Can Kala-azar transmission be interrupted?

Session Date: Saturday, October 27

Session Time: 1:00pm – 4:00pm

Session Location: Endymion, 8th Floor

Session Description: Currently, Visceral Leishmaniasis (VL), known as Kala-azar on the Indian subcontinent (ISC) is being controlled, and Nepal, Bangladesh and India have seen decreases in the incidence of disease that are consistent with achieving the 2020 goal of "elimination as a public health problem". The question then arises whether to maintain this level of control, or push for further reduction, especially elimination of infection/interrupting transmission. During this session, arguments in favour and against pushing for interrupting transmission will be discussed based on recent evidence from epidemiological and control trials performed in the ISC. The session will conclude with a discussion on some potential new tools required to interrupt transmission and how they can be incorporated into the national program.

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KEY DISCUSSION POINTS

This session consisted of 10 presentations and two discussion periods. The following is a summary of key points raised during the presentations and/or discussions.

Overview of VL (Kala-Azar) in India

There are currently four endemic states in India: Bihar, Jharkhand, West Bengal, and Uttar Pradesh. Sporadic cases occur in other states. The control program, which is based on intensive disease management (case finding and treatment) and Indoor Residual Spraying (IRS), has been highly successful in reducing the number of cases and deaths.

The SPEAK India consortium provides a platform for all stakeholders involved in VL efforts to plan for sustainability of elimination and identify areas of collaboration to ensure optimal use of resources. The coalition, which consists of representatives from the national program, research, donors, and the World Health Organization/TDR, aims to define key knowledge gaps and data needed to achieve the elimination goal. SPEAK works in the areas of surveillance, transmission, health systems, and modelling.

Is the current target appropriate and attainable?

The current Roadmap goal for VL in the South-East Asia Region is "Elimination as a Public Health problem," defined as an annual incidence of less than 1 case per 10,000 population at the district level in Nepal, upazila level in Bangladesh, and sub-district (block) level in India. The SPEAK India consortium has examined whether this is the appropriate goal in the Indian context, assessed the feasibility of achieving it, and arrived at the following conclusions:

- The more stringent goal of Elimination of Transmission (true elimination) is unlikely to be attainable in India at this time with currently available interventions.
- The wording of the current target could become a barrier to control by discouraging detection/reporting of cases.
    - The target could be improved by rewarding case detection and planning for outbreaks with inclusion of a time element to control them.
- Drug procurement, quality, delivery, resistance and program fatigue are potentially important barriers to reaching the current goal.

VL is a regional disease with little respect for political boundaries and high outbreak potential. This means that achieving any control or elimination target in India will be strongly dependent on the situation in Nepal and Bangladesh. Elimination or sustained control must be considered in a regional context.

Surveillance tools

In order for programs to reach their elimination targets, it is essential that they have access to tools capable of measuring progress. Two ongoing studies were presented which evaluate the use of sero-surveys as measures of transmission and surveillance. One study is assessing the Direct Agglutination Test (DAT) and rK39 ELISA for use in monitoring transmission. It is trying to answer questions relating optimal sensitivity and specificity, and economic feasibility. The other study is aimed at improving VL surveillance at the Primary Health Care (PHC) level.

In a post-elimination or surveillance setting, ideal diagnostics would be non-invasive, cheap, and capable of distinguishing current from past infections. Diagnostics that can detect parasite antigens are therefore highly preferred. The Leishmania Antigen Detect ELISA (InBios, IDRI) shows promising early results, however it has not been fully validated. Cost and scale-up are likely to be challenges to large-scale programmatic implementation.

In the absence of an antigen test, tests that detect antibodies are frequently used as proxies for measuring transmission. Two such tests, the DAT and the rK39 ELISA/rapid diagnostic test are widely used for this purpose. Because they detect antibodies, they are unable to distinguish between active and past infections and cannot be used to measure response to treatment. Given these limitations, studies evaluating the use of these tools for surveillance are essential.

Xenomonitoring as a measure of transmission

Xenomonitoring is another potential surveillance tool that can be used to measure ongoing transmission. It relies on detection of the parasite within the sandfly vector, rather than the human host. In a post-elimination setting, it will be very challenging to do active case detection, so xenomonitoring could serve as a less costly and less invasive mechanism of passive surveillance.

A study is currently ongoing to assess and optimize xenomonitoring as a tool for measuring transmission. The first objective in this study is to determine the best collection method for capturing the infectious portion of the *Phlebotomus argentipes* population. Three sampling methods were compared to assess the following:

- Total number of sandflies caught
- Proportion of bloodfed to unfed females
- Species specificity
- Proportion of infected females

Preliminary results indicate that the Prokopack performed best in capturing bloodfed, female *P. argentipes,* however infection status has not yet been assessed.

