in areas where RAPLOA prevalence was >40%, 24.5 million people live in areas where RAPLOA prevalence was >20% but less then 40%, and even more live in areas with RAPLOA prevalence >0% and ≤20%. The current working opinion for research studies is that it is safe to treat communities where <1% of individuals have >20,000 Mf/mL. This will result in some risk of SAEs. However, there are risks associated with any public health programme, including NTD programmes. For example, 1-3% of children who receive medications for deworming have a choking incident, and albendazole can rarely result in Stevens-Johnson syndrome. Even if everyone is tested with the LoaScope, it may miss people with >20,000 Mf/mL. Who is the appropriate convening body to discuss this ethical issue and which stakeholders should be involved? Perhaps the OTS should weigh in on this. When we balance the risks and benefits, discussions should include not only the risk of SAE, but the benefits of ivermectin for people with onchocerciasis and loiasis, and perhaps other diseases as well. The cost of programme resources that must be committed to testing everyone, and thus not used for other activities, may also be a factor. It is worth discussing the working definition created by the MEC of treating when there is <1% prevalence of individuals with >20,000 Mf/mL. Having a high Mf count does not guarantee that an SAE will occur. The higher the count is the greater the risk. The predicted risk of a neurological SAE is 0.7% when the counts are 30,000 Mf/mL. The proposed strategy has already added a layer of safety by targeting a lower threshold. There are other strategies available to assist with the loiasis issue. Rigorous mapping of onchocerciasis in co-endemic areas would allow programmes to ‘shrink the map’. If there is no
onchocerciasis in an area, TnT would not be needed. A strategy that allows areas to be excluded as having loiasis would be another option. Environmental data coupled with Loa antibody data might provide strong enough evidence for the absence of loiasis that TnT would not be needed. Although antibody tests for use in the field are not currently available, work is in progress and such tests are 2-6 times more sensitive than detection of Mf. It might be possible to define an antibody prevalence that excludes high risk infections in populations. A third option would be to perform evaluations in a variety of epidemiologic settings, similar to what Nigeria did, and determine if the relationship between infection prevalence and infection intensity differs by setting. Epidemiologic models might also be used to make treatment decisions at the community level. The model presented at this meeting would have allowed MDA to proceed without TnT of the entire population in 19 out of 24 communities. It also required TnT in 5 communities that, when evaluated with TnT, did not find prevalence above the 1% threshold. The major question about this model strategy is whether it can be used to make district level decisions. This is where the benefit of a mapping strategy versus a TnT strategy everywhere would be seen and thus is a priority to be addressed. TnT should be used everywhere it cannot be demonstrated that ivermectin MDA is safe. All of these possibilities lead us back to the original question. What is the accepted threshold of safety? What is the burden of proof? In conclusion, we have many tools that can and should be used in complementary ways to make safe treatment decisions. But we need some convening body, perhaps WHO, to help determine the safety threshold for MDA with ivermectin where there is risk of SAEs.

Presentation: Cost and cost-effectiveness of the TnT strategy

An analysis using data collected in Soa, Cameroon, was performed to determine the district level cost of one round of the TnT strategy and identify the main cost drivers. The output of the analysis was the cost per person treated per round of TnT, though other indicators were examined. The inputs included direct costs (e.g. per diems, fuel for vehicles), indirect costs (e.g. utilities), financial costs, and economic costs (e.g. lost opportunity to earn income). Some costs were directly calculated from financial records and others were estimated using questionnaires. The preliminary results are based on the costs associated with implementation in 5 of the 6 health areas in the study area. This included a population of 36,254 people, 30,390 of who were eligible for ivermectin MDA and 44% of whom accepted the treatment. The total global cost of the TnT strategy was 326,451 in purchasing power parity (PPP) dollars (or US$ 139,385). The cost per person tested was 11 PPP and around 20 PPP per person treated. Considerations that should reduce the final cost analysis include: per diems for routine programme activities are less than study per diems, which contributed significantly to the total cost; a portion of the personnel cost may not be attributable to this particular activity; supervision is much more intensive in this research setting than would be expected in a programme implementation setting. Additionally, the cost of avoided SAEs and cost of failed MDA were not factored into the analysis. This current estimated cost is currently about 4 times higher than the standard benchmark for a standard NTD programme.

Presentation: Potential use of the LoaScope in hyper- and meso-endemic areas

As the data suggest that the LoaScope is good at identifying people at risk for SAEs, it is probably time to consider other situations in which we may want to use the scope to prevent SAEs or other
situations in which a little operational research might be helpful in making a decision about expanding the use of the LoaScope. One option is to use a TnT strategy in currently treated meso- and hyper-endemic areas that are already known to have a significant presence of loiasis (e.g. where SAEs have occurred in the past). This could involve testing everyone or just those individuals who have never taken ivermectin or perhaps those who have not taken ivermectin in the past year. Is there enough data on the impact of ivermectin on loiasis to make it possible not to test those who have received the medication in the last year? Operational research might be required to determine how to reliably identify those individuals who would not require testing before MDA. If a TnT approach were used, would this allow programmes to stop enhanced surveillance for SAE and what would the cost implications be versus the cost of managing an SAE and maintaining enhanced surveillance if TnT were not used? Using the LoaScope in high risk areas could help us better define those areas that need TnT or mapping if we were able to identify environmental or other factors that would contribute to exclusion mapping of loiasis. Certainly, using the LoaScope in areas already under ivermectin MDA would help demonstrate that its use on the programmatic level is feasible and help identify potential problems with its use that need to be planned for when used in the onchocerciasis hypo-endemic areas.

**Discussion:**

**Overlap of onchocerciasis and loiasis.** The appropriateness of using district administrative boundaries vs ecological zones to show data was raised. It was pointed out that countries need data to be presented in an actionable, but conservative way; even if one community has information on loiasis or onchocerciasis, then the entire district is highlighted to reflect that category. This does not mean that countries should not refine their understanding of the district or cannot divide activities on a sub-district level. There was the concern that RAPLOA of 0% may not mean absence of risk and that focal areas of endemicity could be missed in small areas with appropriate ecology to support the vector. Areas that had RAPLOA = 0% but that are found in ecologically suitable zones could be mapped as part of operational research to help determine if this areas need additional mapping for *Loa loa*. Refinement of exclusion criteria would be helpful in further shrinking the map of areas that need mapping. ESPEN has begun and will continue the process of cross-checking the district level data with country programmes in order to resolve discrepancies on the endemicity of the two infections.

**Update on tools.** The group discussed potential limitations of the LoaScope. There were some problems with the screen freezing in older models, but this is not expected to be an issue with the newer models. It will be important to identify and report on which model of the LoaScope is being used and tested, so as not to create confusion about its performance. Anemia can result in problems in obtaining a result with the LoaScope, so that will need to be incorporated into training materials. Also, since Mf die quickly the same sample should not be read multiple times. As with blood films, the results of the LoaScope will be affected by the periodicity of microfilaremia, so the blood draws will continue to need to be obtained between 10AM and 4PM. Although software and internet connections are required to upload data, these are not required to use the LoaScope to obtain results in the field. The LoaScope and the blood smear remain the only tools that can define the prevalence of microfilaremia in a population and determine the Mf density. The availability of the LoaScope will increase over the next 12-18 months. Antigen testing, which has the potential to
be quantitative, will take longer to develop. Antibody testing could potentially become available in the 12-18 month time frame, but it will not likely be quantitative. Serology might be able to be used to exclude areas from needing to use the TnT strategy.

