THE TASK FORCE FOR GLOBAL HEALTH

NEGLECTED TROPICAL DISEASES SUPPORT CENTER

# Strategies to identify persistent hotspots of infection

Strategic Technical Meeting
29-30 April 2019

Meeting Report

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**Content:** This document highlights summary notes and action items from the "Strategies to identify persistent hotspots of infection" strategic technical meeting held at the Task Force for Global Health (330 West Ponce de Leon Avenue, Decatur, GA 30030) on April 29-30, 2019. This report was made

available on August 16th, 2019. The Neglected Tropical Diseases Support Center is a program of the Task Force for Global Health. Please contact the Neglected Tropical Diseases Support Center (ntd-sc@taskforce.org) with any comments or questions.

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# Summary of Key Messages from Meeting

- There are many different factors to consider when it comes to the definition, measurement and interpretation of hotspots.
- At the broadest level, a hotspot is an area that requires programmatic action.
- While hotspots, of varying forms, can pose challenges at all stages of NTD programs, an area of pressing concern is how to address hotspots in the context of post-MDA surveillance.
- NTD programs are already collecting rich datasets, using rigorous sampling techniques; however, the programs are not taking full advantage of the information contained in these datasets.
- By aggregating data across clusters to assess a single threshold (e.g., the LF Transmission Assessment Surveys or Trachoma Impact Surveys) cluster-level and spatial information is lost.
- Minor modifications to existing WHO M&E frameworks may lead to significant predictive gains; potential modifications include:
    - The interpretation of cluster-level data to predict whether a site is a hotspot
    - The incorporation of spatially regulated sampling to improve the efficiency of the survey design
    - The utilization of adaptive sampling; using prior survey data to inform where future sampling should take place to reduce areas of uncertainty
    - Cumulative analysis of data collected at different time points to demonstrate the absence of transmission (e.g., a potential means to verify elimination)
- A re-analysis of existing operational research & programmatic datasets may help to answer questions around the predictive gains and feasibility of the aforementioned modifications

# Setting the stage

## Meeting overview

As disease elimination programs succeed, the remaining reservoirs of infection become increasingly focal and difficult to identify. Disparities in transmission intensity, intervention coverage and effectiveness, population shifts, and the environment may result in areas, or foci, with an elevated incidence and/or prevalence compared to their surroundings. New sampling strategies are needed to find these sites of persistent infection (aka 'hotspots') to enable the delivery of targeted treatment or monitoring. While the concept of identifying and addressing disease 'hotspots' has been embraced by other public health programs for quite some time (e.g., malaria), it is a relatively new and important concept for NTD programs looking to reach the final mile of disease elimination. Within the NTD community, the specific use cases and diagnostic tools used to identify hotspots may differ by disease; however, the challenge of identifying and defining the boundaries of persistent infection is a cross-cutting and pressing concern for many infectious diseases including lymphatic filariasis, onchocerciasis, trachoma, leprosy, chagas, visceral leishmaniasis, buruli ulcer, human african trypanosomiasis, yaws, and malaria.

The purpose of this 2-day meeting was to bring together statistical, epidemiological and disease-specific experts to explore and debate the different tools and approaches that might be used to identify focal areas of persistent infection in the context of disease elimination or surveillance. The ultimate goal of the meeting is to emerge with a more clearly defined set of program challenges related to the identification and delimitation of 'hotspots' and the accompanying sampling strategies that can be piloted through OR to address these challenges.

## Specific meeting objectives:

1. Determine a working definition of a hotspot
2. Identify survey methodologies best suited to detecting hotspots
3. Create operational research proposals to evaluate hotspot detection methodologies
4. Encourage dialogue and collaboration around hotspots across disease and methodological domains.

**See Appendix for the pre-read materials, meeting agenda, and a complete list of meeting participants.**

# Presentations of on-going research & programmatic challenges related to hotspots

Meeting participants volunteered to give five-minute presentations of their research or program work, as it relates to hotspots during the first day of the meeting. Each presentation was followed by a brief discussion amongst meeting participants. Below are summaries of these presentations/discussions that were provided by each respective research group. Key themes which recurred through presentations included:

- How do we define a hotspot?
- What types of sampling are most efficient and most feasible?
- What spatial resolutions should we build tools for?
- How can we use existing data, and which uses of data should be avoided?

## LF in Sri Lanka post-elimination

**Presentation:** Link
**Referenced literature:** Rao et al. PNTD 2014, Rao et al. PNTD 2016

Gary Weil of Washington University in Saint Louis and the DOLF Project presented a summary of areas of elevated prevalence and ongoing transmission of LF in Sri Lanka, in the context of a country that recently received WHO validation for eliminating LF as a public health problem.