Strengthening of Health System for VL elimination

A study is ongoing in India's four endemic states to understand the role of the health systems in VL elimination. Researchers are working to analyze the strengths and weaknesses of the health systems in each state and document best practices. This study will provide state-specific

recommendations for health systems interventions that can be applied to address challenges that arise during the post-elimination phase.

Active Case Detection

Case detection is essential for both control and surveillance of VL. Active case detection (ACD) is based on the concept that VL cases tend to be clustered, so the presence of previous cases predicts appearance of new cases. A study is being conducted by CARE India to evaluate and optimize ACD using a "light touch" method. This study is first looking to prove that ACD is more effective in finding new cases than passive case detection. Preliminary results suggest that it does yield a higher number of new cases, particularly Post Kala-Azar Dermal Leishmaniasis (PKDL) cases.

In order for ACD to be programmatically feasible, it must be applied in strategically selected areas in which the number of cases detected and reported will justify the necessary resources. This is largely dependent on being able to accurately predict the location of new cases. It is well understood that a significant proportion of new cases will come from endemic or ever-endemic villages. However, this represents a huge number of villages. So how do programs decide which villages to target for ACD? Researchers are attempting to understand how best to strike a balance between feasibility and the number of cases detected and reported. Finally, researchers will evaluate the overall utility of ACD in reducing transmission and death.

Vector Control

Case detection and Indoor Residual Spraying (IRS) are one arm of the control efforts in India. In order for IRS to be fully effective, it is necessary to understand how best to implement it in a programmatic setting. Reactive IRS has been used successfully for malaria control and is now being adapted for leishmaniasis control. IRS alone does not target the complete transmission cycle. Other vector control strategies are also being evaluated. Studies investigating efficacy of Insecticide-Treated Nets (ITNs) have produced mixed results. Sugar-baited traps and insecticide-treated paints have also demonstrated efficacy against malaria vectors. These interventions could be successfully adapted to target the sandfly vector. It is necessary to investigate the association between all interventions and clinical outcomes.

Post Kala-Azar Dermal Leishmaniasis (PKDL)

PKDL is suspected to be a significant barrier to elimination efforts. While the total number VL cases is decreasing, the number of PKDL cases is increasing. PKDL cases are usually healthy and do not require medical attention. Though the mechanisms behind development of PKDL are poorly understood, it is thought to be a consequence of VL treatment in combination with host factors. Recent studies have demonstrated that PKDL cases can serve as a reservoir of infection. It is therefore necessary to understand both the mechanisms of disease as well as optimal treatment regimens.

A study was conducted in Bangladesh to assess PKDL and VL relapse among cured VL patients treated with single or multi-drug therapy. This study revealed that the probability of developing PKDL and VL relapse peaked at 3 years and 1 year respectively post initial VL infection. Treatment with multi-dose AmBisome or AmBisome plus paromomycin combination was associated with the lowest incidence of both PKDL and VL. Clinical trials are currently ongoing to compare treatment strategies for both PKDL and HIV-VL coinfection.

KNOWLEDGE GAPS IDENTIFIED and RECOMMENDED NEXT STEPS

Transmission dynamics

- Investigate factors that cause resurgence of infection in villages that had previously been below the threshold.
- Investigate foci were transmission has been absent (without resurgence) for many years

- Investigate the role of asymptomatic cases in transmission
- What is the most effective way to draw boundaries around index cases?
- What is the most accurate method in predicting location of future cases?
- What role does socio-economic development play in transmission?

ACD

- Does ACD lead to a reduction in transmission?
- What ACD methods are most sustainable?
- What other methods can be used to reduce the time to diagnosis (and hence time to treatment)?

Vector Biology and Xenomonitoring

- Calculate infection rate
- Calculate entomological inoculation rate
- What is the proportion of infected sandflies that creates risk of human disease?
- Evaluate the cost-effectiveness of xenomonitoring as a surveillance mechanism
- Develop guidelines for VL transmission endpoint assessment
- Adapt the *L. mexicana* metacyclic-specific PCR assay to *L. donovani* to measure the proportion of sandflies that are infectious
- Evaluate vector control activities for association with desired clinical outcomes
- What incidence level should trigger a vector control response?
- Can vector control strategies be expanded to target the entire transmission cycle?

PKDL

- Incidence
- What role does PKDL play in transmission?
    - Can PKDL cases serve as a reservoir of infection?
- What are the mechanisms and important determinants of PKDL development?
    - What is the relationship between primary VL treatment and development of PKDL?
    - What host factors are associated with development of PKDL?
- What VL treatment regimen is most effective in preventing PKDL?
- What is the best treatment regime for PKDL?
- Is there a way to distinguish PKDL from other skin conditions (an improved diagnostic over skin slit)?
- Are there socio-demographic factors related to PKDL?
- Are there regional differences in the association between treatment and development of PKDL?
- What are the ethical considerations of treating a disease that does not cause severe clinical manifestations with potentially toxic drugs that can cause harmful side effects?