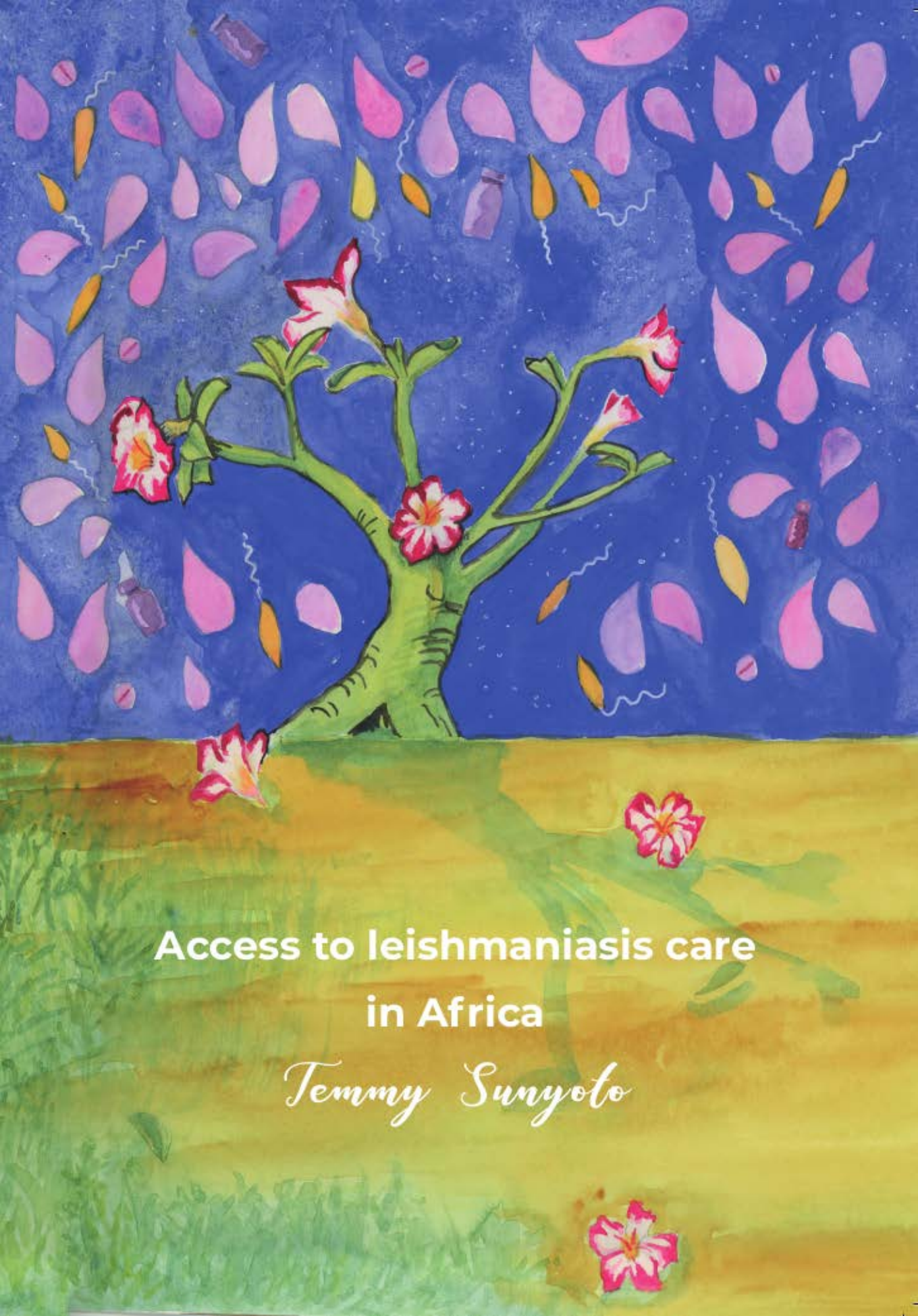
UNIVERSITAT DE BARCELONA

Access to leishmaniasis care in Africa

Temmy Sunyoto



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Cover design by Evelien Jagtman

Description of the cover: *Adenium obesum* or ‘desert rose’ can be found in both Asia and Africa. Here on the front page, the plant symbolises the neglected population which depends on access to resources to flourish. Unprotected from disease and without access to water or medicines, the flowers wilt and the people suffer. The back page, by contrast, depicts the ideal situation where access to resources is adequate, just like it should be.

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Access to leishmaniasis care in Africa

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ACCESS TO LEISHMANIASIS CARE IN AFRICA

Acceso a la atención de la leishmaniasis en África

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“Education is a progressive discovery of our own ignorance.”

Will Durant

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ABBREVIATIONS

AMC	Advanced Market Commitment
API	Active Pharmaceutical Ingredients
CHE	Catastrophic Health Expenditure
CL	Cutaneous Leishmaniasis
COI	Cost of Illness
DALY	Disability Adjusted Life-Years
DAT	Direct Agglutination Test
DCL	Diffuse Cutaneous Leishmaniasis
DHIS	District Health Information System
DND*i*	Drugs for Neglected Disease *initiative*
EML	Essential Medicines List
ERP	Expert Review Panel
FDA	Food and Drugs Administration
FGD	Focus Group Discussions
GBD	Global Burden of Disease
GDF	Global Drug Facility
GF	Global Fund
IDA	International Dispensary Association
IDI	In Depth Interview
IDM	Intensified Disease Management
IDP	Internally Displaced People
IPR	Intellectual Property
IRB	Institutional Review Board
ITM	Institute of Tropical Medicine Antwerp
HIV	Human Immunodeficiency Virus
KAEP	Kala-Azar Elimination Programme
LAMB	Liposomal Amphotericin B
LCL	Localised Cutaneous Leishmaniasis
LST	Leishmanin Skin Test
MCL	Muco-cutaneous Leishmaniasis
MF	Miltefosine
MMV	Medicines and Malaria Venture
MOH	Ministry of Health
MOQ	Minimal Order Quantity
MSF	Médecins sans Frontières
NCE	New Chemical Entity
NDA	New Drug Application
NGO	Non-Governmental Organisation
NTD	Neglected Tropical Diseases
ODA	Orphan Drug Act

OOP	Out-of-Pocket payment
PAHO	Pan American Health Organization
PCT	Preventive Chemotherapy
PM	Paromomycin
PDP	Product Development Partnership
PKDL	Post Kala-azar Dermal Leishmaniasis
PPP	Public Private Partnership
PQP	(WHO) Pre-Qualification Program
PRV	Priority Review Voucher
RDT	Rapid Diagnostic Tests
R&D	Research and Development
SDG	Sustainable Development Goals
SSA	sub-Saharan Africa
SSG	Sodium stibogluconate
TRIPS	Trade Related Aspects of Intellectual Property Rights In
UHC	Universal Health Coverage
US FDA	United States Food and Drugs Administration
VL	Visceral Leishmaniasis
WHA	World Health Assembly
WHO	World Health Organisation
WHO/TDR	WHO Special Program for Research and Training in Tropical Diseases
WTO	World Trade Organisation
YLL	Year(s) of Life Lost

SUMMARY

INTRODUCTION

Leishmaniasis is a group of diseases caused by an obligate protozoan *Leishmania* and transmitted by sand flies. As a neglected tropical disease (NTD), leishmaniasis disproportionately affects the poorest populations and those living in rural, remote areas or conflict zones with limited or no access to health care. Manifesting in cutaneous, mucocutaneous or visceral symptoms, the diseases' complexity and diversity across regions contribute to the challenges in the control efforts. Visceral leishmaniasis (VL) is fatal without treatment, and the indelible scars left by cutaneous leishmaniasis (CL) may have important psycho-social impact.

Eastern Africa region currently bears most of the world's VL burden. However, underestimation of true disease burden is likely, as the paucity of data from unstable contexts may contribute to inaccurate disease estimates. Both VL and CL are known to have limited geographic distribution but may show high variability inter- and intra-countries. Population movement due to conflict or drought, combined with weak or poorly functioning health system have led to epidemics and spread in new areas. Without vaccine or effective vector control, the pillar of control strategy in Africa remains diagnosis and treatment.

Access to adequate, quality diagnostic and treatment services in Africa is challenging. The rk39 rapid test is less accurate and treatment options are limited. A 17-day combination of antimonial and paromomycin is the first line treatment for VL in the region, requiring prolonged hospitalisation and increased economic burden for the patients and their households.

Despite the progress in tackling NTDs, access to care for leishmaniasis is often taken for granted. Especially in Africa, access remains problematic and the current body of literature shows critical evidence gaps. Low coverage of the health services, accessibility and availability of quality care, limited diagnostic and therapeutic options along with inefficient procurement and supply remain significant challenges in the region. Delay in seeking treatment not only increase morbidity and mortality but also sustain transmission.

The hypothesis informing the project is that access to care for leishmaniasis in Africa is still inadequate. The **general objectives** of this thesis are to improve our understanding on access to care in Africa, by documenting availability, affordability and accessibility of care, explore novel ways of enhancing such care, and provide insights into specific elements of access to formulate coherent policy recommendations for leishmaniasis in eastern Africa. Three specific objectives were formulated: the first is to update the disease burden, second to examine access issues 'upstream' i.e. the R&D process and third, assess access issues 'downstream'.

METHODS

Four distinct methodologies were deployed in this research. First, **systematic reviews** (on cutaneous leishmaniasis epidemiological burden in sub-Saharan Africa and economic impact of leishmaniasis), along with **context analysis** (on access to care for VL in Somalia). The systematic review protocols were published and registered in PROSPERO and followed PRISMA guidelines.

On the access upstream part, we conducted a landscape analysis to assess if the public-private partnership (PPP) was a solution to tackle neglected tropical diseases. An **in-depth case study** on miltefosine, the only oral drug for VL, was conducted to analyse its post-licensure access issues. On access downstream, we answered the research questions (a) What were the barriers at the health service level, their supply chain? and (b) What remains the barriers at the community level? through **qualitative research methodologies**. A series of in-depth interviews were conducted with main stakeholders at the global and national level from Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda, as well with former VL patients, community leaders and health care workers from southern Gadarif, Sudan.

MAIN RESULTS

- ***Visceral leishmaniasis care in Somalia***

Somalia has suffered from protracted conflict since 1991 and VL has been reported in southern endemic foci. We reviewed evidence about VL epidemiology in Somalia and appraised control options within the context of this fragile state's health system. The sole VL control option is diagnosis and treatment, which are mostly provided by non-state actors. The availability of VL care in Somalia is limited and insufficient at best, both in coverage and quality. Precarious security remains a significant obstacle to reach VL patients in the endemic areas, and the true VL burden remains unknown. Innovative approaches in VL care provision, adapted to the context and without undermining the health system building process are needed. Existing tools for VL control should be deployed, and critically, efforts to overcome the limitations of the current VL diagnostic and treatment tools in conflict settings should continue.

- ***Epidemiological burden of cutaneous leishmaniasis in sub-Saharan Africa***

We reported the state-of-the-art knowledge on CL epidemiology in sub-Saharan Africa. A synthesis from 54 included papers revealed that 13 of the 48 sub-Saharan African countries had reported CL. Historically, CL has been present for decades in both western and eastern Africa, but unfortunately, data are irregular and patchy. All studies were observational: 29 were descriptive case series (total 13,257 cases), and 24 followed a cross-sectional design. Only 22% of the studies were carried out post-2000. There is a high variability across methodologies, leading to difficulties to compare or combine data. The prevalence in hospital settings among suspected cases ranged between 0.1 and 14.2%. At the community level, CL prevalence varied widely between studies. Outbreaks of thousands of cases occurred in Ethiopia, Ghana, and Sudan. Polymorphism of CL in HIV-infected people is a concern. There is insufficient evidence to have accurate figures, and critical information gaps are population-based CL prevalence/incidence, risk factors, and its

socio-economic burden. It is critical to improve the current fragmented knowledge by increasing commitments to tackle CL and conduct better population studies in sub-Saharan Africa.

- ***Understanding the economic impact of leishmaniasis in endemic countries***

We conducted a systematic review of cost-of-illness studies on leishmaniasis across different settings (Asia, Africa, and Latin America) and the consequences to households. Despite free provision of diagnostics and treatment in the public health care sector, VL cost of illness is a critical barrier in accessing care across different settings, due to both direct out-of-pocket payments and indirect costs of lost productivity. Between 11-57% of the annual household income was spent on VL-related expenses. VL leads to catastrophic health expenditure, continuing poverty and long-term indebtedness despite various coping strategies. The illness cost is decreasing due to shorter treatment regimens in Asia, but the situation remains challenging in Africa. Improvement of control tools is critical. There is a need to update cost estimates to inform policy-making and ensure sustainable solutions to reduce financial barriers to leishmaniasis care, especially in pursuing universal health coverage.

- ***Why miltefosine – a life-saving drug for leishmaniasis – is unavailable for the patients who need it the most?***

Miltefosine, the only oral drug approved for the treatment of leishmaniasis, is considered as a success story of research and development (R&D) by a public-private partnership (PPP). Re-purposed cancer drug in the 1990s, its development showed that PPP is a viable model for promoting R&D in NTDs. At the time, miltefosine constituted a breakthrough treatment. However, access to miltefosine post-licensure remains limited to date. Low availability and affordability have been vital issues globally. The initial PPP agreement which includes access to the public sector is not enforced. Shortages occurred due to inefficient supply chains and use of a sub-standard product led to a high number of treatment failures and deaths. We argued that product development for neglected diseases should aim beyond the registration of the product and ensuring access downstream is imperative. The mechanism(s) to enforce framework and legal agreements between partners need to improve, and loopholes in R&D incentives – such as the Priority Review Voucher – needs fixing. Strategies to expand access to an NTD drug must address affordability as a key obstacle, along with supply-side strategies that assure availability.

- ***Community perspectives on access barriers to leishmaniasis care in Gadarif, Sudan***

Through 24 in-depth interviews (IDI) and 29 focus group discussions (FGDs), with a total of 191 participants, this qualitative study explored the barriers to access kala-azar care in southern Gadarif, Sudan. Our findings describe the multitude of difficulties people face when seeking kala-azar care and illustrate the prevailing hardship in a rural Sudanese context. The various barriers, as experienced and narrated by study participants, is categorised in six emergent themes (the misconceptions, the difficult trajectories to get diagnosed, variable quality of care, taxing journey, gender inequalities and lack of control efforts). Access to health care is always a multi-dimensional phenomenon closely related to the health-seeking behaviour of the population. However, in this region, the perception of illness and care is predominantly shaped by poverty and other structural problems in an extremely resource-constrained setting.

- ***Exploring global and country-level barriers to effective supply of leishmaniasis in eastern Africa: a qualitative study***

An uninterrupted supply chain for leishmaniasis diagnostics and medicines is imperative. On the ground reality is different; quality-assured sources are limited, the procurement process is long, and shortages in health facilities deter care-seeking. Ensuring a reliable supply chain for VL has been chronically challenging due to the context and dependence on external support. From the stakeholders' perspectives, barriers prevail along the supply (manufacturing and selection, forecasting, procurement and distribution) and health system level (financing, regulatory, coordination). Addressing the barriers requires a more unified approach. Our findings indicate that despite the diversity in each country's context, simultaneous efforts and collaboration in policy and implementation are required. Regional coordination and global leadership are vital. Commercial logic of companies needs more bridging towards public health needs in terms of price and availability. With commodities strictly procured by the public and not-for-profit entities, options such as pooled procurement are attractive, albeit hampered by lack of funding and commitment. Drug donations do not erase the need for sustainable access driven from the countries. Availability and procurement of diagnostics have been overlooked significantly.

GENERAL DISCUSSION AND CONCLUSION

Ensuring that all individuals suffering from leishmaniasis have prompt access to effective treatment remains a challenge for resource-constrained health systems. The works in this thesis provide insights into the complexity of access to care for leishmaniasis in Africa, ranging from problematic burden assessment and barriers at the global R&D landscape and further at health system and community levels. Care provision – the primary control strategy in this region through diagnosis and treatment – therefore needs to take into account the persisting barriers. Access programmes operate within complex health systems and contexts; therefore, any isolated strategy may not always or immediately translate into improved patient access. The access framework for leishmaniasis, i.e. care availability, affordability, quality and adoption/acceptance, as used in this thesis, could provide insights into future interventions. Measurement of access should be strived for and further evidence generated.

The current efforts to control leishmaniasis in eastern Africa need to deal first and foremost with access to care, which sadly remains inadequate. Conflict-affected areas require innovative strategies. Developing improved diagnostic and treatment control tools is crucial, and so is ensuring that these tools reach the patients who need them the most.

RESUMEN

INTRODUCCIÓN

La leishmaniasis es un grupo de enfermedades causadas por un protozoo (Leishmania) y transmitidas por flebótomos. Como enfermedad tropical desatendida (NTD, por sus siglas en inglés), la leishmaniasis afecta de manera desproporcionada a las poblaciones más pobres y a las personas que viven en zonas rurales, remotas o en zonas de conflicto con acceso limitado o nulo a la atención médica. Las distintas formas clínicas (cutánea, visceral), la complejidad y la distribución de la leishmaniasis en distintas regiones son algunos de los desafíos para controlar la enfermedad. La leishmaniasis visceral (LV) es mortal si el paciente no recibe tratamiento a tiempo, y las cicatrices dejadas por la leishmaniasis cutánea (LC) pueden tener un importante impacto psicosocial.

Actualmente la mayor carga de LV se concentra en la región de África oriental aunque las cifras disponibles son probablemente una subestimación del número real de casos debido a la falta de datos fiables. Se sabe que tanto la LV como la LC tienen una distribución geográfica limitada, pero pueden mostrar una alta variabilidad tanto entre países como entre zonas en un mismo país. Los movimientos poblacionales debidos a conflictos o sequías, combinado con un sistema de salud débil o con un funcionamiento deficiente, provocan la expansión de la enfermedad a nuevas áreas y la aparición de epidemias. Al no existir una vacuna ni un control efectivo de vectores, el control de la leishmaniasis en África se sigue basando en el diagnóstico y el tratamiento de los casos.

El acceso al diagnóstico y tratamiento adecuados y de calidad para la leishmaniasis es un reto en África. La prueba de diagnóstico rápido disponible (rK39 RDT) tiene una baja sensibilidad y las opciones terapéuticas son limitadas. La tratamiento combinado de antimoniales y paromomicina durante 17 días es el tratamiento de primera línea para la LV en África oriental. Este tratamiento requiere una hospitalización prolongada y representa una mayor carga económica para los pacientes y sus hogares.

A pesar del progreso en la lucha contra las NTD, el acceso a la atención para la leishmaniasis sigue siendo problemático, especialmente en África. La literatura científica identifica deficiencias importantes como la baja cobertura de los servicios de salud, la falta de atención médica de calidad, las opciones diagnósticas y terapéuticas limitadas así como los problemas de suministro de estas herramientas. El retraso en iniciar el tratamiento no solo aumenta la morbilidad y la mortalidad, sino que también mantiene la transmisión de la *Leishmania* en las comunidades. El problema es que las barreras para acceder a la atención sanitaria no se conocen bien.

La hipótesis inicial de este proyecto es que es que el acceso al cuidado de la leishmaniasis en África sigue siendo inadecuado. Los **objetivos generales** de esta tesis son mejorar el conocimiento sobre el acceso a la atención de los casos de leishmaniasis en África, documentando la disponibilidad, la asequibilidad y la accesibilidad de los servicios sanitarios, explorar nuevas formas de mejorar dicha atención y formular recomendaciones de políticas de acceso al cuidado de la leishmaniasis en África oriental. Los tres objetivos específicos son: actualizar los datos sobre

carga de enfermedad así como estudiar los problemas de acceso tanto a nivel de I+D como sobre el terreno.

LOS MÉTODOS

Cuatro metodologías distintas fueron usadas en esta tesis. En primer lugar usamos revisiones sistemáticas sobre la carga de enfermedad de leishmaniasis cutánea en África subsahariana y el impacto económico de la leishmaniasis junto a un análisis de situación del acceso a la atención de la LV en Somalia. Los protocolos de las revisiones sistemáticas se publicaron y registraron en PROSPERO y siguieron las guías PRISMA.

Para estudiar los problemas de acceso a nivel de I+D realizamos un estudio de situación para evaluar si las iniciativas conjuntas entre el sector público y el privado son una solución para hacer frente a las enfermedades tropicales desatendidas. Realizamos un estudio de caso sobre la miltefosina, el único fármaco oral para VL, para analizar sus problemas de acceso posteriores a su comercialización. Para estudiar los problemas de acceso sobre el terreno diseñamos estudios de investigación cualitativa para responder a las siguientes preguntas: a) ¿Cuáles fueron las barreras de acceso a nivel de servicios de salud y de la cadena de suministro? Y b) ¿Cuáles son las barreras a nivel comunitario? Se realizaron una serie de entrevistas en profundidad con las principales actores a nivel mundial y nacional en Etiopía, Kenia, Somalia, Sudán del Sur, Sudán y Uganda, así como con ex pacientes de LV, líderes comunitarios y profesionales sanitarios del sur de Gadarif, Sudán.

RESULTADOS PRINCIPALES

- ***Atención sanitaria de la leishmaniasis visceral en Somalia***

Somalia ha sufrido un conflicto prolongado desde 1991 y se reportan casos de LV en focos endémicos en el sur del país. Revisamos los datos sobre la epidemiología de la LV en Somalia y evaluamos las opciones de control en el contexto del sistema de salud de este "estado frágil". La única opción viable para el control de la LV es el diagnóstico y el tratamiento de los casos que actualmente asumen en su mayoría organizaciones no gubernamentales. La disponibilidad de atención médica de la LV en Somalia es limitada, tanto en cobertura como en calidad. Los problemas de seguridad siguen siendo un obstáculo para acceder a los pacientes con LV en las áreas endémicas, y el verdadero número de casos de LV sigue siendo desconocido. Se necesitan enfoques innovadores para asegurar la atención médica de los casos de LV, adaptados al contexto somalí. Las herramientas existentes para el control de la LV deben implementarse en zonas endémicas, incluyendo zonas donde los conflictos armados persisten.

- ***Leishmaniasis cutánea en el África subsahariana***

Revisamos la epidemiología de la LC en África subsahariana. La revisión de 54 artículos reveló que 13 de los 48 países de África subsahariana han reportado LC. Históricamente, la LC ha estado presente durante décadas en África occidental y oriental, pero desafortunadamente, los datos son escasos e irregulares. Todos los estudios revisados fueron observacionales: 29 fueron series de casos descriptivos (un total de 13,257 casos) y 24 siguieron un diseño transversal. Solo el 22% de

los estudios se realizaron post-2000. Existe una gran variabilidad en las metodologías aplicadas, lo que conlleva dificultades para comparar o combinar datos. La prevalencia de LC en el ámbito hospitalario entre los casos sospechosos osciló entre 0,1 y 14,2%. A nivel comunitario, la prevalencia de LC varió ampliamente entre los estudios. Se produjeron brotes de miles de casos en Etiopía, Ghana y Sudán. El polimorfismo de la LC en personas infectadas por el VIH es un motivo de preocupación para la gestión de estos casos. No hay suficientes estudios para estimar la carga de enfermedad y se desconocen datos críticos como la prevalencia e incidencia de LC en zonas endémicas, los factores de riesgo asociados a la enfermedad y el coste socioeconómico de esta. Es fundamental mejorar el conocimiento fragmentado de la LC y realizar mejores estudios de es esta enfermedad en el África subsahariana.

- ***Impacto económico de la leishmaniasis en países endémicos***

Llevamos a cabo una revisión sistemática de los estudios sobre el costo de la leishmaniasis en diferentes zonas endémicas (Asia, África y América Latina) y las consecuencias para los hogares afectados. A pesar de la provisión gratuita de diagnósticos y tratamiento, el costo de la LV es una barrera crítica para acceder a la atención sanitaria en diferentes entornos, debido a los costos directos e indirectos asociados a la enfermedad. Los estudios publicados estiman que los hogares con un caso de LV gastaron entre el 11 y el 57% de los ingresos anuales en gastos relacionados con la enfermedad. La LV conduce a "gastos catastróficos", pobreza continua y endeudamiento a largo plazo. Aunque el costo de la enfermedad está disminuyendo debido a regímenes de tratamiento más cortos, la situación sigue siendo difícil en África. La mejora de las herramientas de control es crítica. Existe la necesidad de actualizar las estimaciones de costos para desarrollar políticas de salud que reduzcan las barreras financieras a la atención médica de la leishmaniasis, especialmente en la búsqueda de la cobertura sanitaria universal.

- ***¿Por qué la miltefosina, un medicamento que salva vidas, no está disponible para los pacientes que más lo necesitan?***

La miltefosina, la única droga oral aprobada para el tratamiento de la leishmaniasis, se considera una historia exitosa de I+D del modelo de asociación público-privada (PPP por sus siglas en inglés). La miltefosina es un medicamento contra el cáncer que demostró su eficacia contra la leishmaniasis en la década de 1990. El desarrollo la miltefosina demostró que el modelo PPP era viable para promover la I+D en las NTD. En su momento, la miltefosina constituía un tratamiento innovador. Sin embargo, el acceso a la miltefosina después de su comercialización sigue siendo limitado. La baja disponibilidad y la asequibilidad han sido problemas a nivel mundial. El acuerdo inicial que incluía el acceso de este medicamento a través de la sanidad pública en los países endémicos no se cumple en la actualidad. Por ejemplo, las roturas de stock ocurren de forma recurrente debido a cadenas de suministro ineficientes y el uso de un producto de baja calidad llevó a un alto número de fallos terapéuticos e incluso muertes de pacientes. En esta tesis argumentamos que el desarrollo de productos para NTD debe asegurar el registro del producto y el acceso de este por parte de las poblaciones afectadas. El (los) mecanismo(s) para hacer cumplir los acuerdos que aseguran el acceso de estos productos deben mejorar, y los incentivos de I+D para NTD - como el vale de revisión de prioridad de la FDA - deben revisarse. Las estrategias para

asegurar el acceso a un medicamento para el NTD deben abordar la asequibilidad y la disponibilidad.

- ***Barreras al acceso a la atención médica de la leishmaniasis en Gadarif, Sudán***

Realizamos 24 entrevistas en profundidad (IDI por sus siglas en inglés) y 29 discusiones de grupos focales (FGD por sus siglas en inglés), con un total de 191 participantes para explorar las barreras al acceso a la atención médica de la leishmaniasis visceral en el sur de Gadarif, Sudán. Los resultados del estudio describen la multitud de dificultades que enfrentan las personas cuando buscan atención médica para esta enfermedad e ilustran las dificultades para el manejo de la LV en el contexto rural de Sudán. Las diversas barreras, según lo vivido y narrado por los participantes del estudio, se clasifican en seis temas: conceptos erróneos, dificultades para obtener un diagnóstico correcto, la calidad de la atención médica, el coste de acceder a la atención sanitaria, las desigualdades de género y la falta de medidas de control de la LV. El acceso a la atención médica es siempre un fenómeno multidimensional relacionado estrechamente con el comportamiento a la hora de buscar servicios de salud de la población. En esta región, el conocimiento de la enfermedad y la búsqueda de atención sanitaria están determinadas por la pobreza y otros problemas estructurales en un entorno donde los recursos son extremadamente limitados.

- ***Las barreras a nivel mundial y nacional para el suministro efectivo de herramientas para diagnosticar y tratar la leishmaniasis en África oriental : un estudio cualitativo***

El continuo suministro de herramientas para el diagnóstico y tratamiento de la leishmaniasis es imperativo para asegurar la asistencia médica en zonas endémicas. En el terreno la realidad es diferente: las empresas que aseguren productos de calidad son limitadas, el proceso de adquisición es largo y complejo, y hay una escasez de centros de salud que ofrezcan atención médica adecuada. Asegurar una cadena de suministro confiable para LV ha sido un desafío crónico. Desde la perspectiva de las organizaciones implicadas en el control de la LV, las barreras prevalecen a lo largo de la cadena de suministro (producción, adquisición y distribución de diagnósticos y medicamentos) y a nivel de los sistemas de salud (financiación, reglamentación y coordinación). Los resultados de nuestro estudio indican que a pesar de las diferencias entre países, se requieren esfuerzos coordinados para implementar políticas conjuntas. La coordinación regional y el liderazgo global son vitales. Las empresas que producen productos para el control de la LV deben entender las necesidades de los sistemas de salud públicos en términos de precio y disponibilidad en los países endémicos. El hecho que los productos médicos para la leishmaniasis sean adquiridos exclusivamente por el sector público y organizaciones sin fines de lucro hace que estrategias como compras agrupadas o conjuntas sean opciones atractivas para asegurar el suministro de herramientas. Pero estas iniciativas están comprometidas por la falta de financiamiento y compromiso a largo plazo. En los últimos años se han producido donaciones de medicamentos para la leishmaniasis pero estas no sustituyen la necesidad de asegurar un acceso sostenible impulsado por los países endémicos. Disponibilidad y distribución de diagnósticos para la leishmaniasis en estos países siguen sin estar resueltos.

DISCUSIÓN GENERAL Y CONCLUSIÓN

Asegurar que todas las personas que sufren de leishmaniasis tengan acceso rápido a un tratamiento efectivo sigue siendo un desafío para los sistemas de salud en países endémicos. Los trabajos en esta tesis proporcionan información sobre la complejidad del acceso a la atención medica de los casos de leishmaniasis en África, que van desde la falta de información sobre la carga de enfermedad, las barreras en I+D y los problemas a nivel de los sistemas de salud y las comunidades en zonas endémicas. El acceso a la atención médica, la estrategia de control principal de esta enfermedad en África, debe tener en cuenta las barreras de acceso descritas en esta tesis. Los programas de acceso operan dentro de sistemas y contextos de salud complejos; por lo tanto, cualquier estrategia aislada puede no siempre o inmediatamente traducirse en un mejor acceso para el paciente. El marco o estrategia para mejorar o asegurar la disponibilidad de atención médica para la leishmaniasis en África propuesta en esta tesis puede usarse para guiar futuras intervenciones.

Los esfuerzos actuales para controlar la leishmaniasis en África oriental deben ocuparse primero y principalmente del acceso a la atención médica, que lamentablemente sigue siendo inadecuada. Las áreas afectadas por conflictos requieren estrategias innovadoras. El desarrollo de mejores herramientas de diagnóstico y tratamiento es crucial, pero también asegurar que estas herramientas lleguen a los pacientes que más las necesitan.

ARTICLES INCLUDED IN THE THESIS

1. **Visceral leishmaniasis in Somalia: A review of epidemiology and access to care**
   Sunyoto T*, Potet J, Boelaert M*.
   PLoS Negl Trop Dis. 2017 Mar 9;11(3):e0005231. doi: 10.1371/journal.pntd.0005231.

2. **Uncharted territory of the epidemiological burden of cutaneous leishmaniasis in sub-Saharan Africa-A systematic review**
   Sunyoto T, *Verdonck K, El Safi S, Potet J, Picado A, Boelaert M.*
   PLoS Negl Trop Dis. 2018 Oct 25;12(10):e0006914. doi: 10.1371/journal.pntd.0006914.

3. **Understanding the economic impact of leishmaniasis on households in endemic countries: a systematic review**
   Sunyoto T, *Boelaert M, Meheus F.*
   Expert Rev Anti Infect Ther. 2018 Dec 4. doi: 10.1080/14787210.2019.1555471.

4. **Why miltefosine-a life-saving drug for leishmaniasis-is unavailable to people who need it the most**
   Sunyoto T*, Potet J, Boelaert M*.
   BMJ Glob Health. 2018 May 3;3(3):e000709. doi: 10.1136/bmjgh-2018-000709.

5. ***"Kala-Azar is a Dishonest Disease"*: Community Perspectives on Access Barriers to Visceral Leishmaniasis (Kala-Azar) Diagnosis and Care in Southern Gadarif, Sudan**
   Sunyoto T, *Adam GK, Atia AM, Hamid Y, Babiker RA, Abdelrahman N, Vander Kelen C, Ritmeijer K, Alcoba G, den Boer M, Picado A, Boelaert M.*
   Am J Trop Med Hyg. 2018 Apr;98(4):1091-1101. doi: 10.4269/ajtmh.17-0872.

6. **Exploring barriers towards an effective supply of leishmaniasis drugs and diagnostics in eastern Africa: a qualitative study**
   Sunyoto T*, Potet J, den Boer M, Ritmeijer K, Postigo JAR, Ravinetto R, Alves F, Picado, Marleen Boelaert*
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CHAPTER 1
INTRODUCTION

A kala-azar patient rests at a Médecins Sans Frontières hospital in Lankien, South Sudan, 2015

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1. GENERAL INTRODUCTION

Leishmaniasis is the common denominator for a group of neglected, stigmatising, tropical diseases caused by an obligate protozoan parasite - *Leishmania* sp.- and transmitted by sand flies. They either have cutaneous, mucocutaneous or visceral manifestations and disproportionately affect the poorest of the poor with little or no access to care. Visceral leishmaniasis (VL), also known as kala-azar, is a slowly progressive systemic infection that is life-threatening, and represent the leading focus of this thesis. The eastern Africa region reported the highest VL burden in the world in 2016[1], with 30-57,000 cases reported annually[2], though the paucity of data from conflict-affected countries like Somalia may contribute to inaccurate disease burden estimates. Underestimation of the actual disease burden is thus likely. The geographic distribution of VL is generally limited to well-identified foci within endemic countries, but it can also suddenly emerge in new areas, sometimes leading to deadly epidemics. In Europe, VL has (re)emerged as an opportunistic infection for the immunosuppressed people, including those infected by Human Immuno-deficiency Virus (HIV).[3–5] Contextual elements such as social unrest, drought and famine, conflicts leading to population movement, and weak or poorly functioning health systems have further hampered control measures[6].

VL patients in the eastern Africa region face extreme challenges to access effective, quality-assured diagnostic and treatment services for their ailment. The rK39 rapid diagnostic test (RDT) introduction has allowed easier diagnosis at peripheral health centres, but its sensitivity is sub-optimal in Africa[7,8]. The medicines used to treat leishmaniasis are problematic in regards to safety, resistance, cost and varied effectiveness[9]. Pentavalent antimonials (sodium stibogluconate or SSG and meglumine antimoniate) has been the mainstay treatment since the 1940s, and together with an old antibiotic – paromomycin(PM) – comprised two key medicines. Currently, a 17-day combination of SSG/PM is the first-line recommended regimen to treat VL in the region[10]. Though this combination is shorter than the previously recommended 30 days SSG monotherapy, it still requires prolonged hospitalisation and painful double injections. Conventional amphotericin B is an alternative despite its renal toxicity, while its liposomal form (AmBisome®) unfortunately is not as effective in eastern Africa as it is in other regions of the world. The only oral medicine, miltefosine (MF) is only used compassionately, especially for VL/HIV co-infection[11,12]. Better, more appropriate drugs are needed, but the required R&D is lagging behind, for the same reasons as for other neglected tropical diseases (NTD)[13] : little interest from industry because of the non-viable market and little interest from the public sector as NTDs are considered minor issues in the face of competing for health priorities. Public-private partnerships have been proposed as a way out of this conundrum, along with other 'push and pull' mechanisms[14,15].

In eastern Africa, problems with leishmaniasis care are currently rampant from source to the stream. The availability of the drugs mentioned above that are essential for clinical care is compromised by the inability of patients to pay, by a shrinking market volume due to the downward trend in VL incidence in South Asia, and by the lack of competition as most drugs are produced by virtually a single manufacturer[16]. Moreover, the availability and affordability of quality-assured leishmanial medicines in endemic countries are also hampered by weak supply chains and pharmaceutical management[17]. Even where diagnosis and treatment are provided for

free at public health facilities, VL patients and families still have to pay out-of-pocket for other non-medical costs, such as transport or food for caretakers for prolonged periods[18,19]. The cost to seek care results in catastrophic health expenditure for the family and poses as one of the main barriers to accessing quality treatment for leishmaniasis in Africa. Other barriers perceived by the community may be linked to socio-cultural factors and health-seeking behaviour in a particular context. If unaddressed, these barriers lead to delay in seeking treatment which worsens the clinical prognosis for the patient but also foster continued transmission[20]. In eastern Africa, these barriers are still poorly understood.

Ensuring that all individuals suffering from leishmaniasis have prompt access to life-saving effective diagnosis and treatment remains a challenge for resource-constrained health systems. The lack of R&D for leishmaniasis further exacerbates this sub-optimal access. VL care in eastern Africa disproportionately lags behind compared to the standards of care in southern Europe and other regions in the world. Against this backdrop, I conducted this research project focusing on the access continuum for leishmaniasis in Africa. Investigating 'access' to an NTD requires a broad horizon encompassing the dimensions of availability, affordability, quality and adoption. The following paragraphs will provide an overview of the state of knowledge that informed my research questions at the start of this thesis project.

2. LEISHMANIASIS

Apart from being a poverty-related disease, leishmaniasis is characterised by both diversity and complexity[21]. More than 20 species of *Leishmania* genus can cause the disease, with close to 100 medically important species of sand flies (genus *Phlebotomus* and *Lutzomya*) as vectors (**Figure 1**). The parasite reservoir can be human (in anthroponotic forms of the disease) or animal (zoonotic), depending on species. Leishmania parasites are transmitted through the bites of infected female phlebotomine sand flies, which feed on blood to produce eggs. The epidemiology of leishmaniasis depends on the characteristics of the parasite and sand fly species, the local ecological characteristics of the transmission sites, current and past exposure of the human population to the parasite, and human behaviour.

The leishmaniasis is endemic in many tropical and subtropical regions in large areas of South Asia, the Middle East and North Africa (MENA), eastern Africa, the Mediterranean basin and Latin America. The World Health Assembly enshrined the importance of leishmaniasis control in resolution WHA60.13 in 2007[22]. Approximately 1.7 billion people, or one-quarter of the world's population, live in areas where they are at potential risk of leishmaniasis[23]. Leishmaniasis rank as a leading NTD in the 2017 Global Burden of Disease study, in terms of morbidity and mortality, causing an estimated 774 (range 199 to 2720) thousand DALYs (Disability Adjusted Life Years), of which VL contributed to 511(1,02 to 2440)[24].

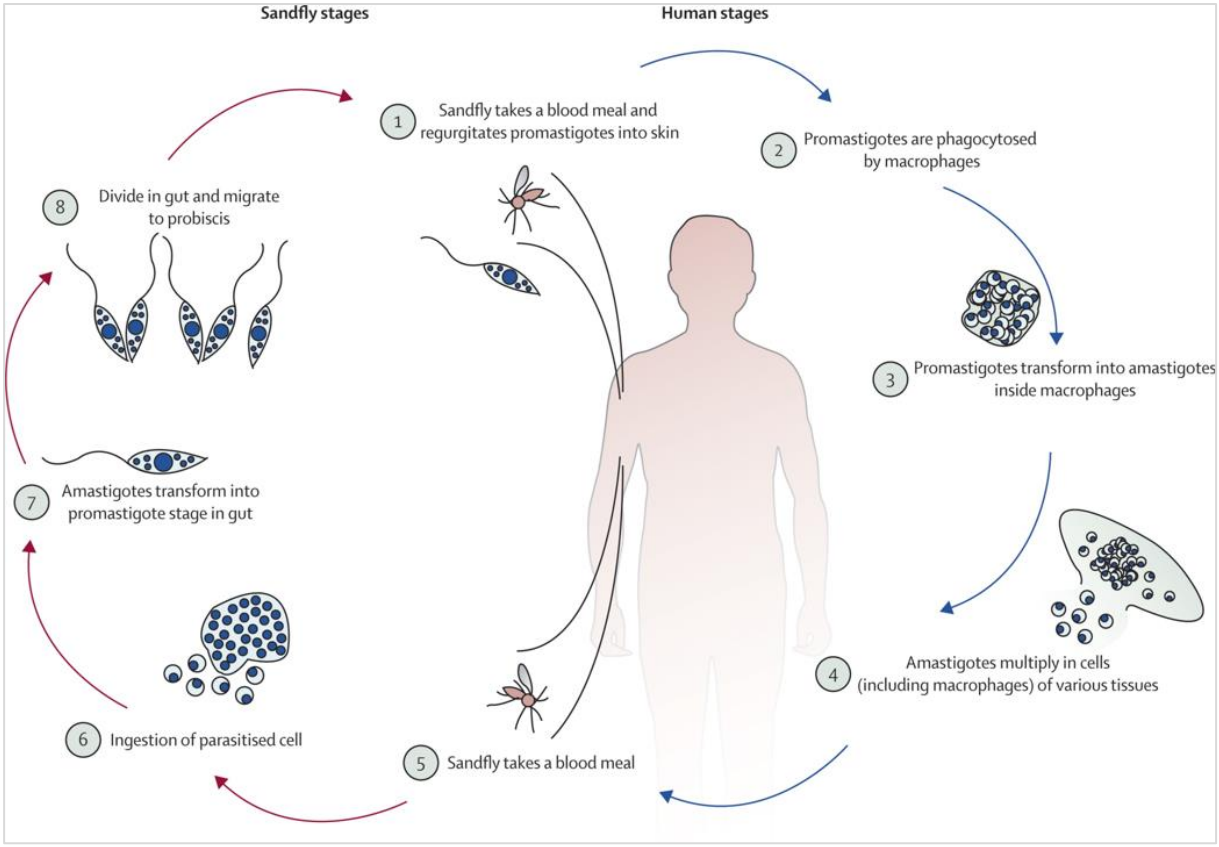

Figure 1. The life cycle of leishmaniasis
Source: Reithinger et al., The Lancet Infectious Diseases, 2007; 7(9): 581-596 doi: 10.1016/S1473-3099(07)70209-82007; reproduced with permission from Elsevier

The most frequent clinical form of leishmaniasis is cutaneous (CL), estimated at 0,7 to 1,2 million cases per year with up to 10% of cases progress to severe manifestations (disseminated, diffuse or mucocutaneous forms)[25]. The CL skin lesions, typically appear as ulcers on exposed parts of the body, may leave life-long scars and serious disability or stigma. Forced migration and lack of control measures were drivers of increased CL incidence in recent years, for example in Iraq, Lebanon, Pakistan and Syria[26]. More than 95% of global CL cases in 2017 are reported from Afghanistan, Algeria, Brazil, Colombia, Iran (Islamic Republic of), Iraq, and the Syrian Arab Republic. Mucocutaneous leishmaniasis (MCL) is the form with partial or total destruction of mucous membranes of the nose, mouth and throat. Over 90% of mucocutaneous leishmaniasis cases occur in Bolivia (the Plurinational State of), Brazil, Ethiopia and Peru. VL is fatal without adequate treatment and may have sequelae in the form of Post Kala-azar Dermal Leishmaniasis (PKDL). PKDL appears as macular, maculopapular or nodular skin rash and may self-heal as observed in Sudan[27], though its importance as driver of transmission has gained importance in the ongoing elimination initiative in the Indian subcontinent[28,29].

GLOBAL EPIDEMIOLOGY AND CONTROL OF VISCERAL LEISHMANIASIS

VL or kala-azar is a systemic disease characterised by persistent irregular fever and hepatosplenomegaly. It is caused by the *Leishmania donovani* in Asia and Africa, and *L. infantum* in northern Africa, the Mediterranean region and Brazil. Previous VL estimates, based on 2008 surveillance data reported to WHO, were 200,000-400,000 cases with 20,000-40,000 deaths annually[2]. Based on 2014 data, the current estimate is between 50,000-90,000 cases per year, distributed in 75 countries (**Figure 2**)[1,22]. Currently, 78% of global VL cases occur in four countries: Brazil, India, South Sudan, and Sudan. Together with Kenya, Ethiopia, and Somalia, these seven countries represent 90% of VL cases worldwide.