- MDA took place in Sri Lanka from 2002-2006, with additional mop up rounds in 2014 and 2015
- The transmission assessment survey (TAS) easily passed in 2013. Contemporaneous and subsequent studies using enhanced surveillance methods documented very active ongoing transmission in large areas in subregions within evaluation units that passed TAS. Low antigenemia prevalence in children suggests that school age children were not an informative sentinel population for post-MDA surveillance in this setting with Culex transmission; similar results have been reported from American Samoa (Aedes transmission) and other areas.
- Research activities including molecular xenomonitoring and serological surveys showed that transmission was ongoing in some coastal areas in Galle district
- The WHO Validated Sri Lanka as having eliminated LF as a Public Health Problem in 2016
- Clear pockets of ongoing transmission were identified in one district along the coast
- Hypothesized drivers of hotspots
    - Suboptimal MDA
    - High Baseline Prevalence
    - Other factors
        - Systematic noncompliance
        - Migration
        - Difficult vector
- Potential solutions to avoid premature stopping of MDA:
    - Move decision-making on stopping MDA to a smaller unit, and use local knowledge
    - Apply different sampling approaches to find hotspots, such as grid sampling or sampling on a smaller spatial scale
    - Utilize adaptive sampling to ensure that TAS can better detect hotspots
    - School-based TAS should be supplemented (or replaced) by surveillance methods that focus on detecting the persistent reservoir of infection rather than documenting recent transmission. Work in Sri Lanka have demonstrated the value of community (adult) TAS

with Mf testing of positives and antibody TAS in children, but neither of these methods is as sensitive as molecular xenomonitoring.

## Persistent hotspots of Schistosoma mansoni in SCORE studies

**Presentation:** Link

**Referenced literature:** Kittur, et al. Am J Trop Med Hyg 2017, Kulldorff. Comm Stat Ther Meth 1997, SaTScanTM v9.4, 2015, Kulldorff et al. Stat Med, 2006, Wiegand et al. J Infect Dis, 2017

Ryan Wiegand of the Centers for Disease Control and Prevention presented on persistent schistosomiasis hotspots in the Schistosomiasis Consortium for Operational Research and Evaluation (SCORE) study, a five-year randomized study of preventative chemotherapy strategies in Kenya and Tanzania.

- The SCORE study found less heterogeneity in outcomes than anticipated, given the randomized design of the trial, and assessed if "hotspots" could provide some explanation for the less-than-expected reduction in prevalence
- Using both operational definitions and spatial analyses, "hotspot" areas were constructed
- Spatial analyses utilized Kulldorff's Spatial Scan Statistic implemented in SaTScan, which aimed to identify spatial subsets of villages with elevated intensity
- Hotspot data were not consistent across countries, and not explained by covariates
- In Kenya, the hotspots identified by SaTScan were consistent, but not so in Tanzania
- There was discussion as to whether a hypothesis test like SaTScan is the right approach for hotspots
- The cutoffs used to define a hotspot can affect which areas receive subsequent intervention, and therefore hotspot definitions should be set with care

## Assessing LF, malaria elimination in Nigeria and the DR

**Presentation:** Link

**Referenced literature:** Keys et al. Infect Dis Poverty, 2019, Willingham et al. unpublished

Greg Noland of the Carter Center presented on hotspots in both LF and malaria utilizing examples in Nigeria and the Dominican Republic, respectively. In LF, hotspots were taken to be areas with high prevalence, whereas for malaria, the concept a 'hotspot' has also encompassed areas at high risk of disease importation.

- Operational research in Nigeria was done in 2016 to assess the differences between the TAS and PacELF survey strategies particularly focusing on using children as a sentinel population and schools as the sampling unit
- As population movement happens and cities grow, particularly into informal settlements in low-lying areas, cities can become potential hotspots of what has formerly been seen as a rural disease
- In the context of malaria, where cases are more visible and immediate, how many cases constitute a hotspot?
- What is the significance of a positive case if they were exposed in a different place from where they were sampled?

## Methods for addressing malaria hotspots

**Presentation:** Link

**Referenced literature:** Bousema et al PLoS Medicine, 2012; Surendra et al In Prep; Clinton Health Access Initiative 2013; Framework for Malaria Elimination WHO, 2017; Druetz & Stresman et al. In Prep; Van

den Hoogen et al. In Prep; Sturrock et al. PLoS One, 2013; Slater et al. Nature, 2015; von Seidlein et al. PLoS Med, 2019; Stresman et al., JID, 2015; Stresman et al.; In Prep, Stresman et al., Under Review; Poithin et al., In Pre;, Wu et al., Nature, 2016; Stresman et al., Sci Rep, 2017; Malaria Zero, In Prep; Fornace et al., In Prep; Reiner et al., eLife, 2015; Wu et al., In Prep

Gillian Stresman of the London School of Hygiene and Tropical Medicine presented on hotspot challenges in malaria, their statistical implications and potential solutions. The presentation first examined how malaria hotspots are defined and detected, and the how to show evidence of impact (i.e., reducing a hotspot), the importance of defining the unit of transmission or intervention, the metrics used to monitor hotspots, the statistical approaches required, and the role of hotspots in an elimination program.