**Risk of adverse events with ivermectin.** Some participants expressed concern about fluctuating thresholds of safety for *Loa loa* Mf density. Although 8,000 Mf/mL has been mentioned as a threshold for AEs, it was not suggested as a new safety threshold. The threshold for SAEs is 30,000 Mf/mL, but experience in the field demonstrated that dropping it to 20,000 Mf/mL increased the margin of safety without significantly increasing the number of individuals excluded from treatment. The LoaScope has been calibrated for that threshold and there are no plans to change the categorization of results (e.g. a ‘do not treat with ivermectin’ result will continue to be given for a count ≥20,000 Mf/mL). It was recommended that qualitative research to determine drivers of non-compliance with ivermectin MDA in *Loa* co-endemic areas could be important, as it is possible the TnT could be used to increase compliance in those areas. Balancing the risk of AEs with the other benefits of ivermectin in terms of its impact on ectoparasites and other helminths, including *Loa loa*, should be considered. Anecdotally, people with loiasis have reported improved feelings of health with ivermectin treatment. It was noteworthy that individuals with a yellow light (Mf counts 8,000 – 19,999 per mL) were counselled about the risk of AEs and all chose to take the medication.

**TnT strategy and elimination of onchocerciasis.** The TnT strategy makes the most sense as a component of an onchocerciasis elimination strategy if it allows programmes to achieve sufficient coverage to interrupt transmission. The coverage of the eligible population in the 1st year using TnT was around 60% in Okola and around 55% in Soa, which includes a large peri-urban area. The coverage of the eligible population in the 2nd year in Okola reached 70%. It will be important to document the coverage of the eligible population when the TnT strategy is used. Equally important are whether the strategy needs to be used multiple years in order to obtain sufficient coverage for elimination and how many years TnT needs to be fully implemented from a safety perspective before regular MDA can be implemented. An additional question raised the concern about potential challenges to implementing TnT in urban areas, such as Brazzaville. While there was general consensus that most elimination activities are challenged in urban areas and that this is an issue that should be investigated, it was felt that this was an issue that should be addressed separate from the utility of the strategy and at a later date.

**Settings for the TnT Strategy.** There was much discussion about the difference in the risk-benefit ratio for using ivermectin in areas that are meso- and hyper-endemic for onchocerciasis and how that might impact where the TnT strategy could and should be used. In the original strategy for implementing ivermectin MDA in areas co-endemic for loiasis, it was determined that the risk of blindness from onchocerciasis, which exceeded 1% in the hyper- and meso-endemic areas, outweighed the risk of SAEs. However, in communities with greater than a 2% prevalence of *Loa loa* microfilariaemia ≥ 30,000 Mf/mL, a system of active surveillance and management of SAEs had to be implemented before ivermectin MDA could be implemented. There are three potential uses of TnT in hyper- and meso-endemic areas. One suggested use was to screen all ivermectin naive
individuals. 80% of the 1300 described SAEs occurred in ivermectin naive individuals (for 8% the history of ivermectin use was unknown, and for 8% ivermectin had been used but not in the previous year). There were objections expressed about requiring the use of the TnT in these areas if there had not been previous SAEs reported in the area. Reviewing the distribution of known SAEs suggests that the correlation between prevalence of loiasis and risk of SAE may not be the same in all loiasis-endemic areas; this concept is supported by the data from Nigeria. Although consensus was not reached about whether testing should be required in this scenario, many felt that it could be used in this setting and that data could be collected on efficacy and cost that would be useful to programmes. The second scenario was using the TnT strategy in areas had already implemented ivermectin MDA but had persistently low coverage. If the low coverage was due to systematic non-compliance because of fear of SAEs, the TnT strategy has the potential to resolve the fears and thus the non-compliance. This was recognized as a reasonable hypothesis that was consistent with observations in Okola, but one that would need to be tested prior to making recommendations. Finally, it was mentioned that there are some ivermectin naive onchocerciasis hyper- and meso-endemic areas. Under current guidelines from the MEC of the Mectizan Donation Program, ivermectin MDA could be started as long as the appropriate surveillance and management systems are in place. The committee felt that the LoaScope could be used to reduce the risk of SAEs, but consensus about whether it was required was lacking.

In areas with hypo-endemic onchocerciasis, the risk of blindness from onchocerciasis is less than 1% and the other manifestations of infection are less well known. The lack of perception of risk of onchocerciasis is likely to influence the population’s willingness to accept the risk of ivermectin MDA. However, there may be perceived benefits of ivermectin MDA for other diseases (e.g. ectoparasites or possibly even from reduced Loa microfilariaemia). From a global perspective, not interrupting transmission in these areas poses a risk to the gains obtained in areas where onchocerciasis used to blind more than 1% of the infected population. These risks and benefits need to be balanced to determine where the TnT strategy might be required. Mapping the risk of SAEs due to loiasis could help shrink the map of where the TnT strategy is required; however mapping requires determining a threshold or risk of SAEs around which the mapping strategy could be designed. Consensus could not be reached about how best to set a threshold, but it was generally agreed that WHO should organize a special meeting that includes all the relevant stakeholders (Loa experts, bioethicists, epidemiologists, and programme managers from affected countries) to try to reach consensus on acceptable risk.

One concern was raised about the fluctuation in what was considered the MF density associated with risk in an individual. In the individual >30,000 Mf/mL was considered as the marker of risk of SAE (though at the level the estimated risk of an SAE is around 0.7%). However, the level was decreased to 26,000 Mf/mL in the TnT study to create a margin of safety and then to 20,000 Mf/mL because of an individual with 25,000 Mf/mL who presented with conjunctival haemorrhage following ivermectin treatment. Others have mentioned that AEs occur about 8,000 Mf/mL. The preponderance of the data presented shows no neurological SAEs below 30,000 Mf/mL. Some non-neurological SAEs have occurred below 30,000 Mf/mL, but there was disagreement of the impact of these SAEs on the performance of the programme. It was clarified that we were not considering lowering the risk threshold to 8,000 Mf/mL and that the majority of these AEs were in people with onchocerciasis and no evidence of loiasis. It was also pointed out that the LoaScope, while accurate, is still dependent on the time point at which the blood was taken. As there will be some variability,
even during the expected peak from 10AM to 4PM, this could result in someone who has a level $>30,000$ Mf/mL being included because the Mf density was below the threshold at the time the blood was taken.

There was some concern about whether there was sufficient data to support the concept that only one round of TnT was required and additional concerns about how one would ensure that only people that had received ivermectin in the past year were allowed to participate in MDA without being tested with the LoaScope. It was explained that the new version of the LoaScope was being made with biometric capabilities to positively identify individuals for 1st and subsequent visits; this could be used by programmes. Or CDDs could be trained to use registers to determine who should not be treated without testing (e.g. people excluded in the past and those who had not participated in the previous MDA). The latter strategy is currently being tested as part of the TnT project.

**Cost of test and treat strategy.** There was significant concern about the presentation on the cost of the TnT strategy. The cost difference between the current system of enhanced surveillance and use of the LoaScope came up. It was noted SAEs cost programs $2,000-$10,000 per event, in addition to the cost of the active surveillance system. TnT should reduce these costs. Participants asked for a cost comparison between the Soa-TNT and Soa-enhanced surveillance conducted in Cameroon, though it was not clear when the system of enhanced surveillance for SAEs would be dismantled if TnT were to be implemented. Certainly, the system would need to continue for the first few years and would need to be set up in areas where ivermectin MDA was scaled-up, but long-term TnT would likely result in cost savings in this regard. This should be examined as part of cost analyses. It was highlighted that the costs incurred for implementing the TnT protocol under a research design has overestimated the expected actual cost, as per diems for study personnel, additional vehicles, etc, were included in the cost. It was recommended that future cost analyses should adjust for this and that future cost studies define the costs for programme scale-up and maintenance.

