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Moving from control to elimination of Visceral Leishmaniasis in East Africa

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Visceral leishmaniasis (VL) is arguably one of the deadliest neglected tropical diseases. People in poverty bear the largest burden of the disease. Today, the largest proportion of persons living with VL reside in the Eastern African countries of Ethiopia, Kenya, Somalia, South Sudan, and Sudan. These East African countries are among the top 10 countries reporting the highest number of cases and deaths. If left undiagnosed and untreated, VL almost always results in death. Subsequently, there is a need for integrated efforts across human, animal, and vector-control programs to address the scourge of VL in East Africa. In the East African region, the challenges including socio-cultural beliefs, poor health system, political instability, and limited epidemiological understanding impede the implementation of effective VL control strategies. The availability of funding, as well as diagnostics and treatment options, are also devastatingly limited. Furthermore, given the realities of climate change and population movement in the region, to effectively address the scourge of visceral leishmaniasis in East Africa, a regional approach is imperative. In this paper, we highlight some of the key challenges and opportunities to effectively move towards an effective control, and eventually elimination, of VL in East Africa. To do this, we underline the need for a fully integrated program in East Africa, inclusive of effective diagnostics and treatment, to effectively reduce and eliminate the burden of VL in the region, subsequently paving the way to achieve global elimination goals.

KEYWORDS

Visceral leishemanisis, Kalazar, rK39, SSG, DAT, East Africa, VL elimination, Leishmaniasis

Background

Leishmaniasis is a neglected tropical disease disease found in South America, East Africa, the Mediterranean, and Asia. It is caused by *Leishmania species*. According to the World Health Organization (WHO), there are over 20 known *Leishmania species* and over 90 known sandfly species that transmit *Leishmania* parasites through bites of infected female sandflies. The three main forms of leishmania are Visceral Leishmaniasis (VL) also known as kala-azar; cutaneous leishmaniasis (CL); and mucocutaneous leishmaniasis (*WHO*, 2021). In East Africa and the Indian subcontinent, VL is caused by *Leishmania donovani*. In Latin America and the Mediterranean regions VL is caused by *Leishmania infantum* (Abongomera, 2020) (1).

VL is the most serious form of leishmaniasis with a 95% fatality rate among untreated cases (WHO 2021) (1). It is endemic in 79 countries with an estimated annual global incidence ranging from 50,000 to 90,000 cases and 20,000 to 30,000 deaths annually (2, 3). The majority (90%) of infections today occur in Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan, and Yemen (WHO, 2021). Currently, East Africa has the highest burden (57%) of VL in the world, with cases reported in Ethiopia, Eritrea, Kenya, Somalia, South Sudan, Sudan and Uganda (4). Ethiopia (35 deaths in 2019 and 31 in 2020), Kenya (43 deaths in 2019 and 21 in 2020), Somalia (9 deaths in 2019 and 11 in 2020), South Sudan (no data in 2019 and 21 deaths in 2020) and Sudan (52 deaths in 2019, 46 in 2020) were among the top 10 countries reporting the highest VL related fatalities in 2019 and 2020. Several factors including conflict and civil unrest leading to cross border migration into VL-endemic regions, poverty, climate change resulting in changes to rainfall patterns, food insecurity leading to malnutrition, and weak health systems contribute to re-emergent VL outbreaks in these countries (5–7).

Characterized by prolonged fever, weight loss and splenomegaly, VL diagnosis often relies on serological and microscopy tests (8) using the RK39 rapid strip test, direct agglutination test and splenic/lymph node/bone marrow aspiration smears (9, 10). Treatment is further complicated by drug availability, affordability, and toxicity which has implications on treatment approaches. VL requires hospitalization and supervision under qualified clinicians. Pentavalent antimonials like sodium stibogluconate (SSG) are the mainstay of treatment for VL and CL despite numerous drawbacks. First line treatment with Ambisome is available in South Asia with paromomycin-miltefosine as the second line despite their sub-optimal performance and high toxicity levels. Amphotericin B is the most effective treatment for patients with refractory VL in India despite its toxicity and high cost (9). In East Africa a combination of SSG and paromomycin is the current recommended first line treatment (DNDi, 2018) (11)

VL remains a serious public health problem which risks being further pushed into the shadows in the midst of global supply chain disruptions and COVID-19 (12, 13). Repercussions of this will be dire if immediate actions are not taken to address current challenges. In this paper we discuss the challenges and opportunities to the elimination of VL in East Africa from the perspective of stakeholders engaged in the funding and implementation of VL programs in five East Africa countries (Kenya, Ethiopia, South Sudan, Sudan, and Uganda). We review ongoing interventions and reference available literature and program reports to develop our recommendations on actions required to eliminate VL in these countries and other affected countries in the East Africa region.

