Alternative Surveillance and Response Strategies for Lymphatic Filariasis Elimination

Session Date & Time:	Tuesday, November 19; 9:00 AM to 12:00 PM
Session Location:	MGM Salon A
Session Description:	Transmission Assessment Surveys have poor sensitivity for detecting residual transmission and hotspots at the end stages of lymphatic filariasis (LF) elimination, when prevalence has reached low levels. Alternative surveillance and response strategies are needed to minimize resurgence risk and protect programmatic gains.
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KEY DISCUSSION POINTS

- The original title of our session included 'Lessons from the Pacific'. Presentations included data from Samoa, American Samoa and Papua New Guinea (PNG) which are at different programmatic stages. The Samoas have previously done many years of mass drug administration (MDA), and both initiated nationwide treatment with ivermectin, diethylcarbamazine, and albendazole (IDA) in 2018. PNG has recently done several MDA rounds in both districts of New Ireland Province, has been the site of IDA trials, and began implementing IDA in 2019 in all four districts of East New Britain Province that last did an MDA (of uncertain coverage) in 2006.
- Data presented were from blood surveys and molecular xenomonitoring in mosquitoes.
- Samoa and American Samoa served as case studies for post-treatment recrudescence of LF. Although American Samoa and most EUs in Samoa had previously passed at least one transmission assessment survey (TAS), all failed TAS subsequently. Multiple studies provide evidence that widespread resurgence has occurred in both Samoa (2018/2019) and American Samoa (2016).
- Alternative surveillance strategies, explored through research projects outside of World Health Organization (WHO) programmatic activities, could potentially have detected resurgence earlier:

  - In **American Samoa**, serum bank screening of adults (collected in 2010) led to identification of two suspected hotspots which were confirmed in a later study (2014). The 2014 study also found that opportunistic testing of adults (at a work place and a clinic) could have provided early signals of these hotspots. A TAS strengthening study (2016) found that a school survey was cheaper but less sensitive at identifying hotspots compared to a community survey; both surveys confirmed recrudescence. Household members of antigen positive kids identified through TAS had significantly higher antigen and antibody prevalence compared to the general population, i.e. positive kids from TAS could potentially provide signals of hotspots.
  - In **Samoa**, a survey in 2018 found that testing household contacts of microfilaria (Mf) positive individuals in TAS or community surveys could lead to identification of hotspots. Purposive surveys of 'suspected hotspots' identified by the ministry of health (MOH) was more sensitive compared to surveys of randomly selected communities, indicating that the MOH was aware of where hotspots were located, and local knowledge could provide useful information about potential hotspots even if TAS was passed.
- In **Papua New Guinea**, the results of a cluster randomized controlled trial in Bogia district, Madang Province, found that IDA was more effective than DA at reducing community-level Mf prevalence. At 12 months post-MDA, there was lower prevalence of Mf in IDA communities compared to DA communities. By 24 months, almost all IDA and DA communities had Mf prevalence below 1%. Results of CFA tests after one year were not informative to guide decision-making about when IDA could be stopped. Xenomonitoring, gender/age specific sampling and filarial test strip (FTS) scoring (semi-quantitative measure) have the potential to be useful tools for monitoring the impact of MDA with IDA.
- **Geospatial analysis** of data from American Samoa (2010) found significant antigen clustering at 1.5 km. No significant clustering of antibody was identified. Geospatial analysis of data from Samoa (2018/2019) found that targeted sampling of households that a machine learning model predicted as high risk has the potential to help identify hotspots in medium prevalence settings. In high prevalence settings, targeted sampling did not perform any better than random sampling because there was high risk throughout.
- **Molecular xenomonitoring** requires significant entomological capacity to catch a sufficient representative sample, and was not possible yet to implement in PNG prior to the recent IDA in East New Britain Province, although was done in other trial areas. Molecular xenomonitoring in Samoa identified more positive villages (before IDA) compared to circulating filarial antigen (CFA) testing and also required about half as much fieldwork as human blood surveys. Identification of mosquitoes at species level apparently offered little advantage over genus level, which would increase the efficiency of this method as a surveillance tool.

