COR-NTD 2020
Virtual Meeting, November 12 – 14
Integrating for Impact

IDM Diseases: What can we learn from each other?

Session Date: 11/14/20

Session Time: 9:00 AM - 12:00 PM EST

Session Description: The NTDs listed under the WHO selection of Innovative and Intensified Disease Management (IDM) have many challenges in common and some particular diseases have successful stories which can lead the others to the final target of elimination as a global health problem and further, with the interruption of transmission.
Chagas diseases (CD), Human African Trypanosomiasis (HAT) and Visceral Leishmaniasis (VL) share most of the same questions and challenges to address. However, their responses can be different depending on the stage of advance towards elimination or control of each disease.
We will address some important questions, such as: Is the mobile test and treat experience of HAT a model that can be applied to others such as CD? What models of other diseases' coordinating bodies can be helpful for VL? How can we improve and evaluate the level of integrating neglected diseases into prioritized diseases' programs as the MTCT+ of CD, for example? Is there evidence from operational research that can contribute to the integration? What are the key components of control programs and how cost-effective are they? What to learn about the approach's shift represented by the "Tiny Targets" initiative on HAT to reduce the density of the vector presence? How to improve the advocacy for a higher investment in the research agenda to adapt the innovation to the real field where these diseases are causing severe damage? How to measure and balance the programs with a people-centered approach? Is the WHO's NTD roadmap on the loop of the three communities? To what extent can new and global data collection systems provide an impact on the three diseases? What is the level of political and financial commitment with these NTDs?

Session Chairs: Kendra Palmer, Javier Sancho and Paul Verlé

Session Rapporteur: Marina Antillon

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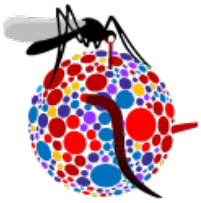
EXECUTIVE SUMMARY

This session focused on Chagas disease, Human African Trypanosomiasis ("sleeping sickness"), and Visceral Leishmaniasis (“kala-azar”) caused by *L. donovani*. These three diseases are all parasitic, though they are largely present in distinct geographic locations – with the exception of Chagas and VL, which are contiguous in certain parts of Brazil. However, these diseases are linked together thematically in their need for intensified disease management (IDM), as the treatment precludes all diseases from mass drug administration (MDA) or preventive chemotherapy (PC) strategies. The sessions were framed around the following themes, of major concerns to all three diseases: **1) transmission control, 2) diagnosis and treatment, 3) surveillance, and 4) advocacy**. Although peripheral to these core themes, there were momentary discussions of vector control (important to efforts against all three diseases) as well as the impact of the current COVID-19 pandemic.

Key knowledge gaps and next steps were identified around each disease but also across diseases. More accurate diagnostics and effective treatment are needed for VL for locations outside of the Indian subcontinent and for the HIV-positive community, as well as an avenue for interdisciplinary coordination for the VL research and public health community. With regards to Chagas disease, there is a need for simplified diagnostics and safer treatment together with a implementation research on integration into the primary healthcare service. Across all diseases, there was a need to clarify the metrics of progress (VL and Chagas) and success (gHAT) to orient the activities of diverse communities. Lastly, the issue of community engagement and empowerment within research and foreign aid programs was addressed.



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KEY DISCUSSION POINTS

What key findings and data did the group identify via presentations? What issues were raised in discussions?

Session 3F brought together the communities of Chagas disease, Human African and American Trypanosomiasis and Visceral Leishmaniasis. The sessions were framed around the following themes, of major concerns to all three diseases: **1) transmission control, 2) diagnosis and treatment, 3) surveillance, and 4) advocacy**. Although peripheral to these core themes, there were momentary discussions of vector control (important to efforts against all three diseases) as well as the impact of the current COVID-19 pandemic.

