Operational Research Priorities for Onchocerciasis Elimination

Session Date: Saturday, November 4

Session Time: 1:00pm – 4:00pm

Session Location: Camden

Session Description: The World Health Organization guidelines provide criteria for stopping mass drug administration and completing post-treatment surveillance. Many of the details for routine monitoring and assessment, integrating onchocerciasis impact assessments with lymphatic filariasis assessments, and demonstrating interruption of transmission were beyond the scope of the guidelines. Additionally, the transition to elimination requires mapping for elimination which is distinct from the mapping done for control of onchocerciasis. The breakout session will review strategies developed by the onchocerciasis subgroup to the NTD M&E working group in order to determine how best to pilot the implementation of the suggested strategies and to compare to alternative strategies developed either by the subgroup or by participants in the breakout session.

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KEY DISCUSSION POINTS

Entomology

Onchocerciasis is transmitted by several species of blackfly which vary in terms of range and efficiency as a vector. *Simulium damnosum,* the most common vector, has an average flight range of 10-15km but can fly much further and can easily cross country boundaries. Breeding sites occur in areas around fast moving water; in the savanna these breeding sites are relatively easy to identify. However, there is seasonal variation in the location of breeding sites, and our ability to identify breeding sites is challenged in forest areas and in low transmission areas (e.g. seasonal streams may be more important in these areas).

Etymological assessments are part of M&E, MDA stopping surveys and post-treatment surveillance, generally using O-150 PCR pool screen. In order to conduct these assessments, one must first determine the location and seasonality of breeding sites. For M&E, the breeding site is used to identify 1st line villages, some of which are chosen as sentinel sites for monitoring, because the risk of infection decreases with increasing distance from the breeding site.

Mapping breeding sites is necessary to identify first line villages. However, incomplete knowledge of breeding sites, particularly in low transmission zones, prevents the identification of all relevant 1st line villages which are key component of the M&E system that has been used in the past by onchocerciasis control programs. Additionally, breeding sites may have shifted since previous assessments, so even previously identified sites and associated 1st line villages need to be verified. Unfortunately, validation of breeding sites is a difficult and, at times, dangerous task and the pool of qualified field entomologists is limited.

Entomologic M&E is required by the 2016 WHO guidelines. Fly collections should occur in association with those 1st line villages that are selected to be sentinel 1st line villages. The current standard is human landing collection. Fly traps are being developed, but we do not yet know how to calibrate them compared to human landing, which will be required in order to calculate the annual transmission potential, which is probably a more useful indicator than prevalence of infection in flies. It will be important to understand how best to time fly collections, as they should align with high transmission period and account for MDA since IVM clears the skin of parasites. Fly collection within 4 months of treatment may yield false negative results.

Discussion:

1) Identification of sentinel 1st line villages and breeding sites
    a) Are we confident (given that the average flight distance is 15km) that assessment of sentinel 1st line villages 30-50 km apart along a river are close enough to ensure that interruption of transmission is occurring?
    b) Data indicate that some sentinel 1st line villages had lower rates of Ov16 positivity in children than non-1st line villages
        i) This could stem from poor MDA coverage in the non-1st line villages or failure to identify a breeding site (e.g. breeding site moved since last mapping or it was small). Understanding the explanation of this finding could inform strategies for identifying breeding sites that contribute to transmission.
2) Number of flies required
    a) Should the number of flies necessary vary based on annual transmission potential and endemicity, perhaps to more than 6,000 flies (the current minimum)? How would we determine what number would be necessary?
    b) Given that fly collection may be difficult, could fewer flies be collected by determining the number of infected flies (as opposed to infectious flies), which represent fly exposure to infectious human host?
    c) If programs were to monitor infected (as opposed to infectious) flies, what level of infection would be concerning for on-going self-sustainable transmission?
3) Screening methods
    a) Given that PCR pool screening is necessary to validate elimination and this requires sufficient laboratory capacity, could an alternative methodology help alleviate this bottleneck?
    b) What about increased capacity? –funders may be interested
4) Neighbouring transmission zones
    a) How do we tell if two geographically neighbouring transmission zones have the same vector population and if flies re-invading can cause a re-emersion of transmission?
    b) TDR is trying to develop a tool to genetically ID the flies to determine transmission zones
5) Is limited vector control (as opposed to elimination) a viable strategy to use at the end of MDA to accelerate elimination?