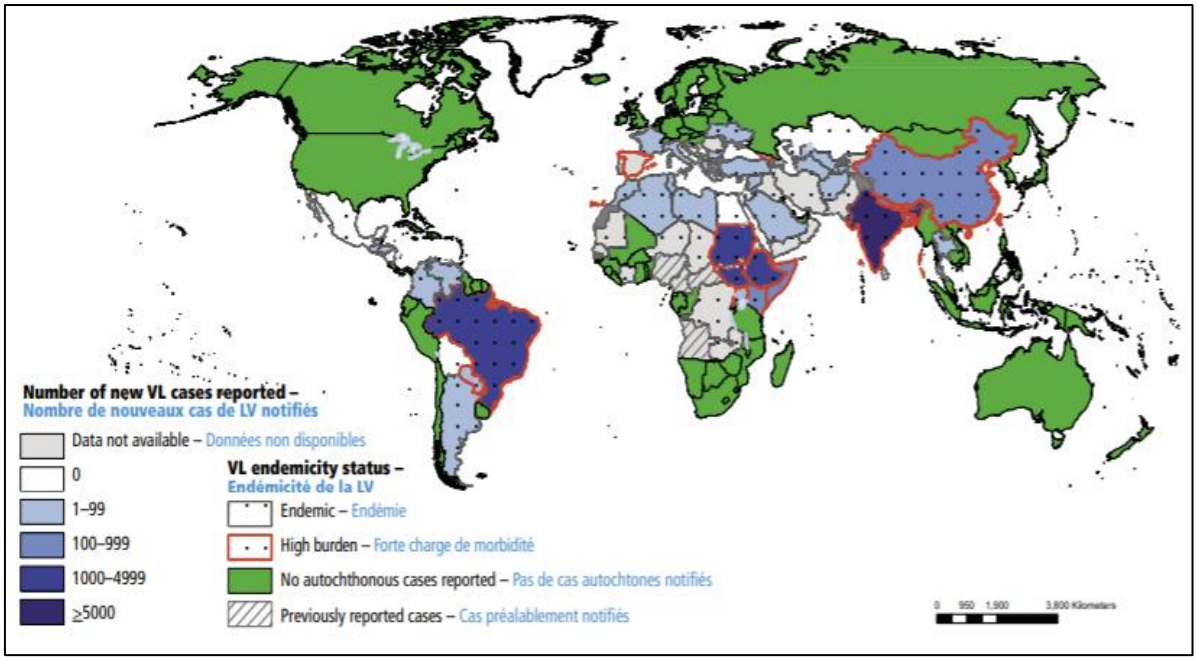

Figure 2. Status of endemicity of visceral leishmaniasis worldwide, 2016
Source: WHO, 2018 available at https://www.who.int/wer/2018/wer9340/en/

The bite of female sand flies, either of the *Phlebotomus* spp. (in the Old World) or the *Lutzomyia* spp. (in the New World), maintain VL transmission, either with humans as the only reservoir (anthroponotic transmission), or involving animals (zoonotic transmission). Domestic dogs, rodents, sloths, and opossums are amongst a long list of mammals that are either incriminated or suspected reservoir hosts[30]. Prevention and control strategies recommended by WHO vary according to the region based on transmission dynamics and available evidence. These include diagnosis and treatment, vector control (using chemical molecules or through environmental management), control of reservoir hosts, along with surveillance and social mobilisation. To this date, the quest to develop leishmaniasis vaccine still continues.

In 2005, the governments of Bangladesh, India and Nepal signed a Memorandum of Understanding to eliminate VL from the region, and this elimination initiative has since drawn considerable support from the international community[31,32]. In the Indian subcontinent, certain epidemiological features render elimination technically possible, i.e. humans are the only reservoir and the only involved sand fly species (*Phlebotomus argentipes*) is still susceptible to

insecticides. Along with the availability of improved control tools (the rK39 RDTs and oral miltefosine) and the level of political commitment, WHO considered it operationally feasible to reduce the burden of VL to a level at which it is no longer a public health problem (defined as incidence of fewer than 1/10,000 cases per sub-district) by 2015. This deadline has since been extended to 2020. The incidence has indeed notably declined since 2005, and Nepal and Bangladesh both reached the target. However, the natural cyclical epidemiological pattern might contribute to the rapidly declining incidence in this region[25].

The VL elimination remains unfeasible in eastern Africa, as the endemic region is affected by civil unrest, the diagnostic and treatment tools are suboptimal, and the epidemiological parameters are different, with multiple vectors and most likely, an animal reservoir[33,34]. In eastern Africa, the VL burden is steady and even increasing, whereby under-reporting of cases remains a continued concern. When control programmes rely on passive case detection only, as they do in eastern Africa, there is a significant proportion of leishmaniasis patients who remain undetected and untreated. Several major VL epidemics of VL have been building up in the past, driven by population displacement due to conflicts, such as in Somalia and South Sudan[35,36]. A high co-infection rate with HIV, up to 20% in Ethiopia, has also made control efforts more challenging[37].

CLINICAL MANIFESTATION, DIAGNOSTICS AND TREATMENT STRATEGIES

A *Leishmania* infection does not always lead to clinical disease as asymptomatic infections outnumber the clinical cases. When symptoms occur, the onset can be acute or insidious; the incubation period of VL varies between 2 weeks and eight months. Suspected cases of VL typically have prolonged fever (of ≥2 weeks), spleen enlargement and weight loss, along with pancytopenia, hepatomegaly and hypergammaglobulinemia. If left untreated, the disease progresses with time, causing debilitation, bleeding, susceptibility to secondary infection and, eventually, death.

Early and accurate laboratory diagnosis is essential before initiating treatment as the clinical features of VL are non-specific and may resemble those of several other diseases including malaria or other conditions (infectious and not-infectious). Furthermore, available drugs are potentially toxic and in general require hospitalisation. On the other hand, undiagnosed cases would result in death without timely treatment and would maintain transmission. Correctly diagnosing VL, therefore, is essential for case management of VL.

Parasitological diagnosis remains the gold standard in VL diagnosis, because of its high specificity. The microscopic examination of Giemsa-stained smears could be done from spleen (highest sensitivity: >90%), bone marrow (sensitivity 50-70%) and lymph node. Spleen aspiration is invasive and carries a risk of bleeding, estimated at 1/1000 procedures[38]. Serology-based tests are available, such as ELISA, immunofluorescence and western blot, but they still require well-equipped laboratory and skilled personnel and therefore their use is limited. Based on this gap, two serological tests have been specifically developed for field use: the direct agglutination test (DAT) based on the freeze-dried antigen and the rK39 immunochromatographic test (generally referred to as the 'rK39 RDT'). The latter offers more advantages as RDTs are simpler to perform and provide result faster, making them convenient for use at peripheral health centres. However,

the rK39-RDTs' diagnostic accuracy varies between regions, with excellent sensitivity in the Indian subcontinent (97%, 95% CI 90-100) but only 87% (95%CI 75-93) in east Africa[39]. Another limitation of antibody tests is their inability to differentiate past and current cases. Several antigen-based tests are being developed to overcome this, though their use is still limited. This includes a latex agglutination test (sensitivity 64% [95% CI 41-86]) and IgG1 based-tests[40]. More sophisticated techniques such as molecular diagnostics are expensive and rarely available outside specialised centres. The health system level where diagnostic tools are deployed or made available have to be considered, for example between primary centres, district hospitals and other tertiary level.

All medicines for VL were initially developed for other indications, except the ancient compound antimony that has been widely used in the early modern medicine (see **Table 1**). Significant advances have been made in the past decades, owing mainly to the efforts of non-profit organisations, including WHO's Special Program for Research and Training in Tropical Diseases (TDR), or public-private partnership entities such as Drugs for Neglected Diseases *initiative* (DND*i*), Institute for One World Health, and Non-Governmental Organisations (NGOs) such as Médecins Sans Frontières (MSF), and others. Treatment guidelines are not uniform because of different levels of efficacy according to regions, and each of the treatment options has significant limitations[41]. Combination treatments with existing drugs have also been advocated to optimise the efficacy and safety of treatment, reduce costs and hospitalisation time, and to prevent resistance[42]. In the Indian subcontinent, the combination of MF+PM is included as second-line treatment, while other combinations such as LAMB+MF and LAMB+PM have also been evaluated in clinical trials[43–45].

Table 1 Currently available medicines to treat visceral leishmaniasis

Medicine	Pentavalent antimonials	Amphotericin B deoxycholate	Liposomal amphotericin B (AmBisome)	Miltefosine	Paromomycin
Dosing*	20 mg/kg/day; 30 days	1 mg/kg on alternate days (15 doses in 30 days)	10 mg/kg (SD for ISC); 30 mg/kg total dose (Africa)	2.5 mg/kg/day over 28 days	15 mg/kg for 21 days
Route	IV or IM	IV	IV	Oral	IM
Efficacy	35-95% (depending on region)	>95% all regions	>90% (Asia, Europe, Brazil)	91% (India), Africa not established	91%$
Resistance	60% in Bihar, India	Not documented	Not documented	Prone (proven in vitro)	Lab isolates
Safety profile	Poor: arrhythmias, pancreatitis, hepatotoxicity, nephrotoxicity	Poor: nephrotoxicity (in-patient care needed), infusion-related fever	High; minor/no nephrotoxicity, mild infusion-related (shivering)	Moderate: gastrointestinal, nephro/ hepatotoxicity, teratogenic	Minor/no nephrotoxicity, reversible audiotoxicity
Issues	Prolonged treatment, painful injections, toxicity	Prolonged treatment needs slow IV infusion	Need slow IV infusion with complex preparation, heat stability (storage <25°C), single quality-assured source (AmBisome®) Efficacy variable across the region	High price; Low compliance if monotherapy, required contraceptive for women in reproductive age; resistance potential, single quality-assured source	Pain at injection site, prolonged treatment Efficacy variable between and within the region

IV-intravenous; IM-intramuscular
* Note that monotherapy is no longer recommended as first-line treatment (except LAMB for India, Nepal and Bangladesh), and the dosage may differ when used in combination therapy. See Table 3. $ when used as combination treatment with antimonials for 17 days in eastern Africa.

SSG, when used alone in eastern Africa, requires 30 days of painful daily intramuscular injections and may cause serious (cumulative) toxic side effects. PM, an aminoglycoside, needs to be administered in combination with another drug in order to optimise its use. African countries switched to the WHO-recommended combination regimen of 17 days SSG/PM (both intramuscular injections) in 2011. Miltefosine (MF), the only oral medicine, is contra-indicated during pregnancy, and is susceptible to develop resistance with a single point mutation due to its long half-life. Used in monotherapy, its treatment duration is 28 days and requires strict adherence, with contraceptive provision for at least three months post-treatment[46]. Conventional Amphotericin-B deoxycholate is a cumbersome treatment that needs to be given in slow intravenous (IV) infusions daily or every other day for 15 doses. Careful hydration and potassium intake of patients are needed to avoid renal toxicity and hypokalaemia. Its liposomal form, LAMB/AmBisome® is administered intravenously and must be stored and transported in a manner that ensures the vial is not exposed to temperature over 25˚C. Its current cost remains an important barrier to treatment[47] though the manufacturer has previously set an access price, and later agreed to donate the drugs for VL treatment in several countries since 2011, facilitated by WHO[48,49]. LAMB has excellent efficacy and safety profile, either when used alone or in combination with an oral drug. However, LAMB in Africa is less effective and requires higher doses compared to the Indian subcontinent[50]. Currently, it is used in treatment failures, severely ill patients, those co-infected with HIV, pregnant women and those under two and over 45 years of age[51–53] . The pursuit of finding the most effective regimen is still ongoing, and particularly for Africa, the quest is longer and admittedly more difficult.

3. LEISHMANIASIS IN AFRICA

EPIDEMIOLOGY AND BURDEN OF LEISHMANIASIS IN EASTERN AFRICA

With the declining incidence in the Indian subcontinent, eastern Africa is now the region with the highest VL burden in the world. Sudan is the most affected country, followed by South Sudan, Ethiopia, Somalia, Kenya, and Uganda[1]. Eritrea and Djibouti have reported leishmaniasis cases in the past. This region showed an increasing trend in the proportion of the global burden of VL, from 9602 cases (40%) in 2015 to 11,215 cases (50%) in 2016[1], and believed to have 6-10 years cyclical patterns (**Figure 3**). Historically, leishmaniasis has been reported since the early 20th century by medical officers during colonial times [54,55]. It is difficult to assess the real burden of VL[56], but a cross-sectional survey in Gadarif in eastern Sudan revealed an overall incidence of VL in 2010 of 7.0/1000 persons per year. 12.5% of the population reported a past VL treatment episode[57]. A considerable variation between villages or clusters has been reported, while evidence on risk factors are mixed[58–62].

[1] South Sudan gained their independence from Sudan in July 2011. In the older literature, Sudan and South Sudan were reported as one country. Sudan and Somalia belong to WHO Eastern Mediterranean Region (EMRO) while Ethiopia, Kenya, Uganda and South Sudan belong to WHO African Region (AFRO)

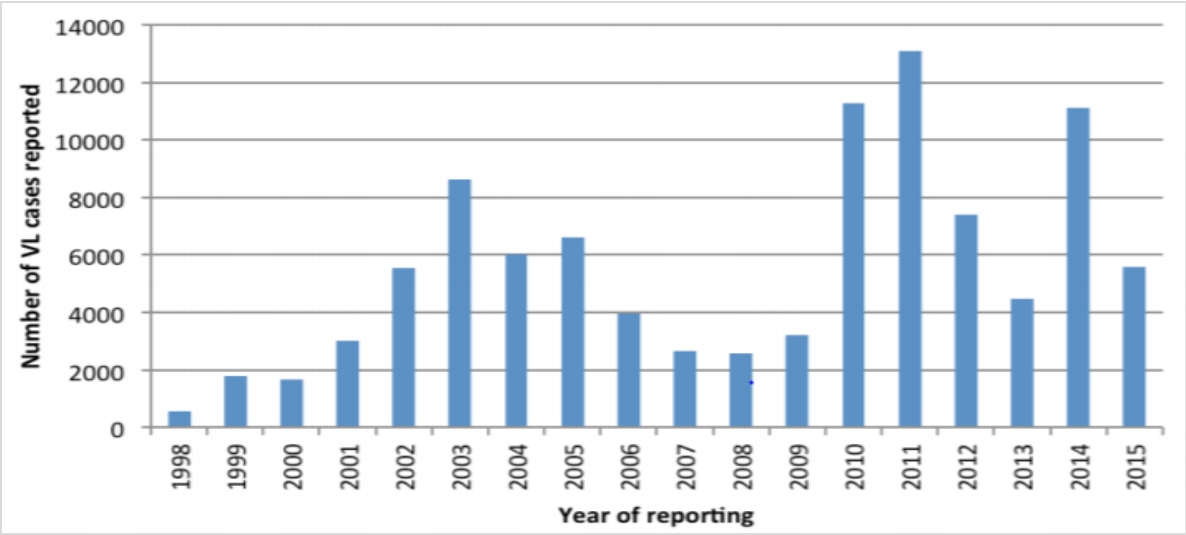

Figure 3. Reported cases of visceral leishmaniasis in the African region (1998-2015). Source: WHO

Transmission is considered as largely anthroponotic in this region[21], and the role of an animal reservoir is unclear despite the discovery of parasite DNA in dogs and rodents[63,64]. The known principal vectors of *L. donovani* are *Phlebotomus orientalis, Ph. martini* and *Ph. celiae*[65]. *P. orientalis* occupy a distinct habitat characterised by the presence of chromic vertisols (black cotton soils) that form large cracks during the dry season, and are covered with *Balanites aegyptiaca* and *Acacia seyal* trees; while *Ph. martini* and *Ph. celiae* are associated with termite mounds. The latter can be found in foci in Somalia, Kenya and Ethiopia. VL spreads over a broad belt from the Atbara river in the north-east along the Sudanese-Ethiopian border to the south of the Sobat river and Nassir and Malakal and extending west across the White Nile (see **Figure 4**).

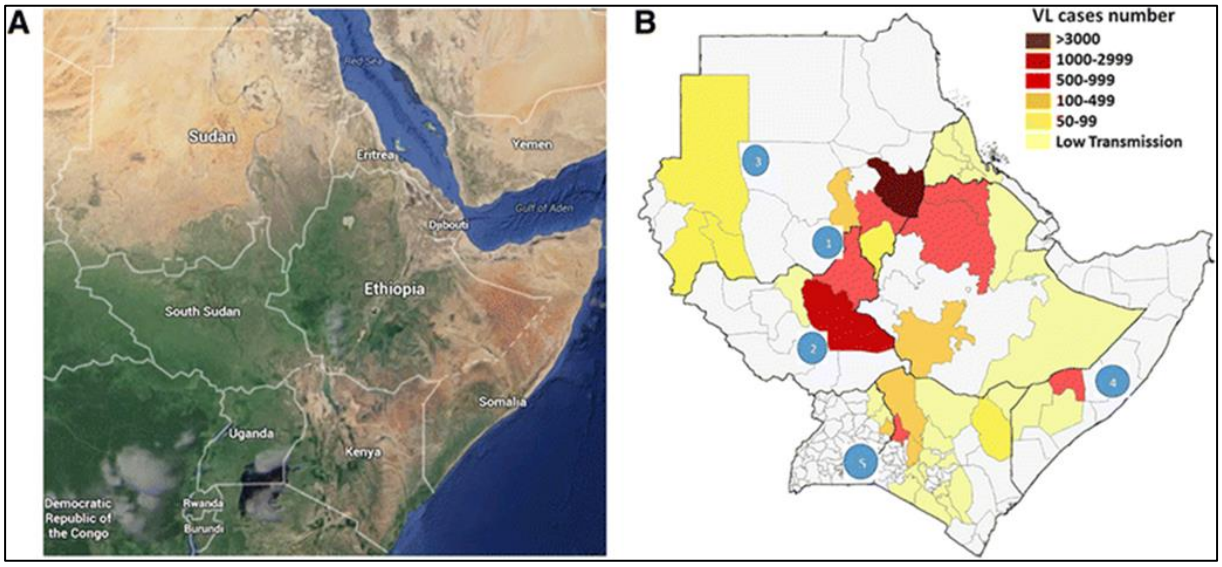

Figure 4. Distribution of visceral leishmaniasis (VL) cases in East Africa.
A. This satellite image is taken from Google Maps; B. The distribution of VL for each region or state within East African countries. The largest affected area in terms of number of cases is the eastern region of Sudan and neighbouring Ethiopia (Area 1), followed by South Sudan (Area 2), Darfur and Western Sudan (Area 3), and Somalia (Area 4), and Kenya with North-East Uganda (Area 5) Source (with permission): Saleem et al. Parasites & Vectors2016, 9:460DOI: 10.1186/s13071-016-1743-7

The epidemiology of VL in eastern Africa is particularly driven by its context. The violent conflicts of the past 40 years have induced massive movements of susceptible or infected populations into VL-endemic or non-endemic areas, respectively, triggering major epidemics. Sustained droughts have led to widespread malnutrition and famine, known to be risk factors for VL. Conflict and drought probably caused the most massive VL epidemic ever recorded, during the 1980s in southern Sudan, where VL killed an estimated one-third of the 280,000 population of a district[3]. An outbreak starting in 2009 in Upper Nile, Jonglei, Unity and Eastern Equatoria provinces of South Sudan caused over 32,000 cases[36,66]. Following a clash in December 2013, another outbreak occurred in 2014 with close to 8000 cases reported[4], and to date the disease trends are unpredictable. Refugees fleeing the conflict in Somalia caused an outbreak in Dadaab refugee camp in Kenya. The ensuing investigation established the existence of a VL endemic area in Bakool region in Somalia, where they came from[67]. Another epidemic in the non-endemic area of Libo Kemkem, Ethiopia was confirmed to be VL, though initially thought to be caused by drug-resistant malaria[68,69]. Partly attributed to seasonal population movement, i.e. the labour migration from highland to the lowland to work in agricultural farms, this phenomenon also reveal another challenge of increasing VL/HIV co-infection[37].

One element affecting leishmaniasis is the socio-economic aspects, either at risk of exposure and access to medicines and diagnostics. Socio-economic burden of VL, its impact and consequences, is well described in India, Nepal and Bangladesh through cost of illness studies. These studies, when conducted well, provide insights to inform policymakers on economic burden from the perspective of individual/household or health care provider or both (societal perspective). From eastern Africa, there is only one study by Meheus, *et al*. (2013) that reported the economic burden of VL with data from Gadarif, the epicentre of VL in Sudan[70]. The median total cost for one VL episode was estimated to be US$450, of which 53% is borne by the households (40% of the annual household income. More than 75% of households incurred catastrophic out-of-pocket expenditures. Further evidence is clearly needed.

CUTANEOUS LEISHMANIASIS IN AFRICA

CL is present in 67 countries in the Old World (Europe, Africa, Middle East, central Asia and the Indian subcontinent). The causative agents of CL in Africa are dermotropic *L. major, L. aethiopica, L. tropica*, and, rarely, *L. donovani.* CL in Africa has complex transmission cycles involving animal reservoir host (e.g. hyraxes) and sand fly vectors (*P. longipes* and *P. pedifer*). Environmental changes such as agricultural, irrigation, migration and urbanisation may increase the risk of exposure for humans. When susceptible populations become exposed, it may result in noticeable epidemics, such as in Burkina Faso, Ghana and new pockets in Ethiopia. In Sudan, an epidemic affecting >10,000 people occurred in 1991 in Tuti island, near Khartoum. Movement of a non-immune population aided by high vector abundance following heavy rains was thought to play a role.

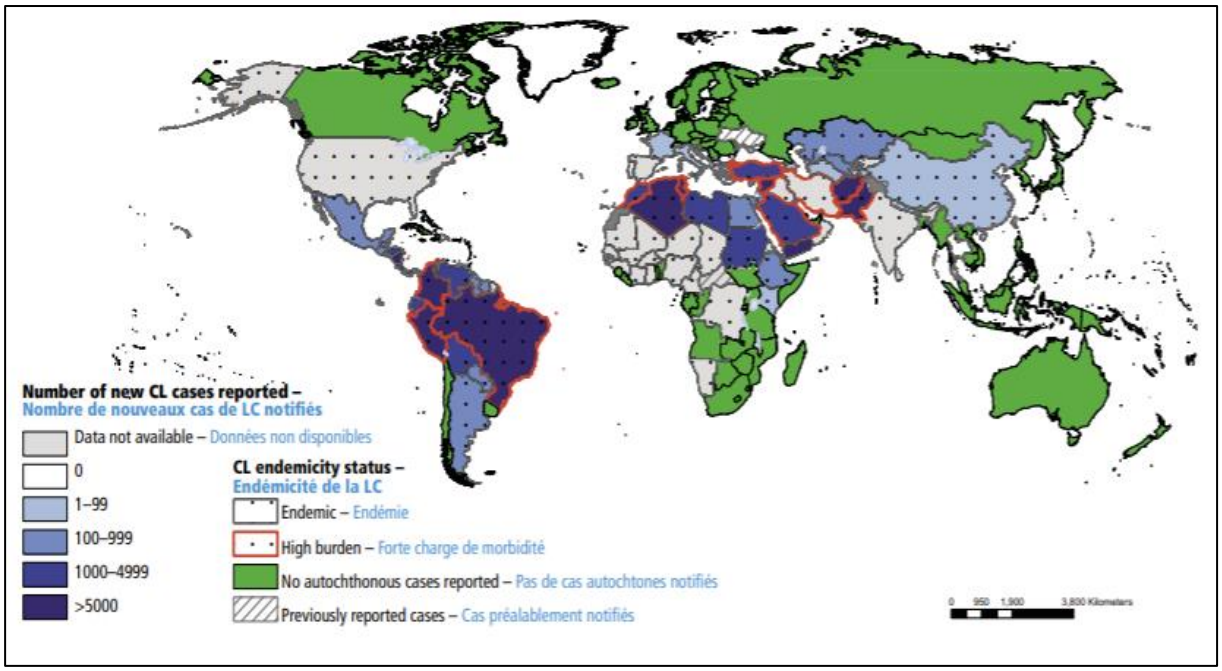

Figure 5 Status of endemicity of cutaneous leishmaniasis worldwide, 2016
Source: WHO, 2018 . Available at https://www.who.int/wer/2018/wer9340/en/

There is a wide variety of CL clinical presentations, depending on different factors such as parasite species, transmission cycle, immunological status or genetic predisposition. In general, CL refers to ulcerative skin lesion(s), which can be developing at the site of the sand fly bite (localised) or multiple non-ulcerative nodules (diffuse). CL may vary in severity (e.g., in lesion size), clinical appearance (e.g., open ulcer versus flat plaques versus wart-like lesions), and duration (e.g., in time of evolution or in time to spontaneous cure). Most *L. major* lesions self-heals in several months. Some complicated forms can be extremely disfiguring or debilitating, such as those caused by *L. aethiopica*. CL lesion may mimic that of other skin conditions, such as staphylococcal or streptococcal infection, mycobacterial ulcer, leprosy, fungal infection, cancer, sarcoidosis, varicose ulcers, or tropical ulcer. Diagnosis is often made clinically and treatment options – using the same medicines as for VL – are mostly prolonged and with low cure rate. Depending on the severity of the cases, treatment can be given topically (including thermotherapy), intralesional injections or systemic therapy but the evidence is lacking[71].

Although rarely fatal, CL can cause substantial suffering because of the related stigma and the disfiguring scars it leaves in a number of cases. Accurate disease burden is challenging since misdiagnosis is common and there are no standard reporting guidelines. There is a major knowledge gap in terms of the magnitude of the problem, in particular for sub-Saharan Africa. The lack of epidemiological burden and distribution makes it difficult to advocate for control activities and further research to inform public health policy.

EXISTING INTERVENTIONS TO CONTROL LEISHMANIASIS IN AFRICA

Vector control strategies for VL include insecticide spraying, use of insecticide-treated materials, and environmental management[65]. Unfortunately, not much evidence exists about their effectiveness in eastern Africa, and they are not widely used. The only evidence on bed-nets was a retrospective study by MSF in Sudan following community distribution of insecticide-treated nets (ITN) in 1999-2001, which reported a 59% reduction of vector density[72].

In the absence of vaccines and effective vector control strategies, case detection and treatment remain the principal VL control approach in this region. In eastern Africa, major knowledge gaps remain and such concerted efforts to tackle VL seem utopic. The public health importance of VL is further underestimated, partly because of the limited knowledge of the disease burden to inform policy decisions.

Nevertheless, there have been several signs of progress. With increased attention to NTDs from stakeholders and support from external partners, control of leishmaniasis was established in each leishmaniasis endemic countries, along with publication and dissemination of national leishmaniasis guidelines (**Table 2**). Leishmaniasis is a notifiable disease in Sudan, South Sudan and Ethiopia, but not in Somalia, Kenya, nor Uganda. Surveillance type also differs, with an integrated approach for Ethiopia and Uganda and vertical, passive surveillance in Sudan and South Sudan[1].

Table 2 Overview of visceral leishmaniasis status and control in eastern Africa

	Ethiopia	Kenya	Somalia	South Sudan	Sudan	Uganda
Endemic areas	6 out of 9 regions	6 out of 47 counties	14 out of 90 districts	28 out of 86 counties	27 out of 187 localities (in 12 states)	52 out of 146 counties
Total Population	99,290,750	46,050,302	10,787,104	12,339,802	40,234,882	39,032,883
Poverty headcount ratio at $1.90 a day (2011 PPP) (% of population	NA	NA	NA	NA	NA	34,6 (2012)
Health expenditure per capita (current US$)	26,6	77,7	NA	30	129,8	41
Out-of-pocket health expenditure (% of total expenditure on health)	32,3	26,1	NA	54,2	75,5	52,3
Population at risk in 2015[A]	3,168,835	3,268,626	2,337,787	2,034,944	8,696,636	No data
VL cases per year (estimate)[B]	3700-7400	610-1200	1400-2700	15,700-30,300	7,400-14,200	350-520
VL cases reported in 2016[C]	1490	954	858	3541	3894	31
National VL guidelines (last update)[D]	Yes (2013)	Yes (2017)	Yes (2012)	Yes (2011)	Yes (2016)	Yes (2019)
National leishmaniasis control programme	Yes, since 2006	Yes, since 2012	Not available	Not available	Yes, since 2012	Not standing alone
Health facilities with VL diagnosis and treatment provision (2016)	22 facilities[E]	18 health facilities	Three health facilities	38 health facilities[F]	44 hospitals	1 Hospital
Treatment provided for free in **public** sector[G]	Yes	Yes	Yes	Yes	Yes	Yes

A Data from 2015 WHO Country Profile on leishmaniasis, available at http://www.who.int/neglected_diseases/news/New_leishmaniasis_country_profiles_based_on_routine_surveillanc/en/
B Estimate from Alvar et al., 2012 based on WHO data since 2008.
C Data from WHO Global Surveillance of Leishmaniasis, available at http://apps.who.int/gho/data/node.main.NTDLEISH?lang=en
D First-line for all the countries are combination regimen of SSG/PM for 17 days
E Ethiopia has 22 facilities, including a refugee camp in Gambella where MSF is present. (source: MSF and KalaCORE)
F South Sudan has 38 facilities that are receiving full support (supplies, supervision and on-site mentorship) and another 8 that are receiving more indirect support (source: KalaCORE)
G Despite official free diagnosis and treatment, patients and household still have to pay other non-medical costs, notably transport, hospitalisation, and food

To avoid treating false positive, RDT should only be used for patients fulfilling a clinical case definition, defined by WHO as someone presenting with persistent fever (≥2 weeks) and splenomegaly in a VL endemic area. DAT and parasitological confirmation are only available at higher level health facility as they require minimum equipment and skills. Adherence to the diagnostic algorithm in daily practice is influenced by the availability of options and training of the clinicians[73]. The rK39 RDT is the most widely used, despite its sub-optimal accuracy (sensitivity 85%) in the African region[39]. Performance variability due to heat stability, different lots and brands have also been reported in the past[74]. Availability of RDT can also be a constraint: in Sudan, due to the United States' economic sanctions, importation of certain rK39 (DiaMed-IT LEISH®, Bio-Rad International) was impossible and as a result, the national programme has rolled out another brand (Kalazar Detect™, InBios International), which has been documented to perform less well (suboptimal sensitivity of 67.6%[18]). There exist other recombinant antigens for RDT such as rK9, rK16, rK26 and rK28[75]. The latest has recently been studied in Sudan with satisfactory result[76,77].

There has been a shift towards combination therapies with shorter treatment regimen as first-line protocol (17 days of SSG/PM instead of 30 days SSG)[10]. It is a fact that to treat a VL patient is more difficult in eastern Africa than in South Asia, where similar treatments have an efficacy of >95%, except for SSG, for which resistant strains have been clearly described in India[78] (**Table 3**). Inter and intraregional variation have also been observed in eastern Africa; for instance, PKDL manifests in an estimated 40 to 50% of patients in Sudan[79], but rare in areas of Kenya and southern Ethiopia. Lymphadenopathy is frequently found in Sudan but not in other regions. Medicines may demonstrate shown variable effectiveness across foci , such as the case with PM in eastern Africa[80]. These differences can partly be explained by the heterogeneity of vectors, host factors, and parasite across and within the region [81–83].

Table 3 Treatment efficacies in South Asia and Eastern Africa*

	% efficacy(ies) (mean and/or range)*									
Region	**SSG**	**LAMB (20-21 mg/kg)**	**LAMB (10 mg/kg SD)**	**MF (2.5 mg/kg/day 28 days)**	**PM (15 mg/kg/day for 21 days)**	**SSG+PM**	**LAMB +SSG**	**LAMB +MF**	**PM+ MF**	**LAMB +MF**
South Asia	35-95	>95	≥95	72-94	94,6	NIA	NIA	>97	>97	>97
Eastern Africa	93.9	85 (71-100)	98 (33-100)	72	63,8 (14-96)	91	87	77	NA	NA

SSG – sodium stibogluconate; LAMB -liposomal amphotericin B; MF -miltefosine; PM -Paromomycin. *Adapted from Alves et al., 2018[9]

Although SSG-PM combination therapy is an improvement over SSG monotherapy, a new therapy for VL should ideally be a safer, more efficacious, and shorter-course oral combination regimen. Control tools need to be suitable for implementation in the remote locations of the populations affected in eastern Africa. Nevertheless, there are myriad of challenges in bringing these existing tools to the people who need it.

CHALLENGES IN PROVIDING VL CARE: ACCESS AND HEALTH-SEEKING BEHAVIOUR

Without treatment, VL is almost always fatal. Delays in detection and treatment increase the risk of morbidity and mortality as well as the dissemination of disease to others. Accordingly, early access to VL care is imperative to improve clinical prognosis and reduce transmission via human reservoirs. Tragically, many individuals may fail to access VL care. Focusing on supply-side intervention, i.e. providing care on health service or health system does not guarantee utilisation by the patients, especially in the eastern Africa context.

Moreover, the care-seeking behaviour for VL is rarely straightforward. Many barriers exist between the onset of symptoms and completing, or even starting treatment. Typically, different health care providers need to be visited before the patients reached a VL diagnosis, with the choice primarily based on proximity and reputation[84,85]. As VL patients mostly live in remote, rural areas, the reach of the formal health system is limited: they arrive at the hospital (where VL care is made available), when the illness has become severe and with complications. Furthermore, a delay occurs already at individual/household level regarding the decision to seek care (if awareness is low), while the physical access to the health services also a determinant (**Figure 6**). Financial constraints play a role; during the rainy season, transport from rural area to the city is more difficult, e.g. can only be done by tractor or private rented vehicle, requiring more time and money. Lengthy hospitalisation period[86] might hinder the perceived benefit of treatment as socio-economic impact to the household is significant[70]. Previous stock-out or shortages of VL diagnostics and medicine might affect the expectation and perception of the care available.

Figure 6 Difficult geographical accessibility in Sudan (left) and **lack of transport means** (South Sudan). (Courtesy of MSF.)

Even when patients do seek care, the diagnosis was not always easy, with the delay to reach diagnosis up to 5 weeks[87]. In Nepal, the time to reach the teaching hospital tertiary care where VL care is provided took up to two months, and in India, the median duration from illness to cure was up to 14 weeks[84,87]. Health service delay is also common, i.e. further delay before the diagnosis is made and treatment is started, for example, due to the unavailability of the health staff or diagnostic tests and medicines.

Inadequate access to VL care is thus reflected in a relatively long duration between the onset of symptoms and the moment the patient seeks treatment, up to weeks and months. One study investigating accessibility of VL care in Sudan conducted 15 years ago, identified the following factors as access barriers: low knowledge, lack of money for treatment and transport, impassability of roads especially during rainy season, work priorities, severe cultural restrictions of women's decision-making power and distance to the next health center[88]. Apart from this study, there is no other published information on the experience and perspective of the VL affected communities.

Another challenge of VL care provision is linked to the health system capacity, which varies widely and also within the country. Quality care is often hampered by high turnover of medical staff or bottlenecks in the pharmaceutical supply chain, including poor stock management (**Figure 7**). Several non-state actors have long been involved with VL control in the region, such as MSF, DND*i* and more recently, KalaCORE consortium[89]. Availability of diagnostics and medicines is vital, but shortages often happen[90]. Lack of reliable data and difficult communication lead to forecasting difficulties and sub-optimal practices. The quality of diagnostics and medicines may not always be ensured if proper storage and transport to the health facilities are not guaranteed. The distribution to the peripheral health facilities is hampered by geographical or climate (rainy season in South Sudan, for example). Counterfeit or sub-standard drugs have been reported before[91] .

Figure 7 Leishmaniasis medicine in the field
(Courtesy of KalaCORE.)

4. LEISHMANIASIS AS A NEGLECTED DISEASE

NEGLECTED DISEASE, A REPACKAGING OF A GLOBAL HEALTH MOVEMENT

Neglected diseases, or the so-called Neglected Tropical Diseases (NTDs), refer to a diverse group of communicable diseases that prevail in tropical and subtropical conditions and affect populations living in poverty[92]. The critical feature of this group of diseases is the '*neglect*'; implying that they are concentrated in the impoverished population living in marginalised areas, those who are left behind by socio-economic development. There is a lack of visibility at all levels: community, national and international; which leads to a lack of incentives to develop medicines for them as the patients are too poor to pay the price. Sadly, even existing medicines may not reach the patients due to access issues and poor delivery system[93]. Neglected diseases affect neglected populations.

Box 1

'*These diseases, many of which have affected humanity for millennia, affect more than 1.4 billion people. They sicken, disable, and disfigure, keeping people in cycles of poverty and costing developing economies billions of dollars every year. Until recently, NTDs saw little attention from all but a small handful of dedicated supporters. Bus as their impact grew clearer, more were urged into action. '*

Uniting to Combat NTDs 2014 (Delivering on Promises and Driving Progress; The 2nd Report on Uniting to Combat NTDs

The concept of NTDs emerged in the early 2000s, almost as alternative 'brand' or repackaging when most attention goes to the big three diseases (HIV, tuberculosis and malaria), and have continued since to generate momentum in the international community[94]. The NTD movement was not launched in vacuum but constructed within the shifting policy landscape driven by the Millennium Development Goals (MDG). Key WHO meetings took place in Geneva and Berlin in 2003, and these initiatives create an initial framework for NTDs, focusing on mass drug administration as the 'rapid impact package' for at least seven diseases[94,95]. Scientists or 'scientists activists' have largely led the global policy movement and create critical mass for policy and public actions, which led to further institutionalisation through WHO and other stakeholders such as London Declaration on NTDs in 2012 (**Figure 8**). In the latter, pharmaceutical companies, donors, academia, endemic countries and NGOs came together to commit to control, eliminate or eradicate NTDs and improve the lives of over a billion people[96,97]. Several multinational pharmaceutical companies have agreed to donate the necessary drugs to eliminate lymphatic filariasis (LF) and blinding trachoma and to control onchocerciasis, soil-transmitted helminths infection (STH) and schistosomiasis[98]. In May 2013, the 66th World Health Assembly passed a new resolution on prevention, control, elimination and eradication of NTDs, urging member states to step up their commitment and resources to tackle NTDs[99].

Initially consisted of 17 diseases[2], through WHO's Strategic and Technical Advisory Group for NTDs, additional diseases have been included in the NTD portfolio[3]. Five broad strategies to tackle NTDs are preventive chemotherapy (PCT), intensified disease management (IDM), vector control, veterinary public health measures and through improved water and sanitation. These interventions are being implemented with variable intensity and resources. Mass drug administration is the central intervention for diseases amenable to PCT, such as soil-transmitted helminths and lymphatic filariasis. Drug donation programme by pharmaceutical companies has mainly directed towards this PCT.

Figure 8. (*left*) **The first WHO Road Map to Tackle NTDs**; (*right*) **Various advocacy and media attention for the global health partnership to tackle NTD** (source: WHO and Uniting to Combat NTDs, https://unitingtocombatntds.org/)

Leishmaniasis, along with Buruli ulcer, Chagas, Human African Trypanosomiasis (HAT) and yaws, belongs to the IDM diseases for which cost-effective control tools do **not** exist and where large-scale use of existing tools is limited. These diseases also share the same characteristics: they are difficult to manage and costly (diagnosis, treatment), poorly understood burden, lack of investment in Research and Development (R&D), and people affected have poor or no access to health care. Intensifying disease management using existing tools basically means to make do with diagnostics and medicines, while at the same time advocate for rapid development and implementation of better control tools and to ensure the full involvement of

[2]Buruli ulcer, Chagas disease, Dengue/Chikungunya, Dracunculiasis, Echinococcosis, Yaws, Human African Trypanosomiasis, Leishmaniasis, Leprosy, Lymphatic Filariasis, Onchocerciasis, Rabies, Schistosomiasis, Soil-transmitted Helminthiases, Taeniasis/Cysticercosis, Trachoma

[3]Mycetoma or chromoblastomycosis and other deep mycoses, scabies and other ectoparasites and snakebite envenoming have been added to the NTD portfolio

national control programmes. There has been a resolution on control of leishmaniasis in 2007 to encourage endemic countries to take ownership of the leishmaniasis programme.

LANDSCAPING OF R&D FOR NTDS INCLUDING LEISHMANIASIS

At present, development of new medicines by the pharmaceutical industry is driven largely by future 'return on investment' based on intellectual property rights (patents) and market exclusivity. Getting a drug in the market The drugs discovery and development process and then getting them to the market is a long, slow haul (**Figure 9**). The associated failures at every stage make the process costly and serve as justification of the product's final pricing[100,101]. Without the for-profit market, pharmaceutical manufacturers have no economic reasons to develop drugs for conditions like NTDs, which primarily affect the poor. This 'market failure' is reflected in the rate of new drugs developed for infectious diseases that are mainly prevalent in developing countries. In 1975-1999 only 15 (1.1%) of 1393 new medicines (New Chemical Entity/NCE) were dedicated to tropical diseases[16]. Between 2000-2011, this proportion did not change and amongst the newly approved products for NTDs, most were new formulation or combinations of existing medicines[13]. There is a vacuum in the drug R&D for diseases of the poor and also for diseases with small market size, often called the 'orphan' or rare diseases.

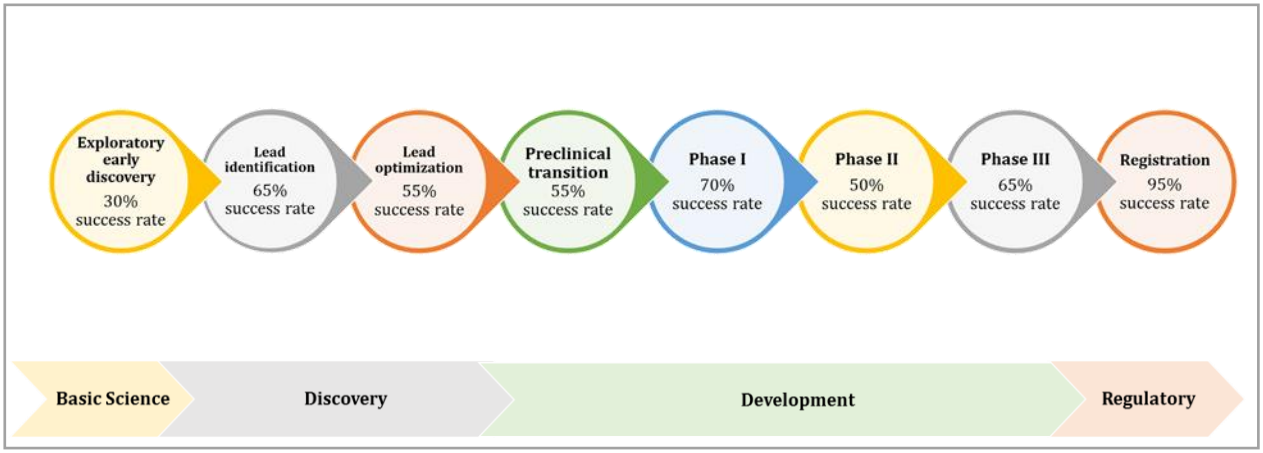

Figure 9 Drug discovery and development pipeline. Graph adapted from Nwaka S and Ridley R (2003). 'Virtual drug discovery and development for neglected diseases through public-private partnerships.' Nature 2: 924

As maximizing profit of sales and shareholders' value are the main incentives for pharmaceutical companies, developing new drugs for NTDs and rare diseases are not prioritised. For these conditions, market mechanisms alone were insufficient and public policy needs to remedy the situation[16,102]. Specific regulatory and economic incentives have thus been created to foster R&D for rare diseases in the United States, Japan, and Europe[103] since the 1980s. Unfortunately, not all problems are solved as the access to these 'orphan drugs' remains problematic due to high cost[104].

Similarly for NTDs, there has been a continuous advocacy for public actions to seek alternative approaches to R&D for NTDs. Public-Private Partnership (PPP), one type of which is Product Development Partnership (PDP), have emerged as one potential solution. PDPs supposed

to knit together the public and private sector, along with NGOs, academia, biotech companies; working virtually to link expertise, provide funding, technical oversight and portfolio management. WHO/TDR, created in 1975, has been involved in driving drug development for neglected diseases in PPP arrangements, encouraging others, e.g. Malaria Medicine Venture (MMV), DND*i*, and TB Alliance, amongst others, since the early 2000s. In fact, three of leishmaniasis drugs (LAMB, MF and PM) were fruits of this approach (see **Box 2).** The success of PPP in this regard was a reassurance of an alternative way to a develop drug in a capital-intensive, market-driven context. However, whether PPPs are the real solution to tackle NTDs remains an open question, especially on its outcomes, policies and practice.

Box 2

Miltefosine (MF): anticancer drug candidate that was discovered as anti-leishmania in the mid-1980s. WHO TDR together with Asta Medica (later Zentaris), supported the development through numerous clinical trials in India. MF was officially registered to treat VL in India in 2002.

Paromomycin (PM): aminoglycoside that originally licensed by Farmitalia, and first used to treat VL in Kenya in the 1980s. WHO sponsored its development in India, which continued by International Dispensary Association (IDA, the Netherlands). Institute of One World Health (currently PATH) took it over for Phase III trial and eventually PM was registered to treat VL in India by 2006. Currently, a pharmaceutical company, Gland Pharma (India) manufactures and markets the drug.

Liposomal amphotericin B (LAMB): since the discovery of the liposomes in the 1970s, trials were ongoing to compare LAMB versus conventional Amp B and/or other lipid formulations. These studies were pivotal to apply for a New Drug Application (NDA) to the United States Food and Drug Administration (US FDA) in 1997. WHO reached an agreement with the company, NeXstar Pharmaceuticals Inc (later Gilead) to evaluate clinically AmBisome for the treatment of kala-azar. Although AmBisome was also initially developed for other purposes, the collaboration between NeXstar, Inc., and TDR has resulted in the first formal worldwide drug development programme for an anti-leishmanial agent.

The landscape in the field of R&D for NTDs has been evolving. In the late 1990s, the effectiveness of PPP is considered unproven, and the plethora of PPPs may be considered as a waste of public money and duplication. In the last 20 years, their main functions shift towards less of a funder but more towards integrating and coordinating multiple industries and academic partners and contractors along the drug development pipeline[105]. The primary source of funding remains the public and philanthropy[106], and PDPs have become the main actor for the majority of neglected disease drug R&D.