Chagas

Chagas is disease caused by the parasite *Trypanosoma cruzi* transmitted by the four different species of the *Triatoma, Panstrongylus, and Rhodnius* genera, colloquially referred to as the 'kissing bug'. Additional routes of transmission include congenital transmission, and transmission through transfusions and transplants. Historically, 21 American countries contain endemic regions for Chagas, putting 70 million people at risk, and it is estimated that 6-7 million people worldwide are infected with the disease. The disease is characterized by two stages: 1) an acute stage of one to two months during which complete remission is possible, and 2) a chronic stage that can last decades during which a cure is more difficult, resulting in cardiac, esophageal, and digestive chronic symptoms that can be fatal if untreated. The WHO's 2030 goal for Chagas is for elimination as a public health problem (interruption of transmission by 2030 in all routes, and 75% coverage of treatment of infected cases). The World Heart Federation, together with the Inter-American Society of Cardiology has published a road map to 2030 with guidelines on the use of existing tools and the outline of adequate interventions to reach those goals.

Prof. Sergio Sosa-Estani of the University of Cordoba, the University of Buenos Aires, and Drugs for Neglected Diseases initiative (DND*i*) presented the key points from a pre-session meeting on the potential synergies of Chagas screening alongside HIV, Syphilis, Hepatitis B. The diagnosis of Chagas relies on one rapid diagnostic test (RDT) for screening and two serological tests for confirmation, taking 30 days. Treatment depends on Benznidazole or Nifurtimox for 60 days, which results adverse events that lead to discontinuation of up to 20% of patients and treatment failture at 12 months in another 20% of patients. Three key challenges remain: 1) the asymptomatic nature of the disease during most of its natural history, 2) its strong correlation to poverty, which impedes access to diagnosis even when symptoms are present, and 3) the complicated nature of treatment. For these reasons, a 'test-and-treat' strategy requires simpler same-day screening and confirmation that can be more ubiquitously available in the peripheral health care system and simpler, safer treatment that reduces loss to follow-up.

It was remarked that congenital transmission, on the other hand, is a domain where integration has progressed. Using the platform of antenatal care visits as a natural touchpoint in the literature, there exists a cross-cutting framework of elimination of mother-to-child transmission of HIV, Syphilis, Hepatitis B and Chagas termed EMTCT-plus. This platform can be used as a case-study to motivate continued integration of Chagas into the efforts against other diseases.

HAT

HAT is caused by the parasites *Trypanosoma brucei gambiense* and *T.b. rhodesiense* and transmitted by the four different species of the *Glossina* genus, colloquially referred to as the tsetse fly. Historically, 24 countries were endemic for HAT, but the geographic reach of gambiense human African trypanosomiasis (gHAT) is diminishing, thanks to a combination of interventions strengthening the health infrastructure

(passive surveillance) as well as mass population screening campaigns (active surveillance). Recently, vector control strategies have been devised and implemented to break transmission in low-incidence areas nearing elimination. At a global level, HAT has reached the 2020 goal for elimination as a public health problem (5-year average in a health districts is fewer than 1 case per 10,000 people at risk) and the WHO has marked HAT for elimination of transmission by 2030.

Dr Paul Verlé of the Institute of Tropical Medicine-Antwerp presented on the comprehensive development of tools towards HAT elimination: spanning better treatment, better diagnostics in terms of both diagnostics as well as access to screening, and vector control. He highlighted the licensure in 2019 and the rollout in 2020 of fexinidazole, a drug that makes the treatment of HAT simpler by allowing for outpatient treatment in stage 1 and early-stage 2 of the disease. He noted that the while the screening test positivity rate has remained the same from 2015-2019 (0.5-0.7% percent of those tested), confirmatory tests have shown that the positive predictive value of these screening tests has fallen: whereas 13% of positive suspects were confirmed in 2014, only 1.8% are confirmed in 2019 due to falling incidence. This context of low incidence underscored the importance of developing new diagnostic approaches but also the work of DiTECT HAT, which is working towards a improved case management. Lastly, he also discussed the new challenges for vector control.