Current challenges

While the current VL program in East Africa is focused on control, countries are adapting their approaches in line with the WHO roadmap for NTDs 2021 – 2030 that includes VL elimination as a public health problem, defined as a reduction to <1% in case fatality rate due to primary disease (14). However, achieving elimination faces a number of interrelated challenges including: socio-cultural, health system, political, epidemiological, diagnostics and drugs, research, little or no vector control and climate change. Addressing these challenges and their interrelation is critical if the 2030 VL elimination targets are to be achieved.

Socio-cultural challenges

The socio-cultural challenges include low levels of VL awareness, misinformation characterized by traditional beliefs, stigma and the use of local remedies. These contribute to late health seeking behaviors that affect treatment outcomes and disease prognosis (15). Furthermore, there is a paucity of research on specific beliefs around the etiologies of VL in affected communities, despite this understanding being essential to developing tailored public health communication strategies around VL detection and health-seeking behavior.

Health system challenges

Health system challenges in VL endemic areas include a limited number of health facilities with the capacity to diagnose and treat VL; long distances to access care in geographically vast locations that are sparsely populated with patients traveling more than 10 km to health facilities (16); and an inadequate number of skilled personnel coupled with their high turnover (7). Based on the WHO-CHOICE's health economics Geo Access work, access is defined as a travel time of 2 h on foot (8 km in rural areas, 10 km in urban areas) (17). Thus, VL affects poor people who live in areas with weak health systems. VL requires long hospitalization, multiple laboratory tests for

confirmation of the diagnosis, and follow-up of patients. This is not only costly for the patient, but difficult in the absence of strong health systems.

Political instability

Political challenges include civil unrest resulting in the movement of populations to new areas coupled with the poor harmonization of activities between central and local levels of government, and limited cross-border public health collaboration and data sharing (5). With the neglected disease considered as low priority for investment in most affected countries, there is minimal funding towards addressing VL and a lack of sustainability in the implementation of current activities. Migration and population displacement resulting partly from climate/environmental changes and civil unrest further contribute to high incidences of VL (18, 19). Civil unrest and VL epidemics tend to occur among immunologically naïve migrants entering VL-endemic areas or when Leishmania-infected individuals migrate to new areas and establish additional foci of disease (20). Military forces deployed from non-endemic areas, or refugees and displaced persons moving to regions that are endemic for VL are examples of naïve migrants who could acquire the disease related to insecurity (21).

Epidemiology

The epidemiology of VL is also poorly understood, with limited data on VL and PKDL morbidity and mortality, partly due to poor reporting and siloed programs with limited scope and funding. VL co- endemicity with malaria, HIV, and TB complicates diagnosis and treatment strategies. This is exacerbated by limited access to the small number of diagnostic tests and medicines (12) supplied to markets where manufacturers have little if any incentives to produce these essential commodities. Furthermore, the affected countries constantly face supply shortages resulting from weak supply chain management systems. The WHO estimates that only between 25% to 45% of VL cases are reported, reflecting significant underreporting (22).

Research

Research gaps due to lack of resources have resulted in limited understanding and oversight of the role of zoonotic transmission and treatment of reservoirs, or infection carrying/transmitting animals. This limited understanding of vectors and reservoirs of the disease has led to limited one-health strategies for control (18). The research gap between academia and health policy makers result in missed opportunities to translate research outcomes into policies and disease control approaches.

Funding

The UK government's decision to reduce funding for NTDs supported through the ASCEND (Accelerating the Sustainable Control and Elimination of Neglected Tropical Diseases) program in April 2021 (23) led to the few actors involved in VL control and elimination in the field scrambling to find ways to secure the resources to maintain momentum. The ASCEND project, conducted in partnership with several non-governmental organizations (NGO) and government partners, trained various cadres of healthcare workers in VL case detection and treatment, ensured smooth supply chain and necessary clinical inputs, and supported treatments for VL patients at health facilities. The ASCEND programme also supported countries' VL prevention and control goals through improved diagnosis and treatment approaches, strengthening surveillance to improve VL outbreak control, improved VL data collection, reporting and integration into national reporting systems, and strengthening existing VL treatment facilities and activities. In East Africa, ASCEND contributed to the control of VL by ensuring the availability of the necessary diagnostics and treatments (13). Such regional coordination activities aimed at addressing all the challenges to VL elimination are required.

In August 2021, the END Fund with co-funding from ELMA Philanthropies, leveraged its regional experience supporting NTD prevention and control and supported four organizations delivering VL prevention and control across 5 East African countries under ASCEND. The END Fund sought to ensure continuity of planned VL diagnostics and treatments and to support countries by addressing key program quality gaps that were observed during the previous phase.