**OTS Recommendations: Loiasis - Test and not Treat strategy**

- OTS felt that there was good data to validate the use of the LoaScope to measure *Loa loa* microfilaremia in the density ranges relevant for the development of severe adverse events ($>30,000$ Mf/mL) and for milder adverse events ($>8,000$ Mf/mL) Data are needed to determine how many years TnT would be needed to achieve and maintain the MDA coverage required to interrupt the transmission of onchocerciasis
- Data are needed to confirm the number of years TnT would need to be implemented from a safety perspective before switching to testing only ivermectin naive individuals
- WHO should convene a meeting of relevant experts and stakeholders to develop, if possible, a consensus around acceptable risk of SAEs in onchocerciasis hypo-endemic areas. This is a requirement for the development of a mapping strategy that does not require the testing of all individuals at risk for SAEs.
- Modelers were asked to estimate how many SAEs we would expect given mapping strategies.
  a. Look at various community prevalence levels of Loa microfilaremia $>20,000$ Mf/mL (e.g. 0.5%, 1%, 2%) and determine the expected number of SAEs
- Continued work on the development of a mapping strategy that would identify areas that require testing all individuals for loiasis and areas in which MDA can be implemented without further testing for loiasis was encouraged.
• Elimination mapping of onchocerciasis may reduce the area that requires mapping for loiasis and should be considered a tool that can be used while the loiasis strategy is finalized.

• Targeting the TnT strategy should be prioritized in areas where the density of Loa infection is thought to be greatest. As a starting off point, additional research could be conducted in Gabon using the LoaScope to establish the risk benefit balance in hyper-endemic areas (i.e. go into areas where there is consensus that the area cannot be excluded, then slowly fill in the map by expanding the concentric circles using TnT). This data can then feed into future modeling, which could then help in providing broader guidance. Countries should be encouraged to implement TnT in previously untreated onchocerciasis hyper- and meso-endemic areas in an effort to reduce the risk of SAEs and gain experience with the use of the LoaScope in programmatic settings.

• Operational research on the use of the LoaScope in currently treated onchocerciasis endemic areas with poor coverage in order to determine its use’s impact on systematic compliance would be useful.

• Operational research is needed to determine which areas with RAPLOA = 0% need additional evaluation. Consideration should be given for storing the new mapping data in the ESPEN portal if acceptable to ESPEN and programmes.

• Strategies need to be developed for how to implement TnT in urban areas and this should be addressed at a future meeting

3. Post-treatment surveillance – the role of entomology

Presentation: Review of entomological methods

Classic entomological methods to assess control of *Onchocerca volvulus* include fly catches using human attractant. The flies can then be assessed for the presence of infection (evaluation for the presence of any larval stage in the body of the fly) and for the possibility of infectivity (evaluation for the presence of L3s in the head of the fly). The number of infective flies can be used to calculate biting rates and the annual transmission potential (ATP). This method is also suitable for both dissection and PoolScreen analysis of PCR, though dissection cannot differentiate *Onchocerca* species. Advantages of human collections include that it requires little equipment and that it selects for flies that bite humans. The disadvantages for human catches include the cost of supervision, ethical concerns, and greater limits on the number of sites that can be sampled. Fly traps have been developed for fly collection such as the Bellecoviposition trap and the Esperanza Window trap, but teams still need adequate training to use them effectively and work needs to be done to determine how to calculate ATP. Advantages include the ability to sample additional sites and reduced need for supervision. Disadvantages include that more post-collection processing is needed, and traps may catch non-vector species and vector cytospecies that do not bite humans. Community collection has also been tried to encourage collection of as many flies as possible.

Fly processing has typically used classical dissection, which detects L1-3 larvae. The benefits include that dissection provides immediate results and normally no preservation is required. The disadvantages are that dissection requires a degree of training and skill, it cannot distinguish *O. volvulus* from some zoonotic *Onchocerca*, and fewer flies can be processed. Processing by PCR
requires sorting, preservation and laboratory capacity for PCR, but many more flies can be processed in a short period of time given adequate logistics and avoidance of bottlenecks.

Post-treatment surveillance requires entomological evaluations. The advantage of testing flies, instead of humans, is that you can catch numerous flies and use molecular techniques to detect low levels of infection in flies more easily that you can in humans. Infection in the heads of flies is a direct measure of infectivity. Unfortunately, as opposed to humans, we cannot be certain of the origin of the flies caught. They could be local or they could be migrants. From the Onchocerciasis Control Programme (OCP) in West Africa, we have considerable information of the potential for vectors to migrate. Although the migration can be quite far (hundreds of kilometers), in West Africa the direction of migration is known as is the seasonality for these areas. It might be important to try to divide onchocerciasis transmission areas into zones. It might be necessary to try to develop different thresholds of transmission (i.e. ATPs or prevalence of infection) for each zone.

Presentation: Experience with PTS in the Americas

A brief review of the progress towards onchocerciasis elimination in the Americas was given, followed by a review of the recommendations for PTS using entomology as the key indicator. PCR in blackflies is felt to be the earliest and most sensitive indicator of the recrudescence of transmission. The experience in the Americas with entomology for stop-MDA surveys and PTS indicated that community educational activities surrounding the meaning of and community role in PTS were important. Entomological surveys were begun during the 2nd year of PTS and completed during the 3rd year. In accordance with current WHO guidelines, serology in children was not performed unless the results of O-150 Poolscreen PCR were near the threshold. Additional surveys are recommended if the blackfly PCR results exceed the threshold to determine next steps. The entomological survey analysis focused on biting rate and infectivity rate, monitoring sentinel site information over time. Good data led to greater confidence. Stop-MDA and PTS results from 4 countries were presented. The number of flies varied by site, with most but not all sites collecting at least 6,000 flies (some catches exceeded 50,000 flies). In the areas where <6,000 flies were caught, the ATP was <20. In the Americas most countries have based their post-elimination surveillance (PES) on nodule surveillance. One nodule in Mexico was found to contain *O. volvuvus* but no other member of the individual’s community was found to be infected, so no intervention other than continued surveillance was needed. Countries have been recommended to perform intermittent serological or entomological surveillance as part of PES. They have also been asked to monitor migrants returning from endemic areas. As an example, Guatemala evaluates military personnel returning from duty in endemic areas in Africa.

Presentation: PTS in the North East Focus of Venezuela

OEPA is very stringent in how it classifies onchocerciasis-endemic and formerly-endemic areas. A focus that has stopped MDA after the appropriate surveys is designated as ‘transmission interrupted’ but still at risk until PTS is completed. It is successful PTS that demonstrates that transmission has actually been eliminated and that allows the population in the focus to be removed from the population at risk. MDA was stopped in the North East Focus of Venezuela (Bolivarian Republic of) in 2013. PTS took place from 2015-2017, with fly collections in 5 sentinel communities and 3 extra-sentinel communities. More than 30,000 flies were collected in the sentinel sites and 49,000 in the extra-sentinel sites over 9 months. In 2015 no infectious flies were found, but some
infectious pools were found in 2016 and 2017. Overall less than 1 infective fly per 2000 flies was identified by poolscreen PCR. The biting rate was 9,843 flies per person per year, so the ATP was 1.8 and the 95% CI was 1.1 to 3.6), so the focus passed WHO criteria. However, the results for 2 communities found >1 infective fly per 2000 flies and 2 other communities had 95% CIs that did not exclude 1 infective fly per 2000 flies. All of the ATPs were <20. Because of concern about the findings in the specific communities, the data were entered into the EuSimon model of transmission, which predicted that a few infected individuals may remain in the communities but that recrudescence would not occur. The Program Coordinating Committee (PCC) of OEPA agreed that the focus had completed PTS, pointing out that it had met WHO criteria (which were focus based), that all of the ATPs were <20, and that the fly results were consistent with model predictions. The PCC also recommended that the country perform a vector evaluation as part of PES in 3 years.