Dr Verlé concluded his presentation by highlighting the potential obstacles of elimination and how much advocacy around these obstacles is needed. First, while specific treatments and diagnostics are under development to serve isolated populations and contexts of low incidence, the health systems might still be too weak to carry this work forward. Second, while the Democratic Republic of Congo (DRC) and select countries are the subject of grant funding for both research and support to the national ministry of health, a few endemic countries remain "orphaned" in the fight against gHAT, and their financial shortfall may delay the elimination of the disease.

Visceral Leishmaniasis

Visceral leishmaniasis (VL) is a disease caused by the parasites of the genus *Leishmania*. There are two species that cause VL – *L. donovani* which is anthroponotic and has a 95% fatality rate if not treated, and *L. infantum* which is zoonotic with a canine reservoir. Leishmaniasis spans four continents and 100 countries; WHO reports about 25,000 cases per annum. *Leishmania donovani* has been targetted for elimination as a public health problem in the Indian subcontinent (aiming to achieve under 1 case per 10 thousand population at the district or subdistrict level), and for control programmes in East Africa, the two main regions affected by VL. VL may cause fever, serious anemia, swelling of the spleen and liver. Like gHAT, VL is almost 100% lethal without treatment. Post-kala-azar dermal leishmaniasis (PKDL), a sequela of VL normally following treatment, is a milder form of the disease that causes skin nodules or macules. Professor Simon Croft of LSHTM presented on the progress of efforts again VL.

First, Prof. Croft relayed the key points of Dr. Dinesh Mondal's presentation during the pre-meeting session, where Dr. Mondal presented on the situation in the Indian Subcontinent. He listed a number of challenges from political and financial commitments to obstacles of procurement and case finding. He additionally noted the preoccupations with both HIV co-infection and particularly highlighted the the concern of PKDL as a potentially competent reservoir that could hamper progress towards elimination as VL prevalence declines. He also noted that absence of vector control and the lack of scientific development around tools for vector control. Lastly, like with other diseases, he pointed to the lack of post-elimination validation guidelines.

Prof. Croft next presented the key points of Prof. Ahmed Musa's presentation during the pre-session meeting. Prof. Musa echoed Prof. Mondal's messages about the concerns surrounding PKDL, but he

especially highlighted that the tools for both diagnosis and treatment that work in the Indian subcontinent are less accurate and effective in East Africa. Moreover, he pointed to the high rate of HIV co-infection in VL patients (up to 20% in some parts), and a lack of coordination in activities across the relevant countries in the region: Sudan, South Sudan, Ethiopia, Djibouti, Somalia, Kenya, and Uganda.

Next, Prof. Croft outlined issues around the global research agenda, which had been presented by Prof Philippe Guerin of the Infection Disease Data Observatory (IDDO). He focused primarily on the quality of clinical trials and dissemination, pointing to existing issues with data standards and coordination of data collection across regional and national borders.

Lastly, a call was made for global coordination of both research and advocacy within the Leishmania community (see the recommended next steps section) that would include both VL and cutaneous leishmaniasis (CL).

Synthesis and emergent cross-cutting themes.

In addition to the exhaustive exploration of the proposed themes, these additional themes emerged in discussions:

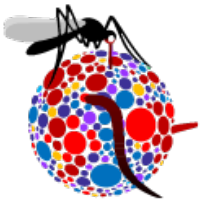
Community engagement

A common theme across the talks was that community engagement was a necessary, though neglected, component of all disease-elimination efforts. Engagement with the communities is often hard to quantify or prove and its development is difficult to report to donors. Easier diagnostics and integration with the health system will help to engage broader sectors of the communities. However, for programs whose sustainability is in question in the absense of international donors, and for which therapeutics often prove uncomfortable to recipients, a lack of trust with the community could jeopardize programs.