The status of VL prevention and control in East Africa

The World Health Organization (WHO) compiles VL endemicity, morbidity, and mortality data from all endemic countries and reports it through its website and Global Health Observatory (GHO) portal. However, reporting is dependent on accuracy, completeness, and timely submission of data from the VL treatment health facilities and its validation by each country's health authorities which is often delayed for several months and impedes a real-time view of VL cases and deaths in each location. Issues related to these delays are context specific, but generally even in countries like Kenya where VL data is entered directly into DHIS2, the delay in reporting is often linked to

infrastructural challenges such as lack of access to computers and no or poor internet connection, challenges accessing transportation to visit VL facilities to collect the data before entering them, duration of treatment (currently 17 days), incomplete data capture by clinicians and lab technicians, lack of clear reporting timelines, and other competing programs that pay better (the same Health Records Information Officers enter data for other diseases like malaria and HIV).

Based on WHO's GHO data, the number of VL cases in East Africa has generally been stable in most countries with a steady decline reported in South Sudan from 2016 to 2020. Prior to this period, an outbreak was reported in 2014 (7,472 cases) followed by upsurges in one of South Sudan's endemic states of Jonglei in 2016 & 2017 (24). the decrease in cases is a testimony to the effects of successful control activities and a period of uninterrupted supply of diagnostics and medicines due to support by KalaCORE –a UK aid funded program that supported elimination of VL in select countries (25). Support under the ASCEND grant included procurement of VL medicines and supplies for South Sudan and other supported countries from 2019 to April 2021. However, ASCEND's exit resulted in the interruption of services in some of the facilities.

Kenya has reported steadily increasing cases since 2017. Besides the upsurge of cases in 2014, 2017 and 2019 due to a major outbreak in Marsabit county, cases were reported in Kitui and Garissa counties in 2020, Mandera County in late 2020/early 2021 and Kajiado and Tharaka Nithi Counties in 2021 (26–30). These outbreaks were detected early due to the improved surveillance system established in endemic counties. The increase is also likely a result of the community sensitization activities that have been carried out to improve health seeking behavior in the endemic population. The trends in VL can also be partly attributed to availability of diagnostic and medicines which allows for increased case detection and treatment. Due to limited resources to cover endemic regions, and the emergence of new cases in non-endemic areas such as Kajiado and Tharaka-nithi counties in 2021, there is an urgent need to expand VL services and ensure adequate and uninterrupted supply of diagnostic kits and medicine.

The way forward: addressing current challenges and establishing inter-country and regional coordination mechanisms

The challenges described above make VL elimination out of reach for affected countries in East Africa unless they are addressed. This in and of itself is a stark example of global health inequities, with little attention paid to a deadly and expensive disease that only affects some of the world's poorest people. If we have learned anything from the COVID-19 pandemic, it is that without investment, these inequities will largely go unaddressed, worsening over time.

Access to improved diagnostics and treatments

The availability of effective diagnostics urgently needs to be addressed. While the reference diagnostic method of VL microscopy is highly specific, it remains invasive and requires technical expertise. Thus, serological tests namely; rK39 RDT (31, 32). Direct Agglutination Testing (DAT) (33) and rK28 RDT (34) are the only tests currently available, with varying degrees of test performance. Of these, only the DAT and rk39 are listed in the current WHO's essential diagnostics list (EDL) (35).

The treatment options for VL have also advanced to some degree. As mentioned above, for several decades, treatment was primarily based on pentavalent antimonials (sodium stibogluconate, SSG), administered by intramuscular (IM) injection (alternatively intravenous) over a 30-day period. However, the large volume needed and the drug itself, results in pain at the injection site, coupled with severe side effects that can lead to death (36–38). The side effects coupled with resistance led to the development of new drugs such as paromomycin (PM), miltefosine (MILT) and liposomal amphotericin B (Ambisome). In Eastern Africa, SSG monotherapy was replaced by a combination of SSG with PM, effectively reducing treatment injections nearly in half, to 17 days. While other treatment combinations are being evaluated, oral treatments will enhance patient's compliance to treatment regimens.

VL drugs and diagnostics are noted to be expensive and donor dependent, with suppliers that have expressed an intention to slow down or halt production of some of the most critical products (39). In the East African context, these challenges are exacerbated by population movement linked with conflict and natural disasters and a notable lack of cross-border coordination of epidemiological data sharing for humans, vectors, and reservoirs, hampering the ability to accurately forecast drug and diagnostic needs.

The implementation of passive case detection and test-and-treat strategies when the patients fulfill the clinical case definition, relying on the use of the antibody detection rK39 RDT, has improved VL control. However, more reliable tests will be required to estimate actual disease burden, track disease trends over time, improve diagnosis-treatment algorithms and verify disease elimination (40). Consequently, antigen detection RDTs for VL diagnosis will overcome the limitations of the current antibody RDTs contributing to the VL elimination in endemic regions. The WHO Diagnostic Technical Advisory Group (DTAG) for NTDs also highlighted the diagnostic needs for VL: "Rapid test – more sensitive and specific especially for Eastern Africa and Latin America regions and

tests (serological or other preferably rapid test) – to monitor treatment response or test of cure". These needs remain high on the elimination agenda and must be urgently addressed towards the 2030 targets.

