Threshold for Stopping MDA for Onchocerciasis: Time for a Change?

Session Date: Friday, October 26

Session Time: 1:00pm – 4:00pm

Session Location: St. Jerome, 3rd Floor

Session Description: WHO guidelines require demonstration of Ov16 seroprevalence <0.1% in children younger than 10 years old to justify stopping mass drug administration. The scientific rationale behind this 0.1% threshold is weak at best. Such a stringent threshold is difficult to measure and may require programmes to continue treatment for years after transmission has been interrupted. Available epidemiologic models suggest that it may be possible to raise the threshold; however, such a revision should be supported by data and experience in the field. There are two main objectives for the session: 1) to review the serologic and entomologic data that have been generated from sites where transmission may have been interrupted to see if they are consistent with a higher threshold; and 2) suggest additional studies that could improve model projections of possible thresholds and/or provide field data to validate a more optimal serologic threshold for stopping decisions.

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KEY DISCUSSION POINTS

- WHO hopes to harmonize recommendations for tests to be used during post-treatment assessments and set associated thresholds based on sensitivity and specificity of each test.
    - There are 5 commonly-used serological tests for onchocerciasis, including the OEPA ELISA, CDC OEPA ELISA, PATH ELISA, SD Bioline rapid diagnostic test (RDT), and SD Bioline ELISA kit. Sensitivity and specificity varies among tests. Although the SD Bioline RDT has been found by two studies to have a sensitivity of 89-91% and a specificity of 97-8%, sensitivity in low-prevalence settings appears to be reduced.

- Mathematical models, including the ONCHOSIM model and the EPIONCHO-IBM model, can be used to predict transmission and infection spread of onchocerciasis.
    - Both models are individual-based stochastic models that simulate transmission in a closed population. The models take into account individual variation in exposure and intensity of infection as well as age- and sex-dependent exposure patterns.
    - The models have not been calibrated/validated against empirical data and make a number of assumptions.
        - Both models assume that the probability of mounting an antibody response on exposure is 80%.

        - ONCHOSIM assumes varied sensitivity and specificity of the Ov16 ELISA, whereas EPIONCHO-IBM assumes 100% sensitivity and specificity.
        - Both models assume that seroconversion is elicited by an adult worm of either sex but EPIONCHO-IBM assumes a delay of 10 months for L3 larvae to become L5 juvenile adults.
        - ONCHOSIM assumes either immediate or no seroreversion. EPIONCHO-IBM assumes no seroreversion.
        - ONCHOSIM assumes that exposure to bites increases until age 20 and that exposure is higher for males than for females. This was informed by data from Guatemala.
        - EPIONCHO assumes that boys have higher earlier exposure but older women are more exposed than men.
    - To estimate threshold with ONCHOSIM, modelers simulated 750 scenarios with variations in pre-control endemicity, and mass drug administration (MDA) frequency, coverage and duration. Each scenario was run 10,000 times with the aim of determining how often elimination outcome would be predicted correctly for a range of serologic thresholds.
        - The probability of elimination declines as the threshold increases. Higher threshold value represents a risk of premature interruption.
        - A higher threshold can be used if children aged 5-14 are sampled compared to children ages 5-9. The ROC curve for ages 5-14 is the most informative.
        - If we assume immediate seroreversion, we cannot measure the 95% probability of elimination even at a threshold of zero.
        - The appropriate threshold declines with increasing baseline endemicity.
        - Using an onchocerciasis pre-TAS to weed out districts where elimination has not been achieved can improve the performance of the model.
        - Both models agree that testing children under age 15 with a threshold around 1-2% would provide a reasonable positive predictive value for the scenarios explored assuming no seroreversion.