Presentation: Uganda Experience with entomology for stop-MDA and PTS

Uganda declared the goal of national elimination of onchocerciasis in 2007 and designed a strategy that employed both ivermectin MDA and vector control. The initial entomological criterion for stopping MDA and completing PTS proved challenging in Uganda because the principal vector in many foci is *Simulium neavei*, which is more readily eliminated. It was unclear how to catch the minimum number of flies, when there were no flies to catch. Additionally, the vector has a complex life cycle which involves freshwater crabs, which created the opportunity to create a system of surveillance based on crab evaluations, instead of fly catches. Thus the programme had to develop criteria specific to its situation, focusing the number of flies caught and crab surveillance to confirm the absence of flies.

The presenter shared some of the specifics of fly catches. Identifying appropriate catching sites in each river basin in the focus and distributing them such that they are representative of the entire focus is key. Human landing catches occur 2 days per weeks during collection. Species are confirmed in the field and again in the laboratory. The O-150 PCR is performed in the Ugandan laboratory though some DNA is sent to the University of South Florida as part of a quality assurance (QA) programme. Challenges, other than low fly numbers mentioned previously, include the occasional failure of PCR due to deterioration of nucleotide solutions, appropriate labeling of the samples, incorrect species identification in the field, issues with field preservation, and the lack of a laboratory network in sub-Saharan Africa for troubleshooting and mutual assistance. Challenges for crab catches include determining suitable sites for trap placements, determining the number of traps to set and the frequency at which to assess a site, and the disappearance of the crabs from some freshwater streams (perhaps due to a virus).

In general entomological activities during PTS are not much different than those performed early in the programme history, except that there is focus on being more rigorous. In areas where the vector was eliminated, the programme does perform PCR on suspected non-vector species to ensure that a new vector has not emerged in the area. Additional fly catching sites are added during to PTS if they are recommended by Uganda’s onchocerciasis expert committee. Fly and crab catches occur on a quarterly basis throughout the PTS period.

Presentation: Entomology experience in Sudan

There were many similarities with the presentation from Uganda. In the Abu Hamid focus the programme had to adjust the breeding sites that it monitored twice. After MDA had been ongoing
for some time an extension area with transmission was identified, and breeding sites had to be identified there. Later, after the Marawi dam was built, many breeding sites were flooded. The programme then had to search for potential breeding sites in the dam spillways. This highlights the need to regularly evaluate the appropriateness of the breeding sites selected for monitoring; they may change over time. Sudan uses volunteer fly catchers from affected communities during human landing catches. They are trained in all aspects of the catching (e.g. catching, sorting, preservation, and labeling). They are also required to give verbal consent to participate in fly catching, although the entomologic evaluations are not considered research, but rather routine programme evaluation. Flies were collected in 4 sites over a 1-year period. Collections occurred from 6AM to 7PM, 5 days per month. In some areas, such as the Galabat focus which extends from eastern Sudan into Ethiopia, they had to increase the number of collections to 10 days per month because they were not catching enough flies. Sometimes collection points were changed due to concerns about suitability. The programme also took into account the flight range of the vector, spacing out collection sites so that each site collected a different population of flies. The presenter also noted that in Galabat focus, MDA could not be stopped in Sudan until the Ethiopian programme was able to stop MDA on the other side of the border. This resulted in a 2-year delay for starting PTS.

**Presentation: Modeling the risk of recrudescence**

The onchocerciasis community is currently faced with several closely related questions: how long will it take to eliminate onchocerciasis using an MDA strategy, what is the threshold for elimination, and how does one prove that an area is free of infection. Models can make use of the limited data from MDA and post-MDA surveillance and natural experiments with the untimely interruption of MDA to attempt to model recrudescence scenarios. Transmission has been interrupted in 11 foci in the Americas as well as multiple foci in Africa, though some areas in Africa have continued to have transmission despite up to 18 years of good coverage. Mechanistic transmission models, such as ONCHOSIM and EPIONCHO, incorporate key biological and transmission processes to make inferences about the current status of transmission in a community. Although models are helpful, they have limitations and there is always concern about the unknown influences on transmission that are not included in the model. There is an ongoing collaboration between two modeling groups whose aim it is to improve the models and minimize the absence of important but unknown variables that contribute to transmission in the models.

Recently the two models were used to evaluate the risk of recrudescence in Mali and Senegal in the areas that served as the proof of concept for onchocerciasis elimination in Africa; the results of the evaluation were published in *Epidemics*. The two models differ in a variety of respects with differences in model type, determination of risk of exposure, description of MDA adherence, modeling of elimination, and density dependencies. As a result the two models make different predictions about the annual biting rate required to maintain a certain population prevalence of infection in humans, and thus breakpoints for elimination. In general EPIONCHO predicts a higher prevalence at lower biting rates than ONCHOSIM; related to this, EPIONCHO predicts that it is harder to interrupt transmission than ONCHOSIM does. When the two models were used to examine elimination in Mali and Senegal, both models captured the trends in decreasing Mf prevalence over time. However, they differed in their projections for what would happen to Mf prevalence after MDA was stopped. ONCHOSIM projected some low level residual transmission but no recrudescence. EPIONCHO projected that in some scenarios recrudescence could occur. In some of
the scenarios the recrudescence was slow. It could take 5 or more years before significant increase in prevalence occurred. The most rapid recrudescence occurred in scenarios with the highest Mf prevalence when MDA was stopped, and recrudescence occurred only in areas that were hyperendemic at baseline. The models differ in their assumption about the efficiency of transmission at low endemicity, which may be driving these differences in the model predictions. There could also be other factors that the models did not capture that could influence the predictions. The models do not incorporate the chance of reintroduction of infected humans or flies from elsewhere. In conclusion, one of the models suggested that recrudescence of infection might occur in settings that had high transmission at baseline and that significant recrudescence could take more than 3 years, which is the minimum time-period for PTS according to WHO recommendations. Highly sensitive surveillance will be needed to ensure that transmission has been interrupted, possibly for longer time periods than currently recommended. The modeling consortium will continue to review model assumptions, particularly those about vectorial capacity and density dependence of transmission. Additionally, an individual-based version of EPIONCHO is being developed.

Presentation: Outstanding questions about PTS

A presentation was given about some outstanding questions about PTS for onchocerciasis. Although WHO guidelines specify a 3-to-5-year PTS period, most countries have performed 3 years of PTS. Modeling has raised concerns of resurgence happening past the 3-year period. In Uganda, additional catching sites have been added during PTS. Could procedures be established to provide guidance on how best to establish additional sites? Making sure that the catching points selected provide a representative sample of transmission in the focus is very important. This may need to take into account the flight range of the vector species in and near the focus. Additionally, does it always make sense to pool fly catching results across an entire focus, or should results be considered at each catching site? How might the distance between sites influence this consideration? Currently, there is no SOP for the number of catching days/month. Would standardization of catching days be helpful for programs? Would a standard of twice per week during transmission season (not at each site) be sufficient, or will it need to be more varied? The goal remains to collect at least 6,000 flies from a focus area, but this is a challenge for some programs due to low densities of vectors. If capture techniques are following best practices and yet programmes are still capturing <6,000 flies, this could be an indicator of low biting rates, which makes interruption of transmission easier. How can one determine that adequate attempts have been made to capture at least 6000 flies? Finally, it was pointed out that QA is very important so that programmes are making decision based on good-evidence. Should there be standards for what percentage of flies should be evaluated as part of a QA programme? How would labs be accredited for the testing that they perform?