KNOWLEDGE AND IMPLEMENTATION GAPS IDENTIFIED AND RECOMMENDED NEXT STEPS

Knowledge/implementation gap	**Priority next steps/research questions**
Alternative surveillance strategies (also see molecular xenomonitoring)	
<u>Changes in antigen and antibody patterns over time and interpretation of these markers</u> - Significant knowledge gaps about the serological patterns of antigen and antibodies over time, including when each serological marker appears, how long they last, changes after treatment, and variability between age groups. - Associated with this are the gaps in knowledge about how to interpret each of these markers of infection. This information is crucial for deciding the most appropriate serological tool(s) to use in different surveillance settings, and the interpretation of the results.	<u>Changes in antigen and antibody patterns over time and interpretation of these markers</u> - Review of existing datasets of antigen and antibodies in different age groups, different numbers of years post-MDA, and hotspots vs non-hotspots, especially in areas with longitudinal datasets. Identify opportunities in ongoing research sites to conduct prospective studies to help answer questions below: - How quickly do CFA and different antibodies appear after infection? - How long does it take for CFA and different antibodies to become undetectable with/without treatment? - Do CFA and different antibodies correlate with other indicators including Mf and MX results? - Do the above vary depending on age? Could existing post-treatment datasets be used to find age-specific correlation between CFA, antibodies, Mf, and polymerase chain reaction (PCR)? - Is CFA in adults a meaningful marker for surveillance purposes? i.e. is FTS positivity in adults a reliable indicator to detect ongoing transmission? If not, what else can be used? - What should the critical thresholds for different tests be? - Prospective longitudinal studies to measure Ag and Ab levels in the same individuals, such as following up of Mf-positive people over time (including pre and post treatment samples) would be particularly useful.

<u>Determining (and responding to) transmission in the post-validation stage</u> - The best surveillance response strategies in the post-validation stage are not known, including evidence on how to conduct targeted sampling of mobile and indigenous populations, and which populations should be targeted for surveillance. This also includes identifying what serological indicator is best for detecting ongoing transmission. <u>Monitoring and evaluation for IDA</u> - More information is needed regarding M&E for IDA including whether it will it be possible to conduct M&E for IDA without using Mf, biological reasons for such low Mf rates after IDA, and how long Mf will stay low after cessation of IDA? <u>Point of care (POC) testing</u> - It was recognized that microscopy requires resources and expertise. An alternative POC test would be valuable in increasing efficiency of surveillance. Is it possible to develop a point of care diagnostic that would serve as a good proxy for microscopy? This would be ideal. <u>Role of baseline prevalence and coverage</u> - More information is needed regarding the role of baseline prevalence and coverage at all stages of the programs, including number of MDA rounds needed, when to do TAS,	<u>Determining (and responding to) transmission in the post-validation stage</u> - Trial and assess different surveillance strategies in post-validation settings - Trial sampling and surveillance strategies in mobile /migratory and indigenous populations - Use existing data to assist in identifying which populations to target for sampling (i.e. particular age groups, genders and areas) - Determining appropriate response strategies when infection is identified (*see Alternative response strategies*) <u>Monitoring and evaluation for IDA</u> - Investigate if it will it be possible to conduct M&E for IDA without using Mf (e.g. decline in antigen intensity; age-specific sampling) - Prospective study to determine if Mf rates will stay low after cessation of IDA <u>Point of care (POC) testing</u> - Develop and test a POC test for Mf as an alternative to microscopy <u>Role of baseline prevalence and coverage</u> Use modeling and existing datasets to investigate: - How do coverage data and baseline prevalence play a role in determining surveillance strategies?

and how these factors affect post-MDA and post-validation surveillance. Evaluation Unit (EU) size - There may be heterogeneity within EUs and uncertainty about what size an EU should be/ or how to undertake sensitive sampling of EUs where there is heterogeneity. Coverage data - It was recognized that there can be limitations in the accuracy of coverage data Personnel - Limitations in the skills of personnel (health care workers and volunteers) was recognized. e.g. This could lead to inappropriate timing of Mf surveys giving poor quality study results Modelling using existing data - There was recognition of extensive existing data which may be useful through modelling to assist in surveillance.	- Would it be beneficial to consider coverage of high risk groups in particular? Evaluation Unit (EU) size - Review data and modelling (e.g. at Erasmus U) on situations where EUs of different sizes have been used, to recommend EU for adequate surveillance, considering heterogeneity Coverage data - Review programme and coverage survey data (especially where different methods have been used simultaneously) and social science surveys to make recommendations on improving coverage surveys and reaching consistent non-compliers. Personnel - Test different ways to improve training and capacity of personnel - Investigate whether additional training improves MDA success and/or data quality from coverage surveys - Review past survey data to see whether Mf data are being captured at the appropriate time of night? - Review programs to assess whether personnel with the right skills and training are being utilized efficiently? Modelling using existing data - Support efforts to collect, collate and use past existing data to inform surveillance strategies