- In 2017, the WHO malaria community defined a foci as, "A defined circumscribed area situated in a currently or formerly malarious area that contains the epidemiological and ecological factors necessary for malaria transmission. Note: Foci can be classified as active, residual non-active or cleared."
- The malaria community has also been operating under the understanding that hotspots are areas that fuel onward transmission, despite little evidence that targeting hotspots clears transmission or leads to sustained reduction
- Spatial scale is an important aspect in the definition of a hotspot (e.g., household as the base unit for transmission of malaria)
- Community based surveys are helpful but are always going to miss some hotspots
- Is receptivity potential, that is predicting future areas of risk, important to consider in identifying and defining hotspots?
- Another challenge is confirming the absence of hotspots; freedom from infection models can be used to assess the absence of hotspots or transmission, using repeated surveys (longitudinal monitoring) and integrated surveillance
- In an elimination setting, surveillance also needs to be able to detect the difference between imported cases and local transmission

## Geostatistical methods for survey design

**Presentation:** Link

**Referenced literature:** Diggle white paper, 2019

Peter Diggle of Lancaster University presented on geostatistical methods for mapping prevalence including spatially regulated sampling and approaching geospatial modeling as a prediction problem.

- Rationale for geostatistical sampling is to borrow strength from neighboring surveyed areas
- Utilizing previous prevalence data and newly collected survey data, it is possible to create a surface of predicted prevalence across an area
- By using spatially regulated sampling strategies, it is possible to greatly increase the efficiency of sampling, as measured by positive predictive value (PPV) and negative predictive value (NPV)
- Utilizing spatially regulated sampling strategies may allow less data to be collected, lessening costs, however many methodologies of spatial regulation require advanced knowledge of all village locations and their populations, which may be infeasible in many NTD settings without additional in-country training and/or close international collaboration.
- Running in-country training courses is important both for building hands-on skills and promoting the benefits of using the most efficient statistical methods, but for the foreseeable future it will not be realistic to expect short-course trainees to be immediately capable of operating completely independently.

## Trachoma hotspots: detection and interpretation

**Presentation:** Link

**Referenced literature:** none referenced

Travis Porco of the University of California, San Francisco - Proctor Foundation presented examples of different types of disease hotspots across a variety of public health settings, along with some statistical tools that can be used to detect them.

- "Hotspots" have been around since the start of epidemiology (John Snow and the water pump)
- Generally, these are identified as a spatial anomaly with more cases than expected by chance in a region, and temporally sustained manifestations provide further support
- With infectious diseases, clustering is expected even if transmission is uniform, which can leave us "chasing ghosts" in areas where prevalence is high but transmission is waning
- Clustering can be assessed by looking at the counts of cases in an area and utilizing goodness of fit testing, Q statistics and assessing mixtures of distributions
- Narrowing a focus from all "hotspots" to those which indicate increased prevalence, increased transmission or perhaps "supercriticality" and the ability to fuel ongoing transmission

## A geospatial hotspot sampling tool

**Presentation:** Link

**Referenced literature:** NTD hotspot village prediction app

Hugh Sturrock of the University of California, San Francisco presented on the concept of spatially adaptive sampling for hotspot detection and shared a tool that he and colleagues have developed, which is designed to fit a geospatial model to predict hotspot locations that then provides two outputs: 1) the location of likely hotspot villages and 2) optimal locations to next visit to collect more data in order to update your hotspot prediction map.

- The tool fits a geospatial model to predict prevalence certainty, then balances adaptively sampling in areas with high uncertainty while ensuring good spatial coverage
- Batch adaptivity is built into the model, allowing people to identify the next X places to sample adaptively; however barriers to applying this approach in low resource settings were noted
- As this tool continues to be developed, questions of remain about the programmatic utility of different spatial resolutions and the incorporation of temporality
- Constrained adaptive approaches, such as building in practicality or cost efficacy to create maps of optimal routes was discussed

## Morbidity hotspots for LF surveillance

**Presentation:** Link

**Referenced literature:** Stanton et al. JMIR Public Health Surveill, 2016

Louise Kelly-Hope of the Liverpool School of Tropical Medicine presented on using LF clinical case and TAS positive data to identify, map and monitor transmission hotspots as part of an enhanced endgame surveillance strategy.

- LF clinical case data are being collected as part of morbidity management and disability prevention efforts, and are one of the few persistent markers that will be collected after TAS 3 has been conducted
- Looking at morbidity and seroprevalence together may provide richer information that what is provided by seroprevalence data alone
- In Nepal and Bangladesh, hotspots for positive students in TAS appear to be similar to morbidity hotspots

- Although LF morbidity hotspots would be influenced by migration, morbidity could serve as a pseudo-baseline for LF, and would be advantageous in areas where no baseline data exist

# Hotspot Definitions

Throughout the previous presentations, as well as in the NTD literature, different working definitions of hotspots have been utilized and proposed. In some contexts, hotspots are defined in relative terms (e.g., areas with elevated prevalence relative to their surroundings), while other definitions are absolute (e.g., prevalence greater than X%). Hotspot definitions may be intervention dependent (e.g., failure to respond as expected to a public health intervention) or independent of the intervention. In some settings hotspots may be a result of poor program performance, and identifying these areas may be a useful tool for better targeting program resources. Additional discussions ensued around whether hotspot detection should be seen as a hypothesis testing or prediction problem.