Elimination Mapping Strategy: Update from the Oncho Technical Advisory Subgroup

As Onchocerciasis elimination activities move forward, greater certainty about where onchocerciasis is present is required. In the control era, the focus on hyper- and meso-endemic areas was necessary, but as we push toward elimination, a more thorough accounting of hypo-endemic and believed non-endemic areas is necessary. Areas mapped via the rapid epidemiological mapping for onchocerciasis (REMO) strategy need to be remapped with more sensitive diagnostics.

To ensure that we are aware of all of the areas where MDA needs to be implemented, the OTS has recommended a conservative (and therefore biased in favour of starting MDA) methodology which aims to shrink the areas in need of treatment and enable resources to be targeted to areas where onchocerciasis has historically been present but treatment has not been performed.

This mapping will involve several steps. First, all unmapped districts are enumerated and then reviewed at the national level to exclude districts which are not ecologically suitable for oncho transmission. For districts not excluded, a sub-district units (IU) can be defined to remove areas in the district that are not suitable for transmission. Elimination mapping should first occur in the higher risk districts (e.g. those adjacent to hyper/meso endemic areas and those with known blackfly biting nuisance). In zones of likely transmission, first line villages will be tested first. This would involve a sample of at least 300 adults and at least 3 villages. Data were shown that suggest testing adults would provide a better signal for transmission in untreated areas than children. If there is no Ov16 signal (via Ov16 RDT) in these sentinel 1st line villages, a random sample of villages in the rest of the district will be chosen and further Ov16 testing done. In zones of uncertain transmission, where 1st line villages cannot be identified via traditional methods, villages will be randomly selected. If there is Ov16 signal at any point, then treatment is required. If there is not, then it is recommended that the absence of Ov16 signal be confirmed by ELISA.

Discussion:

1) Geographical Considerations:
    a) How do we ensure geographical coverage of elimination mapping?
    b) In areas thought to be hypoendemic for oncho, but treated for LF with ivermectin, how will we adjust this strategy to take into account prior treatment?
    c) Are there additional characteristics of sites that we can add to the exclusionary criteria to reduce the total mapping burden?
2) Diagnostics
    a) Some members of the community are uncomfortable with serological tools since they are not always concordant with skin snips or nodule assessments
        i) These diagnostics measure different things, historical versus active infection.
        ii) While the presence of nodules or positive skin snips signify that treatment must be done, their absence does not signify that there is not onchocerciasis in the community and the Ov16 provides a more sensitive test for historical transmission
        iii) Data referenced (Gabon) purportedly shows that transmission evident by skin snip would have been missed by Ov16, though the opposite was more common
    b) Serology: What is the threshold of OV16 which constitutes a signal of transmission? What is the threshold at the community versus district level?
    c) Entomology: How can entomology be used to calibrate what is considered a serological signal for transmission?
3) Participants
    a) Age group
        i) Current testing is performed on adults. Could we instead test “late school age” (10-14) children who might be easier to reach due to sampling in schools?
        ii) 10-14 can be middle school which can aggregate a large mix of people because people travel to school at this age especially in rural areas.
    b) Migration
        i) Add an exclusion criteria for people who lived elsewhere in the last 10 years
        ii) How do we take into account people who live and work in different (sub)districts?
    c) Sampling
        i) In areas that require a random sample how many villages need to be sampled to adequately assess for potential transmission?
        ii) In areas that require a random sampling what size should each village cluster be?