Surveillance of 'hot populations' and hotspots - There are gaps in knowledge about how to conduct surveillance on hard-to-reach, high risk populations. - Areas where data gaps exist may require supplementary surveillance activities.	Surveillance of 'hot populations' and hotspots - Investigate using modeling and/or empirical data whether it would it be beneficial to focus on 'hot populations' in addition to or instead of hotspots (demographic versus geographic)
Detection, definition, and importance of hotspots	
Definition of hotspots and 'hot populations' Hotspots can be defined in terms of geography, demography, thresholds for prevalence in vectors vs people (and depending on what marker of infection in people) - Which monitoring tools are most relevant for the detection of hotspots? - What level of prevalence is important for transmission/resurgence at the local level and at a programmatic 'public health problem' level? - At what geographic scale should hotspots be defined? E.g. household level vs village level. - What is the appropriate geographical scale for response to hotspots? Understanding importance of hotspots in terms of ongoing transmission and resurgence - When is a hotspot is a public health problem or at risk of leading to resurgence which would become a public health problem?	Definition of hotspots and 'hot populations' - Work to develop a geographic element (perhaps varying by context) in the definition of a hotspot - Consider a demographic element to a definition of a hotspot - Consider whether hotspot definition should be based on MX, CFA, Mf, and/or Ab, and if so, at what levels of infection indicators? - Develop definitions of 'hot populations' that are useful for the context – and identify whether these vary across settings. This may be very helpful as a first step in describing and informing appropriate response strategies - Investigate the characteristics of a hot population: low participation in MDA, efficient vector, and/or increased likelihood of exposure? Understanding importance of hotspots in terms of ongoing transmission and resurgence - Model how the presence and attributes of a hotspot relate to its risk for ongoing transmission and risk of resurgence, and test the predictions over time where empirical data are available

<u>Understanding why a hotspot is a hotspot</u>
- In terms of environmental, vector, demographic, compliance, geographic factors. This will help identify and predict hotspots
- How can we predict hotspots in areas that have not been sampled, and assess the role of unidentified hotspots?
	<u>Understanding why a hotspot is a hotspot</u>
	- Conduct multivariate spatial and risk factor analyses to determine the environmental, vector, demographic, compliance and geographic factors (and their combinations associated with hotspots, for regions/countries where these data are available, and examine novel modelling methods for doing so
	- Conduct retrospective follow-up of individuals previously identified as antigen positive (or negative) to assist in identifying risk factors for infection and identifying hotspots (or what is not a hotspot)
	  - Include areas not previously sampled to identify other potential hotspots, especially but not limited to situations where hotspots have already been found.
	  - Determine if there are proxies or predictors that could help identify such previously unidentified hotspots or those in areas not sampled.

Molecular xenomonitoring	
More information is needed regarding the role of xenomonitoring (MX) during TAS and post-validation surveillance (PVS) and how to best conduct MX: <u>Interpretation of MX findings (and informing sample size requirements)</u> - What further evidence is needed for a combined TAS/xenomonitoring? - Does an infectious vector always mean that transmission is ongoing? - What is the efficiency of the vector to become infected with LF parasite? Does this vary by species? This is important to determine the sample size necessary for	<u>Interpretation of MX findings (and informing sample size requirements)</u> - In areas where side by side human/MX surveys have been done, compare and analyze the relationship between mosquito and human infection. (also see 'alternative surveillance strategies) - Conduct more combined studies of TAS/community human studies and MX together.

mosquito collections and may assist in interpreting how positive MX results relate to human infection - What thresholds should be used to define ongoing transmission? Should this vary by vector and parasite species? - More comparison between human and xenomonitoring surveys is needed. - Gaps in understanding the relationship between MX, results and CFA, Ab and Mf results in humans. - Does vector biomass have an important role in transmission?	- Review literature and conduct studies to determine the efficiency of different vectors to become infected with LF parasite.
<u>Mosquito collection methods</u> - What types of traps are best for each species? - When is the best time to collect mosquitoes? Should this be based on season, timing of IRS, etc?	<u>Mosquito collection methods</u> - Compare existing data and/or data on mosquitoes collected for different purposes or programs, and/or undertake mosquito collection at different times to determine best times to collect mosquitoes. - Use existing data/evidence and/or conduct trials of different collection methods in settings with different vectors to determine most efficient methods of collection for different vectors.
<u>Mosquito processing issues, efficiency and cost effectiveness</u> - When is speciation necessary? This is important because it may be more efficient in terms of human resources and expertise not to speciate and may increase the feasibility of MX - How does the cost effectiveness of speciating vs not speciating compare?	<u>Mosquito processing issues, efficiency and cost effectiveness</u> - From available studies, compare results obtained when combining all mosquito genera (e.g. all *Anopheles* in PNG and all *Aedes* in the Samoas) or distinguishing by species. Does this vary by setting depending upon the species present? - Develop and test simplified PCR processing to make it more accessible and less requiring of specialist expertise - Form regional agreements to increase number of PCR facilities that may be more accessible to countries with LF

