Generating Evidence for Moving to Elimination of LF Transmission

Session Date: Saturday, October 27

Session Time: 9:00am – 12:00pm

Session Location: Maurepas, 3rd Floor

Session Description: WHA 50.29 called for the elimination of lymphatic filariasis (LF) as a public health problem. WHO launched the Global Programme to Elimination Lymphatic Filariasis (GPELF) with the aim to interrupt transmission and to alleviate suffering among patients. According to WHO, elimination as a public health problem involves reducing infection below measurable targets at which transmission is assumed no longer sustainable in the absence of further interventions but actions are required to maintain the targets whereas interruption of transmission (or elimination of transmission) represents zero incidence of infection in defined areas. The difference in the stated target has represented a gray area of understanding among stakeholders and limitation in the type of achievement acknowledged by WHO. Additional evidence to standardize both the indicators and the surveillance methods is required to develop WHO guidance for affirming the elimination of transmission.

Session Chairs: **Dr. Jonathan King**, Lymphatic Filariasis Elimination Department of Control of Neglected Tropical Diseases, World Health Organization
Dr. Leda Hernandez, Infectious Disease Office in the National Center for Disease Prevention and Control of the Philippines Department of Health (DOH)

Session Rapporteur: Kira Barbre

KEY DISCUSSION POINTS

As of 2018, 14 countries have met criteria for elimination of LF as a public health problem. Elimination as a public health problem requires continued action after validation to sustain the achievement (surveillance and providing care to affected persons). Elimination of transmission is a more rigorous goal defined as zero incidence of infection in defined areas. To establish such criteria for elimination of transmission of LF, the target indicators and thresholds must be defined, diagnostic tests, sampling methodology and size of the evaluation unit specified. In this session, findings from recent operational research studies were presented, implications discussed, and key areas of research identified.

The Transmission Assessment Survey (TAS) is an established platform that countries are using now to determine when to stop MDA and then during post-MDA surveillance to ensure average incident infection levels across evaluation units are sustained below thresholds. Post-MDA surveillance conducted in 2 provinces in the Philippines found evidence of focal transmission through following

up communities with antigen-positive children in TAS. Data from TAS conducted in Malawi was also used along with a spatial analysis of clinical data as an approach to prioritize areas for post-MDA surveillance to find and respond to focal transmission.

The extensive data collected from ongoing research In Sri Lanka was also presented. In that setting TAS was not sensitive for detecting ongoing, focal transmission. Xenomonitoring identified several hotspots. Antibody prevalence was more sensitive than antigenemia. An adult TAS was also more sensitive than school-based TAS in detecting ongoing transmission in the community.

KNOWLEDGE GAPS IDENTIFIED AND RECOMMENDED NEXT STEPS

Further research is needed to obtain an acceptable, measurable proxy for LF transmission. Years after MDA, historical infections should have cleared if transmission was interrupted. Where there is no transmission, there should be no evidence of recent exposure. The following potential methods could be studied:

- absence or below a defined threshold of infection in mosquitoes by sampling mosquitoes and testing for filarial DNA.
- absence of reservoirs of infection by following up positive cases and searching for hot spots.
- little to no infection in the population by using a cross-sectional survey to determine whether microfilaria or circulating filarial antigen in adults is below a threshold.
- no infection in places where signals were found or are predicted (either from previous TAS or other surveys)
- decline of infection and/or antibody prevalence at a rate consistent with reaching no more transmission.
- absence or below a defined threshold of antibody prevalence

Further research is required on how to enhance TAS to minimize risk of missing ongoing transmission leading to recrudescence and maximize probability of elimination of transmission.