Other approaches to stimulate R&D for NTDs have also been advocated, most commonly categorised as pull and push mechanisms[107]. The 'pull' in the form of research grants, subsidies or tax credits, are meant to stimulate upfront the research costs. Though this signals interest for a change, there is no evidence on their impact. It may address one factor, but as high costs alone do not explain the shortfall in R&D these mechanisms warrant further scrutiny. The 'pull' factors aim to address the lack of viable markets and are designed to create or secure a market (improving likelihoods of return of investments). These include patents or market exclusivity, purchase pre-commitments (or advanced market commitments, exist for vaccines for example) and regulatory

incentives such as the Priority Review Voucher (PRV) programme. PRV was created in 2007 as an incentive for manufacturers when registering a product with US FDA for tropical disease indication [108]. Knight's Therapeutics, the current owner of miltefosine, received the PRV in 2014 and had sold it to Gilead for US$125 million. The overall evidence of PRV impact is so far mixed as impact of PRV on improved access is yet to be confirmed[109,110].

TACKLING NTDS IN THE ERA OF UNIVERSAL HEALTH COVERAGE

Universal health coverage (UHC) is defined by WHO as "ensuring that all people can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship"[92]. UHC[4] has become a guiding principle for countries post-2015: the Sustainable Development Goals (SDG) era, and there has been a strong push to consider NTDs control and elimination efforts within this frame[111].

Within the 17 SDG, health is pronounced under the SDG3 ("Ensure healthy lives and promote well-being for all at all ages") and in specific target 3.3, neglected diseases is mentioned. In the broadest interpretation, NTD interventions may impact poverty (SDG1), hunger (SDG2), education (SDG4), work and economic growth (SDG8) and reducing inequalities (SDG10)[112]. The cross-cutting contribution of the end of NTDs to improve the prospects of attaining the SDGs is linked to the characteristics of NTDs 'sufferers' – the poor, but not only in low-income countries but also in middle and high-income countries[113]. The unequal distribution of NTDs means that the public health impact of NTDs may not be obvious at the country or national level but especially hard for the lower socioeconomic groups[114]. This 'social gradient' for NTDs have been demonstrated for Buruli ulcer, dengue, HAT and VL. For the latest, despite a free provision of diagnosis and treatment, 25-75% of households affected by VL experience some type of financial catastrophe[19,113,115].

Within this context, it is important to note that the two targets set by WHO/World Bank framework to monitor progress towards UHC[116], i.e. 1) minimum 80% essential health services coverage and 2) 100% financial protection from out-of-pocket payment for health services, seem appropriate for NTD programmes. This is because NTD patients and their families often fall into the medical poverty trap, through what is known as Catastrophic Health Expenditure (CHE). CHE is defined as out-of-pocket payment exceeding 10% of annual household spending or 40% of non-subsistence spending[117,118]. Access to NTD interventions reduces the financial burden on health systems in almost all countries[119].

In endemic countries where intervention for NTDs is mainly reliant on case detection and management by the health services, NTD burden can be considered as a proxy for inequitable access to health systems. Universal access is therefore fundamental to achieve universal health

[4] There are three dimensions in the so-called UHC cube: 1) extending coverage to individuals previously not covered; 2) extending coverage to services that previously not covered; 3) reducing direct payments to protect from financial hardship (Source: WHO)

coverage and is often defined in three aspects: physical or geographical accessibility, financial affordability and acceptability (willingness of the people to utilise a service or intervention)[120,121]. For visceral leishmaniasis, access to affordable, quality-assured medicines and diagnostic is a prerequisite, while for other forms (cutaneous or mucocutaneous) the recognition of their psychosocial impact is critical to have better burden estimates.

There is a case to be made towards investment in leishmaniasis control, which is aligned as well with the 'rights to health' approach for NTDs. People affected by leishmaniasis are the poorest of the poor or marginalised groups of the community[122,123], and impoverishment due to leishmaniasis is not unheard of. Translating UHC into reality requires the inclusion of leishmaniasis care, and other NTDs interventions, in the UHC benefit package[96].

Lack of NTD prioritisation is illustrated by very little domestic investment from endemic countries. Despite several NTDs master plan and regional strategies in some region, including Africa, the progress is variable, and NTDs are often absent from national health plans and budgets, let alone in other sectors. Reliance on external support, mainly from big donors or philanthropy foundations, jeopardises sustainability in the long run.

Nevertheless, the current consensus is that access to NTD interventions should form an integral part of UHC, with their positive effect on health gains and reduction in CHE[124,125]. Control and elimination of NTDs are sensitive indicators of poverty alleviation and UHC and should represent how developing countries care for the health of the poorest section of the population. Implementing NTD strategies is an essential element of UHC to 'leave no one behind'.

CHAPTER 2
HYPOTHESIS, OBJECTIVES AND THESIS OUTLINE

MSF clinical officer prepares sodium stibogluconate (SSG) for a child admitted in the kala-azar ward, Xuddur, Bakool region, Somalia. © E. Rasmussen, MSF

HYPOTHESIS

Poor access to care remains one of the barriers to a functioning leishmaniasis control programme in eastern Africa. The diversity and complexity of leishmaniasis mean VL control in this region depends on case detection and management. The current diagnostics and treatment options are limited, but the reasons behind are not fully understood.

Furthermore, even though VL care is made available, it might not be accessed optimally or fairly: much is left unknown on the part of community perspective and motivation to seek VL care. Low coverage of the health services, accessibility and availability of quality care including diagnostic and treatment options, and inefficient procurement and supply– remain all major challenges in the region. Aspects of financial, organisational and socio-cultural barriers that limit service utilisation, and also affordability, physical accessibility and acceptability need to be evaluated. For a potentially fatal disease like VL, the understanding of the determinants of access to care is critical. What is clear is that access to leishmaniasis care in this part of the world remains problematic and that the current body of literature shows critical evidence gaps.

Therefore, the central hypothesis in this thesis is that **access to care for leishmaniasis in eastern Africa is inadequate.**

OBJECTIVES

The **general objectives** of this thesis are to improve our understanding on access to care in Africa, by documenting availability, affordability and accessibility of care, explore novel ways of enhancing such care, and provide insights into specific elements of access to formulate coherent policy recommendations for leishmaniasis in eastern Africa.

The studies included in this thesis were framed around the following **specific objectives** (represented in **Figure 10**)

a. Burden assessment:

- To assess the availability of leishmaniasis care in a fragile context (Somalia)
- To update epidemiology and burden of cutaneous leishmaniasis in sub-Saharan Africa
- To synthesise the economic burden of leishmaniasis

b. To examine access issues 'upstream':

- To summarise the current landscape of RnD for NTDs, especially Public-Private Partnership
- Analyse failures of post-registration access of miltefosine (case study)

c. To examine access issues 'downstream':

- To analyse access barriers to the effective supply chain of leishmaniasis diagnostics and medicines in eastern Africa
- To explore access barriers to care for leishmaniasis from the community perspectives in a high endemic area of Gadarif, Sudan

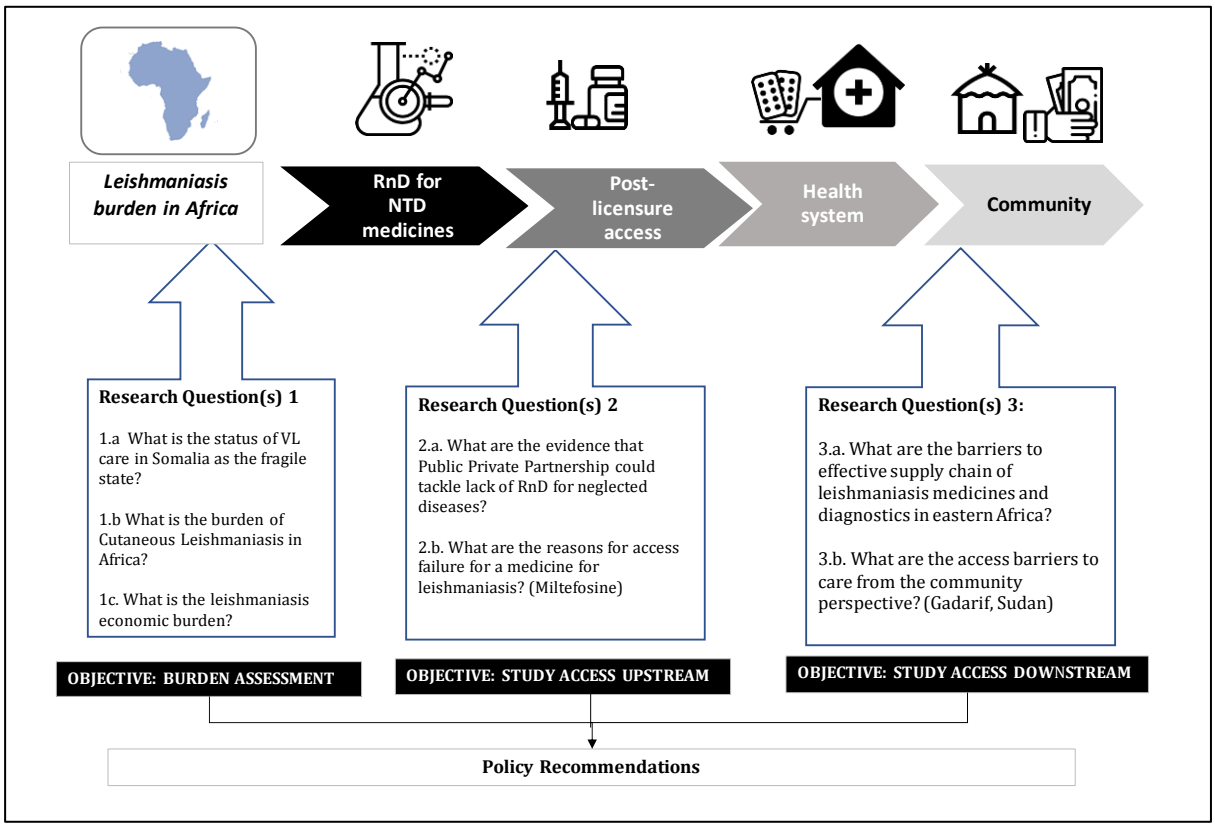

Figure 10 Overview of the thesis by research questions

THESIS OUTLINE

The thesis result is divided into three sections structured around the specific objectives described above, that each look into the different part of the access continuum applied to leishmaniasis care.

In the **first section** on **burden assessment**, we present three studies, primarily based on systematic reviews and my participatory observation during my fieldwork in Somalia, Ethiopia and Sudan. The **second section** provides two studies of the more **upstream aspects** of access, i.e. an analysis of the role of Public Private Partnership as a solution for the gap in R&D for NTDs, and a case study of the post-marketing access to the first and so far the only oral medicine for leishmaniasis, miltefosine. The launch of miltefosine was considered as a breakthrough in leishmaniasis control, but the drug never became as widely available and affordable as anticipated. We looked into the reasons why. The **third section** contains two studies that investigate **the access barriers in the field**, from two perspectives: the health system and the

community. The first analysis, on the health system, examines the supply chain for leishmaniasis diagnostics and medicines in the endemic countries of eastern Africa. In the second study conducted in Sudan, we studied the community perspective in a hotspot of VL through a qualitative study (see **Box 3**). As the last chapter, we summarise critical findings for each of the studies to discuss our findings and formulate policy recommendations

CHAPTER 3
MATERIALS AND METHOD

Windows in feeding centre for the displaced and refugees during the famine in Mogadishu, Somalia, 2011
© E.Laurent-Gascoin, MSF

In 2015 when this project started within the Euroleish network, it was made clear that this research should be done in accordance with current agenda of leishmaniasis control and research in eastern Africa. To do this, we consulted with the main stakeholders namely Médecins Sans Frontières, and members of KalaCORE Consortium (a UK-aid funded programme to tackle leishmaniasis in Africa and Asia, 2014-2018). Based on the unmet needs and not to duplicate efforts, the studies in this thesis were planned and informed to these stakeholders. Apart from that, **Euroleish.net** as a European Union Marie-Sklodowska Curie Innovative Training Network Programme also encourages collaboration with non-academic partner(s), which for this project is represented by MSF Access Campaign, Geneva.

For the burden assessment, the fact that at least two countries in these regions are mired by active conflict (Somalia and South Sudan) made a focus on fragile settings necessary. I worked in these two places as physician and in Bakool region, Somalia, managed a 30-bed kala-azar ward for 6 months in 2009. A monograph on VL care and epidemiology in Somalia, documenting current situation in 2016-2017 was warranted. A systematic review was performed, added with MSF programme data and context analysis.

Another gap in knowledge was for cutaneous leishmaniasis in Africa, as most control efforts are directed for VL. A clear idea on the burden was proposed as possible study, to provide a firm baseline for further research or intervention. A systematic review was planned. Similarly, the economic burden of leishmaniasis was also synthesised through a systematic review.

Though a literature review is needed in every start of scientific endeavour, in this thesis the **systematic review** method was employed in the highest standard (learned from my Cochrane review experience) and strict, meticulous adherence to a pre-defined, published protocols (registered in the international register platform for systematic reviews called PROSPERO: https://www.crd.york.ac.uk/prospero/). PRISMA guidelines were followed in all ensuing publications.

This methodology was also partly deployed, combined with a landscape analysis to build the second part of access upstream. Here, a joint systematic review was performed to assess if public-private partnership (PPP) was a solution to tackle neglected tropical diseases. A synthesis of this research question applied to R&D for leishmaniasis is presented, followed by an in-depth **case study** on miltefosine, the only oral drug for VL. The insights included in this part were complemented with my **participant observations** during the regular meeting of two main core groups that I was invited to be part of *the MSF NTD Working Group* who meets every quarter, and also of the *WHO Working Group on Access to Leishmaniasis Medicines* which was established in 2016 and had met four times to date. Interacting with the key players on leishmaniasis control in my region of interest were useful in understanding issues that are not found in published literature but as well to shape my project in a way that can be impactful, with steadfast focus on public health.

These have contributed to the design of the third part on access downstream: studies on access barriers at two different levels. What were the barriers at the health service level, their supply chain? What remains the barriers at community level? As these research questions fundamentally ask what and why (the reasons behind), **qualitative research methodologies** were chosen as the best to answer them. Admittedly, the lack of quantifiable data on these two

aspects have led also to this choice. Qualitative methods were definitely an eye-opener for me in delving deeper beyond numbers: choosing the right theoretical framework, collecting data through Focus Group Discussions and In-depth Interviews, and eventually analysing the immense text data generated from this method.

For the supply study, in depth interviews were conducted with main stakeholders at global and national level from Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda. The community study was conducted in a hyperendemic hotspot in Sudan, in a collaboration with the Kala-azar Research Center (KRC), based in the University of Gadarif and facilitated by KalaCORE Consortium. Gadarif state in eastern Sudan bears 80% of the VL cases in Sudan, with 12 health facilities providing care (3 with external support, one MSF and 2 DND*i*). The field sites are the 3 main localities in this state, where I spent in total of 6 weeks.

This thesis is presented as collection of 6 articles that are already published in international peer-reviewed journals

Kala-Azar Research Centre (KRC) is part of the Faculty of Medicine, University of Gadarif or al-Qadarif in the eastern part of Sudan. The centre has been created to facilitate research from this endemic area. KRC became a member of Euroleish network since 2017 and helped to implement and facilitate the access barrier study in Sudan.

After the initial visit in July 2016, the field work started in 2017. A training on qualitative research methods was organised for the local teams, prior to piloting the techniques in real life setting.

The people of Gadarif relies on agriculture for their livelihood, with sesame and sorghum as the main crops. The state is considered as one of the pillars for food security in Sudan. Smallholder farmers of the area came from various areas of Sudan and beyond since.

Traditional healers can always be found in the market selling remedies to all kinds of ailments.

Interview and focus group discussions (FGD) were conducted in gender and age specific groups. Facilitators were previously trained using piloted topic guides, and daily debriefing was done to analyse and adjust the topic guides.

Prior to visiting the villages, the team called a community meeting. The village leader(s) were informed, and supported the research team in the study. Former kala-azar patients, caretakers and health care workers made up the groups.

The means of transport in Gadarif are limited. The most common means to move around are these trucks, rickshaws, tractors and donkeys. During the rainy season, some of the roads become inaccessible.

CHAPTER 4
RESULTS

Silhouette of trees in the landscape, a frequent view in eastern Africa. Photos by Javi Lobarda in Unsplash.

1. Part I: BURDEN ASSESSMENT

A child at the kala-azar ward with burnt marks on his belly as a result of traditional healing to the swelling, Xuddur, Somalia 2008. © E. Rasmussen, MSF.

1.1 ARTICLE 1

Visceral leishmaniasis in Somalia: a review of epidemiology and access to care

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REVIEW

Visceral leishmaniasis in Somalia: A review of epidemiology and access to care

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Abstract

Somalia, ravaged by conflict since 1991, has areas endemic for visceral leishmaniasis (VL), a deadly parasitic disease affecting the rural poor, internally displaced, and pastoralists. Very little is known about VL burden in Somalia, where the protracted crisis hampers access to health care. We reviewed evidence about VL epidemiology in Somalia and appraised control options within the context of this fragile state's health system. VL has been reported in Somalia since 1934 and has persisted ever since in foci in the southern parts of the country. The only feasible VL control option is early diagnosis and treatment, currently mostly provided by nonstate actors. The availability of VL care in Somalia is limited and insufficient at best, both in coverage and quality. Precarious security remains a major obstacle to reach VL patients in the endemic areas, and the true VL burden and its impact remain unknown. Locally adjusted, innovative approaches in VL care provision should be explored, without undermining ongoing health system development in Somalia. Ensuring VL care is accessible is a moral imperative, and the limitations of the current VL diagnostic and treatment tools in Somalia and other endemic settings affected by conflict should be overcome.

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Introduction

The global burden of visceral leishmaniasis (VL) is estimated at 0.2 to 0.4 million cases, resulting in 50,000 deaths every year [1]. Eastern Africa is the second-highest-burdened region, after the Indian subcontinent [2]. VL suppresses the immune response, and epidemics in populations affected by malnutrition or displacement can be severe [3,4]. This deadly parasitic disease has been mainly reported in parts of southern Somalia [5,6], though data from Somalia are scarce and the true magnitude of the VL burden remains unknown.

Somalia was conflict-ridden even before the state implosion in 1991, and its health indicators are among the worst in the world [7,8]. With a high burden of infectious disease [9,10] and weak surveillance systems, outbreaks are commonplace [11]. The United Nations–backed government is still struggling to exert control beyond the capital (Mogadishu) and urban towns, while most of the VL-endemic areas in southern Somalia are controlled by al Shabaab, an al Qaeda-affiliated Islamist movement hostile to international agencies [12]. Health care in these areas is mostly provided by multiple nonstate actors that face great difficulty in accessing those in need [13,14].

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Prompt diagnosis plus adequate VL treatment is lifesaving, and in anthroponotic foci, it is the cornerstone of VL control. However, providing VL care is difficult to enact in a fragmented health system [15]. With the establishment of a federal government in 2013, the health system-strengthening agenda has been gaining momentum [16,17], and many unmet needs have been identified [18–20]. In this paper, we review the evidence on the current burden of VL and availability of care in Somalia, from which we derive recommendations for VL control. Our aim is to draw attention to the neglected tropical diseases (NTDs) agenda in fragile state such as Somalia, and hopefully, our recommendations prove useful in similar settings affected by protracted conflict.

Methods

We searched the MEDLINE (via Pubmed) online database for articles with leishmaniasis and Somalia in the title with no date limit and published up to 31 March 2016 without language restriction. Additional search terms used in Medical Subject Headings (MeSH) were "leishmaniasis, visceral"; "kala-azar"; and "Somalia". We searched reference lists from these articles by hand to identify other relevant publications. In addition, we searched documents and reports from agencies, institutions, and organizations with projects in or related to Somalia and contacted the authors of this grey literature for additional information. An experience from a VL control project managed by Médecins Sans Frontières (MSF), a private international humanitarian medical non-governmental organization (NGO), was described.

Ethics Statement: All sources/key informants give consent for the article. The study is exempted from ethical review by MSF Institutional Review Board (IRB).

Results

The literature search yielded 12 papers, all of which were retrieved in full-text and included in the analysis (see Table 1).

VL epidemiology in Somalia

The parasite species causing VL in the east-African region belongs to the *Leishmania donovani* complex, and the same species was confirmed in Somalia in 2000–2001 [21]. The presence of sand fly vectors in this region is generally associated with cracks in black cotton clay soil, *Acacia* and *Balanites* woodland, and termite mounds [22]. Semi-arid regions, where the sand fly *Phlebotomus orientalis* is the vector [23], contrast with the savannah and forested areas, where *P. martini* and *P. celiae* have been incriminated [24]. Exposure to bites mainly happens outdoors—male persons are more at risk because of their cultural roles of herding cattle or forest traversing [25,26]. Women and children are usually infected in and around the house, leading to clusters around VL cases and household contacts [27,28].

In the Bakool region of southwestern Somalia, an entomological assessment identified mainly *P. martini* and *P. vansomerenae* as potential vectors[22]. These sand flies have their optimal breeding and resting in the ventilation shafts of termite mounds, which are ubiquitous in Somalia[24,29]. Being in the vicinity of termite hills (the eroded or pinnacle type) are thought to lead to exposure [30]. The vector microhabitat in these *Macrotermes* termite mounds is also influenced by various factors, such as moisture, humidity, temperature, and rainfall, all of which are highly variable in different parts of Somalia.

The ecological situation in the endemic foci of VL in the south has yet to be described in depth, as these areas differ from the higher-altitude northern zones. Somalia has a generally arid and semi-arid climate with two seasonal rainfalls. Its southern part is a rugged plateau, crossed by two major rivers, the Jubba and Shabelle (from Ethiopia highlands), with fertile

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Table 1. Overview of included studies from the published literature search.

Year, Location	Author	Type of Publication	Summary	Ref
1966, Middle Shebelle	Baruffa	Journal article	Describing the problem of kala-azar in Somalia.	[40]
1968, Middle Shebelle	Cahill KM	Journal article	Describing epidemiology and clinical features of kala-azar patients in east Africa, including in Somalia.	[38]
1971, Middle Shebelle	Cahill KM	Journal article	Description of kala-azar patients seen in Somalia and mapping of the origins.	[39]
1995, Baidoa	Woolhead A	Journal article	Case report of VL in a woman from Baidoa and warning of potential outbreaks because of the war.	[43]
1995, Lower Juba and Middle Shebelle	Shiddo SA et al.	Journal article	Prevalence study using leishmanin skin test (LST) (positive in 26%) and serology (11%) in 438 village inhabitants. Hospital data showed male:female ratio was 3.3:1.	[41]
1995, Lower Juba and Middle Shebelle	Shiddo SA et al.	Journal article	A study to provide baseline data for antibody responses using DAT, IFAT and ELISA- all distinguished well sera from VL patients and healthy controls. DAT is recommended.	[42]
1995, Lower Juba and Middle Shebelle	Shiddo SA et al.	Journal article	Study reporting humoral and cell-mediated immunity amongst VL patients compared to healthy inhabitants.	[45]
1996, Lower Juba and Middle Shebelle	Shiddo SA et al.	Journal article	Study to determine the levels of IgG subclasses and IgE from 22 VL patients from Somalia, compared to healthy controls. Possible diagnostic role for western blot was found.	[46]
2001, northeastern Kenya	Boussery G et al.	Letter	Reported outbreak in 2000 amongst Somali refugees in Dadaab camps in Kenya, with 34 probable or confirmed VL patients. Median age was 15 years. Case fatality rate was 29.4%, and there was concern over situation inside Somalia and the nutrition situation.	[49]
2003, Somalia, northeastern Kenya, southwestern Ethiopia	Marlet MVL et al.	Journal article	In 2000 and 2001, 904 patients with VL were diagnosed from areas which were known as previously nonendemic for VL or had only sporadic cases prior to the epidemic.	[21]
2003, Bakool	Marlet MVL et al.	Journal article	Description of new VL focus in Bakool region, Somalia, an area where VL had not been reported before. In one year, 230 serologically positive cases were diagnosed as VL, with a cure rate of 91.6% with SSG. Additionally, a serological survey of 161 healthy displaced persons found 24 (15%) positive by the LST and three (2%) positive by the DAT.	[22]
2007, Bakool	Raguenaud ME et al.	Journal article	Retrospective analysis of MSF VL data from 2004 to 2006. After an average of 140 admissions per year, a 7-fold increase happened in 2006. 82% of total patients treated for VL originated from Huddur and Tijelow districts. Clinical recovery rate was 93.2% and case fatality rate was 3.9%.	[50]

DAT: direct agglutination test; IFAT: indirect fluorescent antibody test; IgG: immunoglobulin G; IgE: immunoglobulin E; SSG: sodium stibogluconate.

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inter-riverine areas. Seasonality of VL vectors (abundance after rainy season) are well established elsewhere [31], but in Somalia, no information exists to date.

There have been no studies on local determinants, risk factors for VL, transmission dynamics, or vector control in Somalia, but the transmission cycle is supposedly human to human, similar to that in Uganda, Sudan, South Sudan, and Kenya [28,32,33]. Though several animals have been suggested as reservoir hosts (dogs, wild mammals such as the Nile rat, mice, gerbils, servals), their role in transmission in the region is unclear [34,35]. Climatic change has led to frequent floods and droughts in the eastern Africa region, which is thought to influence the transmission or epidemic cycle of vector-borne diseases, including that of VL [36,37]. In Somalia, changes in land use, such as agriculture and deforestation, may lead to desertification and provide habitats for VL vectors.

Contrasting with Sudan, where VL was already described in 1904 [38], in Somalia, it was first reported by Penso in 1934 [39], then followed by a case series in 1955 [40]. In the 1960s, Cahill [41,42] and Baruffa [43] mapped the origin of patients. The coastal areas in Lower Juba and Middle Shabelle River were considered endemic [44,45], with the most recent case report

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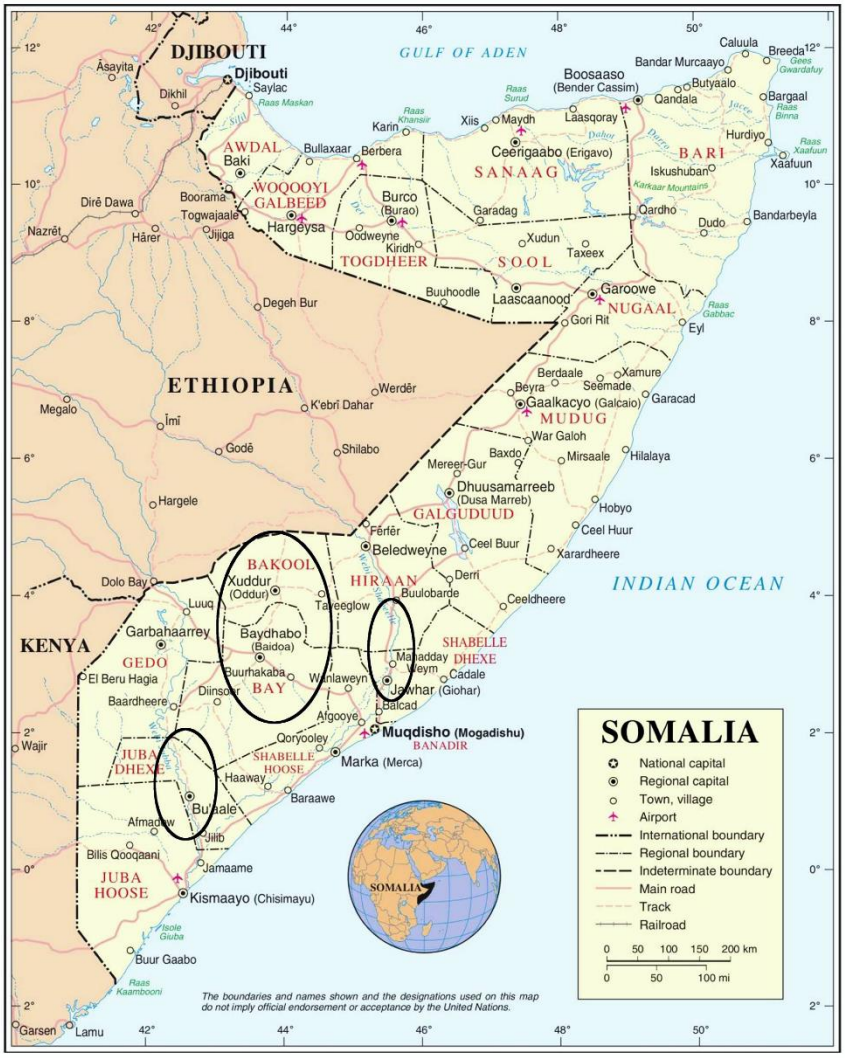

Fig 1. Map of Somalia, with the mark showing approximately the known VL-endemic areas in the country. Adapted from Worldsofmaps.net (under Creative Commons license).

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coming from Baidoa region [46] (see Fig 1). Few epidemiological surveys were carried out, such as the one in Giohar district, Middle Shabelle showing 26% positivity with the leishmanin skin test (LST)—an intradermal test of the delayed-type hypersensitivity response—and 11% with serology [44]. There are no recent population-based estimates of VL incidence or

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prevalence in Somalia. An LST survey conducted in 2001 among displaced people in camps around Xuddur, Bakool region revealed a 15% positivity rate, indicating previous exposure to *Leishmania* infection [22]. Different methods, such as immunofluorescence, ELISA, and direct agglutination test (DAT) [47], were used to measure circulating antibodies to provide baseline data and to explore which methods would be the most suitable for diagnosis or for epidemiological population studies in Somalia [48,49].

To date, there have been no reports of VL from the northern parts of Somalia (Somaliland and Puntland zones). There is also no information available in the literature about it, as highlighted in this review. It is clear that the knowledge on VL foci in Somalia is constrained by the country's emergency situation, which does not allow large epidemiological studies and exhaustive disease mapping to take place. The predictions made by spatial risk maps [50] are consistent, with a significant VL presence in southern Somalia and much less of a presence along the coastal areas of northern Somalia.

VL affects the most marginalised: the rural poor and those lacking access to health services, such as the pastoralists and agropastoralists, who comprise approximately 60% of the population in the south-central zones of Somalia [51]. The socioeconomic impact of VL in a country where almost half the population lives in extreme poverty [52] is not known. In 2000, the confirmation of a VL outbreak among Somalian refugees living in camps in north-eastern Kenya triggered concern about the VL situation inside Somalia [21,53]. From May 2000 to August 2001, 904 VL cases were diagnosed in Kenya, originating from southern Somalia, north-eastern Kenya, and south-eastern Ethiopia. Unusual rainfall patterns, malnutrition, and migration of a population seeking food and security were likely major factors in the outbreak [53]. In this context, an endemic focus was recognized as it was unfolding in parallel in the Bakool region in Somalia, where it was discovered that the "fever and big belly" syndrome that corresponded with the main symptoms of VL had been long known locally [30]. The disease mainly affected children, which had also been observed in Mogadishu hospitals in the early 1990s [44].

MSF VL control project in Xuddur, Bakool region, 2002–2009

The MSF project in Xuddur started in 2000 as a nutrition program and gradually expanded to a 290-bed health centre by 2008. The VL component commenced when an unusual number of malnourished children did not improve despite proper nutritional support. At first, tuberculosis was suspected as the underlying problem, but VL was later confirmed, as described by Marlet et al. [21,22]. In an 11-month period, 59% of patients presenting a history of fever of at least 1 month, splenomegaly, and wasting tested positive on the DAT and were treated for VL.

A total of 1,671 patients were treated from 2002 to 2006, with a steep increase of cases in late 2005, which later peaked in 2006 with 1,002 new cases and then decreased to 715 and 833 cases in 2007 and 2008, respectively. These numbers do not necessarily reflect the real incidence trend at the population level. The treatment used was injections of sodium stibogluconate (SSG) dosed at 20 mg/kg/day for 30 days. Program data shows an overall case fatality rate (CFR) of 4.5%, while 88% were cured during the period between 2002 and 2008. The defaulter rate improved after the rk39 rapid diagnostic test (RDT) was introduced in 2004, as fewer patients had to wait for DAT tests that had to be performed abroad. Health education on adherence was emphasized, and meals for the caretakers were provided. Better awareness among the population about treatment availability was thought to lead to a shorter duration of sickness before seeking treatment[30].

The programme was negatively affected by the reigning insecurity, which led to repeated evacuations and forced MSF to deploy a remote management approach, in which no presence of international staff could be maintained on the ground anymore. Evaluating the risk after a

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serious security incident, MSF decided to close the project in Xuddur in 2009 while remaining in other areas of Somalia until the organization pulled out of the country by August 2014 [54].

Current availability of VL care in Somalia

VL-endemic areas are located in parts of southern Somalia continually mired in conflict. Since al Shabaab rose to prominence in 2008, access to care has been extremely problematic in these areas. At present, there are three facilities able to diagnose and treat VL: two in the Bakool region (Xuddur and Tijeglow) and one in the Bay region (Baidoa). The coverage of these three health centres is not known, as baseline prevalence and population data are missing. The officially reported number of VL cases from the country remains consistent at 400 to 1,000 per year [55,56]. In 2014, an incidence rate of 4.35 per 10,000 inhabitants was estimated by WHO, with an estimated 2–4 underreporting ratio [57].

Adherence to the prolonged VL SSG treatment regimen is a challenge. In the clinic in Baidoa, care is provided on an outpatient basis, and patients who travel from far away have to stay with relatives in town. There is no further referral level for complicated cases beyond the Baidoa clinic. Structured referral is nonexistent. As the VL clinic also provides general health services, its doctors and nurses face a huge workload. It is not uncommon that suspected VL patients travel by their own means to hospitals in Mogadishu to seek care, only to find that no diagnosis tests or drugs for VL are available (M. Dakane, personal communication). In such a context, people tend to use the informal sector, largely composed of privately organized initiatives—pharmacy retailers, traditional healers, and Islamic charities[58,59]. One example is the many children with splenomegaly—one of VL's main symptoms—who demonstrate burn marks on their stomachs, indicating traditional care-seeking pathways followed before reaching the hospital (G. Elders, personal communication).

Despite the issuance of a 2012 National Guideline for VL in Somalia with support from WHO and various NGOs [60], there is no national control programme in place yet. The precarious security situation remains the stumbling block for active case finding or outreach activity; thus, VL care is in practice restricted to patients who are able to reach treatment centres. Wider community sensitisation on VL prevention and treatment is practically nonexistent. The unstable context also affects procurement and supply of VL diagnostic kits and drugs and the possibility of implementation of vector control measures. Since 2011, WHO has supported the implementing partners with procurement alongside on-the-job training in neighbouring countries (J. A. Ruiz-Postigo, WHO, personal communication).

Discussion

What is known about VL in Somalia is very limited, as evidenced from our review of the medical literature. Recent global attention to NTDs [61] has not benefited Somalia, where the overall context appears to be a deterrent for action. With the shift from an emergency service delivery approach towards health system building, life-threatening condition like VL are at risk of being further neglected due to emerging, competing priorities in the health sector [62,63].

Understanding the health system context

The health system in Somalia is a diverse, heterogeneous landscape, mirroring its context [12,64,65]. Apart from al Shabaab's outright ban on Western agencies [66,67], other factors, such as donors' counterterrorism legislation and difficulties in negotiating access, have led to cessation or limitation of activity by many NGOs [15,68]. The political economy of aid, subject to politicisation or clan rivalry [69,70], should be well understood in any planning of a health

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care programme. Thriving private sectors, a weak regulatory environment, urban–rural discrepancies, and the limited reach of state health authorities are features that need to be taken into account.

The Somali social fabric, abiding to customary and Islamic law [71], whereby clans and extended family influence the decision to seek care for illnesses such as VL [72], is important to understand. The cost of health care is almost always borne by households through out-of-pocket expenditure [58]. Although a kinship transfer system—from remittances of Somali diaspora or clan mobilisation—perhaps provides a partial safety net [64], the most vulnerable groups, such as less powerful subclans or nomadic peoples, may not benefit. Additionally, there is urban bias in care provision [16], with the remote, rural areas where VL is endemic being underserved.

VL is unamenable to mass preventive chemotherapy or vaccination; case detection and management is, therefore, crucial. Service delivery through the health system would be the generic mantra in most contexts, but for Somalia, we advocate for exploring nonconservative approaches to mitigate the impact of VL. Local, small-scale, indigenous solutions (rather than nationwide goals) may work better in Somalia, with more focus on local (region or district level) priorities and action.

Way forward

VL care provision cannot wait until peace returns; with the current climate-related famine threat in the Horn of Africa, alertness and preparedness for another VL outbreak is important for the whole region [50,73]. A mobile team strategy has been implemented successfully in South Sudan (M. den Boer, personal communication)—recruited from local tribes, their tasks include training, health education, bringing drugs and diagnostics, and going to places where there are outbreak rumours to provide immediate assistance. Innovative thinking in improving care would also benefit VL patients. Examples include disease risk mapping using a spatially referenced population database in Somalia [74,75] or use of technical support platforms, such as telemedicine, encompassing teleconsultation and telementoring. The latter has already been deployed in Somalia in paediatric and tuberculosis (TB) services, with encouraging results [76–78]. Surveillance, using up-to-date geographical information on the distribution of VL, can assist in targeting the villages where most patients come from to carry out a more active approach if and when circumstances allow. In a complex, protracted conflict like the one in Somalia, the surveillance system suffers from the breakdown in health services and routine data collection, and without a functional governmental health system, the classical approach to epidemiological surveillance as a centrally operated public sector information management system is not obvious. Therefore, innovative approaches to VL surveillance should be explored, starting with improved coordination of various stakeholders (WHO, NGOs, the community) and proactively building on innovative approaches and new technologies. A few examples that can be considered are using crowdsourced information, event-based or community-based surveillance, and exploiting the digital potential of the Somali community, who are using cell phones and internet on a large scale. WHO has paved the way in this case by proposing the online DHIS2 platform as a uniform and flexible platform that allows various stakeholders to participate in the surveillance endeavour in this complex context[79]. Improving the spread of information and awareness about the disease could be done simultaneously thanks to technological advances in communication tools[80].

Qualified health cadres are lacking at all levels in Somalia [8,81], and local initiatives to bring care closer to the community should therefore be supported. To deal with VL, these capacity-building efforts could be better targeted, with basic in-service skills being provided to

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the local workers, as opposed to formal qualification. The plan to recruit and train female community health workers [17,81], if rolled out in endemic areas of southern Somalia, could include detection of suspect VL cases. Increasing awareness of VL among the population and availability of care are as important as improving the quality of curative service itself. Working with various actors in the complex backdrop of health care provision is labour-intensive, but it may provide better outcomes than what has been implemented in Somalia in the last decades. Commitment from the local communities, through their own structure, would be crucial in ensuring access to care for this deadly disease.

Looking at the local dynamics through a different lens would help in adapting how care should be organized and delivered. However, there are technical obstacles: the existing tools to diagnose and treat VL in the eastern African region are imperfect and extremely difficult to use in conflict settings with scarcity of health staff. The current treatment option of 30 days' daily SSG injections or 17 days' combination of SSG and Paromomycin [56,82] are far from ideal, as not all patients are able to travel to the treatment centres or to afford prolonged in-patient care. A short-course oral treatment for self-administration at home would be a breakthrough in such settings. Likewise, better RDT's with improved accuracy and that differentiate between past and present infections are needed, as current treatment cannot be justified to be given empirically without diagnosis confirmation. Clinical diagnosis by community workers would still require certain training and supervision and should be in conjunction with RDT use. There is a clear gap in the current research and development landscape to invest in user-friendly tools that are easier to roll out in unstable contexts such as Somalia. The operational challenges in conflict-ridden areas like parts of Somalia or South Sudan should also be considered when formulating global research portfolios as well as resource allocations (see Table 2 for complete recommendations).

Table 2. Recommendations for addressing VL in Somalia.

For policy makers	• **Show awareness and commitment toward VL (and other NTDs) as important causes of ill health and suffering of the Somali people** • **Ensure mobilisation of resources to tackle VL through focused and concerted efforts with all stakeholders** • **Maintain the policy intent, which includes VL control through macro-, meso-, and micro-level planning in endemic areas** • **Commit to ensure security and access for health care workers and programmes**
For programme implementers, NGOs, and support agencies (e.g., WHO)	• Continue ensuring availability and access to the VL National Guidelines for health care staff, including through training and supervision • Optimizing the reach and coverage of free care provision • Ensure availability of needed diagnostic kits and treatment • Strengthen the surveillance mechanisms • Explore innovative approaches to spread awareness of VL and availability of care • Manage VL programme sustainably and toward capacity building • Advocate for continuing the provision of access to diagnosis and treatment of endemic clusters of VL and strengthening emergency capacity for outbreak
For research community	• Contribute to and lead in building in-country research capacity to enlarge the evidence base of VL in Somalia, including operational and implementation research • Identify the most relevant research questions, including those related to disease burden, understanding the economic and social cost of VL, barriers to care, and vector control • Identify and innovate in research methodology to address these questions in the context of a difficult-to-access, conflict-affected country • Continue to address the gaps in VL epidemiology and VL control knowledge and practices, especially for the east Africa region, including Somalia; accelerate the progress for improved tools to be implemented in the field to overcome limitations of diagnosis and treatment regimens

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Conclusion

To ignore the burden of neglected diseases in conflict-affected areas is not only detrimental to public health, but also to our morals [83]. VL in Somalia should not be left as just another neglected disease in a neglected conflict. Existing tools for VL control—albeit imperfect—should be deployed, their outcomes monitored, and efforts continued to develop better control tools. Innovative strategies—adapted to the stateless context—without undermining the health-system-building process are needed. Addressing VL in Somalia is a moral imperative, as it means averting avoidable deaths for the most vulnerable: the rural poor, internally displaced, and nomadic populations.

Key learning points

- Visceral leishmaniasis (VL), fatal without treatment, is known to be endemic in parts of southern Somalia, with outbreaks reported in the past.
- Information on VL in Somalia in the literature is scarce and the only currently feasible control option is provision of diagnosis and treatment.
- Due to the ongoing conflict and difficulty in accessing the people in need, availability of VL care within the country is limited.
- There is a need to stop the neglect of VL in Somalia through innovative strategies and improve emergency preparedness.
- Further research is needed to improve existing diagnosis and treatment tools to be more adapted to be used in such a context.

Five key papers in the field

1. Chappuis F, Sundar S, Hailu A, Ghalib H, Rijal S, Peeling RW, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? NatRevMicrobiol. 2007;5(1740–1534 (Electronic)):873–82.
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1.2 ARTICLE 2

Uncharted territory of the epidemiological burden of cutaneous leishmaniasis in sub-Saharan Africa – a systematic review

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RESEARCH ARTICLE

Uncharted territory of the epidemiological burden of cutaneous leishmaniasis in sub-Saharan Africa—A systematic review

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Abstract

Introduction

Cutaneous leishmaniasis (CL) is the most frequent form of leishmaniasis, with 0.7 to 1.2 million cases per year globally. However, the burden of CL is poorly documented in some regions. We carried out this review to synthesize knowledge on the epidemiological burden of CL in sub-Saharan Africa.

Methods

We systematically searched PubMed, CABI Global health, Africa Index Medicus databases for publications on CL and its burden. There were no restrictions on language/publication date. Case series with less than ten patients, species identification studies, reviews, non-human, and non-CL focused studies were excluded. Findings were extracted and described. The review was conducted following PRISMA guidelines; the protocol was registered in PROSPERO (42016036272).

Results

From 289 identified records, 54 met eligibility criteria and were included in the synthesis. CL was reported from 13 of the 48 sub-Saharan African countries (3 eastern, nine western and one from southern Africa). More than half of the records (30/54; 56%) were from western Africa, notably Senegal, Burkina Faso and Mali. All studies were observational: 29 were descriptive case series (total 13,257 cases), and 24 followed a cross-sectional design. The majority (78%) of the studies were carried out before the year 2000. Forty-two studies mentioned the parasite species, but was either assumed or attributed on the historical account. Regional differences in clinical manifestations were reported. We found high variability across methodologies, leading to difficulties to compare or combine data. The prevalence in hospital settings among suspected cases ranged between 0.1 and 14.2%. At the community level, CL prevalence varied widely between studies. Outbreaks of thousands of cases

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occurred in Ethiopia, Ghana, and Sudan. Polymorphism of CL in HIV-infected people is a concern. Key information gaps in CL burden here include population-based CL prevalence/incidence, risk factors, and its socio-economic burden.

Conclusion

The evidence on CL epidemiology in sub-Saharan Africa is scanty. The CL frequency and severity are poorly identified. There is a need for population-based studies to define the CL burden better. Endemic countries should consider research and action to improve burden estimation and essential control measures including diagnosis and treatment capacity.

Author summary

Cutaneous leishmaniasis (CL) is the most common form of this group of parasitic diseases, transmitted by sandflies. In sub-Saharan Africa, its extent of the problem is unknown, while elsewhere its disfigurement and stigma may cause a severe impact. This study systematically searched the literature to find evidence on the epidemiological data on human CL in this part of the world. Historically, CL has been present for decades in both western and eastern Africa, but unfortunately, in the last decades, the data are irregular and patchy. The estimated burden, relying on detected cases, may only capture part of the true number of cases. This article shows that there is insufficient evidence to have accurate figures; the diversity of the disease, along with poor surveillance have resulted in unprecedented CL outbreaks in the past. Many knowledge gaps remain, and we highlight the importance of improving the current fragmented knowledge by increasing commitments to tackle CL and conduct better population studies. CL in sub-Saharan Africa appears to be a blind spot and should not remain so.