COVID-19 interruptions

COVID-19 interruptions seemed mitigable for vector control with HAT, where it proved that some management activities can be handed off to the country staff. Otherwise, it was generally acknowledged that COVID-19 diverted resources away from the efforts against Chagas, VL, and HAT. However, there was one exception: vector control activities against the HAT-transmitting tsetse fly in DRC, which were usually led by staff of the Liverpool School of Tropical Medicine, were successfully continued by the country's national HAT control program (Programme National de Lutte contre la Trypanosomiase Humaine Africaine).

Due to the relatively long duration of the disease, in the magnitude of years, short-term COVID-related interruptions would not make a large impact on the progress towards 2030 goals as long as the activities for each disease resume as before, but questions remain about the length of the interruption.



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KNOWLEDGE GAPS IDENTIFIED

What data and tools need to be generated to address the issues raised by the group?

Addressing the needs of distinct patient populations of VL

VL in the Indian Subcontinent for HIV-negative individuals has driven disease decline, but both the diagnostic tools and the treatment regiments are less successful in East Africa, treatments are not as successful for individuals who are HIV-positive, and tools to fight PKDL, the sequalae of VL, are limited.

Baseline epidemiology of Chagas disease

Because of the silent nature of Chagas disease progression, there are notable gaps in the basic epidemiology of the disease. To build a case for integration, baseline epidemiology of Chagas disease as well as other diseases that are asymptomatic and geographically contiguous.

Missing metrics and data quality standards, moving goal posts

Within the context of VL, there is an absense of data standards for consistent collections across studies and across geographic locations. The discussants remarked that the the goalposts to abate the burden of VL are often delayed and are not necessarily aligned with the end of transmission, but rather with lower case-fatality rates. Moreover, there is an absense of post-validation guidelines for elimination of *L. Donovani* in the Indian subcontinent, and to certify the interruption of transmission in gHAT everywhere.

RECOMMENDED NEXT STEPS

What operational research and other actions need to be taken to address the knowledge gaps identified by the group?

Definition of success metrics

As defined in the knowledge gaps, while the WHO set a target for elimination of HAT transmission by 2030, and Chagas and VL for elimination of transmission as a public health problem by 2030, the metrics of progress and success are not clear in all the diseases. For HAT, there are designated metrics of to certify that countries have achieved HAT elimination as a public health problem. For Chagas and VL, the metrics of progress are often changing. For VL in particular, the presenter found that there are inconsistencies in the way that data are collected, making geographic comparisons difficult.

Integration into the peripheral or primary health care system, aided by better diagnostics.

It will not be sustainable to continue to perform large-scale mass screening with declining prevalence of the infection of any of these diseases. While vertical strategies might be easier to apply, implementation research on integration must be undertaken to demonstrate the benefits of such a system in the long run as well as the roadblocks to realization. For HAT, nearing elimination, promising high-accuracy serological tests on dried blood spots (using filter paper) could be a feasible alternative. For Chagas and

VL, especially VL outside of South Asia, more accurate diagnostics with same-day confirmation could ease the connection with treatment.

Make community engagement and empowerment an integral part of the implementation process

The importance of community engagement was strongly embraced by discussants, and the difficulty of "selling" community engagement to donors was brought up, but frustration was expressed around the difficulty of presenting engagement during progress reports of grants.

Develop more professional network around core activities and goals around efforts against VL, modeled after the HAT platform and the Chagas Global Coalition

Prof. Simon Croft pointed out that within the VL and CL communities, there has been some cross-country coordination of activities, but the domains of public health action are not integrated; for instance, there are separate groups pursuing treatment and control in humans and in canine reservoirs. There is one community meeting on leishmaniasis every 4 years, but there is little cross-talk across the separate parts of the community in the intervening time between meetings. As brought up by Dr. Javier Sancho in the context of coalition-building in Chagas disease, defining core three or four goals for the community to rally around would help avoid the frustrations of large groups.