Presentation: Update on laboratory capacity

For a claim of achievement of elimination of transmission to be believable, programmatic decisions need to be based on high quality data that are quality assured. WHO guidelines for onchocerciasis elimination require data generated by ELISA and PCR. There is a clear need to develop a QA system and supply support system for the particular needs of onchocerciasis to ensure high quality data for ELISA and PCR. This has already been done in some countries in Africa and the Americas supported by the Carter Center and the ESPEN laboratory in Ouagadougou is scaling-up. Strong lab systems will be able to address both research and program needs, but this is only possible if we standardize the technology and outputs; it is not clear that we can get similar results from different diagnostics and
methodologies. An initiative supported by USAID, CDC, and the NTD Support Center has been visiting various laboratories in Africa with the goal of understanding the current capabilities, needs, and interests of known laboratories to participate in a network of laboratories that will support diagnostic testing for onchocerciasis. Specifically, laboratories were evaluated to determine the experience with the required or similar tests, the logistics capability, the presence of functional equipment, the commitment on the part of the management to support the testing, the local support given to the laboratory staff, and the region connections/communication systems upon which the laboratory currently relies. An example of the evaluation of the ESPEN lab was provided. Results from country evaluations were not shared at the meeting out of respect to the sovereignty of country labs, but confidential reports have been shared with the relevant countries and laboratories. Labs have been visited in Mali, Burkina Faso, Nigeria, Ghana, Cameroon, Sudan, Ethiopia, and Tanzania. In general, there was a lot of willingness to participate in testing for onchocerciasis, the quality of the facilities ranged from adequate to impressive, the presence of the needed equipment varied but it was clear that some replacements were needed, the supply systems varied, and the QA systems were almost non-existent.

There is a need for a laboratory network that is interconnected and in which the laboratories can rely on each other for mutual support. Onchocerciasis diagnostics could be the catalyst for a network that would eventually encompass other NTDs of relevance to the region. Laboratories would need to adhere to basic QA requirements, use standard reagents, and participate in communication with other laboratories. The QA component of maintaining data quality would include development of standard operating procedures, trainings, maintenance of equipment, traceability of results, and an annual review. The QC component would include standard references and/or spiked samples, use of negative controls, testing in duplicate, and sample exchange between laboratories (to ensure consistent results across laboratories). Organization will be important to ensure that country programmes receive data in a timely manner. The processing of ELISAs can be time consuming, so delays caused by missing reagents or broken equipment could impair programme decisions. An example of the expected time and cost of clearing a 72,000 priority specimen backlog was presented. Depending on the number of technicians hired to complete the work, it could take 2.5 – 3.5 months to complete it. If all of the at least 225,000 existing DBS need to be tested, it will take some time to clear that backlog. Efforts are being made to determine the total diagnostic needs for onchocerciasis. If 10 foci were to be evaluated, with 3,000 DBS and 6,000 flies per focus, the laboratory would need to perform 30,000 ELISAs and 600 PCRs (assuming a pool of 100 flies). Current projections suggest that millions of ELISAs will need to be performed over the life of the programme. This is going to entail a significant cost and a lot of time.

Entomological capacity of the programmes also needs to be addressed. There is a need both for field expertise and for laboratory processing capacity. The needs for O-150 PCR are similar to those with ELISA, with particular need for a good QA system. There are some newer PCR platforms being evaluated currently that may need to be incorporated into current laboratories moving forward.

Key needs for onchocerciasis laboratories include determining the circumstances in which RDTs can be used (which would decrease the need for ELISA), defining the standard operating procedure for Ov16 ELISA, standardizing ELISA and PCR protocols across sites, establishing a robust QA system, establishing a robust data flow system, establishing a robust laboratory supply chain, forecasting the diagnostic needs for elimination, and securing the funds needed to support the system.
Discussion: post-treatment surveillance – the role of entomology

There was some discussion about the models of risk of recrudescence. The fact that the two models reach such different conclusions is concerning. Some efforts have been made to try to get the models to converge, but others disagreed that this was a good idea. Understanding why the models are different (e.g. which assumptions about transmission processes are different) and gathering data to determine the validity of underlying assumptions about transmission would be helpful. It was suggested that reviewing previous OCP data to investigate biting rates might be important given the different conclusion about biting rates in the two models. It would be ideal if the models could capture differences in vector species and environmental factors that affect the relationship between biting rate and prevalence of infection. Although consensus was not reached on whether the model results in regard to PTS are correct, they nonetheless raised some concerns. The current WHO guidelines suggest PTS should continue for 3-5 years. Programmes should not be discouraged from opting for longer periods of PTS, particularly if they have specific concerns about the area under surveillance. The guideline recommends, after all, a minimum time period.

In the setting of PTS, flies clearly are a good xenodiagnostic because MDA is no longer being used. Skin snips would be less sensitive and harder to collect due to reluctance of the local populations. However, it is important to recognize that we cannot necessarily be certain of the origin of the flies caught. They could be local, reflecting local transmission if infected, or could be coming from somewhere, which could result in the reestablishment of transmission. There was some discussion about evaluating heads, which contain L3 and represent flies that can infect humans, and bodies, which contain other larval stages and represent flies that have fed on infected humans. WHO guidelines only require the evaluation of the heads; however programmes are free to test the bodies as well, though they would have to develop their own response to the results. There was also discussion about the heterogeneity of transmission between breeding sites within a transmission area. Biting rates will vary from site to site, and sometimes different vector species are found at different sites. The group thought that these are local considerations that are best dealt with at the local level, with input from national onchocerciasis elimination committees. WHO should continue to specify the minimum standards, though countries may need to exceed these minimums when the local circumstances require them to do so. It was also pointed out that programmes need to evaluate the current productivity of their breeding sites and may need to identify new breeding sites as circumstances may have changed since many sites were identified decades ago. There appeared to be consensus that programs should move towards measuring and reporting ATP, which provides more information than the simple prevalence of infection in flies. The ATP threshold of 20 infective bites per person per year came from research performed in the Americas with the support of OEPA. Different thresholds were used by OCP, which was focused more on control and vector elimination. Currently, determining ATP requires human landing capture. However, as more data support the efficacy of traps, it should be possible to derive an ATP from trap captures. This will require some human landing captures in order to understand the relationship between trap captures and human captures. It is important to remember that ATP requires catches throughout the year in areas where transmission is not seasonal. There was some discussion about whether it is appropriate to average fly infectivity prevalence across transmission areas. Some people are concerned that if one catching point exceeds the WHO threshold of 1/2000 infective flies, stopping MDA may be inappropriate even if the transmission area’s average prevalence of infectious flies is below the WHO threshold. Consensus was not reached about a recommendation other than to recommend that countries...
should review the data carefully in these circumstances. Ethiopia and Venezuela chose different responses to this kind of finding, so the OTS looks forward to seeing follow-up data when it becomes available.

There was general agreement that for laboratory capacity, a centralized laboratory that does all the testing does not make sense. There are many practical issues about transfer of human and fly specimens across national borders, prioritization of analyses, and need for the laboratory to closely collaborate with the national programme that make one central laboratory impractical. However, having a centralized process for training laboratories and for maintaining QA/QC would be a good mechanism for supporting country laboratories. Countries that want to support a laboratory to support their programmes should be encouraged to do so; however it will be necessary to identify laboratories that can assist programmes in countries that are not interested in supporting a laboratory. As programmes need to be able to base their decisions on high quality laboratory data, it was suggested that there be a centralized accreditation process for onchocerciasis laboratories. Whether a formal accreditation process was needed or whether a process of documenting compliance with a standard QA/QC process would be sufficient was unclear. A WHO collaborating center that can assist with QA/QC is under development. Such a process would allow programmes to use multiple laboratories to meet their testing requirements if needed.