Introduction

Cutaneous leishmaniasis (CL) is the most common clinical manifestation of leishmaniasis, a parasitic neglected tropical disease (NTD) [1]. Caused by an obligate intracellular protozoa from the *Leishmania* species and transmitted by the bite of Phlebotomine sand flies, the clinical presentations of CL include localized skin nodules (often called oriental sores), diffuse non-ulcerated papules, dry or wet ulcers, and, in the mucocutaneous form, extensive mucosal destruction of nose, mouth, and throat. Transmission of CL may involve animal reservoir hosts (e.g., rodents, hyraxes) in zoonotic foci, while anthroponotic CL (where humans are the main parasite reservoir) occurs in urban or periurban settings [2]. Environmental changes in rural contexts such as agricultural activities, irrigation, migration, and urbanization may increase the exposure risk for humans and result in epidemics. Likewise, outbreaks in densely populated cities or settlements have occurred, especially in conflict-affected zones such as Afghanistan or Syria [3,4], in refugee camps and contexts of large-scale forced migration of populations.

Globally, the World Health Organization (WHO) considers CL as endemic in 20 countries in the New World (South and Central America) and in 67 countries in the Old World (southern Europe, Africa, the Middle East, parts of southwest Asia) [5]. Between 700,000 to 1,200,000 CL cases are estimated to occur annually worldwide, with >70% of cases in 2014 reported

from Afghanistan, Algeria, Brazil, Colombia, Costa Rica, Ethiopia, the Islamic Republic of Iran, Peru, Sudan and the Syrian Arab Republic [5,6]. Multiple parasite species cause CL: in the Old World, these are *L. major*, *L. aethiopica*, *L. tropica*, and, rarely, the viscerotropic *L. donovani* (in Sudan), resembling similar a phenomenon more known for *L. infantum* [7–10]. Though CL is often considered self-healing, the duration varies for different species and can take months, or years [11].

Due to the clinical and epidemiological diversity in CL, its geographic clustering and lack of reliable surveillance data, estimating the CL burden are challenging [12]. The most widely used measure of disease burden known as the Disability Adjusted Life Year (DALY) combines estimated prevalence, incidence, and mortality, with an assigned disability weight for each disease [13]. However, the disability weights are defined using different approaches with regards to the expert panel composition, health state description, and valuation methods [14,15]. The specific stigma and psychosocial distress generated by a non-fatal condition are often overlooked [16,17], although the social impact of CL is potentially severe and has been well-documented [18,19].

Moreover, in sub-Saharan Africa (SSA), not only the disability but also the number of CL cases is largely underestimated. A recent global burden analysis listed 19 countries in SSA in the top 50 high burden countries [20]. The passive epidemiological surveillance system that prevails in these countries leads to the patchy data from this region. According to WHO, only Sudan and Ethiopia reported cases of CL [21]. The objective measures of burden such as prevalence and incidence of CL are scarce in this region, making it hard to advocate for funding and resources to tackle the disease.

Whereas attention has been given to CL in Northern Africa (Algeria, Libya, Morocco, Tunisia, Egypt) and the Middle East [22–24], data for sub-Saharan Africa is critically lacking, particularly in countries where CL is not a notifiable disease. This study focuses on SSA because it is a blind spot on the CL epidemiological burden map and the overall picture of what has been documented on CL is not known. We undertook a systematic review of the literature to synthesize current knowledge on CL burden in SSA.

Methods

Search strategy and selection criteria

We searched the following electronic databases: National Library of Medicine through Pubmed, Cochrane Register, Web of Science, CABGlobal Health, African Index Medicus and Google Scholar. We did an initial keyword search and subsequent searches based on Medical Subject Headings (MeSH) with various combinations of search terms "cutaneous leishman*" AND "Africa, South of the Sahara" (which also included "Africa, Western"; "Africa, Eastern"; and "Africa, Southern") OR "Leishmaniasis, cutaneous" OR "Leishmaniasis, diffuse cutaneous" OR "Leishmaniasis, mucocutaneous" AND each individual sub-Saharan countries. The World Bank classification was used to define sub-Saharan African countries and to group them according to the region (i.e., southern, eastern, western, and middle Africa- see Box 1). No language restrictions were set for searches, while we limited the publication date until 31 May 2018. We hand-searched the reference lists of all recovered studies for additional references. We also explored and summarized information from the Global HIealth Observatory for leishmaniasis maintained by WHO for CL.

We included studies if they are reporting primary data that help to determine the burden of CL in countries in SSA. The burden is defined as elements of 1) severity of the problem (clinical, disability, case fatality,. . .) in human patients; 2) frequency (prevalence, incidence,. . .) and 3) economic cost (from patient, societal or health system perspective). We excluded animals or

Box 1. Countries of sub-Saharan Africa

Angola, Benin, Botswana, Burkina Faso, Burundi, Cabo Verde, Cameroon, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Republic of Congo, Cote d'Ivoire, Equatorial Guinea, Eritrea, Ethiopia, Gabon, (the) Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Sao Tome and Principe, Senegal, Seychelles, Sirra Leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe

vector studies, studies on pathogenesis, immunology, histopathology, or on *Leishmania* species only, studies on diagnostic tests or treatment for CL and cases of Post Kala Azar Dermal Leishmaniasis (PKDL)–skin sequelae of VL. Case reports and case series of fewer than ten patients were also excluded. Sub-Saharan Africa as the main geographical interest refers to the settings where the studies were performed/conducted. Reviews about CL in a specific country or region without original data were excluded.

The systematic review was conducted in line with PRISMA guidelines [25,26]. The review protocol was registered in PROSPERO, an international prospective register of systematic reviews, in July 2016, number 42016036272 [27].

We selected the articles in a two-step process. In a first stage, titles and abstracts of all retrieved records were independently reviewed by two investigators (TS and KV). In a second stage, the selected full-text articles were again reviewed (by TS, KV, and a third person) for eligibility. When full-text articles were excluded, the reason for exclusion was registered and reported. Any discordances were resolved through discussion or seeking consensus with a third investigator (MB).

Data extraction and synthesis

The data were extracted in parallel by two independent readers, using a specific data form, including information on the published record (year, author), setting (country), aim, study design, and main outcomes. We sought data on prevalence or incidence of CL among patients in health facilities and the community; demographic and clinical characteristics of CL patients, and the association between CL and other morbidities, notably Human Immunodeficiency Virus (IIIV). We attempted to use the STROBE checklist (for reporting epidemiological studies) to assess the 'risk of bias,' but could not continue due to a large number of historical studies that are not in line with current reporting standards. The data analysis thus resulted in a narrative, qualitative synthesis of the included studies.

Results

Search results

The flow diagram in Fig 1 shows the selection process: we identified 340 published articles, and after removing duplicates, we screened the title and abstracts of 289 articles, and exclude 184. The full-text articles of the remaining 105 were assessed for eligibility, after which a further 51 were excluded. The remaining 54 articles were included. (See *Supporting Information 1* for all the included studies and the key information).

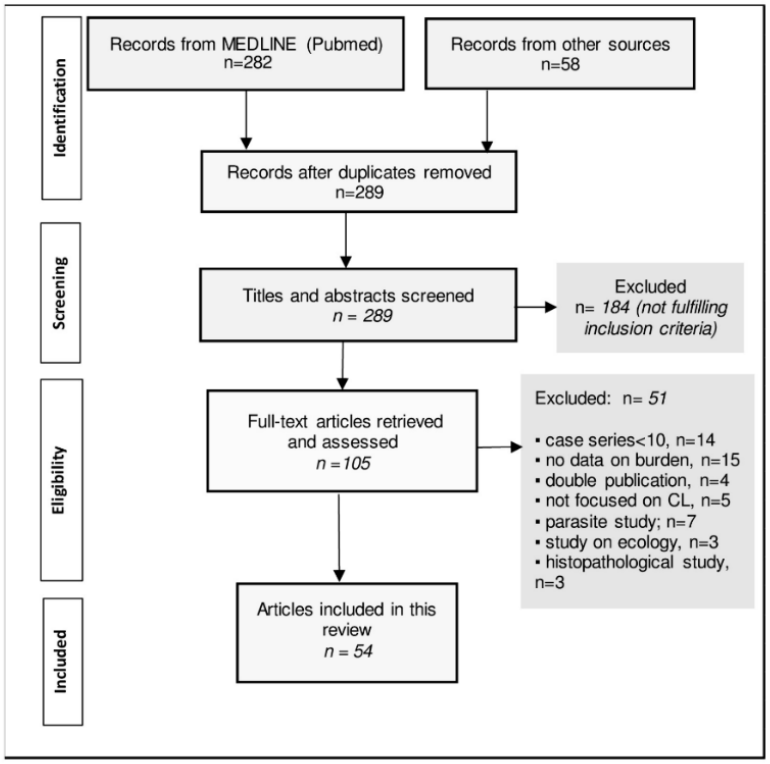

Fig 1. Flow diagram depicting the selection of eligible articles.

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Description of the included studies

The studies were published between 1955 and 2016; with only 12 (22%) after 2010. The studies were conducted in 13 out of the 48 countries in Sub-Saharan Africa: in eastern Africa (Ethiopia, Kenya, Sudan), western Africa (Burkina Faso, Cameroon, Chad, Ghana, Guinea, Niger, Nigeria, Mali, Senegal) and southern Africa (pre-independent Namibia). More than half of the studies were from western Africa (30/54), notably Senegal (6), Burkina Faso (5) and Mali (5). Twenty-three studies studied CL in the community (including three among school-children), and 28 used data collected in health facilities (including 18 dermatology specialized services). The remaining three studies were mixed. All 54 studies were observational: 29 (54%) were descriptive case series (numbering a total of 13,257 cases), and 25 (46%) followed a cross-sectional design, usually survey with various tools employed such as clinical screening or questionnaires.

Historical accounts of cutaneous leishmaniasis in sub-Saharan Africa

In eastern Africa, CL has been known for more than a century, with the first indigenous CL case recorded in 1911 in Sudan [28]. In Ethiopia, CL has been known since 1913, and diffuse

CL (DCL) clinical form was documented in 1960 in the highlands [29]. The first report of *L. aethiopica* as a distinct taxonomic entity was published in 1978 [30,31], and since then, the species has also been found in the mountainous region of Kenya [32]. *L. tropica* was later reported from certain areas in Kenya during the 1990s, and since then considered to have a more restricted distribution than *L. major* [33,34].

In western Africa, only *L. major* has been thought to circulate in this region. The oldest case reports of CL come from Niger in 1911 [35], then from Nigeria in 1924, and from Senegal in 1933 [36]. Later more cases were reported from Cameroon, Mali, Mauritania, Burkina Faso and Guinea [37,38]. During the first half of the 20th century, the colonial medical officers documented sporadic case reports from an area that later became recognized as the 'CL belt' [38]. Several comprehensive ecological and epidemiological studies took place in suspected hyperendemic foci in Senegal [39–42], Mali and Niger [43]. Current Namibia (previously South West Africa), reported dozens of CL cases in the 1970s [44], but the disease was not considered as a public health problem by the authorities [45].

Exposure to the parasite: Frequency of leishmanial infection measured through population surveys

Twelve studies (Table 1) reported prevalence estimated by the Leishmanin Skin Test (LST)—also known as Montenegro test—to detect exposure to the parasites in CL foci. Through intradermal injection of *Leishmania* antigens, the induration is being read 48–72 hours later as a demonstration of a delayed type hypersensitivity reaction, much like a tuberculin skin test [11]. LST does not differentiate between past and present infection and not species specific, yet it is often used as a marker for cellular immunity against CL [46].

These studies were conducted at the community level in CL foci, and have shown fluctuation over time (Table 1). Changes from 4% to 91% in LST positivity rate were observed in the

Table 1. Overview of studies describing the frequency of exposure to *Leishmania* based on Leishmanin Skin Test (LST).

Region	Author, Year, [Ref]	Study year	Country, Location	Setting	Number of people subjected to LST	The proportion of positive LST results
Eastern Africa	Mengistu, 1992 [49]	1989	Ethiopia, Ocholo (west Rift Valley)	Community	120	57%
	Berhe, 1998 [51]	1994–1996	Ethiopia, mid-Ethiopian Rift Valley	Community	1809	3%
	Kadaro, 1993 [48]	1990	Sudan, Khartoum province	Community	1479	91%
	Abdalla, 1973 [47]	NA	Sudan (Blue Nile, Kartoum, Darfur)	Community	560	22%
	Abdalla, 1975 [52]	NA	Sudan, eastern part	Hospital	15 (cases)	80%
Western Africa	Pampiglione, 1977 [37]	1976	Guinea, Kamsar	Community	388	15%
	Imperato, 1970 [43]	1969	Mali, Nioro in Kayes region (western)	Community (school)	550	61%
	Imperato, 1974 [53]	1973	Mali,Mopti (central)	Community (school)	249	5%
	Oliveira, 2009 [50]	2006–2008	Mali, Segou district (central)	Community	1530	31%
	Traore, 2016 [54]	2014	Mali, central/western and southern	Community	1412	39%
	Dedet, 1979 [55]	1976–1978	Senegal, Thies Region	Community	NA	58%
	Dedet, 1979 [56]	1978	Senegal, Fleuve Region	Community	1489	47%

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same villages following an outbreak in Sudan [47,48]. High variability across foci within one country has also been reported, for example in Ethiopia: in Ocholo, 57% of school children without CL lesions were LST positive [49], while another study in the central-Ethiopian Rift Valley, LST positivity was maximum 5%. A study conducted in two neighboring villages in central Mali also demonstrated high variability: prevalence of *Leishmania* infection in Kemena was 45%, with the incidence of 19% and 17%; higher than Sougoula with 20%, 6% and 6% for the same years [50]. Reasons for these discrepancies are not known but possibly linked with hyper-clustering of reservoirs and vectors, leading to different intensity of peridomestic transmissions in Kemena [50].

A 2014 study from Mali complemented LST surveys with PCR and finger prick blood sample to measure antibody levels to sand fly saliva in endemic districts [54]. The results showed uneven prevalence of LST positivity across three different climatic areas (49.9%, 24.9% and 2.6% in Diema, Kolokani, and Kolondieba respectively), linked with north-south declining vector density. PCR was used to confirm *L. major* as the causative agent. LST positivity was also shown to be correlated to higher levels of antibodies to sand fly salivary proteins [54].

Across the studies, a consistent finding is that the proportion of positive LST increased with age and areas where CL transmission is active, at least a third of the population have had exposure to the *Leishmania* parasite [37,43,47–51,54–56].

Prevalence and incidence of cutaneous leishmaniasis in sub-Saharan Africa

Twenty-one studies reported estimates of CL prevalence or incidence; five were using medical records from hospitals, and the remaining were population estimates obtained through active screening for CL lesions and scars at the community level. All diagnosis was based on clinical examination. Though additional confirmatory methods (microscopy/smear, histology, culture in NNN or combination of these) were mentioned in all studies but two, it is unclear whether these were used in some or all or none of the patients. Among the five studies that were hospital-based, two used the number of dermatology consultations as the denominator, and the CL cases proportion found is 2% in Ouagadougou, Burkina Faso [57] and 14% in Addis, Ethiopia [58]. If suspected cases were to be denominator to calculate the CL cases proportion, they were found to be 78% (251/320) in Mali [59] and 93%(74/80) in Burkina Faso [60].

In most of the studies in the community, the prevalence of active CL was less than 5%. In endemic areas, the frequency of CL scars usually exceeds that of CL active lesions, except in a few special settings (Table 2). In Utut, Rift Valley in Kenya, a higher lesion versus scar rate (50% vs. 18%) in migrant charcoal workers suggested a non-immune population's encounter with the disease in an area where transmission occurs [34]. Also during an outbreak in a new focus in Silti, Ethiopia, the frequency of CL lesions was considerably more than that of CL scars [63]. In Sudan, 36% of the community were found to harbor active lesions during an outbreak [68].

To complement the findings from published studies, we also examined the data from the country official reporting system to WHO. The system record data from 1996 onwards, but clearly there are missing data (Fig 2A and 2B). The absolute number of CL cases reported from eastern Africa is always higher than from western Africa, with Sudan bearing most of the burden. In western Africa, the number of cases reported from different countries is highly variable, and recurrent outbreaks were occurring in a 5–7 years cycle [74]. The increased cases in Ghana during 2002–2003 was prominent, yet there was a vacuum between 2007 and 2010, and cases were reported again starting in 2011. Other countries contribute little, with <100 cases per year (Nigeria, Senegal). No data was reported from this region during 2015–2017 [75].

Table 2. Prevalence and incidence of active lesions and scars of cutaneous leishmaniasis.

Region	Author, Publication Year, [Ref]	Country, Location	Setting	Number of people screened	Prevalence CL (active lesion)	Prevalence CL scars	Incidence
Eastern Africa	Wilkins, 1972 [61]	Ethiopia, Meta Abo	Community	1635	0.6%	3.2%	0.1%
	Lemma, 1969 [62]	Ethiopia, highlands	Community	>2000	2.9%	2.9%	
	Negera, 2008 [63]	Ethiopia, Silti (SNNPR)	Community	1907	4.8%[A]	0.3%	
	Mengistu, 1987 [64]	Ethiopia, Ocholo (southwest)	Community	2689	6.0%	40.0%	
	Mengistu, 1992 [49]	Ethiopia, Ocholo	Community	3022	3.8%	34.3%	
	Bsrat, 2015 [65]	Ethiopia, eastern Tigray	Community	2106	7.1%	6.9%	
	Bekele, 2014 [58]	Ethiopia, Addis Ababa	Hospital	1651	14.2%		3.5%
	Sang, 1993 [66]	Kenya, Mt Elgon	Community	1979[A]	1,3%		
	Sang, 1993 [67]	Kenya,Nairobi+Rift Valley	Community	3743	0.5%	0.3%	
	Sang, 1994 [34]	Kenya, Utut	Community	167	49.7%	18.0%	
	Abdalla, 1978 [68]	Sudan, Shendi Atbara	Community	308	36%[B]		
			Dispensaries	NA	20–50%		
	Kadaro, 1993 [48]	Sudan, Khartoum province	Community	458	4.0%	47.0%	
Western Africa	Bamba, 2013 [57]	Burkina Faso, Ouagadougou	Hospital	12708	2.0% [C]		
	Guiguemdé, 2003 [60]	Burkina Faso, Oudagougou	Hospital	80	92.5% [D]		
	Keita, 2003 [59]	Mali, Bamako	Hospital	320	78.0%[E]		0.6%
	Obasi, 1991 [69]	Nigeria, Kaduna	Hospital	18000	0.1%[F]		
	Ngouateu, 2012 [70]	Cameroon, Mokolo (north)	Community	32466	0.4%	0.8%	
	Oliveira, 2009 [50]	Mali, Segou district (central)	Community	1530			9.4%
	Okwori, 2001 [71]	Nigeria, Kaduna	Community	10226	3.9%	3.0%	
	Ikeh, 1994 [72]	Nigeria, Keana	Community	5046	3.9%		
	Dedet, 1979 [73]	Senegal, Thies region	Community	1049	3.7%	8.7%	0.2%

NA- Not Available;

[A] General survey outside the survey's two villages yield prevalence of 0.1% (18/18528);

[B] This study was done during an outbreak (see text)

[C] During 1999–2007; 251 confirmed CL cases among all consultations in the Dermatology Service of University Hospital

[D] Confirmed CL amongst suspected cases (74/80). Also reports the prevalence of CL and HIV

[E] During 1997–2001; 251 confirmed CL cases among suspected file

[F] During 1979–1988; 21 CL cases among 18,000 dermatology consultations in Ahmadu Bello University Teaching Hospital

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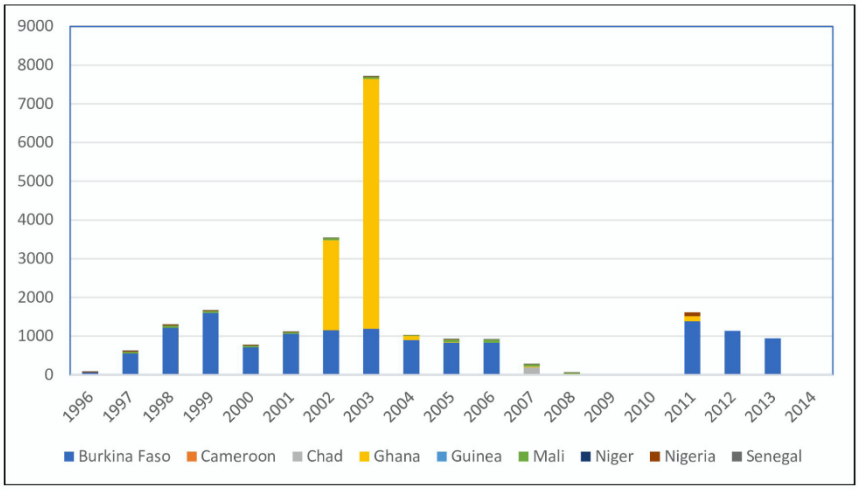
Cutaneous leishmaniasis case series

The majority (n = 28) of the included records are clinical case series based on medical files from dermatology clinics or hospitals as the main data source. These studies describe a cohort of CL patients over a certain period, ranging from two to nine years. Chronologically, 10 studies reported CL cases in periods before 1980 [41,45,47,52,74,76–80], 11 described patient groups observed between 1980–2000 [35,57,59,67,69,81–87], and seven between 2000 and 2013 [58,60,88–92].

Hospitals reported that CL patients mainly came from surrounding areas or outside the cities or capital, such as Dakar, Senegal [74,88,93] or Niamey, Niger [84]. Eighteen studies report



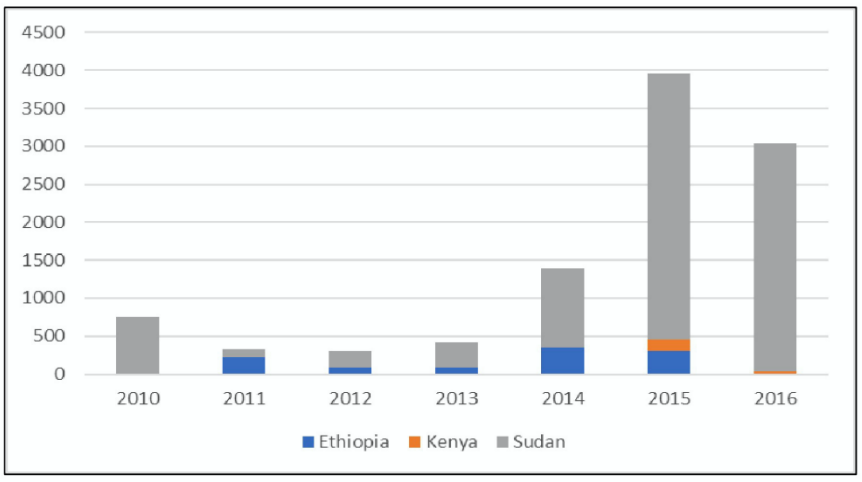


Fig 2. A.) Reported cutaneous leishmaniasis cases in western and central Africa, WHO Global Health Observatory. B.) Reported cutaneous leishmaniasis in eastern Africa, WHO Global Health Observatory.

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cases seen in specialized dermatology services. The proportion of CL cases among patients seen in those dermatology clinics is consistently less than 5% [59,69,94]. In the context of an outbreak, CL patients who seek care in specialized services represent only the tip of an iceberg, as shown in Burkina Faso (further described below). Between 1999 and 2005, a total of 7444

cases were recorded from various health centers in the capital Ouagadougou [95,96], but during the same period, the dermatology hospital had only seen 251 CL cases [57]. Diagnosis in all the case series is obtained through clinical examination and smears or histopathology. In Chad, a hospital close to the Sudanese border reported a very high proportion of CL confirmed cases (580 out of 680 cases between 2008–2012) [89].

Cutaneous leishmaniasis outbreaks

Three countries have published studies on CL outbreaks: Sudan, Ethiopia, and Ghana. The first ever epidemics in Sudan were reported in 1976–1977 along the Nile, in Shendi-Atbara north of Khartoum [68], while the second and third outbreaks occurred in 1985 and 1986–1987, respectively [97]. The last epidemic in Sudan was in Tuti island, and it affected at least 10,000 people in 7 months. Underestimation is likely mandatory reporting only started after the epidemic reached its peak [86]. People of both sexes, all age groups and all socio-economic classes were affected, which is suggestive of a disease ravaging in a non-immune population. The causal parasite was *L. major* LON-1 [98] and the outbreak was attributed to various factors such as immigration from west Sudan, the heavy rainfall in the year of the outbreak after a long period of drought—which led to increase in sandfly density as well as the rodent reservoir population—and waning of herd immunity of migrants from CL endemic areas in western Sudan (*Sayda el-Safi, personal communication*). In Ethiopia, a CL outbreak occurred in 2005 in a district 150 km south of Addis. A survey then established an overall prevalence of 4.8% (92/1907), and 1 in 5 cases had mucocutaneous lesions [63].

In Ghana, an outbreak of localized skin lesion consistent with CL occurred in Ho municipality, Volta region in 2003 [90]. The usual triggers of CL epidemics such as intrusion of humans into vector habitat through deforestation, road construction, wars or migration were not at work here. Previously, only one CL case had been reported from the country in 1999, although the arid, Sahelian area of northern Ghana is considered to be part of the West African CL belt. Through passive case detection (with biopsy as a confirmatory diagnosis) with medical records review and active case finding, it was estimated that there were about 8876 CL cases between 2002 and 2003 in Ghana (Fig 2A). All age groups were affected, and since then CL is considered endemic in this area. A study in the same district later found 60% parasite-confirmed cases among active CL suspects (41/68). A phylogenetic analysis identified this Ghanaian parasite as new member of *Leishmania enriettii complex*, a possible new subgenus of pathogenic human Leishmania parasites [99].

Clinical aspects of cutaneous leishmaniasis

Thirty-two studies described the clinical presentations of CL lesions. The most commonly used categories of the lesions are as followed: the localized CL or LCL, otherwise known as the classic oriental sore, refers to the lesion at the site of sand fly bites that may get ulcerated. LCL may appear as dry, papular forms with crust, or the wet, ulcerative forms with indurated edges. LCL can be singular or multifocal. When the nodules are multiple and nonulcerative, this is typically called a diffuse CL or DCL. In Sudan, mucosal leishmaniasis is described as lesion(s) that involves destructive mucosal inflammation which does not always start with a cutaneous lesion. This differs from New World mucocutaneous leishmaniasis (MCL), which refers to a metastatic dissemination to the mucosal tissues starting from a distal cutaneous lesion [52,100]. Bacterial superinfection is common along with pain, itchiness, fever and the secondary inflammation often complicates clinical diagnosis [11,101].

The diagnosis documented in the medical files are often missing. A dermatology hospital in Addis, Ethiopia reported that among 234 confirmed CL cases, only 22% were categorized—

consisting of 9% DCL, 10% MCL and 3% LCL [58]. The higher proportion of complicated or atypical lesions are frequently reported from teaching hospitals or specialized services. This includes sporotrichoid CL with painless subcutaneous nodules along the lymphatic vessels in Sudan [80,87], or the diffuse CL in Ethiopia, which appear pseudo-lepromatous and can result in fungating or tumor-like lesions [52,80].

In the majority of the studies, the natural history of the lesions is only briefly described (n = 51). The duration between the first bite to lesion formation for LCL varied between 3–12 weeks [62,90]. Although CL can heal spontaneously, this seems to be dependent on the reported parasite species: *L. major* heals within approximately 2 to 12 months and *L. tropica* within 15 months, with a terminal scar appearing after about 24 months [11]. The description of diffuse CL caused by *L. aethiopica* suggests that it presents initially with nodules which do not heal or ulcerate but can metastasize widely [76] and are known to be very difficult to treat. In the case of DCL, spontaneous cure almost never happens. Mucocutaneous leishmaniasis is rare in Africa, but cases have been reported from Sudan and Ethiopia [52,80,100]. The lesions tend to be infiltrative and result in chronic edematous inflammation involving the lips, nose, buccal mucosa and larynx are.

With regard to the locations of CL lesions, there appears to be a regional difference. CL lesions from eastern Africa are mostly found on the head (i.e., face including cheek, nose, forehead, ears, lips) and less on the arms, legs or trunk, while from western Africa the highest proportion of lesions are on the upper and lower extremities.

Amongst the 42 studies reporting the sex ratio of the patients (Fig 3), only 12 recorded more females than males affected [49,50,56,63,70,72,82,95,102] while the remaining described

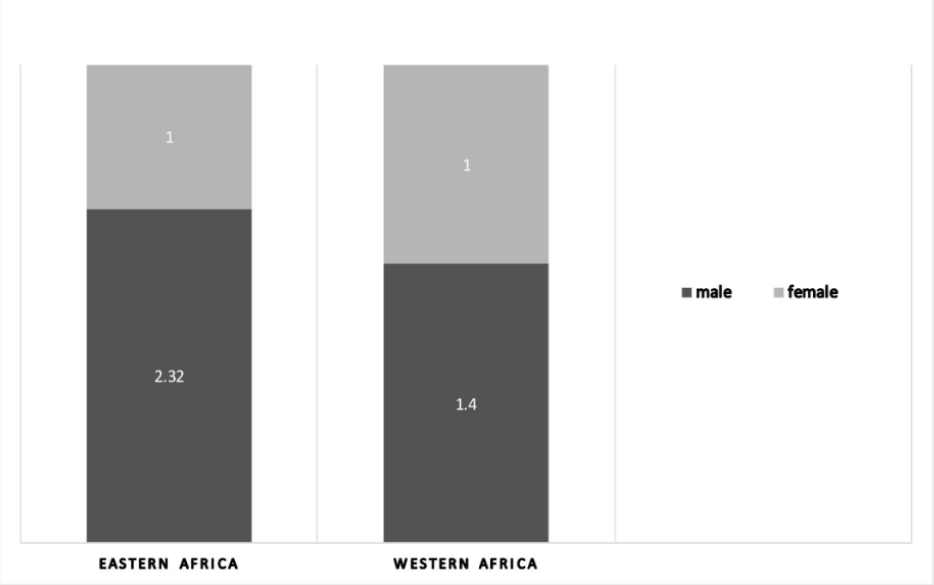

Fig 3. Sex ratio among cutaneous leishmaniasis cases in sub-Saharan Africa. Source: Studies included in this review that reports sex ratio amongst the CL cases (n = 18 studies from eastern Africa; n = 24 studies from western Africa).

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male preponderance, either due to hypothesized occupational exposure or males' easier access to seek care in a health facility. Thirty-six out of the 54 studies reported the age of the CL cases: people of all ages are affected. However, when stratification according to age was reported, there is a broad tendency towards younger age groups (between 10–30 years old.

Cutaneous leishmaniasis co-infection with Human Immunodeficiency Virus (HIV)

CL and HIV co-morbidities has been described in Burkina Faso [57,60,103], Cameroon [70], Mali [59], and Ethiopia [91], while sporadic cases have also been reported from Guinea, Ghana, Senegal, Nigeria, Ivory Coast and Sudan. Burkina Faso has recorded 13.5% (10/74) HIV positivity in a cohort of CL patients in 2000, and another cohort of 32 CL/HIV patients was described in 2003–2004 [60,103]. Six out of 10 DCL cases in Ouagadougou were co-infected with HIV [57]. In Bamako, Mali, the prevalence of HIV among CL patients was 2.4% [59]. In Tigray, Ethiopia, a study reported an HIV prevalence of 5.6%, which increased to 8% two years later in 167 CL patients [92,104]. The only study reporting CL/HIV prevalence in the community was done in Cameroon in 2008. Here, a total of 32 466 subjects were clinically screened, and amongst 146 active CL patients, seven (4.8%) tested positive for HIV-1 and/or HIV-2 [70].

The consistent finding is that the clinical forms of CL are more diverse and complex in HIV co-infected patients, posing significant challenges in diagnosis and treatment. The lesions tend to be more severe: there are reports of infiltrative, leprosy-like, diffuse, psoriasis-like, verrucous, sporotrichoid, and angiomatous or Kaposi-like. Patients are more likely to have more than one lesion and more than one clinical forms [103]. Also, the time to lesion healing was longer in immunosuppressed individuals [70], and particularly in atypical and severe CL patients with poor response to treatment [91].

Discussion

Our review shows that CL is reported in at least 13 countries in SSA but the true burden remains unknown. Several foci in Mali, Guinea, and Senegal have been studied intensively in the last half of the 20th century, but the published literature on CL can best be described as irregular and patchy. There is a lack of population-based or longitudinal studies to measure prevalence and incidence. The current CL burden is difficult to estimate accurately as primary data are scarce and CL cases often clusters in pocket areas. The prevalence in western Africa appears to be low, yet unprecedented outbreaks have occurred, such as in Burkina Faso and Ghana. Several CL outbreaks probably never get reported [105,106]. In eastern Africa, although the number of CL cases are high, there is insufficient evidence on CL prevalence and incidence outside the context of CL outbreak or its spread to new areas.

The findings from this review provide further insights vis-à-vis the official data reported to the WHO's global surveillance system. Based on reported cases in 2002–2009, WHO estimated a global CL incidence of 214,036 in 2012 with 35,300–90,500 cases from eastern Africa and a mere 790–1500 cases from the rest of SSA, albeit with 5–10 fold underestimation [5]. Data reported to WHO in 2005–2015 put the figure of global CL incidence at 187,855, and the estimated contribution of SSA remains negligible [107]. From the 2013 Global Burden of Disease (GBD) study which primarily used modeling, Sudan and Burkina Faso are the only two countries from SSA with significantly greater DALYs from CL than the global mean [20]. Our findings are in line with these, thus emphasising the critical need to improve on-the-ground data as sources for future estimates.

The quality of evidence found in our review is inadequate to establish a more accurate CL burden in this region. Case series provide a snapshot of a specific situation in a certain time and place, yet are hard to extrapolate. A considerable part of the data we reviewed originated from specialized dermatology services which only represent a small proportion of all CL cases. The patchwork distribution of CL within a country further hampers surveillance. The CL belt in SSA from West Africa to the Horn of Africa [38], confirmed with a modeled distribution map of CL [108], appears to be mainly supported by historical accounts. The currently available evidence is clearly limited.

Various factors have been attributed to the poor CL data from SSA [2,12,109]: 1) CL is not a notifiable disease in many of the endemic countries; 2) Patients do not seek care due to perceived self-healing nature of CL; 3) Poor access to health facilities as most affected people live in remote, rural areas; 4) Lack of control tools, including unavailability of diagnosis and limited capacity to offer effective treatment. Compared to other regions, the neglect of CL is obvious. For New World CL in Latin America, the Pan American Health Organization (PAHO) has coordinated efforts to standardize and centralize surveillance data [110]. A Regional Information System called SisLeish was eventually developed to become an essential tool to prioritize areas and guide control actions [111]. Understandably, the region bears a much higher burden than SSA (from 2001–2015, 843931 cases were reported from 17 countries in the Americas). Currently there is no regional approach to improve CL surveillance for SSA. Sudan is part of the WHO Eastern Mediterranean Region (EMRO) [112] while the rest of the SSA countries belong to the WHO African Region (AFRO).

Our review identified the fragmented knowledge on burden as one of the key challenges for CL control in SSA. Being a largely zoonotic disease, the control efforts for CL remains limited to care provision, while vector control or environmental measures are not feasible. The risk of outbreaks, however, should not be undermined. Co-infection with HIV, already a concern for VL, might pose further challenges in CL management. What can be done in the face of all these adversities?

In lights of the scanty data, steps should be taken to improve existing surveillance systems or establish one where it is non-existent. Each country could undertake a thorough review of CL epidemiological situation, using standardized methods, enabling compilation and comparison. The future actions must be adjusted to the country context. An integrated paradigm should be adopted: either in setting up rapid epidemiological assessments for CL alone or in taking opportunities to include CL with other skin-NTDs [113,114]. Recognising the common challenges of a vertical approach to each NTD affecting the skin, a common tool to monitor disability has been piloted [115]. Furthermore, WHO has recently released guidelines for the training of skin NTD for frontline health workers [116,117]. Building capacity in case detection through training or inclusion of CL in clinical guidelines is starting in Sudan and Ethiopia, following an algorithm developed for Eastern Mediterranean region by WHO [118].

The strengths of this review are the systematic search of the literature and the stringent process and reporting following a published protocol in PROSPERO. Furthermore, standardized reporting according to PRISMA guidelines is adhered to. The exclusion criteria for case series of fewer than ten patients have been chosen as the aim is to provide an idea on disease burden though we might risk missing individual case report(s) and may exclude countries which only has case report publications. By systematically assessing all published articles we aimed to draw attention to the importance of the disease and identify research priorities.

The major limitations of our study are first, the publication bias. Sub-national studies that are not published nor listed in the international electronic databases might be missed. Secondly, the weakness of passive detection and clinical case reporting. We could not provide a meta-analysis nor compare the results between studies, due to the high variability across

Table 3. Major topics on CL epidemiology and burden in sub-Saharan Africa identified in this review.

Research topic	Total number of identified studies	Comment
CL incidence	5	Better field data and regular, standardised reporting
Outbreak-associated with CL	3	Outbreaks are often overlooked and not documented
Risk factors for CL	0	Important to inform health messages and design control
The social impact of CL	0	The psychosocial distress has never been reported here
Economic burden of CL	0	Access barriers and access to care need to be prioritized
Factors that sustain transmission of CL	0	More studies needed on transmission dynamics of CL (vector, reservoir, hosts)

https://doi.org/10.1371/journal.pntd.0006914.t003

individual studies (denominator, sampling strategy, . . .). We could not systematically assess the risk of bias in the individual records and apply the current standard of as many studies pre-dated this era. The quality of the data in the studies is relatively poor. However, with the limited data we had to rely on, we understand better the state of the evidence in regards to CL in SSA: still an uncharted territory.

Based on the gaps identified in this review, there are some research priorities to be addressed (see Table 3). Improving epidemiological knowledge on CL will help to advocate for actions and resources in SSA, where the burden of NTDs surpass all other regions [119]. Future studies on CL burden should explore not only physical but also the socio-economic impact of this morbidity. CL in sub-Saharan Africa should not remain an enigma.

Conclusion

The epidemiological burden of cutaneous leishmaniasis in sub-Saharan Africa appears to be poorly documented. There is a paucity of robust evidence on prevalence and incidence on CL in this region. The diversity of CL epidemiological characteristics in endemic countries is not yet fully investigated. Nevertheless, the burden of CL morbidity remains important and most likely to be underestimated. Surveillance and mapping should be improved to mitigate outbreak risk and address dual co-infection with HIV. The current fragmented knowledge should be approached regionally, and awareness must be raised. In addition to population-based studies that better define the CL burden in sub-Saharan Africa, health systems should consider studies and action to improve CL essential diagnosis and care.