- How many positive children represent a concern even if below critical cut-off value?
- Does the spatial distribution of schools with positive children matter?
- Should previous TAS-positive schools be included in subsequent TAS sampling?
- Do we need to collect extra sampling from border districts?
- Should additional efforts focus on high-risk EUs only? How to define high-risk EUs?
- Should we consider other markers such as morbidity cases?
- Should TAS be supplemented by parallel indicators or surveys to improve sensitivity of detecting areas of ongoing transmission?
- What is gained if TAS 1 and TAS2 results are used to create an adaptive TAS 3 design (reform EUs, sample size, selection)?
- What is gained from both random and targeted sampling (increased sampling in areas/populations suspected to be at higher risk)?
    - Ex.: occupational risk (fishermen), geography (border areas, ring testing around known cases, high prevalence of morbidity), adult men

Proposed studies: In EUs with known, persistent low-level transmission (e.g., areas that have failed TAS), compare results from purposeful sampling, random sampling, combined purposeful/random sampling, and 2-3 diagnostic tools to determine which strategy is the most sensitive at detecting transmission.

Can current data predict populations and locations at high risk to be targeted for surveillance? Are the risk factors the same everywhere or setting specific?

Further research is needed to determine whether a standardized survey, developed for implementation after validation could be used to verify elimination of transmission? To design such a survey the following questions must be answered:

- Is the signal from adults and children the same but shifted up/down?
- Which measurable indicators decrease most rapidly over time once adult worms lose fecundity or die?
    - Review available data to find sites and specimens that can be studied.
    - Need to revisit the same communities over time to observe kinetics in the population
    - How can we combine convenience and random sampling in a programmatic context? (hospital-based? TAS-based?)
        - Can we demonstrate a decrease in antibody and a very low level of antigen?
- Proposed studies:
    - In EUs with known, persistent low-level transmission (e.g., areas that have failed TAS), compare results from purposeful sampling, random sampling, combined purposeful/random sampling, and 2-3 diagnostic tools to determine which strategy is the most sensitive at detecting transmission.

Further research around hot spot definition, identification and response is needed.

- What is the definition of a hot spot?
    - What thresholds should be used?
    - What geographic area should be used?
    - What are the risk factors for a hot spot?
    - Can a model be developed to predict hot spots?
- What survey methodologies or platforms can feasibly identify hot spots?
- What is the appropriate response to a hot spot (MDA, test and treat, vector management)?
- Under what conditions and when do hot spots lead to recrudescence?

Research on how spatial data can be used to identify and respond to hot spots is needed.

- Questions to address:
    - What are the spatial sampling strategies that can help identify LF hot spots in different transmission settings?
    - What are the drivers of (transmission in) hot spots? (MDA uptake, socioeconomic, environmental, vector, etc.)
    - What is the spatial relationship between infected humans and infected mosquitoes?
    - How can this information be used to develop spatial targeted surveillance strategies, including xenomonitoring?
    - How should decisions to stop or restart treatment account for spatial dynamics of transmission, either through hot spot detection or other modeling to identify areas in which transmission persists due to low MDA coverage or ecological factors?
- Proposed studies
    - Use current global program data to implement a geospatial model including environmental covariates to detect potential areas of ongoing transmission.

  - Risk mapping using historical data and prospective survey data
    - Make use of risk mapping tools already available
  - Population-based studies to pick up signals
    - Randomized cluster surveys
    - Conduct targeted/adaptive sampling including community/household-level studies in humans and vectors.
  - Spatial overlay of diagnostic tools to define hotspots and inform surveillance strategies.

Research to inform mathematical models and validate assumptions for stopping MDA is needed.

- Validate model predictions with prospective data collection in settings where current elimination goals have been met.
- Use mathematical models to estimate threshold of LF infection at the community level, accounting for differential participation in MDA by sex, age, and other factors.
- Conduct simulations of the performance of different sampling strategies to detect varying levels of prevalence
- Identify a monitoring framework to evaluate sub-implementation unit (IU) transmission potential and the risk that transmission is ongoing.
- Identify predictors of TAS failure by evaluating cluster-level results.
- Determine transmission thresholds for different diagnostic tests.