## Hotspot Characteristics

When coming together to discuss important characteristics of hotspots, several themes emerged. First, the group sought to interrogate whether the objective is finding prevalence hotspots, transmission hotspots or vulnerability hotspots, as well as relationships between these three concepts. Though vulnerability hotspots (areas that are conducive to supporting transmission but where transmission is not presently ongoing) are of interest in malaria, they are less of interest in NTDs given that re-introduction of NTDs has not been widespread or well-documented. Nonetheless, in a post-elimination context when areas that have eliminated a disease share borders with those that have not, vulnerability hotspots may be of more interest to the NTD community. Similarly, morbidity hotspots are informative for MMDP efforts and provide a proxy for potential transmission, but given the lag between transmission and the development of disease in NTDs, prevalence can be misleading. The group also discussed the implications of defining a hotspot at different stages of a program: is the aim to conduct preemptive treatment, enhanced treatment, mop-up, or watchful monitoring? At its core, the group agreed that hotspot detection is essentially a stratification problem; identifying hotspots helps programs know where to allocate resources based on some measure of risk.

In the context of this meeting, it was agreed that the focus is on transmission hotspots that occur during the post-intervention, surveillance stage.

## Proposed Definitions

Following this discussion, suggestions for an over-arching “hotspot” definition were solicited and several were shared and discussed including:

- A connected spatial region in which, given all available information, there is a high probability (“high” being chosen to balance positive and negative predictive values in-context) that a policy-relevant property of the region in question exceeds an agreed threshold that, if met, would indicate the need for a local public health intervention.
- A population with current, or the potential for, sustained transmission that would benefit from continuation of, or a change in, its current intervention package.
- An area of ongoing transmission that requires modification or (re)introduction of an intervention.
- A place where the presence of cases is more than we would wish.

Ultimately, the group settled on the following working definition: A hotspot is an area that requires programmatic action.

The group also discussed the programmatic goals of hotspot detection, including:

- To focus intervention on high-risk groups
- To protect against recrudescence and identify candidate areas for enhanced surveillance
- To identify areas not meeting agreed control targets
- To identify areas for prioritization of resource allocation
- To establish absence of transmission, particularly in the context of verification
- To reduce disease burden/prevalence/transmission in problematic areas independent of targets
- To discover why some spots are hot
- To understand risk to wider population
- To monitor progress in areas of concern

## Considerations for Operational Research Proposals

Based upon the working definition that a hotspot is an area that requires programmatic action in the context of surveillance, the group worked to identify the priority programmatic hotspot challenges on which to focus the breakout discussions and OR protocol development. It was agreed that designing strategies to improve existing tools to contribute towards hotspot detection was more reasonable than developing a new tool and most likely to lead to improvements in WHO guidance in the near future. Additionally, the group agreed that finding hotspots during post-MDA surveillance posed a different question than detecting hotspots (or demonstrating their absence) after validation of elimination. At this point the group divided into 3 breakout groups around the following program challenges:

1. How to identify hotspots during post-MDA surveillance, prior to validation of elimination? (2)
2. How to conduct post-validation surveillance and demonstrate verification of elimination? (1)

Disease domains, spatial resolutions, and design strategies were not specified when the participants broke into their breakout groups. Despite this lack of specification, all three groups independently chose to focus on assessing hotspots for Lymphatic Filariasis (LF), with the two post-MDA surveillance groups focusing on ways to improve the TAS design. A brief background on the TAS is provided below to give context to the research proposals arrived at by the three groups.

## TAS Survey Background

The TAS is a 30-site cluster survey, typically performed in schools, which is performed to determine whether transmission in an Evaluation Unit (EU) is below a set threshold such that MDA can be stopped with minimal risk of recrudescence. The TAS involves testing 6 and 7 year-old children for circulating filarial antigen (or antifilarial antibodies in *Brugia* areas) and is predicated on the assumption that in an area where MDA took place for 5-7 years, any infection in children of this age group indicates that transmission is ongoing. The number of positive cases observed at the EU level is compared against a decision rule (based on the upper 1-sided 95% confidence limit for the EU-wide prevalence estimate of <2% in areas where *Anopheles* or *Culex* is the primary vector, and <1% where *Aedes* is the primary vector).

EUs in which the number of positive cases observed is equal to or below the threshold are said to have "passed" the TAS and the EU can stop MDA and enter into a period of surveillance. Provided the initial TAS (aka 'TAS 1') is passed, the country conducts two subsequent TAS assessments, each three years apart, as a surveillance tool to confirm that transmission remains below the specified threshold. Currently, the selection of sampling sites for these TAS 1, TAS 2 and TAS 3 surveys is conducted independently, using geographically ordered systematic random sampling.

# Breakout Group 1: Post-MDA hotspot detection

**Objective:** Build on the existing M&E framework to identify hotspots requiring programmatic action

**Background and Assumptions**

Elimination programs such as LF, Trachoma, Oncho, Schisto and Malaria have existing M&E tools (TAS, TIS, Stop MDA survey, future elimination surveys, and EAD, respectively) which have WHO backing and provide potentially useful information for identifying hotspots. These M&E tools can be adapted and their data reanalyzed to estimate community level prevalences and the probability that each location in an EU exceeds a hotspot threshold, all the while maintaining the ability to accurately measure exceedance from the policy-relevant threshold. This work will focus on the TAS, but some of these proposals could be adapted to other disease domains.