Supporting information

S1 Diagram. PRISMA flow diagram.
(DOC)

S1 Checklist. PRISMA checklist.
(DOC)

S1 Table. Key information from the studies included in this review.
(DOCX)

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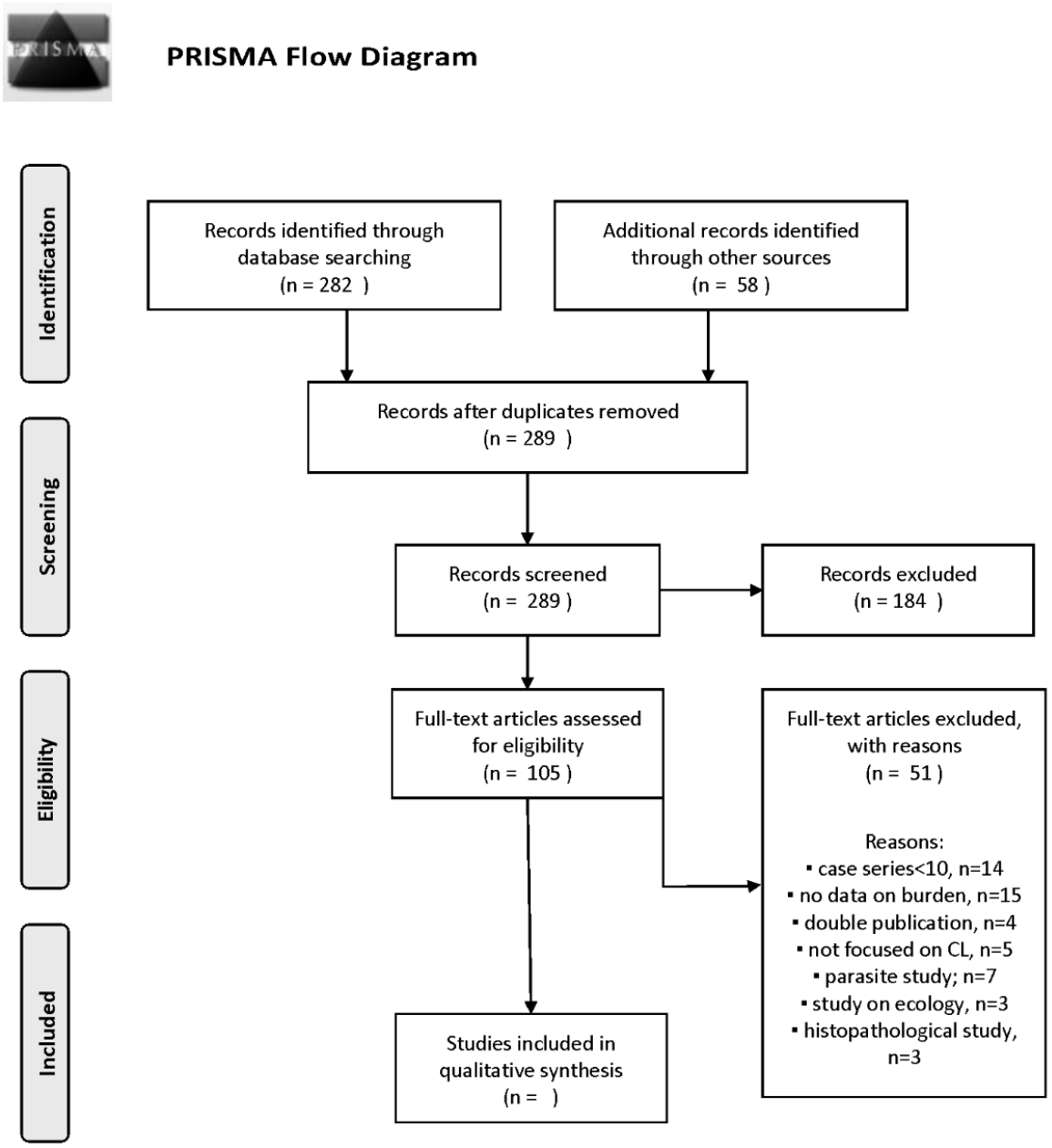
SUPPORTING INFORMATION

S1 DIAGRAM. PRISMA FLOW DIAGRAM



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title, page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract, page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraph 1-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, Paragraph 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, paragraph 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, paragraph 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, paragraph 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods, paragraph 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, paragraph 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, paragraph 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, paragraph 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, paragraph 5

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, paragraph 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, paragraph 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, paragraph 4-21
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA (no meta analysis done)
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA (not possible)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, paragraph 1-4

PRISMA 2009 Checklist

Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, paragraph 6
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Conclusion, page 22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding, page 23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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S3 TABLE: KEY INFORMATION FROM THE STUDIES INCLUDED IN THIS REVIEW

Study	Country	Study design	Study setting	Characteristic(s) of study participants	Number of cases reported	Prevalence/Incidence reported	Diagnostic method	Parasite(s)	Clinical presentation	Male/Female ratio
Abdalla et al, 1973	Sudan	Case series	Civil Hospital	Patients	21	0.22% LST+	Smear + histopathology	NA	nodular/noduloulcerative, ulceratuve, diffuse	9.5:1
Abdalla et al, 1975	Sudan	Case series	Hospital		51	LST+ 12/15	Smear + blood + histopathology	NA	oral, nasal, oro-nasal, laryngeal	Only male
Abdalla et al, 1978	Sudan	Cross-sectional	Community	along the Nile	308	29% skin lesions in Trajama, 59% skin lesions in Kijeik	Smear	NA	multiple, nodulonulcerative/nodular, mean è-28 lesions	NA
Bamba et al, 2013	Burkina Faso	Case series	dermatology service of CHU YO	Dermatology patients	251	251CL/12708 patients. 6VIH/10DCL	Smear	L major assumed	crusted40%; papuloulcerated16%	0.89:1
Bamba et al, 2011	Burkina Faso	Case series	Health centers of city Ouagadougou	Patients	7444 (1999-2005)	0.1%+-0.04*	NA	NA		0.89:1
Bekele et al, 2014	Ethiopia	Case series	Dermatology service	Dermatology patients. 53% rural, 47% urban.	234	234 cases/1651 suspected cases	Microscopic examination	NA	plaque, ulcer with nodules	1.3:1
Berhe et al, 1998	Ethiopia	Cross-sectional	Community			36positive/1167reported	LST			NA
Bryceson et al, 1969	Ethiopia	Case series	Leprosarium	Patients	33	NA	Smear, NNN	NA	single lesion not ulcerate, spread during 4m to 11 y (mean 3 y), not involving mucosa except 4. Extensive graphics. Involvement of lymphoedema and lymphadenopathy. Comorbidities such as filariasis and leprosy	1.75:1 (among whose are sick, but it was not proportional)
Bsrat et al, 2015	Ethiopia	Cross-sectional	Community		NA	P. 14%	Clinical examination + smear and culture NNN	L aethiopica		NA
Dedet et al, 1982	Senegal	Cross-sectional	Community		NA	Inc. 1976 : 3.31/1000, 1977 : 0.98/1000. 1978 : 0.26/1000. Prev 1978 : 12.39% scars 8.67%, active case 3.71%. Immunity : 57.8%	Physical examination + LST	NA		0.68:1
Dedet et al, 1982	Senegal	Case series	Clinic	Patients	60 (1976 : 24, 1977 :		NNN	NA	no halo de Faye, ulcerated with thick crusts, 11%	1.4:1 (* Men are more

					30, 1978 : 6)				protruding,. 25% has lymphatic trajectories	likely to go to town). Urban : 1.2:1
Dedet et al, 1979	Senegal	Cross-sectional	Community		1489	695/1489 LST+	LST	NA	NA	1.5:1
Develoux et al, 1990	Niger	Case series	Dermatology clinic	Dermatology patients	64		Smear + Biopsy	L major assumed	dry ulcerocrusted and humid ulcerous, multiple, 10 with lymphangitis	2:1
Develoux et al, 1991	Niger	Case series	Dermatology center of Boukoki	Dermatology patients	64 confirmed (/96 suspected)		smear + Histology	NA	ulcer crust, pseudosporotritrichosic, pseudotumoral	2:1
Diop et al, 2016	Senegal	Case series	Dermatology department of the Social Hygiene Institute	Dermatology patients	87 recensed, 50 included	3 diabetes /50CL	Clinical + parasitology + histology	NA	ulcerative crusty, spporotrichoid, ulcerative w secondary infection	1.6:1
Djibrilla-Kaou et al,1979	Cameroon	Case series + cross sectional	Community + "Centre de Médecine Préventive"		58		Microscopical examination + smear	NA	nodule which ulcerates in the middle, always evolving and leaving scars	1.15:1
El-Safi et al, 1991	Sudan	Case series	Hospital for Tropical Diseases	Patients	736	23/736 have diabete, 18% have a secondary infection	Smear	L major LON-1	multiple. ulcerative44%, noduloulcerative31%, nodular31%. 11%lymphatic. Itching61%, pain38%fever17%, secondary inf18%	1.32:1
El Safi et al, 1991	Sudan	Case series	Commission of Health Affairs	Non-immune population?	736		Smear + Culture	L major LON-1	typical of L major	1.56:1
Gaafar et al, 1994	Sudan	Case series	Dermatology clinics + community	Dermatology patients	177 SUD + 100 S.AR.		Biopsy + clinical examination	L major	multiple noduls, painless, occasionally ulcerated	1.08:1 (SUD), 5.67:1 (S.AR.)
Grove et al, 1989	South Africa				34		Skin biopsy	L major MON-74		NA
Grove et al, 1978	South Africa	Case series		Patients	18	NA	Histologic	NA	painless red papules to large ulcers	NA
Guiguemde et al, 2003	Burkina Faso	Case series	Dermatological units	Dermatology patients	80	74 confirmed cases/80 patients ; 10 co-infected with HIV/80	Biopsy + NNN + Smear	NA	Chronic non healing ulcers	1:1 (LC); 2.33:1 (Co-infection)

Ikeh et al, 1994	Nigeria	Cross-sectional	Community	Farmers	5046 examined	4.5% female lesions, 3.2% mle lesions. 197/5046 active lesions	Clinical examination + microscopy	NA	papular, fungating, ulcerating-multiple, painful and itchy, healed ulcers leave tissue-paper thin scars	0.71:1
Imperato et al, 1974	Mali	Cross-sectional	Ecole Fontamentale	Students		12/249 positive reactions	LST	NA	NA	2.5:1 (Positive rate)
Imperato et al, 1970	Mali	Cross-sectional	Niori's School	Students	550	61.3%	LST	NA	NA	1.88:1
Jeliffe RS, 1955	Nigeria	Case series	Outpatient deparment City Hospital + ??	In and Out-patients	23		NA	L tropica assumed	sores	NA
Kadaro et al, 1993	Sudan	Cross-sectional	Community	Volunteers (?? Bad traduction??)	Population : 1479	12/303 had active lesions, 19/303 had no active lesions + negative rate, 276/303 had a positivity rate + 147/303 had scars	Smear + LST	NA		1:1
Keita et al, 2003	Mali	Case series	Dermatology-lepro service of CNAM	Dermatology patients	251	I:6.27/1000. HIV:6/251diabete: 1/251	Physical examination + smear/biopsy	NA	multiple in 200, single in 50	3:1
Kodindo et al, 2015	Chad	Case series	Hospital	Patients		580positive/680 exam	Laboratory	NA	NA	1.7:1
Kone et al, 2012	Mali	Cross-sectional	Community	49/50 Dogon (+60% unemployed)	50 suspected cases		Blood, smear, biopsy	L major MON25 26	multiple ulceration, w or w o crust	1.38:1
Kweku et al, 2011	Ghana	Case series, survey, seeking	Community + Volta Regional Hospital	School-children farmer, trader, students, teacher, self-employed		<2003 : 2426, 2003 : 6450 cases	Smears + biopsy	L major MON 26 117 74	pustule, nodule ulcerated	Female dominant (case series)
Lariviere M, 1966	Senegal	Case series	Dermatology service, clinic	Dermatology patients	39			NA	polymorphous (oriental sore; ecthymatous, ulcer, dry/psoriasis like/lichenoid, lupoid	1.29:1
Lemma et al, 1969	Ethiopia	Cross-sectional	Community	Peasant farmes, school-children, villagers	NA	57/2000 with active lesion & 58/2000 with scars. No new cases of DCL	Intradermal inoculation	NA	nodular, later ulcerate, scars very characteristics	Male dominant

Mengistu et al, 1992		Cross-sectional + Propesctive	Community	Ocholo Farmer's Association		P active LCL in 1987 : 3.55%, in 1989 : 3.97%. Positivité in 68% active lesions, 61% scars	Smear + NNN	NA	slight bleeding and local pain- fungating tumor in oral mucosa, or diffuse ulcerative lesions in nasal mucosa	01:01
Mengistu et al, 1987	Ethiopia	Cross-sectional	Community	Ocholo Farmer's Association		53CL/146Elephantiasis cases. 6% active lesion + 40% scars	Clinical	L aethiopica	single, ulcerative	0.63:1 (population)
Milosev, 1969	Sudan	Case series	ENT department	12/16 from an endemic zone (kala-azar)	16	NA	Smear + Animal inoculation	NA		Only male
Morrone et al, 2011	Ethiopia	Case series	Italian Dermatological Centre	Dermatology patients	471	15HIV/186LC	Smears + biopsy	NA	86%LCL,11%mucosal,	2.5:1
Ndiaye et al, 1984	Senegal	Case series	Dermatology dakar and polyclinic Cap-Vert	Dermatology patients	260 cases (1973 : 25, 1974 : 27, 1975 : 32, 1976 : 25, 1977 : 42, 1978 : 41, 1979 : 33, 1980 : 35)		NNN, vaccinostyle	NA	polymoprh, different between balck and white- there is halo, often multiple and ulcerated,	NA
Negera et al, 2008	Ethiopia	Cross-sectional	Community	Kibet 5291, Woliya 6029, Boze 5723 (population).		92/1907 active cases.	NNN, biopsy, skin scrapings	L aethiopica	46.7%has single	0.92:1 (Not SS)
Ngouateu et al, 2012	Cameroon	Cross-sectional	Community			146/32466 active cases, 261/32466 had scars. 4.8% with HIV among the 146	Parasitological	L major	nodule with or without ulcers, multiple	0.95:1 (infected)
Niamba et al, 2006	Burkina Faso	Descriptive & prospective study	dermatology service of CHU YO	HIV patients	32 cases	NA	Smear	L major asssumed	classic but atypical, unusual and atypical	01:01
Obasi et al, 1991	Nigeria	Case series	Ahmadu Bele University Teaching Hospital	Dermatology patients		21/18000 in dermatology	Clinical + physical diagnosis	NA	papular, fungating, ulcers non healing-dry with satellite papules	2:1 (infected)

Okwori et al, 2001	Nigeria	Cross-sectional	School	School-children	10226	394/10226 active lesions. 6.8% of active lesions and/or scars (overall prevalence)	On-sight clinical case detection + parasitological examination	NA	dry and moist types	NA
Oliveira et al, 2009	Mali	Cross-sectional	Community	663 from Kemena, 867 from Sougoula		LST + :: Kemena : P 45.4%, I1 18.5%, I2 17.0%; Sougoula P19.9%, I1 5.7%, I2 5.7%	LST	NA		0.89:1
Padovese et al, 2009	Ethiopia	Case series	Italian Dermatological Center	Clinically suspected patient. Schoolchildren (45%), farmes (33%)		5.6% HIV among the Leish.	Biopsy + parasiitological diagnosis	NA	LCL 109	3.05:1 (infected)
Pampiglione et al, 1977	Guinea	Cross-sectional	Community	Near rail and port	388	LST 14.7%	Physical examination	NA	NA	Only male
Sang et al, 1993	Kenya	Case series	Referral hospitals + community	Population + patients		53/11167 lesions, 28/11167 scars**	NNN, physical examination	L tropica	large non ulcerous if long duration.	NA
Sang et al, 1993	Kenya	Cross-sectional	Community	Children from a sedentarity farming communities		18 New cases/18528 population : >1900m 0/8725, <1900m 18/9803.	Smears + physical examination + NNN	all 3	NA	NA
Sang et al, 1994	Kenya	Cross-sectional	Community	temporary settlers, migrant workers	Residents : 425	83/167 active lesions, 30/167 scars	Smear + NNN	L aethiopica	NA	7.33:1 (sample), 11.7:1 (infected)
Sarojini et al, 1983	Ethiopia	Case series	ALERT Addis Ababa	Patients	104 cases	NA	Smear + biopsy + NNN	L aethiopica assumed	98 with LCL	1.6:1
Seid et al, 2014	Ethiopia	Cross-sectional	Community	NA	NA	NA	Smear + culture	NA	NA	NA
Traoré et al, 2001	Burkina Faso	Case series	Health facilities in Ouagadougou	Patients	1845 cases (1996 : 61, 1997 : 55é, 1998 : 1218)	NA	Smear	L major in 1	ulcerocrusted form	0.99:1
Traore et al, 2016	Mali	Cross sectional	Community		NA	5.5/1000 active case	NNN, biopsy and smears	NA	NA	0.5:1
Wilkins et al, 1972	Ethiopia	Cross sectional	Civil Hospital	Farmers	21	0.22% LST+	Smear + histopathology	L major assumed	crusted40%; papuloulcerated16%	9.5:1

1.3 ARTICLE 3

Understanding the economic impact of leishmaniasis on households in endemic countries: a systematic review

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REVIEW

Understanding the economic impact of leishmaniasis on households in endemic countries: a systematic review

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ABSTRACT

Introduction: Leishmaniasis is a poverty-related disease that causes a significant socioeconomic burden to affected households. Visceral leishmaniasis is fatal if untreated, yet illness costs may lead to delays in accessing care. Skin manifestations of leishmaniasis cause a psychological burden and even longer treatment trajectories. The objective of this review is to evaluate illness costs associated with leishmaniasis across different settings (Asia, Africa, and Latin America) and the consequences to households.

Areas covered: Through a systematic review of cost-of-illness studies, we documented the distribution of costs, the health-seeking behavior, and the consequences of leishmaniasis. We discuss the value of cost-of-illness studies for leishmaniasis.

Expert commentary: Despite the free provision of diagnostics and treatment in the public health care sector, out-of-pocket payments remain substantial. There has been progress in addressing the economic burden of leishmaniasis, particularly through the elimination initiative in the Indian subcontinent. Though the illness cost is decreasing due to shorter treatment regimens and better access to care, the situation remains challenging in Africa. Improvement of control tools is critical. There is a need to update cost estimates to inform policy-making and ensure sustainable solutions to reduce financial barriers to leishmaniasis care, especially in pursuing universal health coverage.

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KEYWORDS
Economic burden; cost-of-illness; direct cost; indirect cost; leishmaniasis; kala-azar

1. Introduction

Leishmaniasis is one of the neglected tropical diseases (NTD) – also known as infectious diseases of poverty – with serious health and socioeconomic consequences [1]. Poor living conditions, malnutrition, conflicts and displacements, and immunosuppression have been associated with leishmaniasis [2–4]. Second only to malaria as the world's largest parasitic killer, leishmaniasis is caused by an obligate protozoan parasite *Leishmania sp* and transmitted by the bite of infected female sand flies. The three main clinical manifestations of leishmaniasis are cutaneous (CL), which is the most common, visceral leishmaniasis (VL), which is fatal without treatment, and mucocutaneous leishmaniasis (MCL), which leads to the destruction of mouth, nose and throat's mucous membranes. In Asia and Africa, transmission of the parasite (*Leishmania donovani*) is thought to be limited to humans only, while in the Mediterranean region and South America, VL caused by *Leishmania infantum* is zoonotic with the dog as the main reservoir host [5]. Post-kala-azar dermal leishmaniasis (PKDL) is a skin manifestation that appears months or years after successful VL treatment [6]. For CL and MCL, several transmission cycles exist, but all share the fact that the parasite is transmitted between the mammal species by a sand fly, genera *Phlebotomus* in the Old World and *Lutzomyia* in the New World.

There is no effective human vaccine for leishmaniasis. Leishmaniasis control programs thus rely on case detection and management and vector control [7,8]. However, due to the diversity of transmission dynamics and the varied effectiveness of diagnostic tools and treatments, there is no one-size-fits-all intervention. Regional characteristics dictate what is feasible. Since 2005 India, Nepal and Bangladesh have undertaken an initiative to eliminate VL as a public health problem, with a target to reduce the incidence rate of VL below 1/10,000 population per year in each intervention unit [9]. The Kala-azar Elimination Program (KAEP) in this region combines several strategies: early case detection and treatment, vector control, surveillance, social mobilization, and operational research [10]. The high-level political commitment combined with the availability of improved control tools (rapid diagnostic test (RDT), oral drug) and international support seems to have borne fruits in recent years. Whereas India reported 33,187 kala-azar cases in 2011, this figure dropped to only 5758 in 2017 [11]. India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil used to account for 90% of global VL cases, but currently, the highest number of VL cases is reported in eastern Africa. This region is particularly prone to VL outbreaks due to population displacement, droughts, and conflicts [12]. Co-infection with Human Immunodeficiency Virus (HIV) has also been emerging as a cause for concern [13–15].

Assessing the true burden of leishmaniasis is complex and challenging [16]. The World Health Organization (WHO) estimates

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Supplemental data can be accessed here.

that approximately 0.2–0.4 million VL cases and 0.7–1.2 million CL cases occur each year in 98 endemic countries (6). Currently, to compare burden across diseases, the metric Disability Adjusted Life Years (DALY) is used, combining premature mortality, morbidity, and disability [17]. The 2013 Global Burden of Diseases study (GBD) estimates the leishmaniasis burden at 1.42 million DALYs, of which 1.37 million DALYs for VL (YLL) [18]. These current estimates on leishmaniasis underestimate the burden of non-fatal morbidity due to CL, though its stigma and psychosocial impact can be substantial [19,20].

Poverty is an important determinant for leishmaniasis [21]. Poor housing conditions that are conducive for vector breeding, forced migration to endemic areas, or lack of nutrition intake, are risk factors for the disease [22–25]. In rural, remote areas where the disease is most common, patients may not seek care or delay it due to the significant cost of diagnosis and treatment [26,27]. In India, the 'poorest of the poor,' often of the lowest caste, disproportionally suffer from VL and have poor access to care [2,3]. Despite the free provision of diagnostics and medicines, other non-medical costs (such as transportation or food) and loss of wages due to the illness could push patients and their households further into destitution leading to what is known as *catastrophic health expenditure* (CHE) [28]. The impact of leishmaniasis on affected households has mainly been documented through cost-of-illness (COI) studies.

COI studies are often considered as the initial step in economic evaluation and are descriptive in nature. COI studies aim to identify and measure all the costs generated by a health problem, and this includes the collection of primary data on the costs burdens on patients and their families. COI studies can contribute to the in-depth understanding of the economic burden of disease on society, and eventually feed a range of further economic analyses (such as cost-minimization, cost-effectiveness, cost-benefit, and cost-utility studies), modeling, and health care planning [29]. For NTDs such as leishmaniasis, COI studies are usually conducted to raise awareness and advocate for much-needed resources for control or research in specific geographical settings. The objective of this paper is to systematically review the COI studies of leishmaniasis and try to summarize the global impact of this disease on individuals and their households in endemic countries.

2. Methods

2.1. Literature search

We conducted this systematic review following PRISMA guidelines [30] and registered it in the PROSPERO register (CRD42018088950) [31]. We searched PubMed (through Medline), Web of Science, CABGlobal Heath, NHS EED, LILACS, and IDEAS-RePEc to identify records published from 2000 until 31 August 2018, without language restriction. We also checked the reference lists of all identified records. Search terms were 'cost of illness' which in MeSH term covers [Illness Costs; Illness Cost; Sickness Cost; Costs, Sickness; Burden of Illness; Illness Burden; Illness Burden; Cost of Disease; Economic Burden of Disease; Disease Cost; Cost, Disease; Costs, Disease; Disease Costs; Cost of Sickness; Sickness Costs; Costs of Disease] AND ('Leishmaniasis'[Mesh] OR 'Leishmaniasis, Diffuse Cutaneous'[Mesh] OR 'Leishmaniasis, Visceral'[Mesh] OR 'Leishmaniasis, Mucocutaneous'[Mesh] OR 'Leishmaniasis, Cutaneous'[Mesh]).

2.2. Study selection

We first reviewed the titles and abstracts of all identified records (Figure 1). The inclusion criteria were studies that report on the costs of human leishmaniasis, from either the individual (patient/household), the health services', or the societal perspective. We excluded conference abstracts, case reports, letters, comments or editorials, and economic evaluations, such as cost-effectiveness, cost-benefit, or cost-utility studies.

2.3. Data extraction and methodological quality assessment

We used a standardized data extraction form to collect information on manuscript authors, study design, year, perspective used, method of cost calculation, and characteristics of the sample/study population. The main outcomes extracted included the unit cost (direct medical, direct non-medical, indirect, and total costs) and the unit of analysis (cost per episode, per patient, or household cost). The household is the preferred unit of analysis for assessing economic costs as treatment decisions are negotiated within the household, and this illness often affects several members of the same household [32]. We also extracted evidence on health care seeking behavior, health service characteristics that influence illness cost, the strategies to deal with these costs, and the impact and consequences of the illness cost (see Figure 2).

To capture the latter, we recorded, where possible, the CHE as a measure indicating financial hardship [33]. Health spending is viewed as *catastrophic* when a household must reduce its basic expenses over a certain period in order to cope with the medical expenses [34]. The definition of what is considered catastrophic varies across studies, but commonly used thresholds are either 40% of non-subsistence income (defined as total income minus expenditure on food) [28] or a range of values, usually 10%, of total income [35,36]. We use the latter threshold since none of the studies included in this review reported non-subsistence household income. More specifically, we documented the proportion of out-of-pocket payment (OOP) out of the yearly household income. OOP or direct payment refers to the payments made by households when utilizing health services, typically including consultation fees, laboratory tests, medicines, and hospital bills. OOP often represents the largest share of health care financing in resource-limited settings and is the main determinant of CHE [37].

An internationally endorsed standard checklist for reviewing the quality of COI studies is still lacking; therefore, we used a customized version of the checklist developed by Drummond and Jefferson [38] and adapted for COI studies by Molinier et al. [39]. We applied this checklist for all included studies, see Supplemental file 1.

2.4. Data analysis

COI studies most often distinguish between direct and indirect costs. We did not include data on a third category of 'intangible

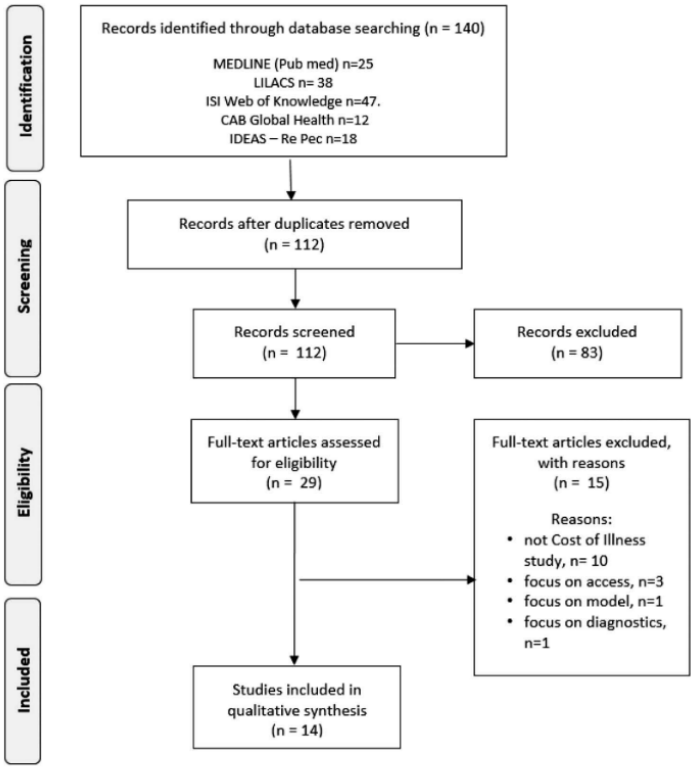

Figure 1. PRISMA flow diagram depicting the selection of eligible articles.

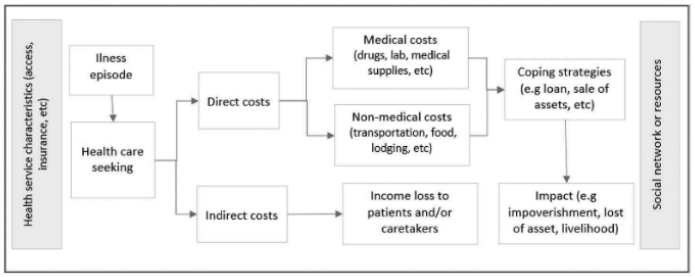

Figure 2. Conceptual framework on the economic burden of leishmaniasis to households.

cost' (such as suffering, grief, social exclusion) because of the difficulty to quantify these costs. Direct costs are defined as the costs related to providing and obtaining health care interventions and include diagnosis, treatment, transportation, and other costs incurred before and during the process of seeking health care. Direct cost can be further categorized as medical and non-medical (see Figure 2).

The term 'indirect' in COI studies refers to the value of lost production or earnings (i.e. productivity losses) due to morbidity and mortality, borne by the individual, family, society, or the employer [40]. We defined indirect costs in this review as individual productivity losses, measured by income or wage loss either to the individual patient(s) or the caretaker(s), or the value of potentially lost production (or potentially lost income) as a

consequence of disease (see Figure 2). This can be due for instance to hospital stays that require patients and caretakers to forego their usual economic activities. These are most often estimated using the 'human capital' method whereby the daily wage rate is multiplied by the numbers of days lost [41]. The total cost is an aggregate of direct and indirect costs.

To facilitate comparisons between studies, we converted all cost data presented in this review to 2016 US dollars. The cost data in the original country currency were first converted to 2016 prices using the Consumer Price Index of that particular country [42] and reported in 2016 US$ using the official exchange rate from the World Bank [43]. If the year of the cost data was not reported, it was assumed to be the publication year of the article. In all cases, both the original cost provided in the publication, as well as the equivalent costs in 2016 US$ were reported.

Due to heterogeneity in the methods, cost analysis and reporting across studies, a quantitative meta-analysis to aggregate cost data could not be performed. Therefore, we performed a narrative (descriptive) synthesis of the included studies.

3. Results

3.1. Description of included studies

The literature search yielded 112 records. We identified 14 studies meeting the inclusion criteria. Of these, 10 were from the Indian subcontinent: Nepal ($n = 5$) [44–48]; India ($n = 3$) [49–51]; and Bangladesh ($n = 2$) [52,53]. The remaining studies were from Brazil ($n = 2$) [54,55] and one each from Sudan [56] and Morocco [57]. One study in Nepal had two records, once as a letter to the editor [58], which we excluded. Two studies from Nepal [46,47] using the same dataset but with a different focus, were both included. Thirteen studies described the cost of VL, except one on PKDL in Bangladesh [53]. Amongst the 13 VL studies, one from Morocco reported the costs specifically for pediatric VL.

The majority of studies ($n = 11$) used the perspective of the individual patient or their household. Three studies reported costs from the societal perspective: one each from Sudan [56], India [51], and Brazil [54]. The societal perspective from Brazil consisted of costs from the public health system combined with indirect costs of the household. Two studies examined the cost from the health system perspective, one for pediatric VL in Morocco [57], and one on the direct cost of VL treatment in Brazil [55]. The time horizon in all included studies was usually limited to a year. Table 1 summarizes the characteristics of the included studies and their methodology.

3.2. Costs from the household perspective

Table 2 summarizes the direct cost estimates provided by studies conducted from the patient/household perspective in the Indian subcontinent and Sudan. Five studies distinguished between costs incurred before VL diagnosis (the care-seeking phase) and post VL diagnosis (including hospitalization) [45,48,50,51,56].

Direct medical costs were found to be dominant during the care-seeking phase, with patients visiting different options, such as traditional healers, chemists or pharmacists, clinics and hospitals, while the direct non-medical costs were higher during the treatment phase and hospitalization [48]. In Charigua hamlet, Nepal, where 15% of the residents had VL in the last three years, 75% of the total direct costs were incurred before the patients received any VL treatment [45]. After VL diagnosis, most patients were hospitalized, which increased the non-medical costs considerably, such as food for the patients and the caretakers during this period [51]. In Sudan, 85% of the direct non-medical costs for a VL episode were food costs of patients and caretakers during hospitalization that lasted on average 30 days [56].

An early study from Danusha and Mahottari districts in Nepal showed that out of the total direct cost per patient, medical costs were highest (57%), followed by food costs (28%), transportation costs (5,4%), and other costs (9,5%) [44]. A study conducted in Siraha and Saptari districts in Nepal used a similar breakdown of costs whereby medical costs were highest (67%), followed by food (23%), travel (9%) and other costs (2%), such as small offerings to staff and payments to middlemen in the hospital [46].

Apart from the type of providers visited, direct costs also varied according to the type of VL treatment provided, the source of the drug, and depended on the year in which the study was conducted. This was related to the fact that the drug policy for VL changed over the years (see Figure 3).

In India, due to emerging resistance to antimonials, the first-line regimen was changed to oral miltefosine (MF) for 28 days in 2006, and later to single-dose liposomal amphotericin B (LAMB) in 2014. However, the actual medicine received by the patient in the first years of the elimination initiative could differ from the recommended policy due to various factors, including drug supply issues and lack of private sector involvement [59]. Back in 2005, a private charity hospital specialized in VL care, treated 88% of patients with conventional amphotericin B [51]. A community-based study in Bihar conducted in 2006 reported that 32% of VL patients in the past year had received conventional amphotericin B as treatment, 29% SSG, 2% MF, and 36% unknown [49]. In 2008, this had not much improved, with 47.9% of patients receiving SSG, 30.3% MF, and 21.8% amphotericin B in another community study [26]. In Nepal, 83% of the patients were treated with oral MF in 2010, yet 15% still received conventional amphotericin B, and 2% SSG [48]. VL medicines were provided in the public sector in Nepal, India and Bangladesh from 2008 onwards, and this determined, of course, the direct medical cost of patients significantly. For instance, Sharma et al. in a study conducted in Bangladesh in 2004 found that 34% of the total direct cost were drug costs for SSG if patients had to purchase a full course from the private pharmacies [52]. Before restriction of VL drugs in public sector, patients obtained their drug from various sources: in Bangladesh, only 14% received SSG full course in public facility [52]. Adherence was a concern, as shown in India that 25–60% of patients received incomplete treatment [50].

Indirect cost refers to the lost labor time due to illness, which reduces the household capacity to earn income and was estimated in 10 of the 14 studies [44,46,48–54,56]. There was substantial variation in the reporting of indirect costs, with some reporting working days lost for patients, or patient and caretakers, or only the income (wage) loss alone. In Nepal, the median days of loss of productivity for patients and HH

Table 1. Overview of cost-of-illness studies on leishmaniasis included in this review.

Author, year	Country	Disease	Perspective	Study Design	Data source	Year of valuation[$]	Currency
de Carvalho et al., 2017 [54]	Brazil	VL	Public health system and societal #	Cross-sectional	National data of illness notification; official MoH disbursement systems	2014	Brazilian Real (R$)
De Assis et al., 2017 [55]	Brazil	VL	Provider/public health system~	Cross-sectional	Microcosting – comparison with the cost of treatment reimbursed to public services	2015	Brazilian Real (R$)
Tachfouti et al., 2017 [57]*	Morocco	VL	Provider	Cross-sectional	Hospital survey using pro forma		Moroccan Dirham (MAD),
Meheus et al., 2013 [56]	Sudan	VL	Societal^ (provider and households)	Cross-sectional	Hospital exit survey with questionnaire; Provider: step down accounting with ingredients approach and data from medical records (randomly sampled)	2010	USD (converted from Sudanese pounds)
Uranw et al., 2013 [48]	Nepal	VL	Patient/Household	Cross sectional	Interview using HH questionnaire	2010	USD (converted from Nepalese rupees)
Adhikari et al., 2009 [46][b]	Nepal	VL	Patient/Household	Cross-sectional	Official records from 3 hospitals, survey with questionnaire	2004	Nepalese Rupees
Rijal et al., 2006 [45]	Nepal	VL	Patient/Household	Cross-sectional	Interview using HH questionnaire	2004	USD (converted from Nepalese rupees)
Sharma et al., 2004 [47][b]	Nepal	VL	Patient/Household	Cross-sectional	Interview using HH questionnaire, Focus Group Discussions (FGD)	2003	Nepalese Rupees
Adhikari and Maskay, 2005 [44]	Nepal	VL	Patient/Household	Cross-sectional	Interview using HH questionnaire	2000	Nepalese Rupees
Samoff et al., 2010 [50]	India	VL	Patient/Household	Cross-sectional	HH survey of stratified multistage sampling, interviews with HH chosen by systematic random sampling	2010	Indian rupees (also converted to US$)
Sundar et al., 2010 [49]	India	VL	Patient/Household	Cross-sectional	Interview using HH questionnaire	2006	USD (converted from Indian Rupee/INR)
Meheus et al., 2006 [51]	India	VL	Societal	Cross-sectional	Provider's financial reports and interview using HH questionnaire	2005	USD (converted from INR)
Ozaki et al., 2011 [53]	Bangladesh	PKDL	Patient/Household	Cross-sectional	Interview using structured questionnaire	2009	USD
Sharma et al., 2006 [52]	Bangladesh	VL	Patient/Household	Cross-sectional	Structured interviews with questionnaire to HH	2004	USD

VL – visceral leishmaniasis; PKDL – post-kala-azar dermal leishmaniasis; USD – US dollars; INR – Indian Rupees; HH – household; MoH – Ministry of Health.
$If not stated, we take the year of the study.
#Health system – is the payer, in this case, the Brazilian public health system through the centralized Notifiable Disease Information System.
^Societal: all costs, including from the patients/households and health system.
~SUS, Table of prices from CMED/ANVISA, Pricing database MoH*.
*Tachfouti: Unit costs – multiplying the use of resources in terms of number of days in hospital, tests performed, medicines. Hospitalization cost (official day rate) includes equipment, infrastructure, overhead costs, personnel.
[b]Adhikari et al., 2009 used the same data from Sharma et al. 2004 to assess impoverishment.

Table 2. Direct medical and non-medical costs incurred by households affected by VL, as reported by studies in the Indian subcontinent and East Africa.

Author, Year	Country	Sample size (HHs)	Medical cost	Non-Medical cost	Total Direct Cost[a]	Total Direct Cost in $2016
Meheus et al., 2013 [56]	Sudan	75	$14	$126.5	$185	$760
Uranw et al., 2013 [48]	Nepal	168	Rs2390	Rs2300	Rs4905	$76
Adhikari et al., 2009 [46]	Nepal	61			Rs4805	$120
Rijal et al., 2006 [45]	Nepal	16			$29	$78
Sharma et al., 2004 [47]	Nepal	61			₹7,076[b]	$176
Adhikari and Maskay, 2005 [44]	Nepal	18			₹6,583	$188
Sarnoff et al., 2010 [50]	India	214			INR6079[c]	$189
Sundar et al., 2010 [49]	India	171	$83	$33	$127	$265
Meheus et al., 2006 [51]	India	77	INR2510	INR1410	INR3920[d]	$137
Sharma et al., 2006 [52]	Bangladesh	113	$51	$25	$87	$220
Ozaki et al., 2011 [53]	Bangladesh	134			$179	$293

HH – household,; INR Indian Rupee; ₹ Nepalese rupee; $ US dollars.
[a] The original data from the studies; median cost to direct cost per treated patient is reported here unless stated differently. It is the sum of medical and non-medical costs; [b]mean; [c] to household, mean total direct cost per patient is INR 5388/US$167 (2016); [d]from household perspective, while the study also reported costs from societal perspective: INR 9900/US $347 (2016).

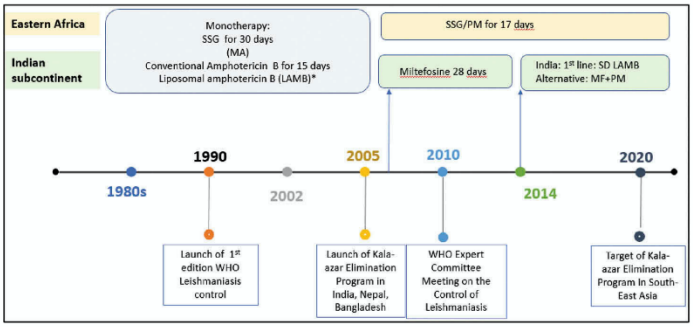

Figure 3. Evolution of recommended VL treatment in eastern Africa and Indian subcontinent.*
SSG - Sodium Stibogluconate; MA – Meglumine Antimoniate; MF – Miltefosine; PM – Paromomycin; Amph B – conventional Amphotericin B; LAMB – Liposomal Amphotericin B; SD LAMB – Single Dose Liposomal Amphotericin B at 10 mg/kg, WHO – World Health Organization

members was 57 days [45,48], 120 days in India amongst those economically active [50], and 51 days in Sudan (62). For PKDL, the median missed work days per PKDL treatment for both patients and caregivers was 123 days in a study conducted in Bangladesh [53].

Total costs as a % of annual HH income from the perspective of the household is shown in Table 3, while Figure 4 depicts studies that reported direct costs as a % of HH income. If 10% is used as threshold for CHE, the economic cost of VL in most cases poses a heavy burden to households. The main driver of costs varied across countries: in Nepal, direct costs represent 53% of total VL expenditure in 2004 (50) and 47% in 2011 [48], while in India, indirect costs made up 59% of the total cost [51]. In the only study from east Africa, the total cost of one VL episode in Sudan for the household was $238, equal to 23% of annual household income and 122% of annual per capita income [56]. Direct costs, in particular non-medical costs, constituted 86% of the median household cost, whereas 14% were indirect cost [56]. One needs to exercise caution in comparing these studies because of differences in methods and types of cost data collected.

3.3. Costs from health systems perspective

Table 4 summarizes five studies reporting cost from the perspective of the health system or health provider. A recent study from Morocco looked into the cost of caring for pediatric VL incurred by hospitals using a micro-costing approach [57]. The current first-line treatment for VL in Morocco is meglumine antimoniate (Glucantime®) for 20 days. Health-related costs in this country are covered by national health insurance, including tests that are done in private facilities that are sometimes paid out-of-pocket first by the patient. The median cost per VL patient was $520 (IQR 316–658) consisting of the cost of hospitalization (50%), diagnosis and treatment (15%), and other costs for drugs or tests not related to VL (33%). Costs were significantly reduced when care is provided on an outpatient base compared to hospitalization ($307 vs. $636).

Another study in Brazil assessed costs at the national level, combining direct costs incurred by the public healthcare system (using a top-down approach) and indirect costs due to morbidity or premature mortality (using the human capital method) [54]. Using data from the national disease information system, the costs of 3,453 cases VL cases in 2013 were estimated. Forty percent of costs were hospitalization, followed by treatment (22%) and prophylaxis (18%). De Assis et al. [55] also estimated the direct cost of treatment including the route of administration of meglumine antimoniate (intramuscular vs intravenous) and the required personnel to administer the treatment, showing the economic feasibility of replacing the antimoniate with liposomal amphotericin B, if using the WHO negotiated price for the latter.

Table 3. Direct and indirect costs of leishmaniasis in the Indian subcontinent and Sudan.

Author, Year	Country	Disease	Sample size (HHs)	Total Direct cost[a]	Total Indirect Cost[a]	Total cost	% Total Cost of HH income
Meheus et al., 2013 [56]	Sudan	VL	75	$760	$415	$1175	
Uranw et al., 2013 [48]	Nepal	VL	168	$76	$80	$186	11%
Adhikari et al., 2009 [46]	Nepal	VL	61	$120	$426	$546	44%
Rijal et al., 2006 [45]	Nepal	VL	16	$78	$107	$185	16%
Sharma et al., 2004 [47]	Nepal	VL	61	$176			NA
Adhikari and Maskay, 2005 [44]	Nepal	VL	18	$188	$255	$433	NA
Sarnoff et al., 2010 [50]	India	VL	214	$189	$186	$355	21%
Sundar et al., 2010 [49]	India	VL	171	$265	NA	$265	28%
Meheus et al., 2006^ [51]	India	VL	77	$137	$193	$330	37%
Sharma et al., 2006 [52]	Bangladesh	VL	87	$220	$101	$321	21%
Ozaki et al., 2011 [53]	Bangladesh	PKDL	134	$293	$148	$441	

[a]The cost data in original country currency were first converted to 2016 using the Consumer Price Index of that particular country, and reported in 2016 US$ using the official exchange rate from the World Bank.

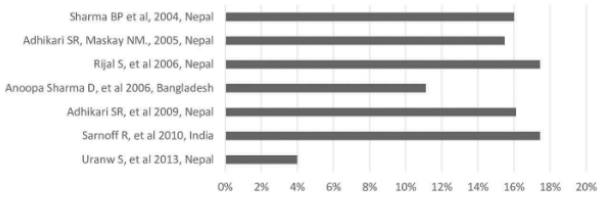

Figure 4. Proportion of direct expenditure to annual total household income.

3.4. Care-seeking behavior, its consequences on VL and VL consequences on household

The process of diagnosis and treatment of VL is rarely straightforward. Many barriers exist between the onset of symptoms and completing, or even starting treatment. Most studies examined the health-seeking behavior of VL patients and the different health care providers that were visited before the patients reached a VL diagnosis. Traditional healers, private providers (both qualified and unqualified) were prominent in India, Nepal, and Bangladesh [44,45,47–49,52,53,56]. Multiple visits (between 2 and 6) are common before the correct diagnosis was made [52]. Costs were significantly higher for patients who consulted private practitioners in India [49]. Ancillary drugs and laboratory investigations made up the bulk of the direct medical cost in this phase [48,50]. The utilization of public provider as patient's first point of contact was 55% in Nepal in 2010 [48].

The choice of health provider was primarily based on proximity and reputation [45]. However, the lowest level of the formal health system, such as a village health center, is often not equipped to provide VL diagnosis and treatment. In Bangladesh, the scarcity of drugs and diagnosis also drove up costs; at the time of the study in 2003, the rK39 RDT was not widely available and was relatively expensive (5–9$) with country-wide shortages of SSG [52].

The access barriers lead to delayed diagnosis and care. Delays are broadly categorized into patient delay (decision to seek care, to reach care) and health service delay (in establishing correct diagnosis and prompt treatment after the patient presented his/her complaint). Prone to bias, these data have to be interpreted with caution. In Nepal, the time to reach the teaching hospital where VL care is provided took up to two months (IQR 4–12 weeks) [45]. In India, the median duration from illness to cure was up to 14 weeks [49]. Decision to seek care is influenced by awareness of the disease, while the physical access to the health services is also important (37). Even when the patients seek care, the diagnosis was not always immediate, with delay to reach diagnosis up to 5 weeks [49]. In Nepal in 2010, the median delay from the patient delay until diagnosis was 25 days (IQR 20–30), and further 31 days (IQR 23–35) until start of treatment [48].

Most households in the various studies included in the review were living below the poverty line. They depended for their livelihood mostly on daily labor or subsistence farming and possessed few assets [48,50]. The burden of VL illness cost is substantial: the median cost of one VL episode were 11% of median annual HH income in India, 12% in Nepal [48], and 23% in Sudan [56]. The percentage of households that incurred CHE (using a 10% cut-off) in 2010 in Nepal was 51%, and as high as 74% if the drugs were not provided for free [48]. VL pushed families below the poverty line in more than 20% of HH in Nepal [44,46]. Meheus et al. reported that 75% of households incurred CHE, and 89% if indirect costs were included [56].

Coping strategies to manage the considerable costs due to VL are diverse, especially in the Indian subcontinent [44,46–48,52]. The main strategies include mobilizing cash or savings, taking loans, selling assets including livestock, and gifts. Several strategies were often used simultaneously. Up to 87% of households reported taking on a loan, either from neighbors, friends, or family with no interest. If loans were taken from moneylenders, households had to deal with high interest rates resulting in long-term indebtedness [46].

Furthermore, the burden of VL is regressive, with the poor incurring higher costs as a % of their income. In India, the most vulnerable households (as defined with assets value

Table 4. Overview of studies on visceral leishmaniasis economic burden from the health system perspective.

Author, year	Country	Sample size	Methodology	Direct cost	Indirect cost	Total cost
Tachfouti et al., 2017 [57]	Morocco	7 hospitals (127 records of VL patients)	Micro-costing approach: Hospital survey using (demographic, clinical, management data); Unit costs calculated by multiplying the use of resources in terms of a number of days in hospital, tests performed, drugs with official price from national insurance agent. Hospitalization cost include equipment, infrastructure, overhead costs, personnel cost was included in the official day rate of hospitalization	$520 (IQR 316_658)	Not estimated	NA
De Carvalho et al., 2017 [54]	Brazil	3453 cases in 2014	Direct medical cost: top-down approach, using values paid and reimbursed by public health care system (SUS), with data from the hospital information system, management system, health prices index and MoH. Include: diagnostic, other tests, treatment, hospitalization, ambulatory care, and secondary prophylaxis. Indirect cost: human capital method, potential years of work lost calculated based on Brazilian law and minimum wage. For morbidity average hospitalization days (14) and recovery days (15)* times daily wage	Cost category: VL diagnostic: $345 249 VL treatment: $ 414 087 Hospital and ambulatory care: $ 770 305 VL/HIV secondary prophylaxis; $ 344 042 TOTAL VL MEDICAL DIRECT COST: $1 873 682	Work absence due to hospitalization (productive age 18–65 man and to 60 for women) as patient or caretaker (of children and elderly). 230 death – 128 in productive age (wage lost $11 421 863). Due to morbidity: 83,856 work days lost TOTAL INDIRECT COST: $12 317 019)	$ 14 190 702**
De Assis et al., 2017 [55]	Brazil	NA	Micro costing: Direct costs (costs of the drugs, remuneration of HCW, consumables, PPE, complementary tests): a) *N*-methylglucamine antimoniate IM 20 mg/kg/day 30 days; b) *N*-methylglucamine antimoniate IV 20 mg/kg/day 30; c) amphotericin B deoxycholate 1 mg/kg/day 21 days; d) LAMB 3 mg/kg/day 7 days (price CMED/ANVISA) e) LAMB 3 mg/kg/day 7 days (price WHO/MoH)	a) US$ 418,52 b) US$ 669,40 c) US$ 1522,70 d) US$ 11 559,15 e) US$ 659, 79	Not estimated	NA
Meheus et al., 2006* [51]	India	1 NGO hospital for VL (KAMRC)	Provider costs: data from annual financial reports 2003–4 from medical center and hospital administrative	Total medical cost: a) accommodation INR2736; b) investigations INR2700 Total medicine cost (including medical supplies: INR8490	Total indirect costs; INR5500: b. Income loss (patient) INR4400 c. Income loss (attendant) INR900 d. Monthly interest on loans INR200	INR15400 ($554)
Meheus et al., 2013* [56]	Sudan	3 public hospitals	3 hospitals: Step down accounting with ingredients approach (data from 2008), medical cost from random retrospective sample of 250 medical records (Kassab and Bazora);	Medical cost $45 (IQR 28–75)[a] Cost per patient: a) Kasab $154(IQR137–186) b) Doka $366 (IQR 349–399) c) Bazora $117 (100–147)	$22 (IQR 0–114)	a) Total provider direct cost: $211 (IQR 197–244) b) Total provider + HH cost (total societal cost per VL episode): $450 (IQR 387–544)

*These two studies reported data from societal perspective, consists of the direct and indirect costs borne by household (reported in Tables 2 and 3), while the direct costs borne by the health care provider is reported here. All values are median, unless reported differently.
[a]The variation is caused by the difference in the (hotel) unit cost per inpatient day; the average hotel unit cost is $5,74 across the three hospitals.
HCW – Health Care Worker; HIV – Human immunodeficiency Virus; IM – intramuscular; IV – intravenous; KAMRC – Kalazaar Medical Research Center; LAMB – liposomal amphotericin B; MoH – Ministry of Health; PPE – Personal Protective Equipment; VL – Visceral Leishmaniasis; CMED/ANVISA – Brazilian Drug Regulation Board/National Health Surveillance Agency.

lower than INR 50,000 in this study) faced higher impact as total VL expenditure was equivalent to 72% of the total assets, versus only 5% in the households with total assets >INR 50,000 [50]. Similarly, low castes (Dalits) have been disproportionately affected in Nepal, with VL costs consuming 57% of household income as opposed to 38% in non-Dalit households [47]. In addition, due to the clustering of VL cases, often more than one member of the household has VL further increasing the economic impact to the household [52]. This is also the case for PKDL, the sequelae of VL that have even longer delay of detection [53]. Higher costs for male patients have been reported in Bangladesh and Nepal [49,52].