iii) It is important to remember that we should not expect programs to perform as stop-MDA survey to demonstrate lack of transmission in an area where there is low suspicion for transmission

Stop MDA Decision: Update from the Oncho Technical Advisory Subgroup

Onchocerciasis transmission can be interrupted after 12-15 years with 80% or higher coverage, a milestone some countries are reaching. The stop MDA guidelines recommend a survey to assess Ov16 serology in 2,000 children at risk for infection and under the age of 10. In order to pass the assessment, the upper limit of the confidence interval needs to be below a threshold of <0.1% seroprevalence in these children. However, the details of how the survey should be conducted are sparse, and therefore countries have developed different types of stop-MDA surveys which vary on primary sampling unit, secondary sampling unit, and sampling methods, though all have a similar sample size, use the Ov16 ELISA and the 0.1% threshold.

While 2,000 children is the minimum sample size suggested, the sample size must account for sampling strategy, Ov16 ELISA sensitivity, desired power, and expected non-response rates. The sample size recommended by the 2016 guidelines yields a low power of around 22% even in ideal settings, meaning that many programs that may have met the serologic criterion may not pass the stop-MDA survey. Given non-response, lower than desired sensitivity, and need to adjust for clustering if part of the sampling strategy, the sample sizes needed to detect and adequately assess transmission are 4,000 or more. Additionally, given that perfect specificity is unlikely, we should expect some false positive results. For example, if the specificity of a test is 99%, we would expect 20/2000 false positives, which is far above the threshold of 0.1%. The current Onchocerciasis Technical Advisory Subgroup (OTS) recommendation is that a minimum of 3,000 children be tested, with further adjustments to be anticipated as more data emerge on test performance and target age group. Modellers found the 5-14 year old age group the best indicator of ongoing transmission by ROC analysis. Including older participants would make the evaluation more conservative.

Given the imperfect understanding of transmission of onchocerciasis, particularly in areas of low transmission, the OTS has also discussed the establishment of a two-stage approach to stop-MDA surveys. The first stage would involve evaluation of identified 1st line villages followed by a random assessment of the remaining evaluation area. A recent study in Nigeria supports the concept that a two-stage process may be required. In Nigeria, an integrated transmission assessment survey (iTAS) for lymphatic filariasis and onchocerciasis was performed. In this two-step assessment, the first step, called pre-iTAS, sentinel villages are assessed. If passed, the iTAS, which is a full cluster randomized survey, is implemented. The result from Nigeria showed that sentinel 1st line villages for onchocerciasis sites often had lower seroprevalence of Ov16 than non-1st line villages. The reason for this is unclear but certainly reflect imperfect knowledge of transmission in the area. This could be due to difference in MDA programme performance, unidentified breeding sites that have more intense transmission dynamics that identified breeding sites, or movement of previously 'known' breeding sites to new locations. Only through both purposive and random sampling was transmission defined in the evaluation area.

Given the time and resources necessary to conduct a stop MDA survey, the OTS recommends that a Pre-Stop-MDA survey be developed. This survey would ideally be limited, using minimal time and resources to evaluate whether assessment areas are ready for full-stop-MDA survey. If a country passed it would proceed to a full stop-MDA survey. If failed, the program would continue MDA and assess the reason for the failure. A possible pre-stop-MDA survey strategy would collect a convenience sample of at least 300 children in 3 or more 1st line villages. Operational research would be needed to determine the threshold for passing the survey. Again, the Nigeria iTAS example supports this approach.