- Empirical epidemiological and entomological data was also presented.
    - In Malawi, 2018 data from 10 districts that had had at least 14 years of therapeutic treatment coverage showed Ov16 RDT seroprevalence of >0.1% among children ages 5-15 in most districts. Children over age 10 had higher seroprevalence than younger children. However, most of the fly-catching sites in the same districts had <0.5% infected flies. Human and entomological studies were conducted in different sites.
    - Tukuyu, Tanzania has been under MDA consistently since 2000. A study found Ov16 seroprevalence by ELISA in children under age 20 to be <2% but >0.1%. A study of >8,000 flies found no infective flies.
    - Kozah, Togo, has been under biannual ivermectin treatment for 20 years. A study found seroprevalence below 6% among children under age 20. Xenomonitoring results are pending.
    - Yoto, Togo, has been under annual ivermectin treatment for 20 years. A study found seroprevalence below 3% up to age 15. Xenomonitoring is pending.
    - In 2017, the Metema focus in Ethiopia met the WHO criteria for interruption of transmission based on both <0.1% prevalence in young children (seropositive results were negative by skin snip) and <0.5% PCR in flies. However, in 2018, 15 children

were seropositive. The area in which the positive children lived also had flies that tested positive by PCR. This area was delineated as the Wude Gemuz hotspot and will be undergoing further testing.

- In the Budongo focus in Uganda, no flies have been observed since September, 2012. However, the Ov16 results among children are still above the 0.1% threshold for interruption of transmission.

KNOWLEDGE GAPS IDENTIFIED

- Empirical data to validate assumptions of the mathematical model are needed.
    - It is not clear how long it takes for seroreversion to occur, which proportion of people serorevert, and what factors (e.g., age) are associated with seroconversion and seroreversion. Longitudinal data on people of all ages could help answer these questions as well as provide data on changes in incidence over time and timing of interruption of transmission.
    - It is not clear whether male worms elicit the same antibody response as female worms. Improved data on this are needed.
    - It is not clear what positive results from children older than age 10 mean. Are these indicative of infections from long ago? How long does it take children to serorevert?
    - Assumptions on age- and sex-dependent exposure patterns can be validated with data on mf prevalence and intensity versus age/sex. It is particularly important to collect these data on children under age 15.
    - There is a need for measures of diagnostic performance, as determined by datasets in which individuals were tested with multiple tests.

- More data are needed to define optimum age group and threshold. These data should come from all age groups and use multiple diagnostic methods.
    - Field data suggest that the serologic threshold is too low. Sites failed serologic threshold even if they passed the entomologic threshold and even if no flies were present.
    - Should threshold vary based on the performance of the test?

- It is not clear whether children are good sentinels for onchocerciasis transmission. It is possible that they are not exposed while adults are still infected and serve as reservoirs.

- It is not known how the efficiency of the vector can influence the appropriate stopping threshold. More entomological work to determine whether vectors vary in efficiency is needed.

- Modeling data suggest that the threshold should be lower in areas with higher baseline prevalence. Hyper-endemic areas are most prone to recrudescence. More work should be done to establish whether threshold should vary by baseline endemicity.

- Feasibility and cost data should be gathered and considered when setting a threshold.

- Entomological data paired with epidemiologic assessments could be used to determine the appropriate stopping threshold.

RECOMMENDED NEXT STEPS

In general, the group was supportive of revising the threshold for stopping MDA but felt that the following information will be necessary:

- **Examination of existing data:** Existing data on Ov16 seropositivity in areas where onchocerciasis has never existed (e.g., Mali) can be used to determine the background level of positive results in the absence of infection. This can be used to determine whether the threshold of 0.1% is too low on account of background noise when using certain tests.

- **Collection of new longitudinal data:** Both the threshold and modeling questions could be answered by conducting a series of cross-sectional studies in Tukuyu, Tanzania (and other similar sites where the entomology is below the 0.5% cutoff but Ov16 serology exceeds 0.1%). MDA should be discontinued and studies should then monitor serology and entomology over time for recrudescence.
    - Studies should be conducted in both savannah and forest areas.

- **Consideration of test-specific threshold**: Additional data are needed to determine whether the threshold should vary by diagnostic test. It is possible that the optimal sampling frame could also vary by test. Comparison studies on different tests should be conducted. Cutoff values for ELISA should also be considered.

- **Improving our understanding of entomology:** Additional entomological studies to determine the efficiency of various vectors would be useful to determine whether this is a factor in onchocerciasis elimination.
    - Methods for determining the best places for fly catching should be refined and not based on historical data.

- **Understanding the best timing for revising the threshold:** The community needs to come to a consensus on whether the threshold should be revised now, or whether it is best to wait 3+ years to generate the above data before revising.