4. Discussion

VL causes a substantial economic burden on the HH, as shown in all studies, whereby the proportion of VL-related expenses ranged between 11% and 57% of the annual household income [46,49–51,56]. The impact of VL illness is obvious when looking at the level of CHE, leading to various coping strategies [60,61]. The long-term impact of VL in terms of continuing poverty and long-term indebtedness was demonstrated [46], in agreement with an early study on the consequences of VL in a Bangladeshi community [62]. Clustering of VL in households with multiple cases within a short period further exacerbates the economic impact [50]. Although the vast majority of VL households are poor, the cost of illness has also been shown to be unevenly distributed across households – a study in India showed that households with less income or assets spend a higher proportion of it for a VL episode [50]. This is in line with the inequalities that are frequently found also among other NTD [63].

The distribution of costs (direct medical, non-medical, and indirect) depends on the context, in particular the availability, access and pathways to appropriate diagnosis and treatment. Indirect costs have been found to be the main cost driver, but this is related to a long journey pre-diagnosis followed by a hospitalization period. Once admitted, the costs varied by type of anti-leishmanial drug received and the patient management process in each country. Studies from the Indian subcontinent included in this review which used data collected prior to 2011, illustrated the reality on the ground at the time whereby various drugs were used [48–52]. In 2008, 50% of the patients in a primary center in Bihar (India) were treated with SSG that requires lengthy hospitalization since miltefosine was not yet available despite being the recommended first line regimen [26].

Poor access to care for leishmaniasis is a critical barrier to control and elimination [64,65]. The studies in this review have clearly demonstrated delays to diagnosis and treatment to be an important factor that exacerbates the costs of a VL episode. Prior to the integration of VL care into the public health sector in the Indian subcontinent, the treatment seeking journey was long with patients seeing multiple providers, such as traditional healers, local chemists or private practitioners, and was common as recent as 2012 [66]. Although in principle diagnosis and treatment is for free in the public sector, the various costs that are incurred during the process may have been underestimated.

Nevertheless, efforts have been made in addressing these barriers. Studies from Nepal at different time showed that delay from symptoms onset to start of treatment may have halved [45,48]. In the Indian subcontinent, public facilities appear to be more utilized when it comes to VL. In Africa, the private sector is rare in remote endemic areas, but other access barriers remain significant [27,67]. There may be a number of explanations for the reductions in delays. Increased awareness of the disease may have led to the observed decrease in the delay of patients presenting at a health provider after the onset of symptoms, while the reduced health systems' delay may be the result of advances in the diagnosis and treatment for VL. An important gap in the literature is the lack of recent COI studies after roll-out of a single dose LAMB in the countries committed to elimination. Patients receiving LAMB are usually treated on an outpatient basis which would reduce the costs associated with hospitalization and productivity losses. Similarly, the only study from Sudan was from the period when the SSG/paromomycin (PM) combination was given for 30 days instead of 17 as recommended by WHO [68]. There is clearly a need to update the current costs estimates, especially in light of the adoption of new, shorter treatment regimens in Asia and Africa.

Another clear knowledge gap is that there is no published study examining cost of illness to households for CL and MCL. In some endemic areas in western Africa, CL patients may not seek care due to perception of its self-healing nature [69]. CL is the most common form of leishmaniasis and may cause lifelong scars and serious disability which may lead to patients seeking various treatment trajectories [70,71], but the costs have never been documented. Furthermore, with the current sub-optimal treatment regimens [72,73], the costs associated with complicated CL, such as caused by *Leishmania aethiopica* in Ethiopia and Kenya, or MCL in Latin America would certainly appear to be substantial. Currently, treatment options are limited to local therapies (thermotherapy, cryotherapy, paromomycin ointment, local infiltration with antimonials) or systemic regimens (azole drugs, miltefosine, antimonials, amphotericin B formulations) for complex cases [74,75]. As treatment choice should be based on *Leishmania* species, geographic regions, and clinical presentations, the economic consequences may vary widely across different geographical settings. Further research is needed, e.g. on the cost-effectiveness of diagnostic-therapeutic options for CL and MCL and insights on socio-economic impacts of these conditions.

This review has certain limitations. The review is based on a set of studies that are mostly on VL, and predominantly from the Indian subcontinent, dating from before 2010, the early phase of the elimination initiative. As such, the synthesis is quite specific for that geographic context and period. VL as the fatal form has indeed been the main focus of COI studies so far, with only one study examining the cost of PKDL, and none on CL. COI studies on VL were popular in the early years of the elimination initiative for advocacy reasons. And, importantly, since the policy change to single-dose Ambsiome, not many COI studies have been repeated, but the impact of VL on HH today is likely to be much less than it used to be 15 years ago. Another limitation of this type of review is also the difficulty to compare studies because of differences in the

definitions of costs and methods used to measure and quantify costs, and the confounding factors related to the heterogenity in health service organization. Some studies classify costs differently, for example transportation costs and lodging are sometimes considered as indirect cost [50], and not all cost elements were collected in some studies [44,76]. Calculating indirect costs may include only the productivity loss due to morbidity (and not premature mortality) [56], while premature mortality was included in one of the studies conducted in Brazil [54]. The contextual factors are important, including the population characteristics, organization of health services, and available social network and resources, but they are not always comprehensively described. In addition to the need for a coherent and standardized approach of the costing methodology, there is also the issue of the timeframe. The current COI studies are cross-sectional, estimating direct and indirect costs for a limited period and retrospectively. To better understand the vulnerability and resilience of households to one (or more) VL episodes, a longitudinal approach would provide us additional insights into the impact of leishmaniasis on the household and the dynamics of coping strategies on a longer term [77]. The disadvantage of such studies is that they are relatively expensive to conduct.

Finally, leishmaniasis remains a disease of poverty (3) and substantial efforts are needed to break the cycle. Health system strengthening play a critical role to reduce the systematic barriers linked to service provision. This should be done in adjustment with local contexts, to further mitigate the economic impact of VL. For example, transportation voucher and loss wages incentives were piloted in Nepal and India [78]. With an increasing number of countries pursuing universal health coverage (UHC), it is important to include the diagnosis and treatment for leishmaniasis in the UHC benefit package. Results from COI studies show that the economic burden of leishmaniasis is severe, and a recent report by the WHO showed compelling reasons to invest in its control and elimination [79]. With studies justifying efforts to tackle NTDs for its health gain [80], investing in a disease like leishmaniasis represents good value for money [81]. Pro-poor policies that help to address access barriers should continue and be sustained.

5. Expert commentary

Effective case management, involving early diagnosis and appropriate treatment, is a cornerstone of VL control and elimination efforts. With earlier detection, VL could be treated before it becomes too severe and would reduce the costs to households. Free diagnosis and treatment (at point of care) is a minimum requirement to avoid CHE, but other forms of social protection will also be required to reduce the adverse economic effect of leishmaniasis. Advances in diagnostics and treatment have not been the same across endemic regions, with few options outside the Indian subcontinent. For instance, RDT perform less well in Africa and treatment still relies on two injectable drugs (SSG/PM), and therapeutic innovations will only be available in 5–10 years from now [82].

Innovation is only one aspect, ensuring country access to diagnostics and treatment is equally important. This was clearly demonstrated with miltefosine, the first oral drug for leishmaniasis in the first years of the elimination initiative [83]. In additional to its high cost in the early year of the VL elimination initiative, substantial problems were encountered with the procurement process within countries. With fewer and fewer leishmaniasis patients, a stable supply of anti-leishmanial drugs needs to be guaranteed. An important milestone in current elimination efforts has been the donation of Liposomal Amphotericin B (AmBisome®) by Gilead Science in 2011 which was renewed in 2016 [84]. However, currently there is no other quality source of liposomal amphotericin B apart from AmBisome and the regulatory vacuum has delayed potential new producers [85,86]. AmBisome remains a crucial drug as a safe alternative in Africa and Latin America, and also for treating HIV/VL co-infection. Continued efforts are needed to avoid access issues when the donation program comes to an end. Although a preferential pricing already exists, the US$ 18 per vial remains a significant investment for national program to procure.

The KAEP program in India, Nepal and Bangladesh has gone a long way in addressing access barriers for VL patients. Albeit there has been no definitive evidence that the KAEP has also reduced the socio-economic impact of VL, the progress is welcomed. As diagnostic and treatment pathways become less arduous, there is a need to regularly monitor the ongoing interventions. The momentum of elimination needs to be captured and sustained, with plans for the post-elimination phase. Resources that have been put in place through international consortia and networks are laudable, but we need similar commitments and investments from national health authorities. With improvement in the front of case management, economic evaluations on preventive measures, such as vector controls are called for. Studies addressing knowledge gaps, such as optimal treatment of PKDL and strategies for asymptomatic cases in the post-elimination phase are needed, and eventually also necessitates modeling to assist better evidence-based policy-making.

6. Five-year view

Current evidence on the COI for leishmaniasis is limited. This review did not identify COI studies for CL and MCL, while the studies for VL were done prior to the implementation of shorter treatment courses. Understanding the costs, financial and other barriers encountered by patients and their household in their search for appropriate and timely diagnosis and treatment is vital, especially in the era of Sustainable Development Goals (SDG). The special role of NTD including leishmaniasis to the SDGs is not driven by its impact at the country level, but by its impact on the distribution within populations, especially among the most vulnerable socioeconomic groups. There is a need to set in place appropriate mechanisms for financial risk protection and obtain high coverage for these interventions.

For the Indian subcontinent, where the 2020 elimination target is looming, the concerted efforts cannot afford to be complacent. The number of VL cases have been steadily decreasing in India, Nepal and Bangladesh, yet sustaining elimination is still a challenging task. The post-elimination strategies should include innovative surveillance and monitoring, while at the same time

VL care should be integrated in the comprehensive package of essential health care services in the UHC. The financial protection from OOPs for health services is one of the three elements in the UHC (after extending coverage to those not covered and extending services to those not covered) and particularly of relevant for leishmaniasis. Monitoring VL elimination target is complementary with monitoring UHC target in equity across population groups. Similarly, other endemic countries where elimination is not (yet) feasible, such as eastern Africa and Latin America, the provision of leishmaniasis care should be free at the point of use. Though cost of diagnosis and treatment in most cases has been covered, other safety nets are paramount to cover other expenses that cause heavy toll to the households (transport, accommodation, and food), as has been shown in our review.

Key issues

- Leishmaniasis, including its fatal form visceral leishmaniasis (VL), typically affect the poorest of the poor in the endemic communities.
- Poverty has been associated with VL, and the dynamics have been captured through cost-of-illness studies.
- The cost of illness for VL pose as critical barrier in accessing care across different settings, with both direct out-of-pocket payments and indirect costs of lost productivity.
- Understanding the economic impact of VL to the patients and the households are critical to assess VL control and elimination intervention strategies. Cost estimates need to be updated in elimination region and as well availability of shorter treatment regimens elsewhere.
- There is critical gap in recent evidence on the economic burden of the non-fatal forms of leishmaniasis, the cutaneous (CL) and mucocutaneous leishmaniasis (MCL).
- Reducing financial barriers to leishmaniasis care is important in efforts to attain Universal Health Coverage, at the minimum it should be included in the essential package of health services that are provided for free at the point of use for leishmaniasis patients.
- More studies are needed to build an investment case for leishmaniasis and NTDs within UHC era.

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Author contributions

T Sunyoto, F Meheus and M Boelaert conceptualized, designed and analyzed the study. T Sunyoto wrote the first draft. F Meheus and M Boelaert contributed in writing and critical revision of the manuscript.

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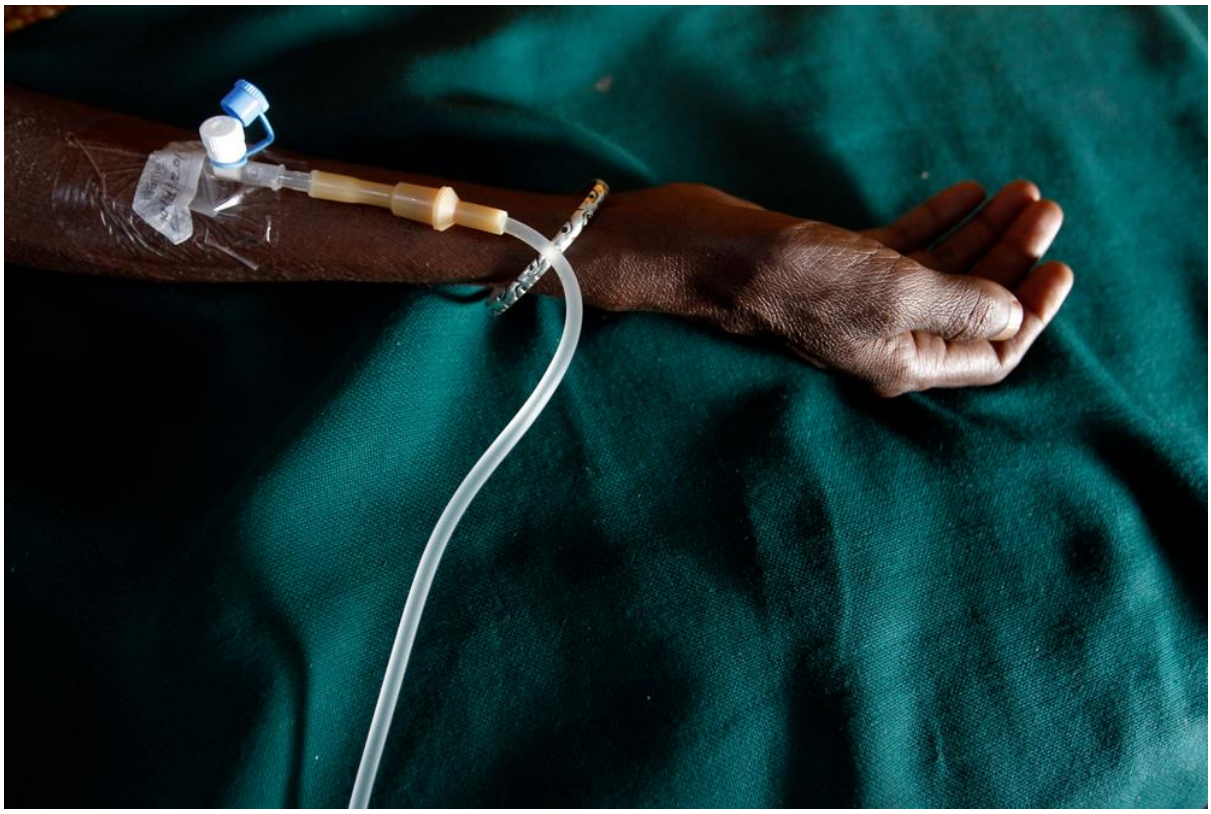
2. Part II: ACCESS UPSTREAM



A kala-azar patient receiving liposomal amphotericin B. Injectables made up most of the medicines used to treat this deadly disease. ©J. Shah, MSF

2.1 Role of Public-Private Partnership in R&D for leishmaniasis**

This chapter provides a brief summary on the state of knowledge of neglected diseases research and development which as a context for leishmaniasis. I synthesised the shortcomings of the current research and development (R&D) system for neglected tropical diseases (NTDs) that result in the lack of effective diagnostics and medicines, followed by an overview of existing remedies specifically on the role Public-Private Partnership (PPP) as an alternative approach.

Current R&D for NTD: diagnosis of problems

The current system for R&D of new medicines does not adequately meet the needs of the majority of the world's population[1]. Research priorities do not reflect the public health interest and has been termed as 10/90 gap, i.e. an imbalance between what is spent on medical research for health needs of people in developing countries (10% of global funding) and the percentage of preventable deaths occurring in those countries (90%)[2]. The R&D process has traditionally been rewarded through profit expected from a market exclusivity either through patent or other 'monopoly' (data)[3]. For diseases such as NTDs that primarily affect populations with little purchasing power, there is virtually no (lucrative) market and therefore, insufficient incentive for industry to invest in R&D for them. This is evident when two systematic assessments show that between 1975-1999 only 1% new therapeutic products had been developed for neglected diseases[4]. Between 2000-2011, among the 336 new chemical entities, only four compounds (1%) had neglected diseases as indication (and these were malaria and tuberculosis)[5]. Latest data revealed that between January 2012, and September 2018, 256 therapeutic products reached the market, but only eight (3 %) targeted neglected diseases[6]. During this period, only two new chemical entities (1%) were approved for neglected diseases: bedaquiline for tuberculosis in 2012 and tafenoquine for malaria in 2018. Approved products for NTDs were typically repurposed compounds, new formulations, or drug combinations.

** The information contained here is loosely informed by a paper 'Are public-private partnerships the solution to tackle neglected tropical diseases? A systematic review of the literature'. Aerts, C, Sunyoto, T. et al Health Policy , Vol. 121, No. 7, 2017, pp. 745-754

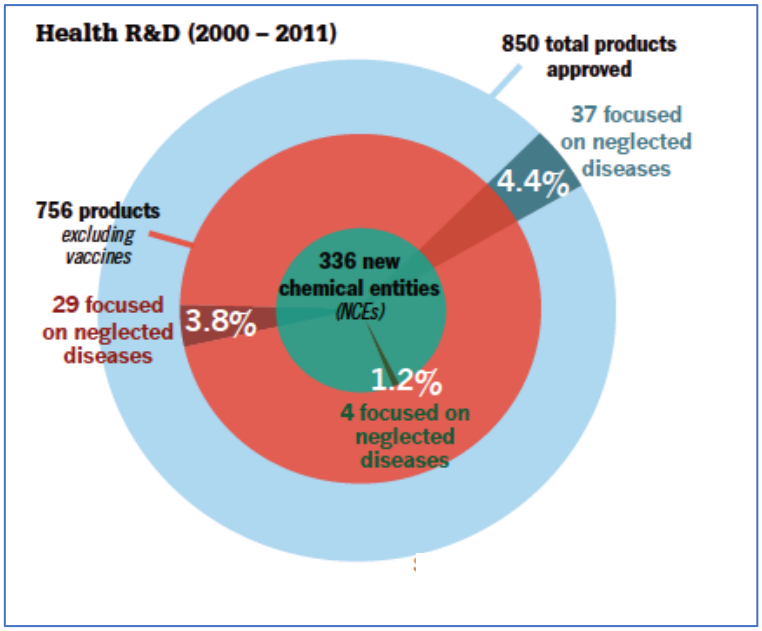


Figure 1. Proportion of products focused on neglected disease between 2000-2011. Source: Pedrique et al, 2013. Lancet Global Heath https://doi.org/10.1016/S2214-109X(13)70078-0

In 2016, G-Finder estimated that the total global funding for neglected diseases reached US$ 3,2 billion, but 70% were still allocated for HIV, tuberculosis and malaria[7]. The R&D process can be described in short as follows. Governments fund the early-stage basic research through mostly public laboratories or academic institutions. The pharmaceutical industry then takes up promising leads and invests further in the development of a product, carrying out clinical trials to test if a medicine is safe and efficacious, then filing for regulatory approval. If successful, firms then market, sell, and distribute the medicine, usually under the protection provided by one or more patents and other regulatory measures; the higher prices enabled by these patents allow firms to recoup their R&D investments and are paid by consumers or by public or private health insurance.

Initially, intellectual property or patent protection was designed to motivate investment to pharmaceutical R&D. By incentivizing innovation, as exchange the invention is disclosed and the public is meant to benefit from the innovation. Patents prohibit the manufacture, use or sale of an invention without the patent-holder's permission, for a minimum 20-year period. However, it has been shown to be inefficient over the years as number of new drugs approved by the US Food and Drug Administration (FDA) per US$ billion spent on R&D halved every nine year[8]. With only few true breakthrough innovations, practices such as 'evergreening' to extend patent duration and increase of 'me-too' drugs (those that merit another patent despite little or no significant therapeutic benefit compared to existing drugs) are common. Diseases that do not offer such profit are simply sidelined, for example vaccines or medicines for Ebola – the viral

haemorrhagic fever which caused a massive outbreak in 2014-2016 in West Africa- though the candidate has been sitting on the shelves since 2005[9]. Lifestyle medicines provide more longer term sales profit than short-course antibiotics, thus pipeline for new antibiotics is empty despite an impending global health crisis of antimicrobial resistance[10].

Focusing on short-term profit also encourages less data sharing and a rise in the business practice of the major pharma to target biotech companies (often the smaller, productive ones) for acquisition or partnering to avoid riskier stages in the R&D cycle[11]. Big pharmaceutical corporations spend almost twice as much on sales and marketing than R&D. Practices to inflate share prices, such as share buybacks - when a company buys back its own shares from the marketplace in order to boost the value of the remaining stock still held by shareholders – are prevalent.

In recent years, drug prices have been increasing and create a significant barrier for patients and health systems[12]. One example is the new antiviral to treat hepatitis C, sofosbuvir, which was priced at $84,000 per treatment course, or $1000 per pill — despite the actual cost of production of $62. Gilead, the drug's manufacturer has earned $40 billion in profit in three years[13]. In addition, sofosbuvir was the product of over 10 years of research funded by the public sector (US Department of Veterans Affairs and NIH-funded research at Emory University as well as NIH small business innovation grants), which then developed by Pharmasset and later acquired by Gilead Science[14,15]. Old, off-patent drugs have become also source of revenue. One archetypal example is pyrimethamine (Daraprim®) for toxoplasmosis whose price was hiked by 5500% from to $750 per pill[16]. Other examples abound, ranging from off-patent drugs to treat diseases such as heart failure, epilepsy and multi-drug-resistant tuberculosis to newer cancer medicines [3]. The high prices of medicines have led to treatment rationing and public outcry. The high price tag is charged according to what the market can bear , even when the company has not invested in the drug's development process[17–19].

The pharmaceutical industry justifies the high drug price based on recouping their R&D investment. The cost to develop new drug from the industry-supported research by the Tufts Center for Drug Development estimated the cost of bringing a successful therapy to market at US$2.6 billion[20] (up from US$1 billion a decade earlier[21]) which consists of $1.2 billion out-of-pocket from company and $1.4 billion time costs (expected returns that investors forgo when the drug is in development). Product development partnership such as Drugs for Neglected Disease *initiative* (DND*i*) estimated the cost to develop a New Chemical Entity (NCE) at US$39-52 million, but up to $130-195 million when risk of failure is taken into account[22].

However, for NTDs including leishmaniasis, the cost for R&D has been argued to be a less credible barrier than the lack of viable market[23]. The 'market failure' has been compounded with the 'public policy failure' that allow the situation to persist. This means that the pharmaceutical

industry does not operate in free market but a highly manipulated one with various regulatory loopholes that can be exploited[24]. Furthermore, neglected diseases often require solutions that go beyond single drugs, such as interventions and approaches which include combinations of drugs (treatment regimens) diagnostic tools, and knowledge of how best to administer drugs for different patients (e.g. children).

In summary, the main shortcomings of the current R&D for NTDs lie in the bigger picture of the insufficiencies of the pharmaceutical R&D system. First, patients' needs and public health impact are not necessarily prioritised. Second, innovation is not linked to equitable access even more when there is no commercial incentive to drive it. Market incentives aligned with intellectual property/exclusivity do not adequately address health needs in low and middle income countries. The out-of-reach high price of medicines and the financialization of the pharmaceutical R&D are symptomatic of deep-entrenched problems. It has increasingly become evident that development of new tools for NTDs cannot be incentivised through the usual patent system and corrective actions from the public are needed. Governments are ultimately responsible for ensuring that people's health needs are met.

Bridging the gap between public health needs and private commercial interests – is it possible?

Initially, to fix the "broken system", several schemes or proposals were suggested in order to attract private sector R&D capacity back into needed areas, what are called "push" and "pull" mechanisms. The drug discovery and development process is risky and difficult, with bottlenecks looming at various steps (see **Figure 2**).

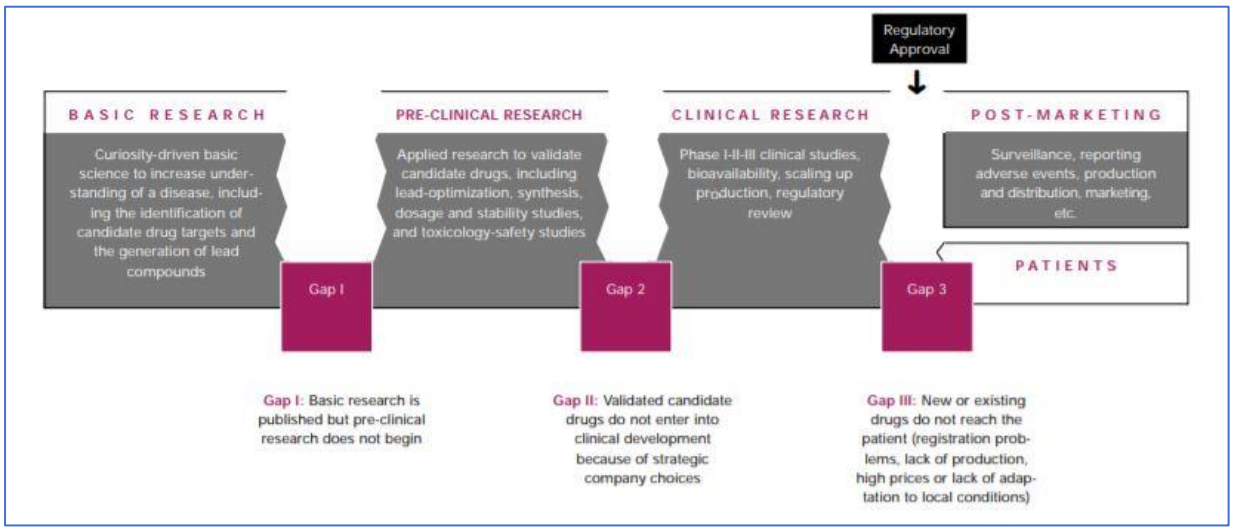


Figure 2. **Gaps in the drug development process for NTDs can arise**. Source: Fatal Imbalance, The Crisis in Research and Development for Drugs for Neglected Diseases, MSF/DND*i* report, 2001

"Push" mechanisms are meant to reduce upfront costs inherent to R&D activities, and can include tax credits, R&D grants, and support for clinical trials. "Pull" measures help create a market for drugs or increase their profitability through a variety of rewards that are contingent on successful drug discoveries. Examples include the creation of purchase funds, advanced market commitment (AMC) or forms of "patent exchange," whereby a company would invest in developing a drug for a neglected disease and gain advantage for other drug, either through accelerated approval or time to market, such as the Priority Review Voucher (PRV) programme (see **Table 1** for overview of some of these pull and push schemes).

Table 1 Push and pull mechanisms for research and development of neglected diseases[a]

Push mechanisms	**Advantage(s)**	**Disadvantage(s)**
R&D grants	Encourage small companies to step in	Moral hazard; asymmetry of information or adverse selection (exaggerate R&D to get more funding)
R&D tax credit	Widely used to stimulate research in specific area	More benefit for large companies with large tax burden
Patent pools	Avoid negotiation with each patent holder, better collaboration and transparency	Have been poorly used. Critic says risk of anti-competitive behaviour due to cartel information
Pull mechanisms	**Advantage(s)**	**Disadvantage(s)**
Advanced market commitment (AMC)*	Reward is only granted once the product is developed	Time-inconsistency problem; difficulty in setting the right AMC price; may not appeal to small companies
Transferable IP right**	Potentially attractive for big company	
Priority Review Voucher (PRV) $	Earlier market access in high-income countries for the awardees	May not reward true innovators (drugs may have been used for long outside USA) No obligatory access strategy

[a] The list is not exhaustive. Adapted from Aerts et al (2017); IP- Intellectual Property, * AMC: donors make a prospective commitment to purchase a successful product at a pre-specified price for a fix quantity; ** Transferable IP Rights: companies are awarded an IP extension for a product of their choice conditional on successfully bringing an NTD product on the market; $ PRV is granted by USFDA upon successful registration of NTD product which can be used by the awardee (or can be sold to third party) for faster review (6 months instead of 10) of a potential blockbuster drug candidate

The combination of the two or mixed schemes tend to be preferred over push and pull schemes, but the equilibrium between push and pull incentives is still to be defined in the context of NTDs. One example comes from for rare diseases, through regulation such as the Orphan Drug Act in the United States (since 1983) and in Europe (since 2000)[25]. Though there are different details between US, Europe, Japan and other countries with similar law, the orphan designation was basically put in place to stimulate R&D for with insufficient expected return on investment to justify the investment. These 'rare diseases' definition also varied, e.g. diseases affecting

<200,000 cases in US, and in EU with prevalence below 5/10,000 population. The incentives ranged from market exclusivity (7-10 years), reduced/waived fee, regulatory or technical assistance, and tax credits or subsidies for clinical trial. Recently there has been increasing call to review these regulation as precision medicine is on the rise and concern that these orphan designation does not benefit the patient[26–28]. Societal agreement is clearly needed[29].

Although the PRV appears to be a good idea at first sight, there has been little evidence in the last decade that their benefits are going to where they were intended. PRV started in 2007 for tropical diseases[30], then extended to rare paediatric diseases in 2012 and medical countermeasures in 2016 (the latest for example, new drug with smallpox indication, given to SIGA and has been sold for US$ 80 million to Ely Lilly). As of February 2019, 22 PRVs have been awarded (eight for tropical diseases -for malaria, tuberculosis, leishmaniosis, cholera, river blindness, and Chagas-, 14 for rare paediatric diseases, and one for a medical counter-measure). (see **Table 2**).

Table 2 Priority review voucher recipients for neglected tropical diseases since 2007

Drug	Year	Company	Disease	Use of the voucher
Artemether-lumefantrine	2009	Novartis	Malaria	Unsuccessfully used by Novartis to accelerate the review of Ilaris (canakinumab).
Bedaquiline	2012	Janssen	Multi-drug resistant tuberculosis	*
Miltefosine	2014	Knight Therapeutics	Leishmaniasis	Sold to Gilead Sciences for $125 million. Gilead announced it had used the voucher in support of its NDA filing for its HIV drug Odefsey. FDA approved the drug in six months on 1 March 2016.
Vaxchora	2016	PaxVax	Cholera (prevention)	Unused. Likely sold to Gilead for ~$200 million
Benznidazole	2017	Chemo Group	Chagas disease	**
Moxidectin	2018	Medicines Development	Onchocerciasis (river blindness)	**
Krintafel (tafenoquine)	2018	GSK and MMV	Malaria	**
Triclabendazole (Egaten®)	2019	Novartis	Fascioliasis (liver flukes)	

The first three PRVs for tropical disease were awarded to an antimalarial drug (Coartem®), a multidrug resistant tuberculosis medicine (bedaquiline) and the first oral treatment for leishmaniasis (miltefosine). Among these 3 drugs, two were already developed and registered outside the US well before the voucher system was launched [31,32]. The voucher has been valued speculatively based on the competitive benefits from earlier entry relative to competitors. To date, the sale prices range from $67.5-$350 million, and the most recently

disclosed sale price was $110 million. At least two companies have used the voucher for their own drugs, and the sale prices of eight PRVs have been publicly disclosed. Critics of the scheme have mainly pointed out that companies may win the voucher despite not being involved in the drug development (such as the case for miltefosine)[33]. Furthermore, the recipients are also not obliged to ensure access. Amendments to fix these loopholes have yet to The true impact of PRV in stimulating R&D for NTDs have yet to be determined [34,35].

The rise of Public-Private Partnership (PPP) in the field of R&D

Partnerships, coordination and better governance have been emphasised as a necessity for NTDs[36]. International control initiatives have naturally brought different stakeholders together, but responding to the lack of treatment for diseases associated for poverty was recognised as one of the motives behind emergence of PPPs since late 1990s[37]. PPPs†† are indeed diverse in nature and exist in various fields (other than health). In the field of R&D for NTDs, it has gained prominence as an example of the ideal way when the drug development expertise of the pharma industry combined with neglected disease expertise of the public sector[38]. They are considered to have positive impact on health outcomes, innovation, development speed and cost-efficiency[39,40]. Some of these PPPs have been evaluated and they all invest a lot in promotion and public relations. There is however little conceptualisation and in-depth empirical investigation into how PPPs actually work[41].

The roles of partnerships in NTDs are – but not limited to – product development partnerships (PDPs) and partnerships based on products delivery and uptake (PPPs Access). Respective examples of such partnerships include the Onchocerciasis Control Program, Medicine for Malaria Venture, Drug for Neglected Diseases *initiative* (DND*i*) and many others. Other types of PPPs include financing and coordinating partnerships. The different types of partnerships are not mutually exclusive: while it is more common for partnerships to dedicate themselves to one particular activity, some use a hybrid model.

Some of the key dimensions of PPPs include: shared objectives, joint investments, bundling, sharing of risks, sharing of benefits, inter-organisation relationships, contractual governance, power and information sharing. The typical strength of a PPP that is often mentioned lies in the distinct roles of the private and public parties involved. Private companies bring in certain technical knowledge and skills and they are generally considered good at innovation, with a certain dose of entrepreneurship and managerial efficiency. Public parties are considered

†† One of the many definitions of a PPP is the following: 'An arrangement – formal or informal – between two or more entities, of which one public and one private party, that enables them to work cooperatively towards shared or compatible objectives, and in which there is some degree of shared authority and responsibility, joint investment of resources, shared risk taking and mutual benefit'.

necessary for creating the right enabling environment, promoting social justice and ensuring public accountability. Some success factors include: (1) clarity of roles and responsibilities and some ground rules for working together (2) a common understanding of mutual benefits (3) a clear vision of objectives (4) sound communication, shared planning and decision making and (5) leadership. These should not be taken for granted as corporate cultures in the private sector, are often quite different from those in (semi-) government institutions. This means that smooth cooperation is not automatic.

The evidence that PPPs are actually instrumental in achieving better health or development in general has varied so far[11,37]. PPPs in health are diverse, which makes it challenging to evaluate their performance. There is a large diversity in the extent to which they are successful – or claimed to be successful – even though the empirical evidence is scanty[41,42]. Some of the critical success factors for PPPs have been reported on and appear to be universal. There is much less consensus about the precise criteria to be used, but several sets of criteria already have been created. More research on what tools and ways to evaluate a particular PPP is desirable. For PDP, defining research priorities and the target product profiles (TPPs) – as has been done by WHO in the case of medicines, vaccines and diagnostics for malaria – can promote targeted use of resources to respond to public health needs[43].

Table 3 PPP for leishmaniasis*

Partnership(s) or Organisation leading the partnership	Tools
The Special Program for Research and Training in Tropical Disease (TDR)	PDP: Drug development (Miltefosine and Paromomycin)
WIPO Re:Search Consortium (World Intellectual Property Organisation)	Facilitate coordination for product development
DND*i* (Drugs for Neglected Disease Initiative)	PDP: Drug development Access
The Infectious Disease Research Institute	PDP: Vaccine development

*Adapted from Aerts et al, 2017

Transformation of the innovation system

International debate and proposals for reform have ensued, including the recommendation that governments begin negotiations over a binding medical R&D convention to address systematic, long-standing problems with innovation and globally equitable access to medicines. Despite the emergence of many new approaches to generating R&D that meets the needs of poorer populations, efforts remain *ad hoc*, fragmented, and insufficient. An R&D treaty

or agreement has been proposed in effort to address four areas where the system remains particularly weak: affordability, sustainable financing, efficiency in innovation, and equitable health-centred governance. Transforming the current system definitely requires effective tools to enforce medical R&D as a global public good, based on the understanding that a politically and financially sustainable system will require both fair contributions from all, and fair benefit-sharing for all.

The World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) is the most relevant international legal framework that sets minimum requirements for the protection of intellectual property for WTO Members. Its use must be encouraged and actually served as opportunity for governments more frequently than previously thought[44]. Another novel tool developed by WHO/TDR is the Portfolio-To-Impact (P2I) Model with the aim to estimate minimum funding needs to accelerate health product development from late stage preclinical study to phase III clinical trials, and to model the impact of such product[45].

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2.2 ARTICLE 4

Why miltefosine — a lifesaving drug for leishmaniasis — is unavailable to people who need it the most

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Analysis

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ABSTRACT

Miltefosine, the only oral drug approved for the treatment of leishmaniasis—a parasitic disease transmitted by sandflies—is considered as a success story of research and development (R&D) by a public-private partnership (PPP). It epitomises the multiple market failures faced by a neglected disease drug: patients with low ability to pay, neglect by authorities and uncertain market size. Originally developed as an anticancer agent in the 1990s, the drug was registered in India in 2002 to treat the fatal visceral leishmaniasis. At the time, miltefosine was considered a breakthrough in the treatment, making it feasible to eliminate a regional disease. Today, access to miltefosine remains far from secure. The initial PPP agreement which includes access to the public sector is not enforced. The reality on the ground has been challenging: shortages due to inefficient supply chains, and use of a substandard product which led to a high number of treatment failures and deaths. Miltefosine received orphan drug status in the USA; when it was registered there in 2014, a priority review voucher (PRV) was awarded. The PRV, meant to facilitate drug development for neglected disease, was subsequently sold to another company for US$125 million without, to date, any apparent impact on drug access. At the heart of these concerns are questions on how to protect societal benefit of a drug developed with public investment, while clinicians worldwide struggle with its lack of affordability, limited availability and sustainability of access. This article analyses the reasons behind the postregistration access failure of miltefosine and provides the lessons learnt.

Summary box

- Miltefosine is a major therapeutic advance as the only oral drug for leishmaniasis. Its development showed that public-private partnership (PPP) is a viable model for promoting research and development (R&D) in neglected tropical diseases (NTDs).
- However, access to miltefosine postlicensure is limited. Low availability and affordability have been key issues globally, despite an agreement between the manufacturer and public institution(s).
- PPPs focusing on product development for neglected and other diseases thus should aim, beyond the registration of the product, on the following:
  - Mechanism(s) to enforce framework and legal agreements between partners need to improve.
  - Ensuring access downstream is imperative: any new NTD tools being developed should include a postmarketing or postregistration access plan.
- Drug pricing structures should be transparent: manufacturers should not take advantage of a monopolistic situation to overcharge.
- Priority review voucher as an incentive to enhance R&D for NTD needs fixing; applicants should seek regulatory approval and demonstrate appropriate access strategies.

INTRODUCTION

Miltefosine, the only oral drug approved for the treatment of leishmaniasis, is an example of successful research and development (R&D) for a neglected tropical disease (NTD) that fails to reach the people who need it. Leishmaniases (infectious diseases caused by multiple species of *Leishmania* protozoan parasites and transmitted by the Phlebotomine sandfly) result in 700 000 to 1 million new cases annually worldwide.[1] More than 1.5 billion people are at risk in 97 endemic countries.[2] The disease is associated with malnutrition and immunosuppression as well as with poverty, poor housing and population displacement.[3–6] The visceral form (kala-azar or visceral leishmaniasis, VL) is fatal when untreated. VL is the cause of the second largest parasitic disease burden after malaria. Each year, the infection causes 50 000–90 000 cases and 20 000–30 000 deaths.[7] Stigma and disability due to cutaneous lesions and mucocutaneous form—involving the destruction of mucosa of nasopharynx—are devastating.[8 9] The Indian subcontinent, eastern Africa and Brazil in Latin America are regions enduring a high burden. Transmission can be human to human, but animals are reservoir hosts in zoonotic areas such as southern Europe.[10] In the absence of vaccines and effective vector/

reservoir control, diagnosis and treatment remain the cornerstone of public health programmes in most parts of the world.[11]

Treatment options for leishmaniasis are limited.[12] Medicines for such a disease are not attractive targets for the profit-driven pharmaceutical industry to invest their R&D efforts because most of the patients are poor. This situation has been described as an example of market failure, a modern welfare economy concept, defined as inefficient outcomes in markets where standard assumptions (perfect competition, symmetrical information) are non-existent or violated, leading to a net society loss.[13 14] In the context of pharmaceutical R&D, the term has been aptly used.[15–17] The main incentive for the producers—the ability to sell products at high prices—does not apply to NTDs, and market challenges are further compounded by perceived lack of intellectual property rights protection in developing countries. For more than 50 years, VL was treated with a single regimen—injectable pentavalent antimonials—until alarming failure rates and drug resistance were shown in India.[18] Other medicines for leishmaniasis (amphotericin B, paromomycin, pentamidine or liposomal amphotericin) are all parenteral, toxic or too expensive. Thus a new, better drug was sorely needed.[12]

In 1995, the Special Programme for Research and Training in Tropical Diseases at WHO (WHO/TDR) engaged in a public-private partnership (PPP) with a pharmaceutical company, Asta Medica[19] for the clinical development of miltefosine. This development involved repurposing what was originally an anticancer compound.[20 21] Clinical trials proved miltefosine administered orally was superior to antimonial injections. In 2002, India's Central Drug Standard Control Organisation approved miltefosine (Impavido) as the first-line regimen for the treatment of VL.[22] This therapeutic breakthrough was a major factor behind the launch in 2005 of a VL elimination initiative on the Indian subcontinent. Oral administration enabled more patients to be treated in primary care settings.[23 24] Subsequently, miltefosine was registered in various countries for both VL and cutaneous leishmaniasis (CL) and was included in the WHO Model List of Essential Medicines (EML) in 2011.[25 26]

Nonetheless, access to miltefosine after it was approved—the postlicensure or postregistration phase—has been less of a success story. The medicine never became as affordable and widely available as originally anticipated. The price of miltefosine made the medicine unaffordable for the majority of patients, most of them poor and marginalised.[27] Even when provided for free by the public health system in the Indian subcontinent, the supply of the drug never quite met the demand.[28] The Bangladeshi VL elimination programme opted for a locally sourced, less expensive alternative product. However, this generic version was clinically ineffective, and on verification, the capsules lacked the active pharmaceutical ingredient.[29]

To this day the drug remains valuable as a partner drug in combination regimens to treat VL and for several other clinical indications, yet miltefosine is hardly available in countries where leishmaniasis burden is high. Widespread adoption of miltefosine was challenging, due to various reasons that this paper attempts to unravel.

Fifteen years ago, WHO/TDR made a substantial R&D investment with a clear goal to reach people in need of life-saving medicine, yet access to this medicine remains compromised. We analyse the lessons learnt in the context of R&D for NTDs, the postlicensure phase and recommend strategies moving forward to increase access to this drug.