Alternative response strategies (i.e. how to respond to CFA-positive people identified in surveys, hotspots, recrudescence)	
<u>Reaching hot populations</u> - These populations have high prevalence and/or low participation in MDA, so may provide a reservoir of infection enabling ongoing transmission and resurgence <u>Response to identified hotspots</u> - Once a hotspot has been identified, there are currently knowledge gaps about the response required in order to prevent ongoing transmission and elimination of LF as a public health problem - The programmatic feasibility of different response strategies <u>Impact of positive people and ineligible populations (e.g. pregnant women) on ongoing transmission</u> - Antigen positive people and groups ineligible for MDA may serve as important sources for ongoing transmission, but the extent of this is unknown <u>Response strategies tailored for different settings</u> - It is not known if different response strategies are required for different settings.	<u>Reaching hot populations</u> - Investigate and compare (by modeling and testing on the ground) ways to reach and engage 'hot populations' in MDA uptake to determine which are most effective and efficient <u>Response to identified hotspots</u> - Once identified, what should be the programmatic response to hotspots? Is a response always required or is it dependent upon the scale (i.e. household/cluster of households/village-level/region)? E.g. further testing and individual treatment of individuals/ localized MDA? What further surveillance should occur following identification of a hotspot? - What response is programmatically feasible at a hotspot (are there resources to undertake individual test and treat or MDA of a whole village? Which response would be more feasible, effective and cost effective?) <u>Impact of positive people and ineligible populations</u> - Those ineligible for MDA should be included in surveillance - Is it important to treat CFA (and Mf) positive people, but also investigate local test and treat responses to limit potential for ongoing transmission. This includes testing how broad the test and treat response should be i.e. the household of the CFA and/or Mf positive person? Surrounding households? <u>Response strategies tailored for different settings</u> - Model the best response strategy for a setting to determine whether this varies by setting and if so, what criteria/spatial factors are important in identifying best response strategy

<u>Learning from other disease control programs</u> - There may be opportunities to learn from other public health disease control programs on ways to eliminate LF, especially once prevalence becomes low and heterogenous <u>Surveillance activities following different response strategies</u> - It is not known if the type of surveillance should vary depending upon what response strategy has been used to limit ongoing transmission <u>Cross-border transmission</u> - It is not known whether there may need for tailored response strategies if there is suspected or potential cross-border transmission <u>Decision-making process</u> - It is unclear what process should be undertaken to make decisions (i.e. recommendations) on key programmatic actions, e.g. surveillance and response under situations of uncertainty and imperfect evidence. It is unclear how new evidence (e.g. those presented in this session) and expert opinion (e.g. when there is no or limited evidence) should be considered and acted upon, and taken into account when updating recommendations.	<u>Learning from other disease control programs</u> - Review other disease control programs to determine lessons that can be learned and/or potentially trialed or applied to LF elimination. <u>Surveillance activities following different response strategies</u> - Link surveillance strategies to the type of response strategy used. E.g. following identification and response to a hotspot, investigate what surveillance should be prospectively undertaken and whether this should vary from the standard surveillance <u>Cross-border transmission</u> - Review data from neighboring areas where there is potential or suspected cross-border transmission and data available from both sides, to investigate what combined surveillance and response strategies are indicated. <u>Decision-making process</u> - Develop explicit and transparent decision-making process to decide upon response and surveillance strategies tailored for different scenarios with varying levels of uncertainty, with a decision-making tool/framework to assist in thorough consideration of important elements. The process should take into account risks, potential impact of action/inaction, missed opportunities, and be able to adapt to new information as it becomes available. Other considerations include the precautionary principle, benefits vs harms, resource use, values and preferences, acceptability, and feasibility.

	- Ideally, action should be evidence-based, but what do we do if there is no robust evidence? Or if there is high uncertainty about available evidence? Whilst waiting for evidence to be generated, how do we best incorporate expert opinion into decision-making? How do we prioritise what evidence is most urgently needed? - Do we need operational research on decision making under uncertainty? What are the barriers to decision making? What type of support would decision makers find most useful? How do we best deal with setbacks, and how do we use them as opportunities to learn and improve?