RESPONDING TO FAILED TRANSMISSION ASSESSMENT SURVEYS REPORT OF AN AD HOC MEETING

STRATEGIC AND TECHNICAL ADVISORY GROUP FOR NEGLECTED TROPICAL DISEASES
SUBGROUP ON DISEASE-SPECIFIC INDICATORS

4 DECEMBER 2015
WASHINGTON (DC), USA

World Health Organization

Responding to failed transmission assessment surveys. Report of an ad hoc meeting

Meeting of the Neglected Tropical Diseases Strategic and Technical Advisory Group's Monitoring and Evaluation Subgroup on Disease-specific Indicators

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1. Opening session

Dr Luis Castellanos welcomed participants and stated that the Pan American Health Organization considers elimination of neglected infectious diseases as a step towards permanent sustainable development in the Region of the Americas. “Every single person counts”, particularly in working towards equity, and the Organization focuses not just on diseases that affect high numbers of people.

2. Purpose and objectives

Dr Jonathan King explained the purpose of the meeting, which was to respond to requests by national lymphatic filariasis elimination programmes for the best available guidance on: (i) investigating failures of transmission assessment surveys (TAS); and (ii) identifying corrective actions to both prevent and respond to failures. The meeting aimed to agree a framework of standard operating procedures for national programmes to follow including:

- activities to be implemented to prevent TAS failure;
- investigations to be completed to determine reasons for TAS failure;
- actions to be taken in response to TAS failure based on the reasons identified during investigations, including enhanced mass drug administration (MDA) and vector control.

The group will submit draft procedures to the Working Group on Monitoring and Evaluation for discussion and broader input before presentation to the Strategic and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTD) for endorsement.

Dr Pat Lammie, the Chair of the STAG-NTD Subgroup on Disease Specific Indicators of the Working Group on Monitoring and Evaluation, led the meeting. Declaration of Interests forms were submitted by participants before the meeting and reviewed by the WHO Secretariat. None of the experts declared interests that would prevent their participation in this meeting.

The agenda is included in Annex 1 and the list of participants in Annex 2.

3. TAS issues arising from regional programme review groups during 2015

Regional programme review groups have raised four main issues about TAS:

1. What confirmatory tests should be done in areas where lymphatic filariasis is transmitted by *Wuchereria bancrofti* and *Brugia* spp.?
2. Should diagnostic tests be used consistently during pre-TAS, TAS1, TAS2 and TAS3?
3. Why are areas of *Brugia* spp. failing TAS?
4. How should national programmes respond to failed TAS during post-MDA surveillance?

4. WHO global TAS results and current guidance for responding to TAS results

The World Health Organization (WHO) recommends the TAS to determine whether levels of filarial infection have been reduced below a target threshold at which continuing transmission cannot be sustained. TAS is a decision-making, standardized survey that employs a robust statistical, yet practical sampling design. Evaluation units (EUs) “pass” TAS when the prevalence of infection among heavily exposed children (positive cases) is less than or equal to the critical cut-off value. Surveyed EUs “fail” TAS when the prevalence of infection among positive cases exceeds the critical cut-off value. WHO further recommends implementing TAS to decide when to stop MDA and also to determine whether levels of infection have been sustained below target thresholds during post-MDA surveillance. During post-MDA surveillance, TAS should be conducted at 2–3 years and again 4–6 years after stopping MDA.

Table 1 summarizes the percentage of EUs that pass TAS by species of causative filarial parasite. In areas where *W. bancrofti* causes lymphatic filariasis, TAS failure is rare. However, in areas where *Brugia* spp. causes lymphatic filariasis more failures occur and the percentage of EUs passing subsequent post-MDA surveillance surveys decreases. In four of five WHO regions at least one country has failed TAS, including Bangladesh, Burkina Faso, Comoros, Haiti, Indonesia, Nepal, Niger and Samoa. At least one TAS failure has been reported in settings for each complex of vector species (*Aedes*, *Anopheles*, *Culex, Mansonia*).

Table 1. Transmission assessment survey (TAS) "pass" rate: percentage of evaluation units (EUs) passing TAS out of those implemented, by parasite species

Etiological species	TAS1 (EUs pass/EUs surveyed)	TAS2 (EUs pass/EUs surveyed)	TAS3 (EUs pass / EUs surveyed)
Wuchereria bancrofti	**97%** (7/278)	**100%** (20/20)	**100%** (3/3)
***Brugia* spp.**	**72%** (31/43)	**57%** (12/21)	**0%** (0/1)

WHO guidance on TAS includes the following key points[1,2]:

- The BinaxNow filariasis immunochromatographic test (ICT) and the Filariasis Test Strip (FTS) are the diagnostic tests[3] recommended for use during TAS in areas where *W. bancrofti* is endemic to detect circulating filarial antigen of adult worms in human blood. A positive ICT or FTS indicates infection.
- The Brugia Rapid point-of-care cassette test (BRT) is the diagnostic test recommended for use during TAS in areas endemic for *Brugia* spp. to detect the presence of BmR1 antibody in human blood. A positive BRT indicates heavy exposure or infection.
- Identification of microfilaraemia in thick blood films is recommended for mapping and for sentinel and spot-check site surveys only.
- All persons who test positive during TAS should be treated. Microfilaraemia can be collected from positive cases at night, or at a time appropriate to the periodicity of the species. The residency status of positive cases (that is, cases having lived in an area for at least one year) should be assessed as an indicator of whether infection has resulted from local transmission and if any significant migration has affected the impact of MDA.
- The detailed protocol proposed during TAS includes an algorithm to follow up positive cases in children, including an investigation of the history of exposure to, and an assessment of the focus of, infection by testing family and neighbours. The protocol is suggested irrespective of whether the EU passes or fails TAS. If additional positive cases are found, the algorithm suggests expansion to community surveys.
- If TAS1 fails, two more rounds of MDA are recommended in all areas of the EU that failed, with reassessment of eligibility for TAS in sentinel and spot-check sites.
- If TAS2 or TAS3 fail, national programmes should consult experts as continuing transmission is indicated. Possible responses to failure include conducting further investigations, implementing two or more rounds of MDA, continuing surveillance activities, or implementing alternative strategies such as vector control or targeted MDA.

WHO acknowledges that national programmes have requested support to determine how to prevent TAS failure, how to investigate TAS failures and how to implement corrective actions in response.

[1] Monitoring and epidemiological assessment of mass drug administration for eliminating lymphatic filariasis: a manual for national elimination programmes. Geneva: World Health Organization; 2011 (also available at http://apps.who.int/iris/handle/10665/44580, accessed June 2016).

[2] Training in monitoring and epidemiological assessment of mass drug administration for eliminating lymphatic filariasis (http://www.who.int/lymphatic_filariasis/resources/TAS_training_materials/en/, accessed June 2016).

[3] Both tests are manufactured by Alere, Waltham (MA), USA.

4.1 Discussion

The WHO guidance assumes that a TAS failure represents a programmatic failure. "False" failure resulting from issues with diagnostic tests is not addressed. Because diagnostic tests for *Brugia* spp. and *W. bancrofti* have changed during the course of the Global Programme to Eliminate Lymphatic Filariasis and performance has varied in some historical circumstances, their quality and application should be reviewed.

Few countries are using the algorithm to follow up children who test positive to assess the potential for residual transmission. No specific intervention response is recommended if additional positive cases are found. There is little scientific evidence to suggest that such a follow-up strategy can detect further transmission or lead to effective decisions.

The guidance also does not address whether the TAS critical cut-off thresholds should be adjusted in areas of *Brugia* spp. to account for the ability of antibody to detect exposure to and not necessarily infection. Given the limited evidence, however, this issue cannot be addressed until the results of adequate operational research are available to prove a need to change thresholds. Furthermore, any change of decision thresholds for diagnostic indicators would need to be considered by the WHO Guideline Review Committee. The results from surveys to date indicate that the thresholds may be sufficient and that the responses of BRT to antibody may represent a useful indicator to determine transmission. Areas that pass TAS using BRT and later fail TAS during surveillance with BRT would indicate increased exposure to infection and perhaps continuing transmission.

It was agreed that additional clarification and detailed protocols are needed to investigate and respond to TAS failures.

5. Potential responses to TAS failure

Dr Kapa Ramaiah proposed enhanced strategies for intervention and surveillance in responses to a "true" TAS1 failure.
An enhanced intervention strategy to ensure elimination of infection that includes:

- higher implementation standards of the currently recommended two rounds of MDA, including: target coverage of more than 80% of the total population; strict adherence to directly observed treatment; triple drug therapy if possible (that is, using a combination dose of ivermectin, diethylcarbamazine and albendazole[4]); and treatment of household and household contacts of those children found positive during failed TAS; and
- vector control (recommended but not mandatory) in areas of *Culex* and *Mansonia* transmission but where difficulties due to safety concerns, complex logistics, financial constraints and environmental impacts may arise.

An enhanced surveillance strategy to ensure identification of hotspots that includes:

- "enhanced TAS" after two rounds of enhanced MDA in which the original (failed) EU is divided into five or six sub-EUs containing no more than 200 000 population each and where preferably the population to be sampled is changed from children aged 6–7 years to adults;
- a mini-TAS of each sub-EU sampling a range of 400–600 individuals resulting in a total sample size for the original failed EU in the range of 2000–3600;
- continued sampling of children aged 6–7 years but changing either from antigen testing to antibody testing or adding xenomonitoring to antigen testing; and
- TAS2 and TAS3 using the same method and maintaining the division of EU to sub-EUs.

The advantage of the enhanced TAS that Dr Ramaiah proposed is in obtaining infection prevalence for each sub-EU, leading to targeted interventions in smaller areas that fail, rather than an EU of up to 2 million population