**Proposed Survey Changes and potential for OR**

*TAS 1 (Stop MDA Survey)*

- Consider using a population-weighted model to predict the EU prevalence (as opposed to the unweighted survey mean)
- Estimate the distribution of village-level prevalence in the sampled clusters
- Predict the probability that a site is a hotspot: Hotspot=[p(community>x%)>q]
- *OR - Validate predictive model: Sample N communities to validate model*
- Intervene in hotspot communities/sub-districts (dependent on program resources)
    - Focal MDA
    - Social science: what caused hotspots and how can they be addressed?
- Monitor all or a sub-set of hotspots (dependent on program resources)
- *OR: intervene on some hotspot communities and monitor others in the absence of intervention*

*TAS 2*

- Select the 30 clusters using adaptive sampling, based on the results from TAS 1
- *OR: In previously-identified hotspots from TAS 1: conduct an impact assessment of the intervention (antibody and antigen) across age groups*
- Update geospatial-predicted probability of hotspots: Hotspot=[p(community>x%)>q]
- *OR: compare hotspot communities that have and have not received intervention*

*TAS 3*

- Select the 30 clusters using adaptive sampling, based on the TAS 1 and TAS 2 data
- Calculate the likelihood that the EU will ultimately achieve elimination of transmission, using existing LF models

*Additional OR questions not addressed above:*

- Does hotspot treatment prevent progression of entire EU (i.e., does the EU need to start again at TAS 1 if focal MDA occurs)? – this is a question for WHO/RPRGs
- Could this TAS framework be modified to support integration of multiple diseases?
- How do we make use of an antibody signal in this context?

**OR Questions that can be answered using Re-Analysis of Existing Data**

- Sri Lanka data to see if the hotspots could have been caught via adaptive design.
    - Seems likely to be able to share data of 60 antigen sites and mosquito sites
    - Additional mosquito surveys

- What is the post-treatment relationship between antibody and antigen across the age curve? Is this consistent? (TAS strengthening and IDA baseline, NTDMC)
    - This will inform hotspot predictive models
- What level of antigen/antibody prevalence is indicative of self-sustaining transmission? How does this differ by species? (TAS strengthening and IDA baseline, NTDMC)
    - This will inform hotspot thresholds
- What are the characteristics of EUs that pass TAS 1 and then fail TAS 2 or TAS 3 (countries, WHO, implementing partners)?
    - Can this be used with elimination models to triage areas in need of adaptive sampling/hotspot intervention?
    - Can locations that subsequently fail be identified by the distribution?
- Does model-predicted EU prevalence outperform TAS-based prevalence?

**Proposed Pilot Locations for Prospective Operational Research**

It is important that such studies be performed in areas with some persistence of LF.

Haiti: EUs preparing for TAS 1

- Samoa/American Samoa: Post-IDA
- India
- DR Congo
- Ghana (TAS 2)
- Southern Nigeria

**Discussion**

The group noted that the full proposal described would take 6 years to complete to fully answer the questions proposed (due to the proscribed time delays between each TAS), and that TAS 1 triggers a lot of potential work, particularly if the fully described OR were performed. The presenters emphasized the utility of this in the context of determining which kinds of hotspots need to be mopped up and which will die out on their own. Creating smaller IUs where specialized interventions could be deployed could assist in this process so that the entire IU would not necessarily need to re-start intervention.

Defining a hotspot under this approach could be a two-tiered system: first to identify hotspots where the level of transmission is higher than a threshold/WHO guidance for a particular sub-unit, and second, to determine which hotspots require some form of intervention. The group asked whether molecular xenomonitoring could be utilized to differentiate between these two types of hotspots.

The group also discussed the utility of this protocol for other diseases and what modifications would be necessary. Onchocerciasis and trachoma were discussed as other diseases that could benefit from adaptive sampling (e.g., around the TIS or Stop MDA surveys). STH was also discussed as another disease that could potentially benefit from this approach; however, the group raised concerns about the limitations of the diagnostics, as well as the persistence of an adult reservoir when most monitoring is restricted to children. Nonetheless, it was suggested that the group could look into the degree to which an adult reservoir or community prevalence can be predicted from school data.

# Breakout Group 2: Pre-elimination hotspot detection

**Objective:** To improve TAS surveys to delineate hotspots through mapping and adaptive follow-up as countries approach elimination

**Background and Assumptions**

As with the previous group, this group chose to address changes to the TAS that could improve the quality of information that the survey generates, the way in which that information is interpreted, and the ability to detect hotspots. Due to programs' familiarity with the TAS and the greater feasibility of adapting existing guidelines vs. developing new ones, Group 2 decided that the best path forward is to modify the current TAS.

