

Driving towards 2030 goals for HAT and VL: Accelerating Progress and Indicators of Continued Success

Session Date & Time:	Tuesday, November 19; 1:00 PM to 4:00 PM
Session Location:	Beau Rivage Meeting Room
Session Description:	The World Health Organization (WHO) is defining new targets for control and elimination of neglected tropical diseases (NTDs) by 2030. What will the road to success look like from 2020 to 2030 for human African trypanosomiasis (HAT) and visceral leishmaniasis (VL)? We focus on indicators of progress and maintaining drive with dwindling case reporting.
Session Chairs:	Luc Coffeng and Graham Medley
Session Rapporteur:	Marina Antillon, Swiss TPH

KEY DISCUSSION POINTS

Gambian Human African Trypanosomiasis (gHAT)

gHAT is caused by the parasite *Trypanosoma brucei gambiense* and transmitted by the four different species of the *Glossina* genus, colloquially referred to as the tsetse. Historically, 24 countries were endemic for gHAT, but the geographic reach is diminishing; some historical foci have not observed cases for years and even where the disease remains, incidence is in the decline. This decline is thanks to a combination of interventions strengthening the health infrastructure (passive surveillance) as well as mass population screening campaigns (active surveillance). Most importantly, the fact that incidence is declining in the presence of stronger surveillance efforts suggests a decline in the underlying transmission of disease, underscoring the optimism on the feasibility of the WHO 2030 goal of elimination of transmission (EoT).

Nevertheless, the Democratic Republic of Congo (DRC) remains the country with the highest burden, contending with 67% of the global burden in 2018. Dr. Erick Miaka presented an overview of the situation on the ground in DRC, where most cases come from the former province of Bandundu. He emphasized that the geographic niches of gHAT are usually consistent over decades, suggesting that it is plausible to perform geographically targeted strategies. Strategies have usually consisted of screening and treatment (since gHAT is not a vaccine-preventable disease, and current treatment is not sufficiently safe for mass drug administration). In most places, screening and treatment has led to dramatic decreases in prevalence, and more recently vector control has been carried out in select places where

moderately high prevalence remains. In the future, the efforts towards integration of gHAT screening into fixed/polyvalent health care facilities will be delicate: more than 50% of cases in the last 21 months have been detected via mobile screening units and about a quarter of cases have been detected via specialized detection and treatment centers. Moreover, maintaining the capacity for what is a complicated diagnostic algorithm will be increasingly difficult, and it was mentioned during discussion that there have been worldwide shortage of rapid diagnostic tests (RDTs), which are used in more remote clinics (without electricity) and in expanded mass screening.

The newly approved oral drug, fexinidazole, is due to be rolled out in DRC starting in December 2019, improving the ease of treatment, as well as the transport of the drugs. This drug will remove the need for lumbar puncture to “stage” disease in most cases (except in those with “severe” gHAT symptoms) as it is effective for both stages.

Using the lens of mathematical modeling, Dr. Kat Rock expanded on our view of gHAT epidemiology and the prospects for the next decades. She combined disease epidemiology with operational and economic modeling to examine the feasibility and resource implications to reach gHAT elimination. A recurring theme throughout the talk was that because transmission is only a partially observed process, modeling provides the link between observed cases and operational processes to measure the probability that we have safely reached local EoT. As illustrative examples, two models have been developed to examine the question of the duration and coverage of mass-screening (active surveillance) necessary to confidently conclude that elimination is imminent: both the village- and health-zone-scale models have shown that 3 years of active surveillance in a period of no case detections would be sufficient to have >90% probability of local EoT. It is notable that self-reporting (passive surveillance) would remain in place, and issues were raised in the discussion surrounding the importance of continued passive surveillance for monitoring after active screening has ceased.

Dr. Rock included a brief overview of costs and decision analysis along with a demonstration of a web-based tool to support decision-making by country-level stakeholders. She reviewed the current understanding of resource use in the health zone of Mosango: with current tools, it is believed that EoT is technically feasible, but that the cost may not fulfill our traditional considerations of good-value-for-money, or cost-effectiveness. Some gHAT-endemic regions (e.g. CAR, South Sudan and East DRC) pose separate operational challenges due to access. Dr. Rock’s team is developing a web-based tool that will show not only model-based recommendations, but also the epidemiologic benefits and components of resource of use of possible strategies.

In conclusion, the target appears technically feasible using existing tools. However, EoT would require a step change in the level of surveillance and even the use of additional controls (such as door-to-door screening or vector control) in select regions that show persistent transmission despite historical efforts. The new single-dose-cure drug in the pipeline, acoziborale, could provide further options for modes of active screening.

Visceral Leishmaniasis (VL)

Two syndromes exist caused by *Leishmania donovani* in the Indian Sub-continent (ISC): visceral leishmaniasis (VL) and post-kala-azar dermal leishmaniasis (PKDL), a sequela of VL. PKDL is mainly of concern because of its contribution to transmission; although VL is more severe and contributes to the majority of the burden of disease caused by *L. donovani*, PKDL patients are competent reservoirs.

VL incidence is in the decline, but unlike gHAT, the geographic span is progressively fragmented rather than shrinking. Bangladesh and Nepal reached the 2020 goal (elimination as a public health goal of under 1 in 10,000 cases at the sub-district level) in 2014 and 2017 respectively. India's incidence is also in the decline, but not all sub-districts will reach the 2020 goal. As elimination nears, PKDL cases will be responsible for an increasing proportion of transmission, underscoring the need to attend to these cases.