Discussion:

1) Diagnostic Questions:
    a) What is the upper limit of the false positive rate for all of the tests that are being done?
    b) Do we need to re-calibrate the test in an area with absolutely no transmission?

   i) Biplex data exists from a known negative population of children under 10 in Mali yielded 1 positive Ov16 result from 1700 tests
   c) How do we standardize quality assurance/quality control (QA/QC) for the ELISA tests and how do we tune it? Can QA/QC results be used to define test cut points in nanograms or international units?
   d) Is there a better test for evaluation of potentially false positive results?
   e) Would development of an antigen test or a marker of the presence of adult female worms, measure the actual outcome of interest and simplify the evaluation required?
2) Threshold
   a) Current threshold of <0.1% is extremely difficult to measure, if not impossible given that tests will have false positives and that it may not be necessary to reduce transmission to this level in order to interrupt transmission, so can we find a more appropriate threshold which is measurable that will allows us to safely stop MDA?
   b) Suggestion to find new threshold: Compare area with verified interruption of transmission with another area with low ongoing transmission. At what level could we correctly differentiate these and not fail an area due to false positives? What sample size is needed?
   c) What threshold/sample size should be used for Ov16 ELISA results?
   d) If a pre-stop MDA survey is feasible and acceptable, what is the best protocol design and what should the threshold be for Ov16 ELISA? For Ov16 RDT?
   e) What is the design effect for oncho (or a similar NTD if oncho data are unavailable)?
3) Sampling
   a) What is the most appropriate age group to assess transmission using an antibody test?
      i) Should the age range take into account number of years of MDA completed?
   b) How could we use prior endemicity and other factors to find an optimal sample size?
   c) How can we best sample in urban areas?
   d) Primary Sampling Unit (PSU) — Location
      i) Which setting should be used—communities vs. schools?
      ii) How are 1st-line villages identified and defined?
      iii) What sampling method should be used—purposive, random, other, or a combination to determine if multiple components are needed
      iv) How many PSUs should be selected?
   e) Secondary Sampling Unit (SSU) — Person
      i) How many people per PSU should be sampled?
      ii) What sampling method should be used—census, convenience, other?
      iii) Which age range should be used—5–9 years, 5–14 years, other?
4) Can we incorporate the vector evaluation results into the decision to stop MDA in such a way as to decrease the sample size required for serological evaluations?
5) Should length of post-treatment surveillance vary based on prior status of transmission and endemicity?

Policy will evolve as we learn more, but countries should still progress with current guidelines. Though this is a moving target, provided PTS successful demonstrates no recrudescence of transmission after stopping MDA, a country's verification of elimination dossier would not be threatened if stop-MDA survey methodology changes over time.

KNOWLEDGE GAPS

- Is assessment of sentinel first line villages 30-50 km apart along a river adequate to ensure interruption of transmission?

- Does the number of flies necessary for programmatic decisions vary based on annual transmission potential and endemicity?
- Is there an alternative screening method to PCR pool screening?
- Is limited vector control a viable strategy to use at the end of MDA to accelerate elimination?
- What is the threshold of OV16 which constitutes a signal of transmission (at the community versus the district level)?
- How can entomology be used to calibrate what is considered a serological signal of transmission?
- How do we take into account people who live and work in different (sub)districts?
- In areas that require a random sample, how many villages need to be sampled (and at what size) to adequately assess for potential transmission?
- What is the false positive rate for our diagnostic tests, and how do we build that into our decision making?
- How do we standardize quality assurance and quality control (QA/QC) for the ELISA tests?
- If a pre-stop-MDA survey is feasible and acceptable, what is should the threshold be for OV16 ELISA? For OV16 RDT?
- What is the design effect for oncho?
- Should the length of post-treatment surveillance vary based on prior status of transmission and endemicity?

RECOMMENDED NEXT STEPS

- Assess relationship between OV16 positivity and MDA coverage in the non-first line villages
- Determine whether fewer flies could be collected by determining the number of infected flies (as opposed to infectious flies), and define a concerning level of infection
- Develop a tool to genetically identify the flies to determine transmission zone
- Assess coverage when testing in late school age (10-14 years) children instead of adults
- Add an exclusion criterion for people who lived elsewhere in the past 10 years to oncho surveys
- Develop an antigen test or a marker of the presence of adult female worms
- Determine a measurable threshold to allow safe MDA cessation

Determine the most appropriate age group to assess transmission using an antibody test