**OTS Recommendations: post-treatment surveillance – the role of entomology**

- Programs should be encouraged to train a cadre of field entomologists.
- Blackfly M&E surveys should include identification of breeding sites and establishment of biting rates and transmission seasons; PCR testing of blackflies is not required as a part of baseline mapping or M&E.
- Concerns about the onchocerciasis laboratory network should be forwarded to the WHO NTD M&E Global Working Group for further discussion.
  - In addition to previous OTS recommendations about standardization of Ov16 ELISA and defining the role of Ov16 RDT, it is important to establish a robust system of QA, data flow and storage, and laboratory supply chain.
  - Forecasting the diagnostic needs should be refined as better estimates become available in order to improve cost estimates of this component of the elimination programme.
- The operational manual for vector breeding site selection and entomological surveillance should be updated with standardized approaches to vector monitoring as appropriate, including recommendations on the procedures to follow when minimal sample sizes cannot be obtained.
- It is recommended that country programmes should be encouraged to review their understanding of the location and productivity of breeding sites as this information will inform M&E activities (e.g. identification of 1st-line villages for surveillance) and must be known in order to design appropriate stop-MDA surveys.
- Programmes should be reminded that the 6,000 flies and 3-5 year time period recommended by WHO guidelines are minimums; they should consider catching more flies or for longer time periods when appropriate.
4. Co-evaluation of onchocerciasis and lymphatic filariasis

Framework for the co-evaluation of onchocerciasis and LF

WHO promotes the coordination of programme evaluation activities across diseases at all times, with integration when doing so provides information of value to programmes at a reduced cost. The co-endemicity of lymphatic filariasis and onchocerciasis is extensive in Africa and large areas need evaluation or mapping for one or both of the diseases. Rapid tests are available for joint monitoring and practical experiences with disease mapping suggests that OV16 or OV16/Wb123 RDT can be used as a component of OEM, although ELISA confirmation of negative RDT results may be needed for mapping when the prevalence is below the Ov16 threshold. Several different potential integration scenarios were presented. The LF pre-TAS and the 1st-line village component of OEM have the potential to be integrated when evaluations occur by district, though different age groups may need to be evaluated. Currently, however DBS would need to be collected for OEM and the random stage of OEM could not be combined with pre-TAS. The LF TAS and OEM could be integrated at the second stage of OEM as both use a random sampling frame. The LF pre-TAS could also be integrated with routine M&E for onchocerciasis. Integration of M&E with LF TAS would allow for more detailed transmission in a district but would not allow for longitudinal follow-up of sentinel 1st-line villages. It is currently difficult to recommend integration of the LF TAS and the onchocerciasis stop-MDA survey, as the 1st stage of the proposed stop-MDA survey would involve purposeful sampling. However, the random component of the stop-MDA survey could potentially be integrated if the final protocol is similar enough to the LF TAS.

Table: Potential for onchocerciasis and LF evaluations to be integrated or coordinated

<table>
<thead>
<tr>
<th></th>
<th>LF pre-TAS</th>
<th>LF TAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEM</td>
<td>1st line approach</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Random approach</td>
<td>No</td>
</tr>
<tr>
<td>Oncho M&amp;E</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Oncho Stop MDA Survey</td>
<td>1st line approach</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Random approach</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: Differences in age groups sampled would have to be reconciled or the evaluation would have to be coordinated but not integrated (e.g. sample different age groups in the same villages).

Mapping for LF would be a bit more difficult to integrate with onchocerciasis assessment given the variety of methodologies currently used for LF mapping, however in cases when both programmes require random sampling, integration would be possible. When purposeful sampling is used, coordination for cost savings may make more sense than integration. In the absence of serological surveillance for PTS or PES, there is little potential for integration during these activities.

Presentation: Burkina Faso experience with co-evaluation

The Burkina programme performed integrated pre-TAS and TAS (pre-i-TAS and i-TAS) in 3 evaluation units (EUs), two of which were hypo-endemic for onchocerciasis and one that was meso-endemic. All areas had received 13-19 rounds of MDA for LF. All EUs met the criteria for pre-TAS. For pre-i-TAS, 4 communities were sampled. One was the LF sentinel site, one was the LF spot check site (and
was also an onchocerciasis 1st-line village), and two were onchocerciasis 1st-line villages. 300 people >5 years old were selected using convenience sampling; it was required that 100 of the 300 people be children ages 5-9 years old. All were tested with FTS, the Biplex RDT (Ov16/Wb123) and ELISA. If the EU passed pre-i-TAS with <2% FTS positive in each community and an undefined threshold for Ov16, the EU proceeded to i-TAS. For the i-TAS, 30 communities were randomly selected using probability proportionate to size sampling. 100 children ages 5-9 years old were enrolled in each community. All were tested with FTS, the Biplex RDT (Ov16/Wb123) and ELISA. In 2 districts, all communities had prevalence of LF antigen <2% and Ov16 antibody <5% and in 1 district, which was meso-endemic for onchocerciasis, LF antigen prevalence was 3.5 – 6.0% and Ov16 antibody prevalence was 3.8 – 11.1%. The 2 districts with good pre-i-TAS results implemented the i-TAS. Both districts had results below the LF critical cut off, though in one EU, the number of FTS positives was 7-fold higher when 5-9 year olds were evaluated, as opposed to just 6 and 7 year olds. The Ov16 RDT results were promising in one EU but need to be confirmed by ELISA. The results in the other EU were above the threshold of 0.1% for stopping MDA for onchocerciasis. The cost of the pre-i-TAS was about 40% higher than the LF pre-TAS. The i-TAS was 51-99% more expensive. The programme has decided to stop MDA for LF in 2 districts. ELISA and entomologic evaluation results are needed to better understand the status of onchocerciasis in order to determine if ivermectin MDA is needed for onchocerciasis. Some of the positive children may have been migrants from Ghana and Côte d’Ivoire.

Presentation: Tanzania experience with co-evaluation

In Tanzania, much of the methodology was similar to Burkina Faso’s but the programme experimented with a few variations in the approach that Burkina Faso used. In the 1st scenario, the sample size used for LF TAS2 was increased to allow the programme to collect enough data to meet the required sample size for children 6-7 years old while also enrolling at least 3000 children ages 5-9 years old. In the 2nd scenario a pre-i-TAS was performed that was similar to Burkina Faso except that people who were older than 9 years old were tested only with FTS and that no children older than 9 years old were evaluated in the 2 onchocerciasis 1st-line villages that were not the LF spot check site. In the 3rd scenario, the i-TAS was school-based and not community-based. In the 4th scenario, the Ov16 RDT was added to a LF TAS strengthening study. Results from scenario 1 were promising by RDT, but the programme is waiting for Ov16 ELISA results before deciding the next steps. For scenario 2, 3 districts were found to have Ov16 RDT seroprevalence >2%, and the other 4 had 0-0.6% seroprevalence. Two areas with the high seroprevalence were selected for a trial of twice annual MDA for onchocerciasis and ELISA results are awaited for the other districts. The results for scenario 3 were not yet available. And scenario 4 had some interesting results. The district evaluated was known to be partially co-endemic for onchocerciasis and partially unmapped for possible hypo-endemic onchocerciasis. There were a number of Ov16 positive children in the known onchocerciasis areas and positivity extended into some of the potentially hypo-endemic areas. Some parts of the district had no Ov16 positive children. It appears that there is evidence of transmission outside of the known onchocerciasis transmission areas but that it does not include the entire district.

The programme was able to obtain useful information from co-evaluations using a variety of methodologies. It was able to prioritize some areas for further evaluation including stop-MDA.
surveys for onchocerciasis, make stopping decisions for LF, prioritize the order in which ELISAs were run, and decide to scale up to twice annual MDA for onchocerciasis based on the data collected. The co-evaluations do require effort to coordinate activities well. The programme had problems accessing the Ov16 RDT and performing ELISAs was challenging because of the existence of multiple ELISAs and the time it takes to run the ELISAs.