Strategies for transmission interruption

Passive case detection strategies aim to address the late stages of the disease, reduce the case fatality, and hence are critical to achieve the elimination target of <1% mortality. However, more is needed. Interrupting transmission will be critical in controlling the spread of the disease. Active case detection strategies to mop up and treat active VL cases and PKDL in the communities are needed. In India, Nepal, and Bangladesh the proportion of VL cases detected through active case detection was high compared to cases reported through passive detection (40). However, given the current uncertainties about the availability of the IT-Leish rK39 and the diagnostic performance of other existing tests, innovative strategies towards the use of these tests will need to be explored. For PKDL diagnosis, the evaluation of a portable loop-mediated isothermal amplification device (41) offers the opportunity for implementation research towards its use in point of care diagnosis.

Improved coordination

Coordination between actors that need to be involved to effectively control and eliminate VL is a major obstacle. While Ministries of Health often take the lead in VL programs, it is necessary to integrate other intervention options such as vector and reservoir control to achieve effective elimination targets. Yet these areas fall under different ministries in most countries, with limited inter-ministerial coordination and resources to address VL. This leads to notable challenges in monitoring, evaluation, and surveillance of VL with repercussions on the ability to accurately forecast drugs and diagnostic test needs.

Improving the coordination between funders, implementing partners and other stakeholders is imperative. As observed in Kenya, some implementing partners and funders only support specific counties, with activities left uncoordinated between partners, leading to duplication of efforts. Effective interaction between partners would therefore enhance the elimination activities and targeting of resources where most needed.

Strategic plans

Strategic plans are one way to begin effective coordination, particularly when they bring together the different actors that need to be involved in VL control and elimination. In 2021, Kenya developed its 5-year strategic plan for the control of leishmaniasis (Kenya MOH 2021) (42). The Strategic plan has clear objectives and targets which include reduction of VL incidence by 60% and case fatality rate for primary VL to less than 1%. In Ethiopia the VL strategy lies within the national NTD strategic plan 2021 – 2025. In Ethiopia's strategy, VL is targeted for elimination as a public health problem by 2030 and the targets include increasing VL diagnosis and treatment from 29% to 50% and reducing case fatality rates due to primary VL to less than 1%. Sudan has a 5-year national strategic plan (2021 – 2025) that includes VL. The strategic objectives related to VL in Sudan are to increase the number of health facilities providing VL services from 44 to 159, improve hospital adherence to the diagnosis and treatment guideline to 95%, and increase the proportion of primary health care facilities in endemic areas that provide early detection of VL and referral for treatment to 95%. Sudan's strategic plan does not have indicators for reducing the incidence of VL. In Uganda, the VL strategic plan is also nested within the National NTD strategic plan for 2017 – 2022 with the main objective to reduce VL incidence to less than 1 case per 10,000 population. While in South Sudan, there is no specific strategic plan for VL, the disease is mentioned in the national NTD strategy–a crucial document that aims to guide VL activities of the country.

Other endemic countries in East Africa must be guided and supported to develop their strategic plans, similar to what was done in Kenya. Given the cross-border movement of populations in East Africa and climate change which is enlarging the habitat amenable to breeding of key vector species, a regional strategy (modeled after the Southeast Asian strategy) that ensures coordination across borders in East Africa is imperative (18, 43).

The Southeast Asian strategy included early diagnosis and case management, integrated vector management, vector surveillance, effective disease surveillance through passive and active case detection, social mobilization, implementation and operational research, and capacity building as integrated tenants to the region's approach to eliminate VL (44). In addition, the establishment of a memorandum of understanding for intercountry cooperation, a regional advisory group, the coordination between different partners, and the development of technical guidance documents enabled control and elimination activities in the region to be successful. The joint establishment of a regional alliance to eliminate VL in Southeast Asia with the additional involvement of the Ministries of Health from Bangladesh, India, and Nepal initially supported by the WHO in 2005, can be considered as an example for the countries in the East African region to follow (45). Translation of research into practice in public health is also very important towards the elimination of VL as demonstrated by the experience of the Indian sub-continent (46). This regional strategic plan critically needs to include clear guidance and modalities on collaboration including cross-border collaboration.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

KY- contributed to the study design, analysis, writing. DO- contributed to the study design, analysis, writing. LMB- contributed to the study design, analysis, writing. CA- contributed to the study design, analysis, writing. DS- contributed to the study design, analysis, writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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