**Proposed Survey Changes and OR**

Pre-TAS

- Delineate evaluation units (EU) based on prevalence information from baseline, monitoring and pre-TAS sites to target areas of risk

Overall TAS Structure (modified TAS with OR opportunities embedded)

- Survey Design
    - Cross-sectional, spatially regulated survey across schools in EU to improve prediction of the prevalence surface
    - School-based sampling, X children per age-banded classroom
        - Expand age ranges tested to all elementary school aged children
        - Rationale: wider age range to expand chances of detecting infections [5-15 y]
        - Decision rule for pass / no pass based on existing LQAS decision rule (possibly modified for expanded age ranges)
    - Test for monitoring outcome: Rapid Ag test for LF
- TAS Follow-up
    - Revisit EU boundaries after each TAS
        - Create smaller EUs in higher prevalence areas
        - Refine EUs using information about predicted prevalence
        - Create new EUs around identified hotspots
    - Continue to measure schools with positive children in later TAS surveys
        - Adaptive sampling based on index cases identified in TAS survey
    - TAS Adaptive index case sampling on all children who test positive in TAS
        - Measure antigen in 50 households in a geographically close sample around the index case
        - Sample 20 additional households from the enumeration areas that encompass the index cases
        - Additional samples in adjacent evaluation units if positives are detected

*TAS 1*

- Conduct TAS survey design, as described above
- OR: Collect DBS for antibody testing (OR research only)
    - Rationale: should provide more information about recent exposure than antigen test or TF for predictive mapping.
- Outputs:

    - Prevalence Map: Create a predicted prevalence surface from antigen and antibody measurements in TAS-1 (OR)
    - Identification of hotspots
    - Focal MDA in hotspot areas

*TAS 2, 3*

- Use the information collected from the last TAS and any new EU boundaries:
    - Generate new probability sample of schools, based on standard TAS methodology
    - Include purposeful sample of those schools that had a positive child in a previous TAS
- Outputs
    - Prevalence Map: Update the predicted prevalence surface from antigen and antibody measurements in TAS-1 (and 2 if conducting TAS 3)
    - Refined delineation of detected hotspots

**Proposed Pilot Locations for Prospective Research**

- Countries with upcoming TAS studies

**Discussion**

The group noted that the positive case follow-up methods proposed in this session bear similarities to reactive case detection, a common strategy in the malaria community. However, reactive case detection in malaria has had mixed effects and there is no evidence that it reduces transmission, perhaps because it is not carried out in a standardized way to reduce transmission or because the intervention is not sustained for a sufficient duration. In either case, participants warned that these strategies could lead to over-adaption, where knowledge of existing hotspots is very high but new hotspots are not detected. The group also emphasized that a balance had to be found between the strengths of some adaptive methods and feasibility for the programs. The potential to sample across EUs, with those EUs where uncertainty is the greatest receiving a greater proportion of the sample, was discussed, though it was noted that adjacent EUs do not always conduct TAS simultaneously.

Additional concerns were raised with the indicator age group being tested; some participants posited that teenagers are not the most likely reservoir population that could fuel an ongoing hotspot. It was suggested that social science research may help to better understand which populations are not being reached by MDA and may be fueling hotspots.

**Finally, the group noted that many of these OR questions can be answered with reanalysis of existing data and that this should be a priority next step.**

# Breakout Group 3: Verification of elimination of transmission

**Objective:** Strengthen TAS surveys to increase the quality of information available from the post-treatment phase, then utilize that information and subsequent survey(s) to quantify the likelihood that elimination of transmission has occurred.

**Background and Assumptions**

Verification of elimination of transmission requires confidence that transmission has been reduced to zero. Measuring zero in a survey context is intractable, but it is possible to assess the probability that, if transmission were present, we would detect it. This forms the basis of Freedom From Infection (FFI) models, a framework from the veterinary world which is utilized to assess potential of disease in livestock based on sampling.

FFI models enable an accumulation of information over time and space, accounting for all sources of surveillance information. These models assess the probability that if there were X cases, you would detect them, essentially providing a negative predictive value of your surveillance activities. By adding information to the model over time, the prior is continuously updated providing a cumulative measure. The framework accommodates several design options including risk targeting to increase the probability of detecting infection if it is present. Therefore, to achieve freedom certification, (known as "verification" of elimination in NTD parlance), the final assessment can be one large survey at one timepoint or a series of smaller surveys.

A large portion of the strength of FFI models is derived from their ability to incorporate information from a variety of sources over time. Therefore, the group opted to look at how to re-vamp the TAS to provide the maximum amount of knowledge possible to inform FFI models post-validation in order to achieve verification. Particular focus was placed on utilizing spatial information, to inform an adaptive TAS.

**Proposed Survey Changes and OR**

*Before TAS 1:*

- Utilize all existing information (e.g., baseline data, sentinel data, morbidity data, environmental data) to create a geospatial risk surface which shows the predictive probability that prevalence exceeds a threshold
- OR Needed: Feasibility of risk surface creation
    - Bangladesh, Tonga, and Malawi have a wealth of historical data
    - These areas could represent a best-case scenario in terms of data availability and could be the first test of creating a risk map

*TAS 1->2->3:*

- Using the risk surface, (updated to include information from previous TAS, if TAS 2 or 3) adaptively sample in a spatially regulated manner to over-sample the high-risk areas, ensuring that any hotspots are identified and can be addressed as needed
- Potential OR:
    - Test Adaptive TAS:
        - Haiti and Tanzania have upcoming TAS 3
        - Compare traditional TAS 3 with informed/adaptive TAS 3

        - While some of this could be done through simulations, actually carrying out these two types of survey in the same EU simultaneously would be a powerful example to show the superiority of one survey
    - Risk surface success at hotspot identification:
        - Data from Sri Lanka on known hotspots already exists
        - Using the baselines and assessments, could a risk surface approach be utilized to find these hotspots?