Presentation: Nigeria experience with co-evaluation

Nigeria also implemented pre-i-TAS and i-TAS in areas that had received 16-17 years of MDA for onchocerciasis and 5-6 years of MDA for LF. The methodology used was similar to what was used in Tanzania’s 2nd scenario, except that everyone was tested with FTS, Biplex RDT (Ov16/Wb123) and ELISA. For the i-TAS component, schools were sampled. The pre-i-TAS was implemented in 5 local government areas (LGA) in 3 different states. One LGA was excluded from i-TAS because of FTS results that were >2%. All 4 of the LGAs that passed pre-i-TAS successfully passed the LF portion of the i-TAS. The results in 6-7 year olds only, compared to the other ages were similar but slightly lower in all LGAs. Two LGAs identified no children with positive Ov16 RDT results. One LGA found 2% seroprevalence by RDT and the other found 4%. In general, there was an increase of seroprevalence by age, with a maximum seroprevalence by year of age around 6% in both LGAs. The results were examined by village or school in the two LGAs. The seroprevalence of Ov16 by RDT ranged from 0-3% and 0-8% in the LF sentinel sites and the onchocerciasis 1st-line villages. The seroprevalence in the randomly selected schools ranged from 0-13% and 0-23%, respectively. Many of the schools that had high prevalence were confirmed not to be 1st-line villages. This could indicate an issue with the identification of 1st-line villages or an issue with MDA therapeutic coverage in the areas that had higher prevalence than the 1st-line villages. The results also suggest that just because results are good in 1st-line villages, it does not necessarily mean that they are good elsewhere. But 1st-line villages appear to be a good ‘gate keeper’ assessment. If transmission is ongoing in them, it is probably not necessary to perform more resource intense assessment. However, stopping assessment would require evaluation of non-1st-line villages. The combined i-TAS evaluations took less time than separate onchocerciasis stop-MDA surveys and LF TASs and the testing costs of the i-TAS was also less than if the testing had been done separately.

Nigeria has some unique considerations for integrating onchocerciasis and LF evaluations because the state was determined to be the evaluation unit for onchocerciasis stopping decisions but LF uses districts, which may or may not be combined into EUs with population < 2 million people. Close coordination is required to ensure MDA continues where needed. Nigeria will be able to use the results to stop MDA for LF in several LGAs. Some LGAs may need to intensify efforts to eliminate onchocerciasis while others may be ready for full stop-MDA surveys (e.g. entomology).

Presentation: Implications of co-evaluation for (pre) stop-MDA surveys

Combining EUs for onchocerciasis and LF evaluations could potentially result in savings in terms of costs and personnel time. It may be possible to combine LF districts into one EU that overlaps with the onchocerciasis transmission area. But even when this happens, it may not be possible to stop treatment for both diseases at the same time. One issue arises when the onchocerciasis transmission area overlaps only a part of the district. It will be important to not include villages from
outside the transmission area, otherwise you will dilute your results and risk detecting no transmission when in fact there is transmission.

Two sampling strategies have been discussed so far: purposeful sampling of 1st-line communities and random selection of communities. It appears that onchocerciasis will need to use a two-stage sampling process. Purposeful sampling of 1st-line villages would be useful to evaluate or exclude transmission in high risk areas. This could be used either as a pre-stop-MDA survey or as the 1st step of a stop-MDA survey. Random sampling of the rest of the villages in a transmission area, either in communities or schools, would allow programmes to identify unknown pockets of transmission once transmission has been suppressed in the known high-risk areas. This two-stage combination of purposeful and random sampling is supported by the results that were seen in Nigeria’s i-TAS evaluations, which revealed unknown pockets of transmission outside the known 1st-line villages. Following this example, programmes could have a pre-stop-MDA survey in which only high risk 1st-line villages were sampled; if there was no evidence of transmission in these villages then a larger, random sample of the remaining villages would be needed to meet WHO guidelines for stopping MDA. Sample sizes similar to those used by Nigeria appear appropriate. It was noted that the results in the Nigeria study could indicate problems with the identification of 1st-line villages, differences in MDA coverage in the villages, or differences in baseline onchocerciasis transmission that were not identified during initial mapping.

There are still some unanswered questions about the sample size in the 1st-stage purposeful sampling and the number of villages to be sampled. Interestingly in the pre-i-TAS in Nigeria, one of the LGAs failed the LF pre-TAS because one of the onchocerciasis villages, which would not have been evaluated in a normal LF pre-TAS, had an FTS prevalence of 5%. Higher numbers of villages will increase opportunities to identify pockets of transmission. As the 1st-stage sampling should be less resource intensive than the larger evaluations, it is probably acceptable to use census or convenience sampling.

For the 2nd-stage random sampling, one of the key questions is whether communities have to be sampled, as is traditionally done for onchocerciasis, or whether at this stage school-based sampling would be acceptable, as this would be more easily integrated with other NTD surveys. The two methods should probably be compared in terms of identification of pockets of transmission and cost. It might also be necessary to have different strategies for savanna areas, in which the village distance from the river is more easily defined, and forest areas, where the number of rivers is so large that often all villages are close to a river or several rivers. Eventually the issue of how to evaluate urban areas needs to be addressed. Common definitions for an urban area are needed and special sampling may be needed.

The age group tested is also important for stop-MDA surveys. Modelling suggests that the 5-14-year-old age group is the most informative, but current guidelines require testing of children younger than 10 years old and recent OTS recommendations state that the children included should be no younger than 5 years old.

Finally, it may be time to re-evaluate the threshold for stopping MDA. It is difficult to measure the 0.1% threshold required by the current WHO guidelines. Additionally, the threshold may be overly conservative, meaning that programmes where transmission has been interrupted will fail to meet the criterion and be required to continue unneeded treatment.
Presentation: Remaining operational questions for co-assessment of LF and onchocerciasis

Although OTS has made progress in defining mapping strategies for hypo-endemic in ivermectin areas, the way forward is a bit less clear in areas that have received ivermectin as part of MDA for LF. The LF M&E framework has changed several times over the course of more than a decade. One lesson was that targeting the correct age group to assess transmission was important.

There are several scenarios in which one could envision co-evaluations of onchocerciasis and LF. In one scenario, LF is ready for TAS and onchocerciasis has never been mapped. The programme will want to know whether onchocerciasis was endemic and thus MDA with ivermectin alone will need to continue after stopping MDA for LF or whether onchocerciasis was never endemic. While the TAS platform could be used for OEM, the efficiency of integration will depend on the age group that needs to be evaluated. In ivermectin naive areas, data suggest that adults may be the most informative group. Five years of MDA for LF should have some impact on onchocerciasis, but it cannot be assumed that transmission has been interrupted. However, this may make adults a less informative age group. Would 5-9 year olds or 10-14 year olds be a more informative age group for OEM in these areas? If children are the more informative group, would school-based sampling instead of community-based sampling be acceptable? Would the threshold for continuing MDA be the 2% threshold used for starting MDA in ivermectin naive settings (this threshold is based on results in adults) or the 0.1% threshold used for stopping MDA (this threshold is based on results in children)?

A second scenario is one in which LF is ready for TAS and there is no expectation that the onchocerciasis program is ready for the stop-MDA survey. The results would give a broad snapshot of onchocerciasis transmission that could indicate if there are problems. Additionally, it could inform the programme of potential 1st-line villages that might be useful to evaluate during a stop-MDA survey. The concern about sampling strategy is not relevant, because this really is monitoring for onchocerciasis. But the current LF age group is 6-7 year olds. Is this age group informative enough to be worth the investment required to add Ov16 testing to the FTS for the LF TAS?

A third scenario is one in which both onchocerciasis and LF programmes are ready for a stop-MDA survey. Increasing the sample size and adding 5, 8, and 9 years olds to the sample is fairly straightforward; integration makes sense as long as the sample size for onchocerciasis remains around 3,000. The key operational research question is whether or not sampling schools is an acceptable methodology.