Diagnostics are working well for VL (rK39, a RDT fulfills some requirements for surveillance). Dr. Adams particularly focused on developments in diagnostics, in particular detecting antigens in urine by ELISA, and the use of this test to diagnose HIV-VL co-infected patients, monitor treatment response in all patients and as a highly specific test of progression. However, better diagnostics are necessary for PKDL, both in terms of accuracy and portability to the field, a principal concern for control and elimination of the disease. An additional concern for control and elimination will be the logistical capacity to contact PKDL patients, who might not present to care of their own accord due to the mild nature of PKDL symptoms.

Dr. Epke Le Rutte reviewed the progress and rationale of the 2020 and 2030 goals for visceral leishmaniasis in the ISC. Briefly, while the goal for 2020 was to reduce the incidence to <1VL case per 10,000 at the district and sub-district level. The key indicator of the 2030 goals is a case fatality rate of VL of <1% and to include cases of PKDL. Modeling has shown that PKDL is an increasingly important reservoir of infection, providing a basis for further study into the detection and treatment of the populations afflicted by this condition. Moreover, Dr Le Rutte addressed the risks of halting interventions when targets have and have not been reached. Where targets have been reached, halting interventions would be unlikely to hamper the progress made towards the 2020 goal of prevalence of 1 VL case per 10,000, but where targets have not been met, the prevalence would not only remain above the 2020 goal but it would also rise. Lastly, modeling showed that the patient-reported duration of symptoms appears to be correlated with the intensity of case detection efforts—underscoring the impact of screening efforts on the underlying transmission of disease.

KNOWLEDGE GAPS IDENTIFIED

There remain gaps regarding the undocumented burden of disease for gHAT, the diagnostics to address transmission in the last pockets for both diseases, and the treatment of gHAT in extremely remote areas.

Undocumented burden of gHAT

It is unclear how many gHAT deaths occur outside of care, a metric indicative not only of the existing prevalence (cases infected in the past) but that would help validate current models of the ongoing transmission of disease (cases yet to be infected). Such a metric would also bolster advocacy efforts surrounding the value-for-money proposition of the increasingly more difficult control and elimination efforts. Generally speaking, symptoms of gHAT are not recorded in aggregated case reporting, whilst they are for VL. This additional data type could be valuable for modelling or other evaluations, especially with the anticipated removal of staging data with the introduction of the new drug.

Diagnostics

There are a range of reasonable diagnostic tools (including point-of-care, or POC) for both diseases, although there are gaps in the diagnostic portfolio which, if filled, could help to reach elimination goals. In order to reach EoT of gHAT, it is unclear how existing diagnostics might be able to prove cure in the more remote locations where gHAT remains. Whereas for VL, the biggest diagnostic gap identified is monitoring VL treatment and identifying PKDL patients (both gold standard and field tools are still lacking), as well as implementation schemes to screen individuals for PKDL. Due to the mild symptoms of PKDL, individuals might refrain from seeking care, thereby serving as lingering reservoirs of *L. donovani* in the community.

Learning from mass drug administration (MDA) diseases

A limitation of interventions for these two innovative and intensified disease management (IDM) diseases is the inability to perform MDA, because both require case confirmation before treatment. Discussions ensued around the need for a single-dose medication effective against both stages of gHAT but posing fewer side-effects than existing medications. Such a drug is of special interest primarily to treat gHAT suspects in locations too remote for existing confirmation tools and treatment. This would present an opportunity to go to extremely remote villages on motorcycles and treat gHAT serological suspects. This would increase the coverage of treatment (current algorithms can miss false negatives) although it would inevitably overtreat non-infected people. Even the new (fexinidazole) treatment, which can be administered in the community under some conditions, is too toxic to give to gHAT suspects without confirmation. Treatment of those serologically positive for VL is not currently possible without corresponding symptoms, unless more specific tests were to be made available that could confirm serological suspects, or unless a treatment for all suspects could be delivered.

RECOMMENDED NEXT STEPS

Burden

For both diseases, it is imperative to identify further metrics of the success of elimination goals by 2030, including metrics for unattended mortality in the community. In order to infer on gHAT deaths in the community, verbal autopsies were suggested.

Intermediate goals

Neither the gHAT or VL communities have set specific goals between 2020 and 2030. The group identified that creating a “2025” target could help make sure that we are on track for 2030. It would be desirable to investigate what the individual goals would need to be if the subsequent 2030 goal is to be successful (e.g. what reduction in gHAT cases would we hope to see by 2025, how many countries should have been validated for elimination as a public health problem? What should the spatial clustering of remaining VL cases look like? Do we need a shrinking geographic area?)

Diagnostics

During discussion the central importance of diagnostics was emphasized. There does not exist a market commitment from companies of existing diagnostics of either disease to produce and provide diagnostics at the levels necessary to reach control and elimination goals. In addition, better, novel diagnostics are necessary for the endgame: for the cure of gHAT and a diagnostic that can show the right trade-off between suitability for POC and accuracy for VL, follow-up and PKDL. Furthermore, an area of development that has received concerningly little attention is the possibility to add HAT and/or VL to multiplexed diagnostic platforms, since passive or clinic-based surveillance will become more important towards the endgame. This is especially important for PKDL, where dermatologist might be the primary health system contact for patients. Moreover, manufacturing of diagnostics is likely to become harder under new EU legislation.

Single-dose treatment of gHAT

There was a discussion surrounding the possibility to treat gHAT suspects rather than only confirmed HAT cases if a single-dose treatment with a safer profile than existing treatments materializes. Such an approach would address the last geographic pockets of transmission, some of which are suspected to be too remote for current logistical approaches of intensifies case detection. It was suggested that economic evaluation modeling could help underpin futures discussions around the costs, benefits, and risks of possible approaches.