THE DEVELOPMENT OF MILTEFOSINE FOR LEISHMANIASIS: A PPP SUCCESS STORY

Miltefosine (hexadecylphosphocholine) is the only oral drug currently registered for the treatment of leishmaniasis.[30] Two research groups discovered the compound in the early 1980s: one in Germany investigating the antitumour activity and another in the UK working on anti-inflammatory properties.[21 31] Dose-limiting gastrointestinal adverse events in several phase I and II studies[32 33] resulted in the discontinuation of the drug's development as an oral drug for the treatment of solid tumours.[20] Its development as a topical formulation for treating cutaneous metastases of breast cancer continued though, and Miltex (Bayer, UK) has been marketed in Europe since 1992.[34–36] In 1987, miltefosine's antileishmaniasis activity in vitro and in vivo was described.[37] Excellent oral bioavailability in mouse models was found, in addition to superiority as compared with intravenous pentavalent antimonials in these animals.[38] These results established miltefosine as a development candidate for the treatment of human VL. A proof-of-concept study conducted in India[39] provided encouraging data for further clinical studies.[40–42]

In 1995, WHO/TDR partnered with Asta Medica (later Zentaris, see figure 1), providing funding and expertise to further develop the drug for the treatment of VL.[43 44] The motivation for the company in the partnership was linked to the potential market in South Asia, and substantial in-kind public input from WHO/TDR.[45] Between 1996 to 2004, seven clinical trials were carried out for adults and children in India.[39–42 46–49] A pivotal phase III study conducted on 398 adults demonstrated a cure rate of 94% (95% CI 91% to 97%) in the miltefosine arm. Phase IV studies involving 704 adults and 428 children were conducted in India and in Bangladesh (cure rates were of 82% overall[50] and 72%, respectively[51]). Though trials involving miltefosine were still ongoing for CL[52 53] and VL-HIV co-infection,[54] in 2005—when the elimination initiative was launched—miltefosine was considered a game changer in the VL control strategy.[22 46 55] The short time taken to bring the drug to market illustrates the efficiency of PPP in miltefosine's R&D process: clinical trials started in 1996, and in 2002 the drug received approval

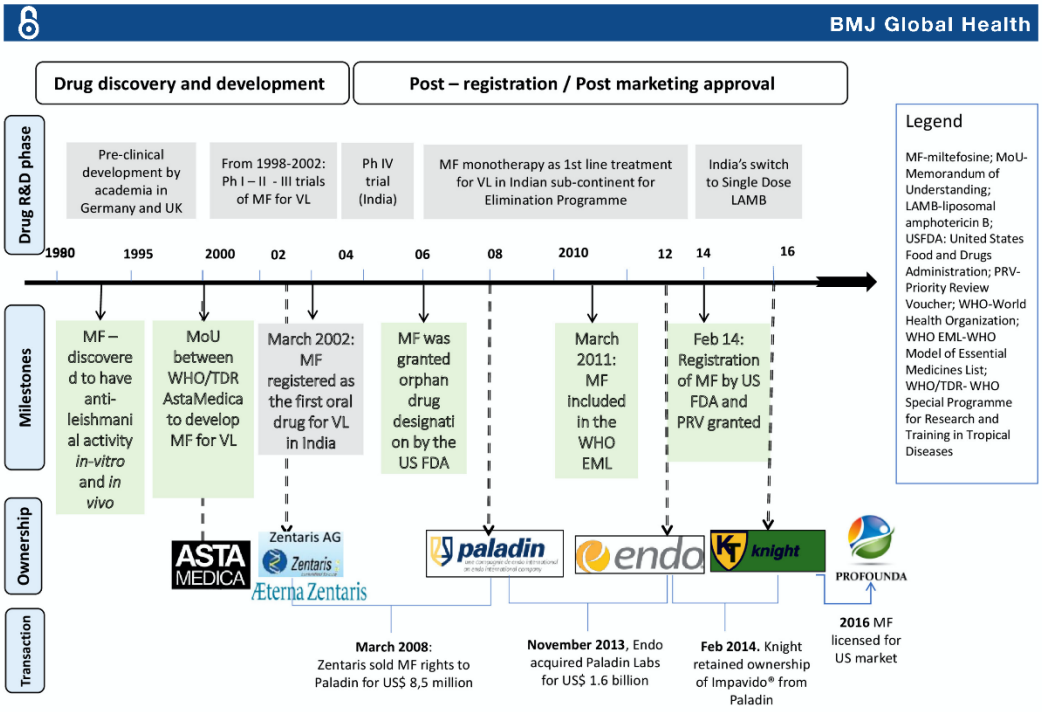

Figure 1 Milestones in miltefosine's journey. R&D, research and development; VL, visceral leishmaniasis.

to treat VL in India and in 2003 it was in the market (see figure 1). Oral administration (enabling straightforward management within primary care), gave rise to hopes for VL elimination.[24 56]

However, implementation of miltefosine treatment faces certain challenges. Miltefosine's reproductive toxicity requires women of childbearing age to avoid pregnancy during, and for at least 3 months after treatment.[57] The required pretreatment pregnancy screening and contraceptive cover severely hindered roll-out through primary care services in resource-limited settings. Gastrointestinal problems are common adverse events: up to 62% patients report vomiting/diarrhoea, although self-limiting.[31 40 47] When the drug is self-administered, even mild adverse events may compromise adherence to a full regimen. Transient elevation of hepatic transaminases and mild renal dysfunction affect up to 10%–15% of patients.[50] In phase IV trials in India and Bangladesh enrolling ~1000 patients, each recorded one death possibly related to the gastrointestinal side effects of miltefosine.[50 51] Adverse events are thus common and need to be managed accordingly.

The difficulty in complying with a twice daily, 1 month treatment course,[58] and a long half-life,[59] all concur to make miltefosine monotherapy vulnerable to emerging drug resistance. The potential for resistance became a major concern in India when the drug was sold in private pharmacies and patients resorted to shorter courses due to affordability issues. India, therefore, restricted miltefosine provision to the public sector from 2008 onwards.[27 60] Preserving efficacy of this valuable drug is crucial, and approaches such as directly observed treatment (DOT) and miltefosine use in combination regimens were thus recommended.[61] After being used as a monotherapy for over a decade, miltefosine effectiveness reportedly declined: in India, 7% of patients with VL on DOT relapsed within 6 months;[62] and in Nepal, the relapse rate was 20% for patients within 12 months on a self-administration schedule.[63] This high failure rate, at least in the paediatric populations, was partly attributed to drug underexposure in paediatric populations at the recommended dose.[64 65]

Meanwhile, other treatment regimens were developed for VL[66–68] and in 2014 the single-dose liposomal amphotericin B was rolled out through the elimination initiative replacing miltefosine monotherapy.[69] Nevertheless, miltefosine remains an important drug in leishmaniasis therapy, as a companion in combination regimens, or in VL/HIV co-infected patients who require rotating multiple regimens. The spectrum of indications for miltefosine increased over time, currently covering VL caused by *Leishmania donovani* and postkala-azar dermal leishmaniasis in Asia, CL caused by *Leishmania Viannia (Leishmania braziliensis, Leishmania guyanensis, Leishmania panamensis)* and mucocutaneous leishmaniasis (MCL) caused by *L. braziliensis*.[69 70] For CL and MCL, miltefosine is a useful alternative for use in paediatric populations

(>2 years old) where existing treatment regimens prove insufficient.[71 72]

POSTLICENSURE ACCESS TO MILTEFOSINE: THE EARLY YEARS AND CURRENT STATUS

Registration

Miltefosine was initially registered in India and Germany. Later, it has been approved for treatment of VL in Nepal, and for both VL and CL in Argentina, Bangladesh, Bolivia, Colombia, Ecuador, Guatemala, Honduras, Mexico, Pakistan, Paraguay, Peru, Israel and the USA—though some licenses may have lapsed and not been renewed by the company. Miltefosine received an orphan drug designation in the European Union in 2002[73] and the USA in 2006.[74] WHO included the drug in its EML in 2011,[25 26] underlining its public health importance.

Cost

Affordability is a critical issue for medicines developed to treat a poverty-related disease. An economic analysis has shown that for miltefosine to be an effective public health tool, the drug should cost no more than US$50–60 per treatment.[45 75] The initial agreements, in the form of a memorandum of understanding between WHO and Asta Medica in 1995 provided the framework to ensure availability and affordability of the drug (see figure 1). The company was allowed to market the drug in the private sector but had to make it available at a preferential price within the public sector in all developing countries, conditional on the free provision of the drug to patients. The agreements stated that this preferential price should allow the company to recover the production cost plus a modest mark-up, while setting the price for the private sector would remain under the company's control.

But, as the negotiation for the preferential price took years, miltefosine was at first only available in the private pharmacies in India at a cost of US$150–200 per treatment.[27] This price is three to four times higher than the preferential one and well beyond the means of the majority of patients with VL, who had to pay out of pocket. The situation improved when preferential pricing was put in place, and after miltefosine was restricted to the public sector in India. Based on the initial agreement, the price of an adult treatment varied between €45–54 (US$54–64) depending on order quantity, at the time set at minimum 75 000 capsules.[76] In the 2004 application for inclusion in WHO EML, the price quoted by Zentaris (Asta Medica spin-off acquired by Aeterna in 2002, later became Aeterna Zentaris in 2004—see figure 1 for complete chronology of ownership changes) was €80–300 for full adult treatment, the former for use in developing countries and the latter for the private sector.[77] However, the preferential price has gradually increased over time, and for a period, it was only applicable when buying a full batch or 200 000 capsules (equivalent to 3500 treatment courses), a challenge for control programmes in countries like Nepal or Bangladesh with lower case numbers. Paladin (the owner company in 2008–2014, see figure 1) expressed in its 2010 application to WHO EML that price would not be a barrier,[25] yet the conditions that need to be met for the preferential price were often unclear. The pricing structure provided by the supplier was not transparent: between 2009 and 2014, the price obtained by a non- governmental organisation (NGO) operating in endemic countries reached €250. Currently, the preferential price, according to Knight Therapeutics, sits between US$120 and US$160 per course, although there is no longer an obligation for minimum quantity (see table 1).

In Europe, the drug is only registered in Germany with one course costs €3000–12 000 (US$3500–14 000).[45] Several access initiatives had been in place: in 2003, the company agreed to supply miltefosine for treating leishmania under special conditions for NGOs through a German medical aid organisation.[78] Compassionate access programmes also exist for special cases, for example, VL/HIV co-infected patients,[79] although many clinicians may be unaware. In the USA, a full drug course is in the range of US$17 000 (for 28 capsules, while a patient weighing >45 kg would need 50 mg thrice daily, amounting to 84 capsules)[80] which health insurance is unlikely to cover.[81] When used for treating free-living

Table 1 Price for one full adult course of miltefosine treatment

Price policy	Price per full course§	Period covered	Remark
Preferential price for the public or non-for-profit sector in developing countries	€45–55 (US$54–64)*	2002–2008	Price varied based on quantity purchased; minimum order quantity (MOQ) was imposed
	€80–110 (US$94–130)	2009–2014	
	€100–140 (US$117–164)†	2016 onwards	No MOQ, but price still varied based on quantity
Market price EU	€3000–12000	2012	Direct order to the producer/distributor
Market price US	US$33000-51000‡	2016	

*This is the original price aimed for in the agreement between WHO and Asta Medica (1995) and published officially in the latest WHO Control of Leishmaniasis guidelines (2010).
†Price quoted by Knight Therapeutics for purchase by non-profit organisations Médecins Sans Frontières (MSF).
‡For 28 caps (https://www.drugs.com/price-guide/impavido). With the recommended dose, in the USA a patient weighing >45 kg needs 50 mg thrice daily, total 84 capsules.
§One full adult course of miltefosine monotherapy uses one pack containing 56 caps. The recommended dose is 2.5 mg/kg daily for 28 days (roughly 50 mg capsule twice daily for adults weighing >25 kg).

Table 2 Overview of miltefosine access issues by region

Region	Year first marketed/ approved	Access issues	Supply and delivery
Asia[27 75 108]	2002	► Large minimum quantities to be eligible for the preferential price (one batch or min 200 000 caps) ► Long lead time or delivery time and frequent stock-outs ► Difficulties in forecasting demand ► Tender system for national procurement: lack of details in the process for the manufacturer, programmes faced with lack of response ► Low affordability for the government and NGO sector	Through national VL control programme
Africa[106]	NA*	► The reluctance of the manufacturer to register the drug in endemic countries ► Governments and end user/patients' affordability ► Limited evidence on its effectiveness in the continent ► The dysfunctional or weak supply system	Usually brought in the country by NGOs or WHO
Europe[31 78]	2004	► Only registered in Germany and very expensive (to buy directly from the manufacturer) ► Can be accessed through the name-based patient compassionate programme ► Liquid formulation for canine leishmaniasis is registered in most countries and widely used to treat pet dogs[109]	To be ordered directly from the company
North America[31 86 97]	2014	► High cost and likely not covered by health insurance ► Governments' and end users' affordability	Available through CDC as an off-label treatment for PAM private market (producer price)*
Latin America[53 110]	2005	► Registration has expired in many countries, no renewal sought by the company ► High cost and limited availability outside research use in most of the countries in the region	Through MoH in coordination with PAHO

*Impavido is available in the USA since Knight Therapeutics provided licensing agreement to Profounda in 2015 (www.impavido.com).
CDC, Centres for Disease Control and Prevention; MoH, Ministry of Health; NGOs, non-governmental organisations; PAHO, Pan American Health Organization; PAM, primary amoebic meningoencephalitis; VL, visceral leishmaniasis.

amoebas such as *Acanthamoeba keratitis*, miltefosine costs have reached US$48 000.[82]

Availability

Table 2 gives an overview of the main availability issues by region. The situation is indeed diverse. In the Indian subcontinent, frequent shortages of miltefosine have been reported by healthcare providers.[28] Small-scale donations made possible by Paladin (see figure 1) did not solve the underlying problems. Obstacles to securing supply include bureaucratic, rigid tender mechanisms for public procurement; inadequate delivery systems; lack of buffer stock and difficulties in forecasting demand, as well as the long production lead time at the manufacturer. The minimum order quantities that were imposed by the company to be eligible for preferential prices for public or not-for-profit sectors seem to play a role, nonetheless. Earlier requirements to purchase a minimum of a full batch were not always compatible with the needs of the procurers (eg, for second-line treatment or clinical trials). The requirement thus had led to oversupply and wastage as the shelf life is limited, while substantial amounts of miltefosine expired in the manufacturer's warehouse and had to be destroyed. Moreover, the global availability of miltefosine has been mostly depending on a single source. The ownership rights have been retained by the private company and have been exchanged over the years through business mergers and acquisitions (see figure 1). The change of companies for miltefosine has led to delays in delivering the drug on time.

Since 2016, Knight owns worldwide rights to Impavido (miltefosine) related to its sale and distribution in all countries other than the USA.[83 84] There, it was initially available through the Centres for Disease Control and Prevention and since 2015 after being approved for leishmaniasis by FDA, through Knight's licensee, Profounda (figure 1). Currently, to say that the drug is freely available in the global market is an overstatement. Entities that need miltefosine have to approach Knight directly and negotiate, with little scope of collective action. Even in the Indian subcontinent where miltefosine is no longer first-line treatment, the medicine is still sorely needed for an alternative regimen, used in combination with paromomycin or liposomal amphotericin B (AmBisome)—and for treatment of HIV/VL. There are no accurate

data on how many patients were treated with miltefosine since it was registered for VL. However, from 2008 to 2014, 163 000 VL cases were reported in India alone.[85] The majority of these patients were supposedly treated with miltefosine.

Miltefosine is considered as a valuable compound in the field of leishmaniasis and beyond, thus several trials are still ongoing. However, no change in the pricing structure is foreseeable in the near future. More frustratingly, the US$125 million earned by Knight for registering miltefosine in 2014 in the USA, did not have any impact on the problematic access in developing countries, despite advocacy efforts by the civic societies.[86]

WHAT ARE THE LESSONS?

Miltefosine represents a major therapeutic advance for the treatment of leishmaniasis, with possible use against other pathogens. The drug's development is a clear success story of a partnership between WHO, a private company and strongly motivated clinical researchers in endemic countries that proved that drug development for neglected diseases by PPPs is a viable model (figure 1).[87–89] However, to date, access to miltefosine is limited, even in a context where preferential pricing should apply, and the manufacturer still has a de facto monopoly of a drug as the only quality-assured source. Based on miltefosine's development history, we present policy recommendations for the wider drug development context and eventually narrow the train of our focus on practical suggestions to improve access to miltefosine for leishmaniasis.

One of the main lessons learnt is that miltefosine's availability has been affected by the multiple changes in the ownership rights (as shown in figure 1) which resulted in changing distribution or marketing licenses for different subsidiaries over time.[90–92] The agreement between WHO/TDR and the initial company—drafted to ensure continuous supply at an affordable price for public health use— could not be enforced with the company's later successors. The case for needing a stronger agreement to ensure access in the postapproval phase is compelling, especially with the expansion of the PPP model for drug development, through organisations like the Drugs for Neglected Diseases initiative, Medicine for Malaria Venture and other entities.

Product development partnerships should set goals beyond mere registration of an NTD drug in endemic countries.[93 94] Pharmaceutical or biotech companies targeting neglected diseases seem to operate a niche business model,[45] seeking profits from both public and private markets in tiered pricing mechanisms. Tiered or differential pricing structure has been argued as a rational way of funding drug or vaccine availability in endemic resource-poor countries if effective access is indeed provided.[95] However, sustained access under preferential pricing may not spontaneously yield robust market mechanisms for demand. Underlying PPP agreements must, therefore, include detailed and transparent provisions for sustained access, including pricing structures and frameworks for monitoring and enforcement.[93 96] The absence of these structures and frameworks was a critical factor in the miltefosine journey. Furthermore, deployment strategies for new NTD drugs should also include long-term pharmacovigilance and feasibility studies for various contexts.

Another lesson is that some current incentive mechanisms meant to enhance R&D for NTDs seem to defeat their purpose. In 2014, the US FDA approved miltefosine registration for leishmaniasis, and Knight Therapeutics—which had acquired the rights to the drug the same year—was granted a reward: the tropical disease priority review voucher (PRV).[97 98] PRV is enacted since 2007 to facilitate the development of drugs for NTDs. If a sponsor achieves approval for a new chemical entity that constitutes a significant improvement for one of the listed tropical diseases, the sponsor receives a PRV which can be used for priority review of any subsequent new drug or biologic under development.[99 100] The voucher is transferable, and its value has been estimated to be up to US$350 million[101].

While the voucher is meant to stimulate R&D for NTD drugs, the overall impact of the programme has yet to be established.[102 103] In the case of miltefosine, as a drug co-developed with public money and already licensed in key countries, the lucrative incentive seems misplaced.[104] Knight Therapeutics subsequently sold its PRV to Gilead for US$125 million,[105] yet no improvements in miltefosine pricing or access in global markets have been seen so far.[86] We suggest that preconditions on PRVs should stipulate that applicants seek regulatory approval of the drug in endemic countries, and demonstrate appropriate access strategies.[103 106]

Miltefosine is not the only leishmaniasis drug produced by a single manufacturer. In the long run, competitors or generic producers might help to secure supply and to stabilise prices. Miltefosine is no longer under patent protection, but generic manufacturers would need time or support to enter the market. It is worth noting that shrinking sales volume, as the number of VL cases decreases following elimination efforts on the Indian subcontinent, may deter potential producers. Nevertheless, as this is the the only oral treatment with potential for additional clinical indications within larger disease groups, efforts to ensure there are more quality-assured producers should continue. The addition of miltefosine to WHO's invitation of expressions of interest for NTD prequalifications in 2017, is a step in the right direction.[107]

Several areas need to be addressed to overcome key access barriers to miltefosine (see table 3). Reducing access barriers to a life-saving drug needs a strong and sustained political commitment from the public sector, governments and global actors alike, supported by coherent policies. International coordinated procurement by multilateral organisations or advance market commitments should be sought to ensure miltefosine's

Table 3 Summary of miltefosine access barriers and strategies to address them

Key area	Access barriers	Access strategy	Action(s) proposed
Governance and coordination	Lack of consolidated coordination to ensure miltefosine access among stakeholders in the public and private sectors	Identify effective leadership; ensure that partnerships developing drugs for NTDs include safeguards to access	► Establish a WHO-led Working Group on Access to Leishmaniasis Drugs and Diagnostics (WHO, MSF, DNDi, IDA, KalaCORE…) which help consolidate approach and coordination[111] ► Identify mechanism(s) to enforce binding agreements ensuring drugs' access ► Include an access plan or strategy in any PDP for NTDs
Affordability	High product price	Lowering prices and ensure a healthy market (non-single supplier)	► Negotiation to decrease the price to an acceptable level for governments and end users ► Advocacy for transparency in the drug production cost and a list price of miltefosine in different markets ► Financial or other support to encourage generic manufacturers ► Curb possibility of a monopolistic situation in setting prices
Availability	Inconsistent supply	► Ensure sustainability of production ► Assure quality ► Expand availability	► Advocacy on the access problem ► Combined procurement, consolidation of demand forecasts or advance market commitments ► Review registration status in endemic countries and renew as necessary ► The supplier should seek registration in disease-endemic countries ► Improve information flow to procurers (on drug availability, lead time, compassionate programmes, etc) and supplier(s) (on tender mechanisms, potential markets, etc) ► Strengthen the supply chain in the country to improve delivery

DNDi, Drugs for Neglected Diseases initiative; IDA, International Drug Association; KalaCORE, UKaid-funded consortium to tackle VL; MSF, Médecins Sans Frontières; NTD, neglected tropical disease; PDP, Product Development Partnership; WHO, World Health Organization.

availability in the short term. In this regard, ensuring sufficient buffer or rotating stock at the regional level seems reasonable, if all stakeholders can reach a consensus. More transparent manufacturing timelines could help to avoid shortages, along with the better consolidation of forecast and orders. In the longer run, miltefosine registration in endemic countries needs to be reviewed and pursued. The inaccessibility of miltefosine should not be taken for granted, thus advocacy must continue. The current monopolistic situation must be challenged, hence encouraging new potential producers to enter the market would be beneficial. Harmonised actions to protect access to an essential public health tool, such as miltefosine, must be provided by the global public policy.

CONCLUSION

The miltefosine story demonstrated the complexity of providing access to a promising NTD drug. Regrettably, apart from being a success story in R&D, the miltefosine journey embodies many flaws along the pathway from drug development to end user, and we observed issues of affordability and availability at global and country levels. Anticipated public health impact was hindered, as access barriers at different levels were not overcome. Strategies to expand access to an NTD drug thus must address affordability as a key obstacle, along with supply-side strategies that assure availability. Benefits of publicly funded medical research should be made broadly accessible to patients—neglect and imbalance should not be the end of the story.

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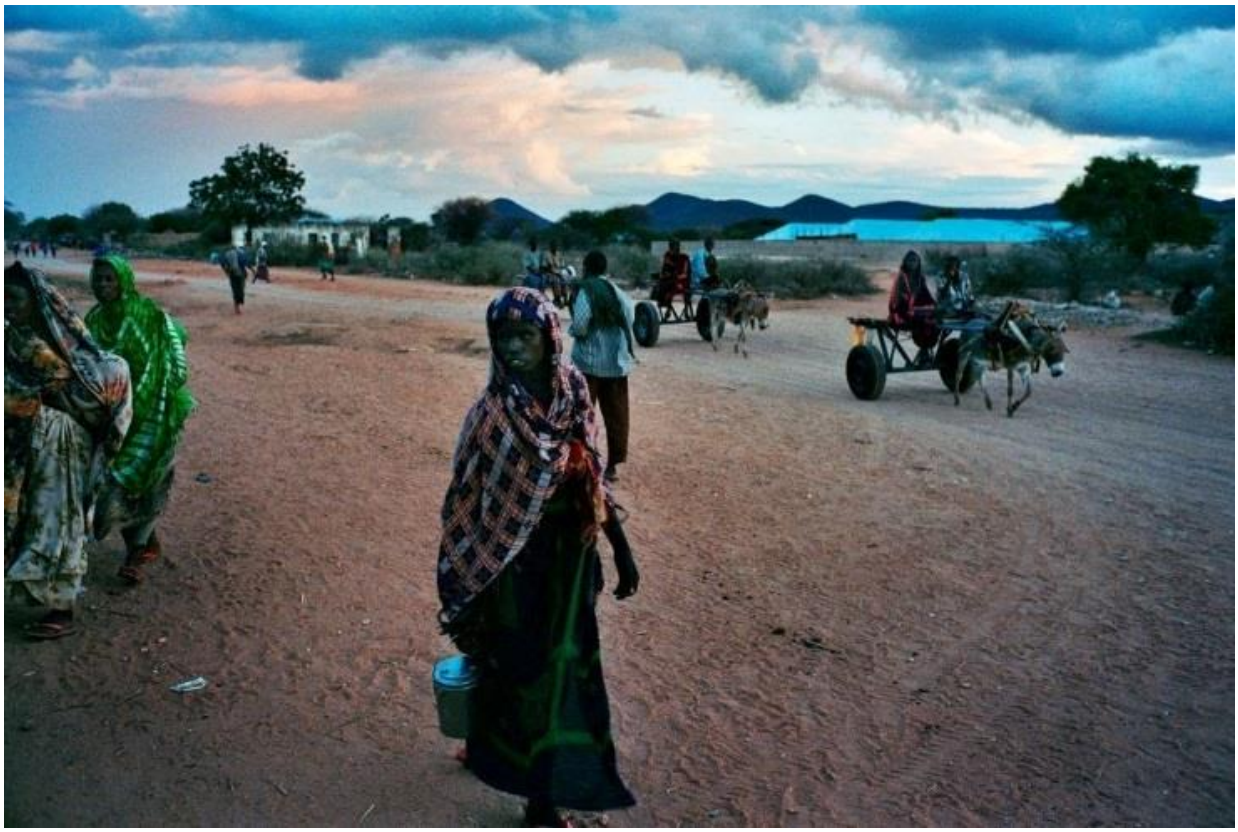
3. PART III: ACCESS DOWNSTREAM



Access to health care remains problematic for people living in remote areas or places affected by conflict. The Baidoa region in southern Somalia is endemic for kala-azar, amongst other health problems.

3.1 ARTICLE 5

'Kala-azar is a dishonest disease': community perspectives on access barriers to visceral leishmaniasis (kala-azar) diagnosis and care in southern Gadarif, Sudan

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"*Kala-Azar is a Dishonest Disease*": Community Perspectives on Access Barriers to Visceral Leishmaniasis (Kala-Azar) Diagnosis and Care in Southern Gadarif, Sudan

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Abstract. Early diagnosis and treatment is the principal strategy to control visceral leishmaniasis (VL), or kala-azar in East Africa. As VL strikes remote rural, sparsely populated areas, kala-azar care might not be accessed optimally or timely. We conducted a qualitative study to explore access barriers in a longstanding kala-azar endemic area in southern Gadarif, Sudan. Former kala-azar patients or caretakers, community leaders, and health-care providers were purposively sampled and thematic data analysis was used. Our study participants revealed the multitude of difficulties faced when seeking care. The disease is well known in the area, yet misconceptions about causes and transmission persist. The care-seeking itineraries were not always straightforward: "shopping around" for treatments are common, partly linked to difficulties in diagnosing kala-azar. Kala-azar is perceived to be "hiding," requiring multiple tests and other diseases must be treated first. Negative perceptions on quality of care in the public hospitals prevail, with the unavailability of drugs or staff as the main concern. Delay to seek care remains predominantly linked to economic constraint: albeit treatment is for free, patients have to pay out of pocket for everything else, pushing families further into poverty. Despite increased efforts to tackle the disease over the years, access to quality kala-azar care in this rural Sudanese context remains problematic. The barriers explored in this study are a compelling reminder of the need to boost efforts to address these barriers.

INTRODUCTION

In eastern Africa, inadequate access to early diagnosis and treatment is a critical barrier to the control of visceral leishmaniasis (VL). Despite a decline in global estimates, the region continues to report high and gradually increasing number of cases.[1,2] Visceral leishmaniasis, also known as kala-azar, is almost always fatal without timely treatment.[3] Delays in diagnosis and treatment not only increase the risk of morbidity and mortality, but also the risk of transmission of infection to others.[4] Visceral leishmaniasis control has been hampered by poorly functioning health services, but, on the other hand, increased supply does not always guarantee optimal uptake of services nor impact on the epidemiological trend.[5,6] Health-seeking behavior toward kala-azar in these sparsely populated rural and underserved areas is complex.

Visceral leishmaniasis is caused by intracellular protozoa from the *Leishmania* species and transmitted by bites of a Phlebotomine sandfly. Its symptoms—prolonged fever, loss of appetite, and spleen enlargement—may mimic other diseases such as malaria, typhoid fever, tuberculosis, or brucellosis. Malnutrition, poverty, and immunodeficiency are known risk factors for developing kala-azar disease,[7,8] and civil unrest, migration, and severe food shortages have led to large VL epidemics in the past.[9,10] The disease disproportionately affects the poor and marginalized, and, in a vicious circle, pushes the affected families into further destitution.[11,12]

Sudan bears one of the highest VL burdens in the world reporting 2,000–7,000 cases per year.[13] Visceral leishmaniasis is thought to be primarily anthroponotic here.[14] Vector control strategies for VL include insecticide spraying, use of insecticide-treated materials, and environmental management.[15] Unfortunately not much evidence exist about their effectiveness in eastern Africa and they are not widely used. In the absence of vaccines and effective vector control strategies, case detection and treatment remains the principal VL control approach. The national VL control program is in place for more than 10 years, providing diagnosis and treatment at public hospitals as a main strategy.[16,17] Diagnosis relies on an antibody detection test, the direct agglutination test, or rK39-based rapid diagnostic test (RDT), or on parasitological examination.[18] Since 2011 the first-line treatment is 17-day injections of antimonial and paromomycin,[19,20] requiring hospitalization for part or the entire course. Late presentations to the hospitals are common, especially in a predominantly rural area such as Gadarif.[21]

Gadarif state of eastern Sudan contributes to 80% of the number of VL cases reported in the country.[22] The southern part of Gadarif is a highly endemic zone with an incidence rate of 75 cases per 10,000 persons per year in a village-level study in 2012.[23] Not all VL patients present themselves to the hospital, although the underreporting seems to improve in recent years.[24,25] Over the past 30 years, several nonstate actors provided support to the Ministry of Health (MoH) to tackle VL, yet the number of cases remains high and access to VL care remains a critical issue in this region. In these large expanses of hard-to-reach, isolated areas there are limited number of hospitals where VL can be treated. During the rainy season (May–October), many roads are impassable, and subsistence farmers and laborers will prioritize the agricultural calendar and postpone dealing with any health matters during these months.[26] Although the governmental hospitals offer VL treatment free of charge to patients, other costs such as transport, registration, admission, drugs for concomitant diseases, and laboratory tests are not for free.[27] Drug shortages have been observed in the MoH services, further reducing access to treatment of many. Cultural barriers exist as well. Nomadic groups lack awareness of the disease.

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Restrictions on women's decision-making power and use of traditional remedies have also been identified as access barriers in a study conducted 13 years ago.[28] All these barriers taken together may result in a long delay between the onset of symptoms and treatment, complicating VL case management, and the chance of treatment success. Treatment defaulters and losses to follow up are common, and the reasons behind are poorly understood.[26] Most interventions in the last decade, however, have been focusing on the supply side of the health service by opening more VL treatment centers, and supplying them with RDTs and medicines. The reasons behind the continued stagnation/increase in the number of reported VL cases, even across villages with similar conditions, are still largely unknown.[29,30] The perspectives of the people themselves, as end users, are rarely investigated.

This qualitative study aimed to explore the perceptions and attitudes of the community to understand the barriers in accessing kala-azar care in this setting. A better understanding of the social context of kala-azar in an endemic area such as Gadarif would generate insights on practical ways to enhance access to care and adjust future control activities.

METHODS

Conceptual framework. In this study, we consider "access" in terms of whether those who need kala-azar care get into the care system and what factors impede this access. We initially adopted the three-delays model from Thaddeus and Maine (delay in the decision to seek care, delay in getting to the facility, and delay in obtaining appropriate care once at the facility)[31] and further incorporate the health behavior model of Andersen[32,33] that focuses on utilization of health services. This model aims to explain use of health services as a function of a set of predisposing factors, enabling/disabling factors, and need factors. This framework guided the structuring of our findings into individual-, population-, and health-system levels barriers that influence health-seeking behavior toward kala-azar.

Study setting and population. Gadarif state has a total population of 1.4 million, spread over 75,000 km^2.[34] It is ethnically very diverse—many Arabic, western Sudanese, West African, and non-Sudanese tribes settled there during the agricultural boom in the 1960s.[35,36] The vegetation consists of a typical dry savannah woodland, with *Acacia* and *Balanites* trees, combined with black cotton soil. Agriculture is the main livelihood, with sorghum, sesame, and millet as major crops. More than half of the population live in rural areas, and only 60% are literate.[37] Most people are subsistence farmers or engage in small animal husbandry. Socioeconomic inequalities are high, due to the expansion of large mechanized farming based on underpaid wage labor. High demand for manual labor attracts seasonal workers (from within Sudan or bordering Ethiopia) during the rainy season.

The study was conducted in three most VL–endemic localities in southern Gadarif – two located along the Atbarah and Rahad river basins (Qureisha and al Rahad, respectively) and one directly bordering Ethiopia (East Galabat) (Figure 1). Al Rahad locality is served by two hospitals, Um el Kher (supported by Médecins Sans Frontières [MSF] in 1996–2005) and Bazoora (also supported by MSF starting in 2017). East Galabat locality, is served by one rural hospital (Basunda) and one specialized kala-azar center (Doka) supported by the research agency Drugs for Neglected Disease Initiative). The al Qureisha locality is served by a kala-azar center supported by MSF since 2009 (Tabarak Allah).

Historically, MoH was in charge of and providing kala-azar care in Gadarif. When a VL outbreak unfolded in 1995–1996, efforts to study and tackle the disease increased, which included collaborations between the Sudanese and international actors. non-governmental organizations (NGO) as MSF have treated thousands of VL cases in dedicated clinics. More recently, the KalaCORE consortium is supporting MoH to improve routine kala-azar services since 2015. In 2017 there were 10 public hospitals designated to diagnose and treat kala-azar, including the referral hospital in Gadarif town.

Study design. We conducted a qualitative study combining in-depth interviews (IDI) with individual key informants and focus group discussions (FGD) to add breadth to the data and triangulate the findings.[38] Data collection took place in March 2017. The field research team was composed of equal numbers of members with biomedical and social science backgrounds, four females and four males, and supervised by the principal investigator (T. S.). We purposively selected three villages from each locality, one with a high number of cases in the last year, one with low number, and one with the worst physical access to any kala-azar treatment centers in terms of roads. We decided on this choice of villages in two meetings between the research team and community facilitators from the localities, using village level kala-azar data from state MoH. The purposive sampling was chosen to ensure maximum depth and variation of information, including typical and deviant cases. Participants for IDIs consisted of three categories: former kala-azar patients or caretakers (as community member), community leaders, and health-care provider. Participants for FGDs consisted of community members only, as involving community leaders or health workers in the discussions may introduce bias.

We introduced the study and the aims to local village chiefs, and community facilitators who previously invited participants for FGDs further approached key informants for a face-to-face interview. If participants were willing to participate, the research team visited them in their home and obtained a written consent before conducting the IDIs. Group verbal consent was taken before FGDs. Health workers in the area were consulted but to avoid bias as much as possible the IDIs and FGDs were not conducted in the health centers. Between 7 and 12 people participated in each FGD which lasted 45–60 minutes, whereas the IDI lasted on average between 40 and 90 minutes.

Focus group discussions were conducted separately for women and men. The interviewer/moderator was of the same gender as a participant(s). All interviews and FGDs took place in the participants' homes or other private and confidential areas and were, after permission, recorded on a digital voice recorder. Semistructured topic guides were used to guide the IDIs/FGDs, and additional items were included as data collection progressed. Data collection continued until saturation was reached and no new information emerged. All interviews were conducted in *Arabic*, the main local language.

Data management. To ensure quality of data, we put forward the following mechanisms during data collection: 1) permanent supervision of the study by the principal investigator (T. S.) and 2) frequent exchange and feedback

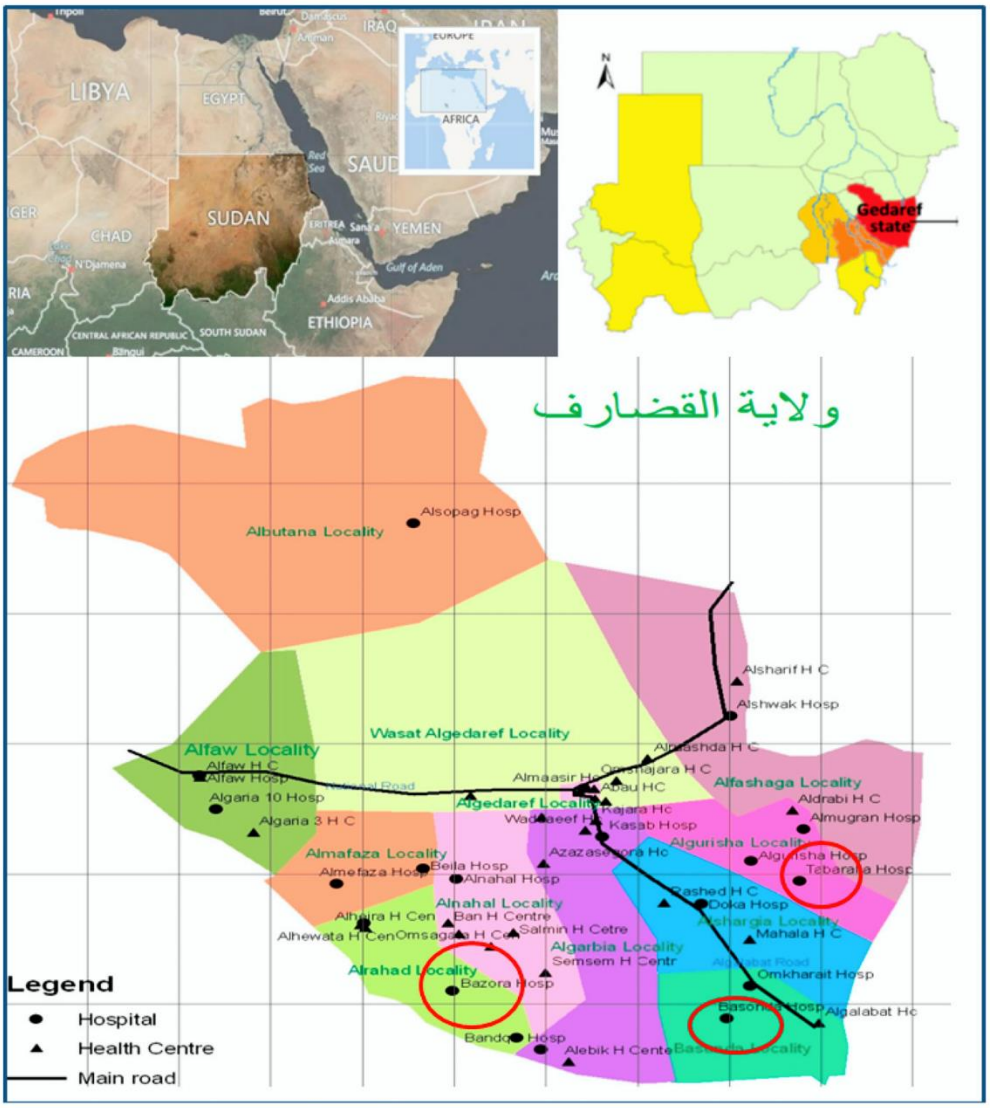

FIGURE 1. Map of Gadarif state in eastern Sudan and localities where the study is conducted. This figure appears in color at www.ajtmh.org.

sessions among the study team in the field. Before study implementation, the team completed a 3-day training workshop, after a pilot test of study tools in one village nearby Gadarif town. Records from the study were transcribed verbatim, while an Arabic language expert and native speaker (G. K. A.) supervised the data transcribing and translation process. The subsequent English translation was carried out by a team from a local English language institution and cross-checked by two researchers (R. A. B. and N. A.).

A public health specialist (T. S.) and anthropologist (C. V. K.) independently analyzed the data using a thematic analysis approach.[39,40] Themes were identified through careful reading and re-reading of the data, and if patterns were recognized, these emerging themes became the categories for analysis. This analysis method combines a deductive

approach - through predefined themes in the questions guide- and data-driven inductive approach allowing for themes to emerge from the data. Three researchers (T. S., C. V. K., G. K. A.) conducted the refinement and reconciliation of coding through frequent discussions about deviations and common themes. All team members were involved in revising the coding schemes, organizing the codes and corresponding quotes to identify consistencies and contradictions in the data and interpretation. NVivo software (version 11; QSR International, Melbourne, Australia) was used to aid the data management during analysis.

Ethical statement. We obtained ethical approval from the National Health Research Ethics Review Committee, Federal MoH of Sudan and from Institute of Tropical Medicine Ethical Review Board. Permissions to conduct the study were obtained from the State MoH, local authorities, and MSF. Written informed consent was obtained from each study participant or their parent/guardian for the nonadult participants, in addition to their assent. Additional oral consent was obtained for using digital voice recorder. Participation in the study was voluntary, and any information provided was kept confidential. Quoted information was anonymized during the analysis and reporting.

RESULTS

A total of 191 individuals participated (see Table 1).

Kala-azar is well known, yet with varying level of misconceptions. Kala-azar is a well-known illness and familiar to many, as almost all participants knew someone who suffered from it. The history of VL goes back a long time in Gadarif. Respondents told that the disease was previously known under the local name *"maraad sayeed,"* literally meaning "disease of the south"—referring to the upstream river basin areas. Other vernacular synonyms for kala-azar were *"tohaal"* (abdominal swelling), *"suffair"* (jaundice), and *"ghibia"* or *"jini wardah"* (recurring fever). Our respondents describe the disease as characterized by bouts of fever, abdominal swelling, low appetite, and weakness. People also linked kala-azar with vomiting, headache, yellow skin, pale eyes, nose bleeding, dry lips, and anxiety.

Table 1
Characteristics of the participants of IDI and FGD

		Females	Males	Total
In-depth interviews		**10**	**14**	**24**
Age group	14–25	2	0	2
	26–35	2	5	7
	36–45	4	2	6
	46–65	3	6	9
Categories	Community members*	8	4	12
	Community leaders†	1	4	5
	Health-care workers	5	2	7
Focus group discussions		**9**	**10**	**19**
Locality	Rahad	4	5	9
	Qureisha	2	2	4
	East Galabat	3	3	6

FGD = focus group discussions; IDI = in-depth interviews.
*Community members: former kala-azar patients or caretaker of a patient.
†Community leaders: members of people's committee, school principals/teachers, merchants, or religious leaders.

Respondents claimed that the name "kala-azar" was only introduced when "outsiders" came to Gadarif to investigate the "killing disease" outbreak in the 1990s. These outsiders were doctors and researchers from Khartoum and abroad and they were the ones who told the villagers about a "sandfly" causing this disease. Respondents from the villages along the Rahad and Atbara rivers were mostly able to correctly identify the sandfly as the transmitting agent, and its association with the *lalob* (*Balanites aegyptica*) and *taleh* (*Acacia seyal*) trees, cracks of the soil and the mud huts, and animal dirt. However, some participants did not know what causes kala-azar and attributed it to hunger, contaminated water, mosquitoes, unhygienic houses, and staying outside the village on the farmland. Some participants believed that the disease could be passed from person-to-person in the same house. Drinking water or sharing food with patients, sleeping in the same bed, and clothes and sweat of the patients were also evoked by some as ways to get infected.

> *"Because when you eat or drink some of the food or drinks meant for the sick person, you will be infected. When this disease infects a person in a family, it must also infect two or three other persons"* [IDI, Male, Community leader]

Some people said that everyone, rich and poor alike, can get kala-azar. However they acknowledged the vulnerability of some groups: children, or the young, in general, were thought to be more at risk, as they play outside close to the trees where the sandfly lives and have "weaker blood." Family members and poor families with food insecurities are also perceived to be at a higher risk to get kala-azar. Certain areas were thought to be more at risk: villages along the river and the deep remote settlements far from the road. A few participants hinted that certain tribes have "more kala-azar": the Hausa and Masaleet were mentioned; although for most respondents the geographic location of their villages matters more. Most respondents linked the abundance of sandflies with the increased number of kala-azar after the rainy season/autumn, also known as the "sesame season." Several mentioned that the general fatigue that people experience after harvesting, makes it easy to contract kala-azar.

> *"Yes, hunger causes it, the sandfly brings it. The person who does not eat enough definitely he will be sick and the illness will increase. When the fly finds that your blood is weak, it (kala-azar) strikes you"* [FGD, Female, Kersyba]

Diagnosis delay and multiple trajectories (getting diagnosed is not an easy feat). Participants who had kala-azar in the past or cared for family members with kala-azar claimed that the search for a definitive diagnosis is a major challenge. People first try to self-medicate, adopting a "symptomatic" approach with distinct healing methods for each affliction. For example, they rub oil and herbal paste against fever, cut or burn skin against the abdominal swelling, drink herbal concoctions from various roots for yellow skin, or drink water that has been blessed by readings from Qur'an (*muhaya*) as a more general measure. The association with "bad blood" led to the practice of bloodletting, "letting the black blood run," after which the wound is tied up with tree barks. If these attempts are unsuccessful, then only people resort to the formal health

system—this might be the village health center or clinic, nearest rural hospital, or pharmacies, depending on circumstances and available money. Private clinics are rare except in Gadarif town.

However, many participants said that the traditional treatment is a thing of the past, from the time when the kala-azar drug was neither known nor available. These traditional or religious practices still have their place if the kala-azar test results are negative. Traditional healing practice seems ubiquitous, not only in remote villages. It is also enhanced by the financial barriers linked to the formal health system.

> *"When we do not know, we treat him traditionally. If not healed, we take him to the doctor to inject him, (but) to take the injection he needs to be tested first. When you go the doctor, regardless if kala-azar appears or not, the doctor gives an injection for malaria and inflammation. If this fails, then we need to take him to the doctor for (another) testing."* [IDI, Female, Former kala-azar patient]

> *"... I have seen it for a long time that local medicine does not cure kala-azar. What is cured by local medicine is "Um-Siffair" - jaundice – trees can cure that. However, kala-azar needs kala-azar medicine. Sometimes, it needs some local medicine to come out and be found. This is the case when it does not show at first in the laboratory test."* [IDI, Male, Former patient]

People mostly believed that kala-azar can only be found after multiple tests. The "easy" type of kala-azar is the one that is detected immediately, whereas the "difficult" one is the one with repeated negative test results. Kala-azar is to a large extent thought to be "hiding" in the body and will only show itself after evolving from malaria, inflammation, or typhoid. In the experience of many, there is a need to be treated for other diseases first.