*Verification Assessment:*

- Use FFI models and potentially additional survey(s) to assess if transmission has been eliminated
- OR Needed:
    - Tonga or the Maldives have a wealth of historical data, are sufficiently past validation and are interested in verification
    - The FFI models could be applied there to see if they will provide enough information in the LF elimination context
    - Using information that we have to assess where we believe there should be no transmission, we can also ascertain what additional survey(s) would be needed to boost our confidence that elimination of transmission has been achieved

**OR Questions that can be answered using Re-Analysis of Existing Data**

- Feasibility of risk surface creation: Bangladesh, Tonga, Malawi
- Risk surface success at hotspot identification: Sri Lanka, Egypt
- Optimal TAS population and serological marker for an adaptive design: Haiti and Tanzania

**Proposed Pilot Locations for Prospective Research**

- Test Adaptive TAS: Haiti, Tanzania
- Test Freedom From Infection Models: Tonga, the Maldives

**Discussion**

Given that this group presented models for adaptive sampling which bore some similarities to prior groups, the discussion focused on the Freedom From Infection models and how these models could inform verification of elimination of transmission. It was emphasized that while FFI models can be a powerful follow-on, they must be well-informed to achieve confidence that cases could be detected if they were present in the population.

An aspect of these models that is particularly attractive in the NTD case is that multiple diagnostic tools can be used as part of FFI (as were utilized in the Rinderpest elimination program[1]) though they do need to be calibrated. However, in order to achieve confidence in FFI models to the level of achieving elimination, specificity of the diagnostic is essential. Therefore, it would be necessary to determine if the level of confidence needed is even reachable with current diagnostic specificity and if not, confirmatory tests could be utilized to ensure specificity.

[1] Roeder P, Mariner J, Koch R. Rinderpest: the veterinary perspective on eradication. Philos Trans R Soc Lond B Biol Sci. 2013 Aug 5; 368(1623): 20120139. doi: 10.1098/rstb.2012.0139

# Next steps

## Meeting objectives revisited

1. Determine a definition of a hotspot ➔ A single definition of a hotspot was not determined but in generally agreed that hotspots are a geographical region in which transmission or cases are high and where intervention or monitoring is warranted.
2. Identify survey methodologies best suited to detecting hotspots ➔ While noting that hotspots come in a variety of spatial resolutions, the group agreed that no survey methodology will be successful in finding all hotspots. However, not all hotspots need to be found to achieve public health impact. In the context of NTDs, adjustments to existing stop MDA and monitoring surveys (such as the TAS) can be made to increase the chances of hotspot detection, particularly adaptive sampling based on predictive prevalence surfaces.
3. Create operational research proposals to test hotspot detection methodologies➔ OR proposal outlines from the three breakout groups can be found on pages 11-16
4. Increase dialogue about hotspots across disease and methodological domains. ➔ Meeting participants expressed their appreciation of the cross-disease and cross-discipline dialogue

## Specific next steps

1. To elaborate the protocols outlined by the breakout groups so that they have the potential to become funded OR studies
    a. Meeting participants are invited to volunteer to take the lead on drafting one or more of the OR protocols
2. To work with NTD programs to identify opportunities to integrate the OR protocols into planned program activities (e.g. TAS or TIS surveys)
3. To identify OR questions that can be answered through re-analysis of existing data and to share these data with the statistical and epidemiological expert groups
4. To pilot a verification survey using FFI design

# Appendix

## Meeting pre-read material

Below is a summary of pre-read materials shared by meeting participants in advance of the meeting:


1. Bousema T, Stresman GH, Baidjoe AY, Bradley J, Knight P, Stone W, et al. The Impact of Hotspot-Targeted Interventions on Malaria Transmission in Rachuonyo South District in the Western Kenyan Highlands: A Cluster-Randomized Controlled Trial. PLoS Med. 2016 Apr 12; 13(4):e1001993. doi: 10.1371/journal.pmed.1001993.
2. Cecere MC, Vazquez-Prokopec GM, Gürtler RE, Kitron U. Spatio-temporal analysis of reinfestation by Triatoma infestans (Hemiptera: Reduviidae) following insecticide spraying in a rural community in northwestern Argentina. Am J Trop Med Hyg. 2004 Dec;71(6):803-10.
3. Diggle PJ. Hot-spot detection: a statistical hunt for buried treasure. White Paper
4. Fernández MDP, Gaspe MS, Sartor P, Gürtler RE. Human Trypanosoma cruzi infection risk is driven by eco-social interactions in rural communities of the Argentine Chaco. Under Review.
5. Kittur N, Binder S, Campbell CH, King CH, Kinung'hi S, Olsen A et al. Defining Persistent Hotspots: Areas That Fail to Decrease Meaningfully in Prevalence after Multiple Years of Mass Drug Administration with Praziquantel for Control of Schistosomiasis. Am J Trop Med Hyg. 2017 Dec;97(6):1810-1817. doi: 10.4269/ajtmh.17-0368.
6. Lessler J, Azman AS, McKay HS, Moore SM. What is a Hotspot Anyway? Am J Trop Med Hyg. 2017 Jun;96(6):1270-1273. doi: 10.4269/ajtmh.16-0427.
7. Rao RU, Samarasekera SD, Nagodavithana KC, Goss CW, Punchihewa MW, Dassanayaka TDM et al. Comprehensive Assessment of a Hotspot with Persistent Bancroftian Filariasis in Coastal Sri Lanka. Am J Trop Med Hyg. 2018 Sep;99(3):735-742. doi: 10.4269/ajtmh.18-0169.
8. Srividya A, Subramanian S, Sadanandane C, Vasuki V, Jambulingam P. Determinants of transmission hotspots and filarial infection in households after eight rounds of mass drug administration in India. Trop Med Int Health. 2018 Nov;23(11):1251-1258. doi: 10.1111/tmi.13143.
9. Stresman GH, Bousema T, Cook J. Malaria spatial heterogeneity: evidence for rational targeting of interventions. Under Review
10. Stresman GH, Mwesigwa J, Achan J, Giorgi E, Worwui A, Jawara M et al. Do hotspots fuel malaria transmission: a village-scale spatio-temporal analysis of a 2-year cohort study in The Gambia. BMC Med. 2018 Sep 14;16(1):160. doi: 10.1186/s12916-018-1141-4.
11. Stresman GH, Giorgi E, Baidjoe A, Knight P, Odongo W, Owaga C et al. Impact of metric and sample size on determining malaria hotspot boundaries. Sci Rep. 2017 Apr 12;7:45849. doi: 10.1038/srep45849.
12. Subramanian S, Jambulingam P, Chu BK, Sadanandane C, Vasuki V, Srividya A. Application of a household-based molecular xenomonitoring strategy to evaluate the lymphatic filariasis elimination program in Tamil Nadu, India. PLoS Negl Trop Dis. 2017 Apr 13;11(4):e0005519. doi: 10.1371/journal.pntd.0005519.
13. Swaminathan S, Perumal V, Adinarayanan S, Kaliannagounder K, Rengachari R, Purushothaman J. Epidemiological assessment of eight rounds of mass drug administration for lymphatic filariasis in India: implications for monitoring and evaluation. PLoS Negl Trop Dis. 2012;6(11):e1926. doi: 10.1371/journal.pntd.0001926.
14. Wiegand RE, Mwinzi PNM, Montgomery SP, Chan YL, Andiego K, Omedo M et al. A Persistent Hotspot of Schistosoma mansoni Infection in a Five-Year Randomized Trial of Praziquantel Preventative Chemotherapy Strategies. J Infect Dis. 2017 Dec 12;216(11):1425-1433. doi: 10.1093/infdis/jix496.

## Agenda

**Monday, 29 April 2019**

09:00 – 09:30 am **Welcome & Introductions, Meeting Objectives: Katie Gass**

09:30 – 11:00 am **Get the Synapses Firing (5 min PPT and 5 Discussion)**

Sharing examples of challenges that programs are facing with hotspots – OR – sharing of applicable research around statistical solutions to hotspots

- **Gary Weil –** LF in Sri Lanka post-elimination
- **Ryan Weigand –** Persistent hotspots of schistosomiasis
- **Greg Noland –** Assessing LF, malaria elimination in Nigeria and the DR
- **Gillian Stresman & Chris Drakeley –** Methods for addressing malaria hotspots
- **Peter Diggle –** Geostatistical methods for survey design
- **Travis Porco -** Trachoma hotspots: detection and interpretation
- ***Subramanian Swaminathan** – Longitudinal follow-up of LF hotspots in India
- **Hugh Sturrock –** A geospatial hotspot sampling tool
- **Louise Kelly-Hope –** Morbidity hotspots for LF surveillance

11:00 – 11:20 pm **Coffee Break**

11:20 – 13:00 pm **What do we mean by 'Hotspot'?**

- Agree on an operational definition for the remainder of the meeting
- Establish survey goals
- What programmatic needs or use cases does a hotspot survey need to address?

13:00 – 14:00 pm **Lunch served at TFGH**

14:00 - 17:00 pm **Group work–** to identify the OR needs & develop an OR protocol outline

**Tuesday, 30 April 2019**

09:00 – 09:30 am **Touch Base –** everyone meet together to discuss progress and plans for the day

09:30 – 11:00 am **Group Work**

11:00 – 11:20 pm **Coffee Break**

10:00 – 12:30 am **Group Work**

13:00 – 14:00 pm **Lunch served at TFGH**

13:00 – 14:00 pm **Report back and discussion –** each group shares proposed protocol(s)

13:00 – 14:00 pm **Next Steps –** where could this work take place? Who will take on protocol/tool development?

*Unable to attend

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