Discussion:

The programme experience with the evaluations shows that carefully considered evaluations can provide actionable information about both diseases to programmes. Different sampling strategies could be needed at different stages of the two programmes, and there are cost implications of the different strategies. Sometimes integration may be appropriate and other times coordination may be the only cost-effective option. Programmes should consider co-evaluation whenever they are planning to evaluate one of the co-endemic diseases.

The results of the co-evaluations have implications for the design of OEM protocols and stop-MDA surveys. The committee was concerned about finding villages that were not identified as
onchocerciasis 1st-line villages that had higher seroprevalence of Ov16 as measured by the RDTs. A combination of several factors could potentially explain the findings. It is possible that programmes failed to correctly identify the 1st-line villages associated with each breeding site, the programme may have failed to identify a breeding site (either it was missed during initially evaluations or a new site had developed), or the MDA therapeutic coverage in the implicated villages was lower than in the 1st-line villages. In any case, the results seem to confirm the thought that knowledge of breeding sites and/or MDA coverage is imperfect. For elimination, a process is needed that may identify information gaps in programmes’ understanding of transmission dynamics. A random evaluation, in addition to the customary 1st-line village evaluations, would help address these gaps in programme knowledge. This would apply to both OEM and stop-MDA surveys. It was also noted that the results suggest that a pre-stop-MDA survey is still a good idea. If transmission is found in a 1st-line village there is no need to go forward with a full stop-MDA survey. Work is still needed to determine the prevalence in 1st-line villages that would result in a full stop-MDA survey.

Discussion around OEM continued, even though it was not the topic of the session. It was agreed that a draft strategy for the random stage of OEM mapping should be presented at the next OTS and that the OTS should finalize a recommended strategy for piloting this component of OEM at that meeting. Although it was felt that during the 1st stage of OEM, in which 1st-line villages or villages of concern are purposively mapped, evaluations should remain village based, it might be possible to use school-based sampling, as was done in some of the i-TAS surveys, in the random stage. A comparison of community-based versus school-based strategies would be helpful. Given the different ecologies of savanna and forest areas, and the increased difficulty of identifying 1st-line villages in forest areas, it may be necessary to develop different OEM and/or stop-MDA surveys for the two different ecologic areas. This should be taken into consideration as operational research studies and the OEM pilot are implemented. Finally the topic of needing strategies for urban areas was brought up but was tabled for future discussion.

OTS Recommendations

- Programmes should consider integrated or coordinated evaluation of both onchocerciasis and LF whenever one of the two diseases needs to be evaluated as well designed co-evaluations have the potential to provide actionable information to both programmes
- Random evaluations of non-1st-line villages help programmes identify gaps in their knowledge and should be incorporated both into OEM mapping strategies and stop-MDA surveys
- A draft protocol for the random stage of OEM mapping should be presented at the next OTS meeting so that a final strategy can be recommended for piloting
- Operational research to validate the utility of pre-stop-MDA surveys is warranted
- Comparison of community-based and school-based evaluations during the random stage of onchocerciasis evaluations should be a priority
- Work is needed to develop a strategy for evaluations in urban areas
- Operational research is needed to identify the age group that should be evaluated as part of OEM in areas that have already received IVM for MDA for LF
Final discussion point. Elimination of transmission is a resource-intensive process. Experience with other diseases has demonstrated how important strong political and financial support is to maintain programme activities when the burden of remaining disease is low. It was suggested that a World Health Assembly resolution for the global elimination of onchocerciasis could help advocate for the resources needed and help maintain political support for the last mile. WHO secretariat was asked to provide information to attendees on the process for submitting a resolution proposal. The secretariat provided that information.

End of Report
Declarations of Interests from Committee Members and Invited Participants

Committee Members – Temporary Advisors

<table>
<thead>
<tr>
<th>Name</th>
<th>Region</th>
<th>Country</th>
<th>Institution</th>
<th>Declarations of interest (i.e., related to the topic of the meeting)</th>
<th>Meeting/review restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Unnasch</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>University of South Florida</td>
<td>Has received funding for onchocerciasis related activities from the Mectizan Donation Programme and the Carter Center</td>
<td>None</td>
</tr>
<tr>
<td>Upendo Mwingira</td>
<td>WHO African Region</td>
<td>United Republic of Tanzania</td>
<td>Ministry of Health, Community Development, Gender, Elderly and Children</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Ricardo Thompson</td>
<td>WHO African Region</td>
<td>Mozambique</td>
<td>Institute of Health</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Katherine Gass</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>The Task Force for Global Health/NTD Support Center</td>
<td>Has received funding for onchocerciasis related activities from the Bill and Melinda Gates Foundation, the U.S. Agency for International Development, and the U.K. Department for International Development</td>
<td>None</td>
</tr>
<tr>
<td>Asam M.A. Zarroug</td>
<td>WHO Eastern Mediterranean Region</td>
<td>Sudan</td>
<td>National Program for Prevention of Blindness, Federal Ministry of Health</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Robert Klein</td>
<td>WHO Region of the Americas</td>
<td>Guatemala</td>
<td>Universidad del Valle de Guatemala</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Joseph Kamgno</td>
<td>WHO African Region</td>
<td>Cameroon</td>
<td>University of Yaoundé</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Thomson Lakwo</td>
<td>WHO African Region</td>
<td>Uganda</td>
<td>Retired</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>
## WHO Invited Participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Region</th>
<th>Country</th>
<th>Institution</th>
<th>Declarations of conflicts of interest (\textit{i.e.,} related to the topic of the meeting)</th>
<th>Review restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amy Klion</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>National Institute of Allergy and Infectious Diseases</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Michel Boussinesq</td>
<td>WHO European Region</td>
<td>France</td>
<td>Institut de Recherche pour le Développement</td>
<td>Has received funding for onchocerciasis and loiasus related activities from the Bill and Melinda Gates Foundation and the Mectizan Donation Program</td>
<td>None</td>
</tr>
<tr>
<td>Chukwu Okoronkwo</td>
<td>WHO African Region</td>
<td>Nigeria</td>
<td>Neglected Tropical Diseases, Public Health Department, Federal Ministry of Health</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Roland Bougma</td>
<td>WHO African Region</td>
<td>Burkina Faso</td>
<td>Ministry of Health</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Sharon Roy</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>U.S. Centers for Disease Control and Prevention</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Peter Diggle</td>
<td>WHO European Region</td>
<td>United Kingdom</td>
<td>Lancaster Medical School</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Frank Richards</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>The Carter Center</td>
<td>Has received funding for onchocerciasis related activities from the U.S. Agency for International Development, the Mectizan Expert Committee, and the Carter Center</td>
<td>None</td>
</tr>
<tr>
<td>Philip Downs</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>Sightsavers International</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>John B. Davies</td>
<td>WHO European Region</td>
<td>United Kingdom</td>
<td>-</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Charles Mackenzie</td>
<td>WHO Region of the Americas</td>
<td>United States of America</td>
<td>Task Force for Global Health</td>
<td>Has received funding for onchocerciasis</td>
<td>None</td>
</tr>
<tr>
<td>Name</td>
<td>Organization</td>
<td>Country</td>
<td>Institution</td>
<td>Funding Details</td>
<td>None</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------</td>
<td>---------------</td>
<td>------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Wilma Stolk</td>
<td>WHO European Region</td>
<td>Netherlands</td>
<td>University Medical Center Rotterdam</td>
<td>Has received funding for onchocerciasis related activities from the Bill and Melinda Gates Foundation, U.S. Agency for International Development, and the Malawi Ministry of Health</td>
<td></td>
</tr>
</tbody>
</table>