> *"We say it is malaria first and then it changes into kala-azar. Sometimes they say typhoid. Malaria becomes typhoid and typhoid becomes kala-azar"* [FGD, Male, Rymila]

> *"Kala-azar is a dishonest disease. If there is any other disease in your body, then kala azar will not appear in the test until you get rid of all the diseases you have."* [FGD, Male, Tabarak Allah]

Most participants indicated that if they suspect kala-azar, they will seek to confirm this through repeated investigations; especially in a bigger town such as Gadarif, where a private laboratory, in particular, is known to be a trusted kala-azar laboratory in the state. The village-level health center and the clinics only perform RDTs for malaria. Hence many respondents described their experience having to undergo multiple tests in various places, either referred or by their own volition, in search of the final kala-azar diagnosis. When the results turned out negative, several respondents attribute it to the lack of experience of the technician or unavailability of "sophisticated machines." Health workers said that the RDTs are not reliable and that only by microscopy the diagnosis can be ascertained.

> *"We are poor. I have two children who had kala-azar. I went to Gadarif five times. All tests and ultrasound exams did not discover the disease, so they told me to go to Ahmad Daneel (the private kala-azar lab). When he saw them, he said it was kala-azar and transferred me to Doka hospital. When I came, they told me to pay 12 pounds for tablets, and I paid, but they gave me nothing. Waited for another day and again nothing. Then I went to Tabarak Allah center, and they started the tests again, my first child and then his brother was found positive but they recovered, and they are well"* [FGD, Male, Rymila]

Participants also discussed specific food items that are believed to force kala-azar to appear, such as banana, chicken, and fish. Some respondents said that this widespread belief was initially promoted by the doctors, although health-care workers refuted this. According to our respondents, this food would make the symptoms worse and push the kala-azar to appear.

> *"Sometimes, when it is too difficult to find kala-azar in laboratory tests, the sick person is told to go home and eat bananas." ..."* [IDI, Male, Former patient]

When kala-azar is finally diagnosed, this is seen as a blessing or good luck. People congratulate the patient with the positive test. People widely felt relieved when kala-azar is diagnosed, as they assume that now cure is within reach and further money expense can be avoided.

> *"The demon accompanying kala-azar is the fact that the disease does not appear easily. So when you meet the doctor for diagnosis, you may feel tired and exhausted. You have nothing at home. Before you do the test, they say 'your medicines are this and that', and 'we test, you give the money' You have no money to pay them. Here you feel worried and anxious... Afterwards when kala-azar appears, you say thanks and praise to Allah. This is a blessing."* [FGD, Male, Bazoora]

The journey to obtain the diagnosis is a huge challenge and these hurdles are evoked as the most important reason to delay coming to the hospital. Treating the initial symptoms with medicines brought from the market is also common and seen as part of the "diagnostic process."

> *"In case someone is sick, he comes here to the hospital and if no kala azar is found [immediately], he goes away and buys the medicine from outside. In reality, he may have kala-azar, yet he buys the medicine from outside and many patients are lost this way. A person's health worsens, and they bring him here when it is too late."* [IDI, Female, Health care worker]

Variable quality of care in different treatment centers. The irregular availability of the kala-azar medicine at the hospital was a source of concern for many respondents. People who have to wait for the drug linger several days at the hospital, and in some cases are referred to places with a higher likelihood to have the drugs. Several respondents experienced this firsthand, and few mentioned that the medicine could be bought outside the hospital. Universally known as "kala-azar injection," it seems that people can purchase the

vials in an informal circuit if they know someone from "inside" this black market.

"By Allah, the reason of death is nothing else than unavailability of medicine. Sometimes it is tough for people to find medicine when they are sick with kala-azar, so they die because of lack of treatment. The medicine is not available all the time, and sometimes you will find a person took two or three injections then the medicine is finished." [IDI, Male, Healthcare worker, Tabarak Allah]

"If you know the right local person, you tell him that you need kala azar drug for your son, they tell you ok, we will give you the drug, and the cost is 500 pounds [US$75]" [IDI, Male, Caregiver]

Most participants said that the injections are the only cure for kala-azar and had no doubt about its effectiveness. However, they also mentioned that the drug is "heavy" and "burns the blood." The change in the duration of treatment, from 30 days to the current 17 days was noticed and to some, generated a concern that kala-azar relapse happens more often with the new regimen. People also said that there is some food to be avoided to prevent kala-azar relapse or skin spots (referring to the post-kala-azar dermal leishmaniasis), such as Sudanese groundnuts (*foul* or *dakwa*) or beans. Participants from kala-azar–affected households expressed their negative feelings toward the health-care system. They mentioned the poor facilities (such as inadequate bed capacity), lack of medical staff, the commercial motives (everything has its fee), and the variable quality across hospitals. The hospitals that are supported by NGO stand out because all care is provided for free and kala-azar patients receive additional support, thus serve as an incentive for the patients.

"During the period of treatment they used to give patients soap, flour, and oil for cooking, the sick person gave multivitamin, milk, madeeda (porridge) so when he gets out of the hospital, he was fit." [IDI, Male, Former patient]

"We did two years without a doctor in the normal (not Kala-azar) ward, while MSF managed the Kala-azar center next to it. The organization is very good, but there is a great difference: the governmental hospital is very poor in everything and the government's doctor is paid a weak salary." [FGD, Male, Tabarak Allah]

The perpetual poverty and the taxing journey to reach care. To deal with a kala-azar episode is costly; this is acknowledged by all IDIs and FGDs participants without fail. Although kala-azar drug is officially provided free of charge, there are many other expenses for the kala-azar patients and their families, which they have to pay out of pocket. These include hospital entry ticket, different laboratory investigations, bed, syringes, medicines for other nonkala-azar conditions, and meals for the caretakers. Participants described their coping mechanisms such as borrowing money, selling cattle/crops, or asking help from the Islamic charity *zakat*. The financial losses are felt both in the short- and long-term, and often stood as the main reason for not taking the sick to the hospital.

"The financial situation is so bad; you find the families (who) are too poor to have food for tomorrow or even the day, they have no money to see a doctor and buy medicine, so he stays with his disease (kala-azar). They say thank god if recovered, if not then it is God's will" [FGD, Male, Um el Kher]

"It is difficult here to be sick with no money because you need two pounds (US$0.3) to get to the hospital and 20 pounds (US$3) to see the doctor, who will give you three tests, malaria, inflammation or typhoid. The result may not show kala-azar, but he has it. Then you start testing again, and that may cost 60–70 pound$ (US$9–10.5), always need to get back (to the hospital) with the sick - such case is normal here, and when your pounds are finished, there is nothing to give him but the traditional treatment" [IDI, Male, Community leader]

The transportation cost to get to the hospital varies with season. During the rainy season, transport costs increase significantly as the roads are flooded. The participants described how the sick were carried by stretcher, on boats or on a tractor that may take days or weeks to reach the hospital. Because of this difficulty, many respondents expressed that people would rather wait until the rainy season is over to seek kala-azar care, and will wait even longer, if there are agricultural chores. The unstable income during this period, to some participants, also acts as a deterrent from seeking timely care.

"Now, in this area for about eight months you [to the interviewer] can't reach us here, I am sure. The tractor was stuck for a day on a stretch where the car can cut in 15 minutes." [IDI, Female, Caregiver]

"First thing is the road, the distance between Barbar and Tabarak Allah is five kilometers, and it takes 6 hours to reach there with the mud…very exhausting. Moreover, people in the rainy season need to buy seed, so they do not have the money to take the patient to Tabarak Allah. From less than 10 pounds (US$1.5) this will now cost 300 to 400 pounds (US$45–60), and you have to rent a special vehicle. Many areas are completely cut-off during the rain. Poor people could not take their son to the hospital even if he was dying in front of them." [IDI, Male, Former patient]

"The problem is that in autumn, people's financial situations are very difficult. The patient's family does not have anything. People collect money for him and write an application to the "Zakat chamber," and you do not get enough money to help you, it is a complicated situation." [FGD, male, Rymila]

Gender inequalities further exacerbates kala-azar impact on the family. Kala-azar is broadly perceived as a dangerous disease and should be taken seriously. The notion of danger is linked to its severity and perception that kala-azar ultimately kills or causes death. Most female participants were aware that kala-azar or its treatment can cause abortion.

"It is the most dangerous disease because it is difficult to be cured. Other diseases can be cured in the nearest hospital but kala-azar only in organizations or centers. It is so expensive, it costs 3000 or 3500 pounds (US $450–525). We think it is the most dangerous disease as it causes death" [FGD, Male, Barbar el Fugara]

When a family member is suspected to have kala-azar, although both parents are responsible to decide what to do, the woman or the mother is in a disadvantaged position. The women are expected to handle multiple tasks: household chores, agricultural work, and childcare. Permission from the husbands or male family member is culturally required, although this is strongly linked to the financial solvency as the husband's prerogative. However, respondents also said that women could help raise the money, either by selling crops or reaching to the collective community resources.

"To get the medicine you have to buy it, so probably sometimes you will not have money, sometimes the father also is not around. A sick child may spend 15 days before going to the hospital, why? The mother tells you that the father was not around and there is no money. She has to wait till the father comes before doing anything. Some people sell their sheep or goat in the market to get money. So money is a major problem, (it) will block everything and that is why there is a delay." [IDI, Female, caregiver]

Many female participants spoke of the impact of kala-azar on the family, the emotional toll to deal with anxiety related to the disease and premature death, and further impoverishment to the family, even if the patient is not the main breadwinner. Having to stay in the hospital disrupts their life, as the work in the field has to be abandoned or delegated to other people.

"The family will be troubled despite their poverty they do what is beyond their abilities. All the family care should be directed to the patient, kala-azar is most dangerous disease here and is still a problem." [IDI, Female, Caregiver]

Limited efforts to control the disease. Participants from villages with a high number of kala-azar cases in the past indicated that the disease has somewhat "decreased" now, although few mentioned that it might increase again. Most people perceived a change in the situation, attributed to various things such as the presence of "organizations," health education, and preventive measures, e.g., spraying campaigns, mosquito net distribution, and cutting trees.

"In the past, kala-azar was more common here, but now and after the organization came the disease is reduced. The people come to our area from different regions to get treatment here. The deaths are also much less. The people nowadays use nets, they know how to control the disease, and there is health education for us. Previously, there were only grass and bushes which are a good environment for the fly." [IDI, Female, Health care worker]

The preventive measures, however, are not entirely perceived as successful. Both the villagers and health-care workers expressed their weariness, as to the use of mosquito nets (too hot in summer time), the ineffectiveness of spraying, and the abundance of trees, even if they are permitted to cut them.

"We are worried about the cause of the disease and treatment. However, we keep asking how to fight the sandfly? From our experience to cut down trees and run after the sand fly to catch it, [everybody laughs] this is a failure." [FGD, Male, Tabarak Allah]

When asked about what more could be done to tackle the disease, many participants expressed that more centers are needed for the hard-to-reach areas, including more laboratory and more doctors. Although some participants wished that kala-azar–specific activities such as spraying, net distribution, and health education programs (in the mosque or school) would be improved, others say that economic programs to tackle poverty would be more critical. Many respondents spoke of the need for more roads and better transportation in autumn.

"I would say that the State should help citizens, treat them & deal with the things that are difficult for them to handle. "The poor citizen cannot get medicine and searches for the cost of treatment." [IDI, Male, Community leader]

DISCUSSION

This qualitative study explored the barriers to access kala-azar care in endemic areas in southern Gadarif, Sudan, from the perspective of the people. Our findings describe the multitude of difficulties people face when seeking kala-azar care, and illustrate the prevailing hardship in a rural Sudanese context. The various barriers, as experienced and narrated by study participants, are depicted in Figure 2. Access to health care is always a multidimensional phenomenon closely related to the health-seeking behavior of the population. However, in this region the perception of illness and care is predominantly shaped by poverty and other structural problems in an extremely resource-constrained setting.

Both the three-delays and health behavior models have been used in many health topics,[41–44] yet this is the first time to apply them to the context of kala-azar in Sudan. Our study was designed to explore what barriers persist from the community perspective on kala-azar care. The predisposing characteristics at community and health system levels influence the "propensity" of individuals to seek care (stage of the decision as the first delay). The second delay in reaching health care is closely linked to the contextual elements, and the third delay in getting quality care is related to the barriers at the health system. Several barriers that we identified were comparable to findings in a community-based study in the same area[28]: lack of money for treatment and transport, distance, impassability of roads, work priorities, and gender inequality. A more recent study in 2012[23] reported that the population around Tabarak Allah (where MSF runs a kala-azar center since 2009) have adequate access to care, but our findings show that this is not necessarily the case elsewhere. Geographical and financial

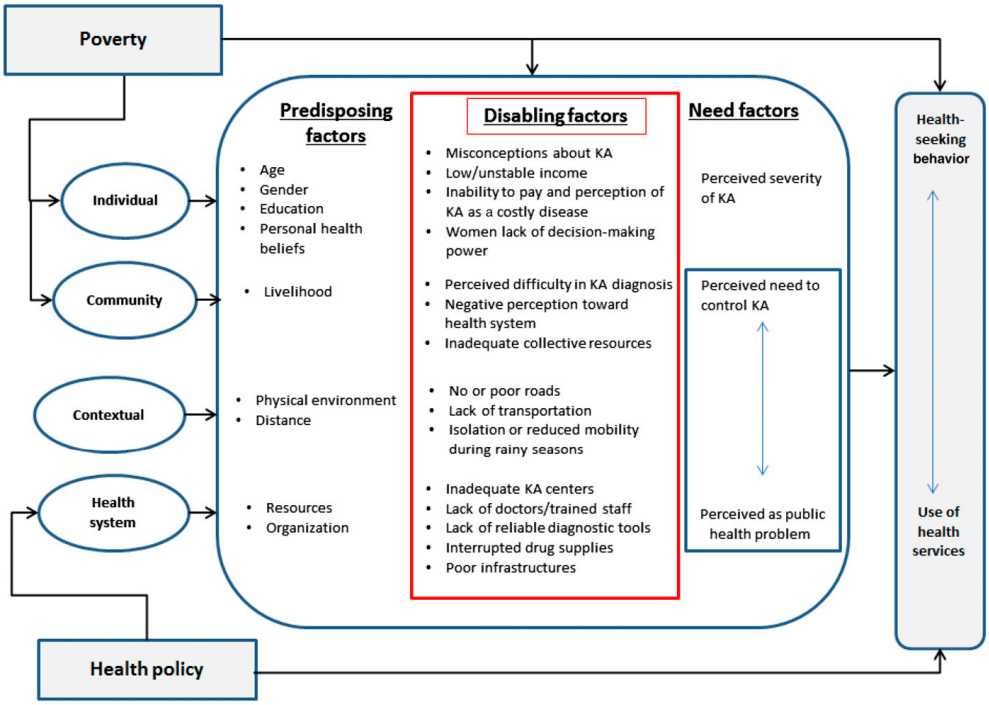

FIGURE 2. Summary of access barriers to kala-azar care in southern Gadarif, Sudan. This figure appears in color at www.ajtmh.org.

barriers are essential,[11,45–47] and the situation is more complicated than assuming that increasing the number of hospitals would be the solution.[48]

In this study, participants were well aware of kala-azar as an important communicable disease, as have been reported in other kala-azar endemic settings.[49–51] The cardinal symptoms are known, although misconceptions of the disease regarding its real cause and transmission remain. The knowledge on sandfly, its habitats in certain trees or cracks were translated to prevention efforts: vector-specific (bed nets, spraying, cutting trees, repellant oil, etc.) or general ones such as improving hygiene. As kala-azar seems to persist in the community; there is a sense of eroded trust in the preventive measures promoted by health providers. The perceived severity of kala-azar is the main drive behind the continuation of such practices, despite the lack of evidence of effective vector control in this area.[15,52,53]

We did not find local explanatory models of disease[54] that are incongruent with the biomedical knowledge that has spread along with efforts to control the disease. None of the participants explained kala-azar as related to the supernatural, magical or religious factors, indicating that the prevailing belief is of naturalistic causality.[55] When asked about the use of traditional medicine, people unanimously said that these things are not for kala-azar. However, people also described these traditional practices for several kala-azar–associated symptoms, such as the swollen spleen (*tohaal*) with burning or jaundice with herbal remedies. Therefore, despite a relatively high level of knowledge about the disease, this may not necessarily mean that there is no "shopping around" for treatment. The study by Gerstl et al.[28] described similar behavior, although they found that disease awareness was low. The care-seeking itineraries for kala-azar are not straightforward; they appear to depend on the symptoms, perceived cause, duration, severity, and role of the person in the households.

Diagnosing kala-azar is seen as a critical difficulty for the people, as the gateway to treatment is only through a positive diagnostic test. Kala-azar is perceived as a disease that is in hiding. Thus various examinations are required, and other diseases must be treated first—most notably malaria and typhoid. There seems to be a low awareness on the type of the tests that is adequate to diagnose kala-azar. Gadarif is an unstable seasonal malaria area, and concomitant malaria among kala-azar patients is estimated to range between 4% and 61%.[56] Hence, the perception of malaria evolving to kala-azar may origin from the standard clinical practice of ruling out malaria first.

The attitude of "doing everything" to get a positive kala-azar test further fuels the frequent belief that certain food would help to diagnose kala-azar. Although perhaps based on observations and experience, the belief reflects the hot–cold dichotomy in a healthy equilibrium state, a symbolic notion found in many cultures.[55,57] People reported that the reason

behind giving banana and chicken to a kala-azar–suspected patient is to amplify the hot power that is raging in the patient's body—the heightened heat would surely make the diagnosis positive. It seems unusual to congratulate someone of being sick (with kala-azar), yet in this context, it symbolizes the end of an arduous journey and hopes that the cure is finally within reach.

Our study found a positive perception toward allopathic treatment: people are convinced that kala-azar needs to be ultimately treated by (medical) injection at the hospitals. Although acknowledged as "hard" medicine because of the side effects, they trust that the drug is making the patients well again, an essential factor for compliance.[58] Negative perceptions prevail toward the quality of care that is provided at the public hospitals, primarily related to the limited resources such as the availability of the doctors and more importantly, the drug. In Rahad and Galabat localities, the recurrent stock-outs of the medicine were criticized as they can lead to interruption of treatment. Illicit trade in medicines adds to the dissatisfaction with the service, especially when they compare with centers/hospitals receiving external support from NGOs. This has led people to take the journey to these centers, or to Gadarif city, thus not necessarily utilizing the closest health facility.

An overarching barrier for accessing kala-azar care is the cost of an episode—being sick with kala-azar implies paying for multiple tests, treatments, and hospitalization. Financial constraints were given as the most plausible explanation for why kala-azar patients wait for weeks and months before going to the hospitals. The fact that the medicine is for free (and not the diagnostic tests) does not compensate for the considerable costs that the family has to spend from the pocket directly, and although we did not find evidence that treatment compliance is jeopardized, several coping mechanisms (such as borrowing or selling assets) were clearly in place. Financial barriers during the rainy season—due to increased transport cost related to the physical barriers—are particularly cumbersome for those without a stable income. Our findings are consistent with an earlier economic analysis of kala-azar in Sudan, which estimated the total cost at US $450 for an episode,[11] totally unaffordable for most subsistence farmers in this area (61% of the population are reported to live below the poverty line of 250SDG [US$37] per month[59]). Although women need their husband's permission to seek care in this culture,[28] the delay is often due to lack of money. People also more readily travel to free-of-charge treatment centers or the ones known to offer more in-kind support (nutrition, etc.). However, the rigidly defined gender roles for women and their unequal access to resources compound more difficulties for women.

The participants indicated that some barriers have been and could be ameliorated through several interventions. Health education to address the misconceptions and to empower the community in negotiating access in the medical system is demanded. Although active case detection was deemed unnecessary in areas with good access to treatment centers,[23] a more targeted approach toward villages with least access to services after the rainy/autumn season should help save lives. The poorest and those who live furthest away could benefit from a targeted support system, such as transport loan funds, health insurance, community loan funds, or charity such as the Islamic "zakat." Quality of care should be standardized, through equitable distribution of resources to the hospitals. Health system strengthening efforts will benefit kala-azar patients through improvement of the supply system and offset the discrepancies between NGO–supported centers and public ones. Another recommendation that goes beyond the health sector is to enhance the propoor policies in Gadarif, and government to step up its actions in reducing poverty. The sustainability of access-to-care for kala-azar needs political and resources commitments.

One limitation of our study was that we did not fully capture the perspective of children and adolescents, who make up most kala-azar patients in Sudan. The group discussions were conducted in gender division, but the varied age in each group may limit the younger participants in expressing their views. We also could not explore fully the ethnic dimensions in the study as it was not possible to conduct the data collection and enroll participants along tribal lines in the current political climate in Sudan. We cannot exclude the social desirability bias in some of the responses, knowing the field team came from Gadarif. Although generalizability is chided as a limitation in a qualitative study,[57] we believed that reasonable extrapolation of our findings is not impossible. The generalizability of this study does not derive mechanistically from the sample but from the concepts emerging from the findings (such as the delay in diagnosis or persistent economic burden) that may well be relevant to other settings or other health problems. The context of Gadarif is specific, yet the suffering is not.

We believe this study offers a timely thorough insight into the community perspective on kala-azar in this area and help explain the reasons behind the delay in seeking kala-azar care documented in quantitative surveys.[60,61] It is essential for policymakers and other stakeholders to understand the barriers explored here as reducing delay would be contingent on addressing these. In regard to the technical tools, there has been progress in the recent decade, i.e., the RDT and a shorter treatment regimen, yet these are still far from optimal. Several factors revealed here merit further research, such as the diagnostic bottlenecks (lack of trust in RDT, an algorithm for prolonged fever such as kala-azar) and more empirical studies to measure the various dimensions of access over time that may predict health behavior, service utilization, and health outcomes. Last but not least, development of better vector control tools and other preventive measures is critical to lessen the kala-azar burden to the communities in the long run.

CONCLUSION

Kala-azar is an infectious disease of poverty in southern Gadarif, Sudan. Despite allegedly more efforts to control the disease, the access to quality kala-azar care remains problematic as is observed for many other health conditions in such settings.[62] To alleviate suffering, the multiple barriers they face should be considered before implementing any interventions. The financial accessibility should be prioritized through a multisectoral approach designed to have wider benefit for health for all.

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SUPPLEMENTAL FILES

SUPPLEMENTAL FILE 1: IN-DEPTH INTERVIEW GUIDE

SUPPLEMENTAL MATERIALS

In-depth interview guide. *NOTE: This guide is to be used after proper solicitation of the information sheet and the informed consent is obtained*.

Visceral Leishmaniasis, also known as kala-azar, is a serious illness common in Gadarif. You have been contacted as you are living in areas where the disease can be found. We would like to ask you some questions about this and also discuss about experience, if you or someone that you know have had it before. We would like to understand better the people's opinion about the disease and challenges in getting care for this disease. The interview should take approximately 30–60 minutes to complete. PLEASE ALSO INTRODUCE YOURSELF.

Part A (this can be filled up at any moment)

1. Interviewer Name: _____
2. Translator: _____- (if relevant)
3. Date of interview: ___/___/___
4. Village of interview: _____ Locality_____
5. Time starting: _____

Part B

1. Sex: M/F (circle)
2. Age: ___ (years)
3. Current occupation: _____
4. Tribe/ethnicity (if you think this is ok to ask, otherwise skip): _____
5. How long have you lived in this village? _____ years _____months
6. Can you tell me something about yourself? (optional)

Part C: QUESTIONS

1. Can you tell me about your experience with kala-azar? (if you have)
2. In your opinion, what is kala-azar? (causes, transmission, symptoms, prevention . . .by asking: *What do you think causes kala-azar? How do people get it?*)
3. What is the specific name of kala-azar in your language?
4. a. How do you see kala-azar as compared with other diseases? (to know perception of severity)
   b. How do people in the village see it? (*How does it affect the community?*)
5. Who do you think can get kala-azar more? (*Who are more at risk for the disease?*)
6. What is generally done when a person gets kala-azar? (*What do people do when they think they have kala-azar? What do people do when they suffer from prolonged fever?*)
7. If people seek treatment of kala-azar, where do they go? Why? (*Beliefs and thoughts, preferences for healing/health-care services including perceptions of services rendered by different providers: traditional healers, hospitals . . .*)
8. If children or young people are sick, who made the decision to seek help? (Why?)
9. Can you tell me if getting care for kala-azar is easy? (*What made it difficult to get care on time for kala-azar?*)
10. Why do you think people with kala-azar sometimes come late to the hospital? (*Try to explore geographic accessibility: seasonal/farming activities, cultural/gender/age, administrative and financial barriers, . . .*)
11. What do you think can cure kala-azar?
12. Why do you go to health centers or hospitals? (explore positive or negative perception toward available care for kala-azar)
13. If someone gets kala-azar, how does it impact the family?
14. And what do you think can make the situation better for kala-azar for you? And for the community?

Closure: Thanks
Time taken to finish the interview: _____
NOTE:

SUPPLEMENTAL FILE 2: TOPIC GUIDE AND GUIDELINES FOR FOCUS GROUP DISCUSSION (IN ENGLISH AND ARABIC)

TOPIC GUIDE AND GUIDELINES FOR FOCUS GROUP DISCUSSION

INTRODUCTION: these guidelines are to be used for conducting Focus Group Discussions (FGD) within a study to understand community perspective on access to care for this disease in Gadarif and the challenges associated with it. Information sheet and informed consent would first be solicited from participant before organizing and starting the FGD.

Participants: Community members from selected villages in the localities of el Rahad, East Galabat or Al Qureiha (representing the catchment area of Um el Kher, Basunda and Tabarakallah hospitals, respectively).

Participant Consent: Participants will sign a consent form to participate in the FGD. One copy of the informed consent form should be given to participants and a second copy should be kept by the focus group facilitator. Participants would be informed if any audio-taping will be used for data collection.

Demographic data: It is important to collect anonymous demographic data from focus group participants. We will use an enrolment form with few key demographic details from the participant (age, sex, occupation, duration of living in the village).

Facilitator/Moderator: only trained person will take this role.

Discussion guides: Note that this topic discussion guide is meant to facilitate structuring the FGD by highlighting the topics that need to be covered. It is not to be used rigidly (like a questionnaire), yet the facilitator encourages participants to explore topics in depth, to reflect, to raise their own issues, etc.

Time and Place: The FGD can last between 45-90 minutes and can have breaks in between for refreshments. Participants need to receive clear details of where and when the focus group will take place and how long it will last.

DISCUSSION GUIDE

Facilitator's welcome, introduction and instructions to participants

Welcome and thank you for volunteering to take part in this focus group. You have been asked to participate as your point of view is important. I realise you are busy and I appreciate your time.

This discussion is designed to assess your current thoughts and feelings, or experience, about visceral leishmaniasis, a disease that is commonly found in this state. The FGD will take no more than two hours. May I tape the discussion to facilitate its recollection ? (if yes, switch on the recorder)

Anonymity: Despite being taped, I would like to assure you that the discussion will be anonymous. The tapes will be kept safely in a locked facility until they are transcribed word for word, then they will be destroyed. The transcribed notes of the focus group will contain no information that would allow individual subjects to be linked to specific statements. You should try to answer and comment as accurately and truthfully as possible. I and the other focus group participants would appreciate it if you would refrain from discussing the comments of other group members outside the focus group. If there are any questions or discussions that you do not wish to answer or participate in, you do not have to do so; however please try to answer and be as involved as possible.

Ground rules

- The most important rule is that only one person speaks at a time. There may be a temptation to jump in when someone is talking but please wait until they have finished.
- There are no right or wrong answers
- You do not have to speak in any particular order
- When you do have something to say, please do so. There are many of you in the group and it is important that I obtain the views of each of you
- You do not have to agree with the views of other people in the group
- Does anyone have any questions? (answers).
- OK, let's begin

Warm up

- First, I'd like everyone to introduce themselves. Can you tell us your name ?

Introductory question: I am just going to give you a couple of minutes to think about what you know about leishmaniasis or kala-azar, or if you know someone who has kala-azar in the past. Is anyone happy to share his or her experience?

Guiding questions

1. What is kala-azar and what do you think about it? (*causes, transmission, symptoms, prevention…)*
2. When someone is thought to have kala-azar, what does it mean? (*perception of severity of disease, meaning...)*
3. What are the attitudes of you or other people towards the disease? (What did people think/say/do?)
4. If people seek care for VL, to where and why? (Beliefs and thought, preferences for healing/healthcare services, including perceptions of services rendered by different providers: traditional healers, hospital...)
5. What made people go to health centre or hospital? (explore positive or negative perception towards available health care…-though this may imply general health seeking behaviour towards any illness, the focus will remain for VL)
6. What are the main issues around about kala-azar here?
7. What made it difficult to get care on time for VL? (explore accessibility: geographic accounting for seasonal difference, cultural/gender/age, administrative and financial barriers…)
8. Has anyone ever had experience/know of an experience when getting care for VL and want to share that? (either positive or negative, including diagnosis, treatment…)
9. What do you think about the current available care for VL? Or Do you think the current available care for VL is good? If not, why not? (similar questions for outcomes, efficiency, teamwork and communication)
10. What are your thoughts to overcome the challenges regarding this disease? Or are there ways that could have been done to make it easier/better for you? (explore different options i.e. linked to shared barriers before, either for specific aspect or more general…)

Concluding question

- Of all the things we've discussed today, what would you say are the most important issues you would like to express about access barrier to this disease?

Conclusion

- Thank you for participating. This has been a very successful discussion
- Your opinions will be a valuable asset to the study
- We hope you have found the discussion interesting
- If there is anything you are unhappy with or wish to complain about, please contact the local PI or speak to me later
- I would like to remind you that any comments featuring in this report will be anonymous

التحكم بسياق المواضيع وإرشادات للنقاشات الجماعية

مقدمة: هذه الارشادات صممت لإجراء النقاشات الجماعية في دراسة لفهم وجهة نظر المجتمع في التحصل على الرعاية الصحية من هذا المرض في القضارف، والتحديات المصاحبة له. بداية يتم التحصل على دفتر المعلومات و استمارة الموافقة من المشارك ومن ثم يتم إجراء النقاشات الجماعية.

المشاركين: أفراد من المجتمع تم اختيارهم من محلية الرهد والقلابات الشرقية (يمثلون التجمع في منطقتي أم الخير ومستشفى باسنده، على الترتيب)

موافقة المشارك: يقوم المشاركين بتوقيع استمارة موافقة عند المشاركة في النقاشات الجماعية، يجب اعطاء نسخة من استمارة الموافقة للمشارك، النسخة أخرى يحتفظ بها الشخص القائم على النقاشات الجماعية. في حال تسجيل النقاشات صوتياً، سيتم إشعار المشاركين مسبقاً.

معلومات الهيكلة السكانية: من المهم التحصل على معلومات عن الهيكلة السكانية من المشاركين في النقاشات الجماعية، سنقوم باستخدام استمارة تسجيل محتويةً على بعض المعلومات عن الهيكل السكاني يملؤها المشارك (العمر، الجنس، الوظيفة، فترة التواجد في القرية)

المنسق/ المشرف: يكون المشرف شخص مدرب ومؤهل.

إرشادات النقاش: لاحظ ان استخدام هذه الارشادات هو لتسهيل عملية إدارة النقاش عن طريق تحديد المواضيع التي يجب تغطيتها. لا يجب استخدامها حرفياً (مثل الاستبيان)، مع ذلك يجب على المشرف أن يشجع المشاركين على الاسترسال وتغطية المواضيع بعمق لعكس أو توضيح مشاكلهم الفردية.

المكان والزمان: فترة النقاشات الجماعية تتراوح بين 45 إلى 90 دقيقة و يمكن الحصول على فترات راحة لتناول المرطبات، يجب على المشاركين ان يتحصلوا على معلومات واضحة عن مكان وزمان قيام النقاشات الجماعية والفترة الزمنية التي ستستغرقها.

إدارة النقاش: يقوم المشرف بالترحيب، التعريف، و توضيح الارشادات للمشاركين.

مرحباً بكم و نشكركم على تطوعكم في المشاركة في هذه النقاشات الجماعية، تم اختياركم للمشاركة نسبة لأهمية وجهة نظركم، أنا أعلم أنكم مشغولون وأشكركم و أقّر لكم الزمن الذي ستقضونه معنا.

تم تكوين هذه الجلسة لنقاش لتقييم أفكاركم، أحاسيسكم وخبراتكم عن مرض اللشمانيا المعوية، المرض الذي أصبح شائعاً في المنطقة، هذه النقاشات الجماعية لن تستغرق أكثر من ساعتين، هل تسمحون لي بتسجيل النقاش لتسهيل عملية جمع المعلومات لاحقاً؟ (إذا كانت الإجابة بنعم، قم بتشغيل جهاز التسجيل).

السرية: على الرغم من النقاش مُسجّل، أود أن أوضح لكم أن النقاش سيحصل على سرية تامة، سيتم التحفظ على أشرطة التسجيل في مكان مغلق إلى حين تدوين الحوار كلمة بكلمة، وثم سيتم التخلص منها، الحوار المستخلص من أشرطة التسجيل سيكون مبهما بحيث لا يمكن ربط أي شخص بأي عبارة في النص، نرجو أن تكون إجاباتكم و ملحوظاتكم على أعلى مستوى ممكن من الدقة والصدق. كل المشاركين يتمنون عدم البوح بما قيل داخل النقاشات الجماعية لأشخاص من خارج مجموعات النقاش. في حال وجود سؤال لا تريد الإجابة عنه لك مطلق الحرية في عدم الرد، لكن نود منكم الإجابة لطفاً.

القواعد الأساسية:

* أهم قاعدة هي أن لا يتكلم أكثر من شخص سوياً، قد يجذبك أحيانا النقاش للرد اللحظي، لكن رجاءً انتظر حتى ينتهي المتحدث من حديثه.
* لا توجد إجابات صائبة أو إجابات خاطئة.
* لا يوجد ترتيب معين للتحدث.
* عندما يكون لديك شيء تريد قوله الرجاء عدم التردد في قوله، يوجد العديد من الأشخاص في النقاش الجماعي، وأريد معرفة وجهة نظر كلٍ منكم.
* لا يتوجب عليك الموافقة على آراء الآخرين.
* هل يريد أي أحد منكم طرح أي سؤال؟ (أجب عليها).
* حسناً، لنبدأ.

بداية:

* أولاً أريد أي شخص منكم أن يعرف عن نفسه. الرجاء إخبارنا اسمك.

سؤال البداية:

بداية سأعطيكم دقيقتين لتفكروا في مرض الكلازار، أو معرفتكم بشخص أصيب بمرض الكلازار مسبقاً، هل يوجد أحد مستعد لمشاركة تجربته.

اسئلة توجيهية:

* ما هو الكلازار، وما رأيك فيه؟ (الأسباب، الانتقال، الأعراض، الوقاية منه ...).
* عندما تعتقد أن أحد ما مصاب بالكلازار، ماذا يعني ذلك؟ (مدى خطورة المرض، المعنى)
* ما هو سلوكك أو سلوك غيرك تجاه المرض؟ (بماذا يفكر الناس، ماذا يفعلون و ماذا يقولون)
* إذا أراد الناس التحصل على الرعاية من مرض الكلازار، إلى أين يذهبون، ولماذا؟ (المعتقدات والآراء، تفضيلات الخدمات العلاجية و المنشآت، متضمناً فهم الخدمات التي يقدمها مزود صحي آخر، علاج بلدي، مستشفى ...).
* لماذا ذهب الناس إلى المركز الصحي أو المستشفى؟ (استرسل معه في فهم النواحي الإيجابية والسلبية في الخدمات الصحية الموجودة، قد تكون الإجابة عامة لأي مرض، خصص النقاش حول مرض الكلازار).
* ما هي المشاكل الأساسية بالنسبة لمرض الكلازار هنا؟
* ما هي الصعوبات في التحصل على علاج الكلازار في الزمن المناسب؟(ناقشه في طرق الوصول، الحالة الجغرافية مع اعتبار التغيرات الموسمية، الثقافة/ العمر/ الجنس، معوقات إدارية أو مالية).
* هل يوجد أحد منكم لديه تجربة في البحث عن الرعاية من مرض الكلازار أو يعرف تجربة شخص ما؟ (سواءً كانت سلبية أو إيجابية، متضمناً التشخيص/ العلاج ...).
* ما رأيك في المستوى الحالي للرعاية من مرض الكلازار؟ أو هل تظن أن المستوى الحالي للرعاية من الكلازار يعتبر جيداً؟ وإذا لم يكن جيداً لماذا؟ (اطرح نفس الأسئلة عن النتائج، الكفاءة، العمل الجماعي والتواصل).
* ما هي أفكارك لتخطي التحديات بالنسبة لمرض الكلازار؟ أو هل هناك طرق أخرى لو اتُّبعت لأدت لنتائج أفضلو أسهل؟ (ناقش الخيارات المتعددة، أي أنها مرتبطة بالمعوقات السابق ذكرها، إما بالتحديد أو عموما).

سؤال ختامي:

* بعد النقاش الذي قمنا به اليوم، في رأيك، ما هي أهم المشاكل التي تعتبر من المعوقات للتحصل على الرعاية الصحية من مرض الكلازار؟

ختاماً:

* شكرا جزيلاً على مشاركتكم، وقد كان نقاشاً مثمراً.
* تعتبر آراؤكم ذات أهمية عالية في الدراسة.
* نأمل أن تكونوا قد وجدتم النقاش مفيداً.
* إذا كان هناك أي أمر يزعجك أو تريد أن تشكي منه، الرجاء التواصل مع الباحث المحلي أو التحدث معي لاحقاً.

* أريد أن أذكركم بأن أي ملحوظة في هذا التقرير ستكون مجهولة الهوية

3.2 ARTICLE 6

Exploring global and country-level barriers to an effective supply of leishmaniasis drugs and diagnostics in eastern Africa: a qualitative study

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Exploring global and country-level barriers to an effective supply of leishmaniasis medicines and diagnostics in eastern Africa: a qualitative study

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ABSTRACT

Objectives To understand stakeholders' perceptions of the access barriers to quality-assured diagnostics and medicines for leishmaniasis in the high-burden region of eastern Africa, and to identify key bottlenecks to improve the supply of commodities for neglected tropical diseases.

Design Desk reviews and qualitative in-depth interview study with purposive sampling.

Methods A landscape analysis through literature and desk review was performed. Next, 29 representatives from international organisations, non-governmental agencies, national control programmes from six countries (Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda) and manufacturers were interviewed between May and July 2018. Participants were selected purposively and expanded through a snowballing technique. Data analysis was aided by NVivo, applying the framework method as a part of the thematic content analysis approach.

Results The barriers along the visceral leishmaniasis (VL) supply chain were identified as emerging themes, grouped across supply chain activities and health systems component(s). Stakeholders expressed the perception of progress, but bottlenecks persist. VL medicines, in general, lack multisource production capacity and with small market volume, expansion of suppliers is difficult. Procurement is plagued by forecasting difficulties, complex regulatory policies and procedures, and distribution challenges. Weak communication and coordination across different levels resulted in shortages and loss of trust among different actors. Cross-cutting issues spanned from limited political and resource commitment due to low awareness and limited in-country capacity. However, study respondents were optimistic to pursue several remedies, most importantly to build bridges between supply and demand sides through continued dialogue and collaborations. Diagnostics supply has mostly been overlooked; thus, improved investment in this area is needed.

Conclusions Addressing supply barriers in eastern Africa requires consistent, specific efforts at the global and national levels, progressing from current partnerships and agreements. Priority actions include pooled procurement, improved forecast, and increased commitment and resources. Sustainability remains an elusive goal, yet to be integrated into discussions moving forward.

Strengths and limitations of this study

- ► We synthesised perspectives from stakeholders of the healthcare sector only in the interviews, and manufacturers of visceral leishmaniasis (VL) diagnostic tools were not reached.
- ► Although important, the country-specific barriers could not be elaborated and quantified in detail as they are beyond the scope of this paper.
- ► As with any qualitative research, there is a possibility of recall and interviewer bias, but we mitigated this through triangulation with the desk reviews and the authors' experiences.
- ► The strength of the study is the qualitative method to document the multifactorial barriers of the supply chain of an neglected tropical disease in eastern Africa.
- ► The comprehensive global and national scope of this study is critical to devise policies and strategies to improve access to VL commodities in eastern Africa.

INTRODUCTION

Ensuring access to essential commodities for neglected tropical diseases (NTDs) is challenging. Diagnostic and therapeutic options for these conditions are limited due to the insufficient investment in research and development.[1 2] Moreover, even when affordable and effective treatments exist, they may not reach the patients in endemic, resource-poor settings.[3]

One of those NTDs is visceral leishmaniasis (VL), or kala-azar, caused by a protozoan parasite of the *Leishmania* species and transmitted by sandflies. The annual global incidence is 50 000–90 000 cases, with 90% reported from Brazil, India, South Sudan, Sudan, Ethiopia, Kenya and Somalia.[4] Eastern Africa region showed an increasing VL prevalence in the last few years, contrasting with decreased caseload on the Indian subcontinent where VL elimination as a public health problem is

Table 1 Overview of current medicines for visceral leishmaniasis

INN	Manufacturer	Unit, administration	Price information per unit*	Limitations
Sodium stibogluconate	Pentostam (Glaxo Smith Klein) Generic: Albert David, India	30 mL vial of 100 mg/mL, IM/IV	Generic: US$8.78/vial†	Toxicity +++ (cardiotoxicity, pancreatitis, nephrotoxicity/ hepatotoxicity); painful injections, prolonged treatment. Resistance (South-East Asia)
Meglumine antimoniate	Glucantime(Sanofi), France	5 mL vial of 81 mg/ mL, IM/IV	WHO-negotiated price: US$1.2/vial	As above
Amphotericin B deoxycholate	Fungizone (Bristol Meyer Squibb) Generic companies	50 mg vial, IV	Variable, ~US$ 7.5 per 50 mg vial	Nephrotoxicity +++, infusion-related fever, prolonged treatment
Liposomal amphotericin B	AmBisome: Gilead Sciences	50 mg vial, IV	WHO-negotiated price: US$16.25‡ Market price US$105–200	Slow IV infusion, heat stability: requires cold chain§
Miltefosine	Impavido: Knights Therapeutics	50 mg and 10 mg capsule, PO	€100–150¶ per pack of 56 caps	Gastrointestinal toxicity, teratogenicity
Paromomycin	Generic: Gland Pharma, India	2 mL vial of 375 mg/ mL, IM/IV	WHO-negotiated price: €1.3/vial	Nephrotoxicity/hepatotoxicity, ototoxicity

*Data provided during meeting with suppliers during sixth World Congress of Leishmaniasis (May 2017).
†Data from IDA quote.
‡This price was offered in 2014, while in 2016 LAMB donation programme expanded for selected countries in the Indian subcontinent and East Africa.
§According to manufacturers' brochure, stable up to 25°C since 2014.
¶Price only valid for selected governments, United Nations organisations and non-governmental organisations: WHO, PAHO, MSF and DNDi.
DNDi,Drugs for Neglected Disease initiative; IDA, International DIspensary Association; IM, intramuscular; INN, International Non-proprietary Name; IV, intravenous; MSF, Médecins Sans Frontières; PAHO, Pan American Health Organization; PO, per oral.

underway.[4 5] Outbreaks, compounded by conflicts, population displacement, drought and malnutrition hamper control efforts.[6–8] VL places a significant economic burden on patients and their families, often the poorest and most marginalised.[9 10] Without treatment, VL is fatal, and as vector or reservoir control is not feasible in this context, early diagnosis and treatment continues to be the cornerstone of VL control strategy.[11]

In this context, reliable supply of VL medicines is vital. However, the therapeutic toolbox is constrained by variable effectiveness in different regions, poor safety profile, stability and cost[12] (table 1). Since the 1940s until very recently, pentavalent antimonials—sodium stibogluconate (SSG) and meglumine antimoniate (MA)—were the mainstay of treatment. Other drugs are miltefosine (MF; the only oral formulation), paromomycin (PM; a broad-spectrum antibiotic), and amphotericin B deoxycholate and its lipid formulations, including the liposomal amphotericin B (LAMB). Combination regimens have gained prominence over monotherapy, as they reduce resistance risk and treatment duration, for a better safety profile and at a lower cost.[13] In VL endemic countries in eastern Africa, the first-line treatment regimen is SSG/PM combination for 17 days, an improvement on the previous 30-day treatment with SSG but still quite long and doubling the painful daily injections.[14 15] LAMB is reserved for severely ill patients or those with contraindications for SSG/PM,[16–18] and also for HIV co-infected patients.[19] The efficacy of treatment varies geographically, for example, the single dose LAMB used as the first-line regimen in the Indian subcontinent is less effective in eastern Africa.[20 21]

The availability of a rapid diagnostic test (RDT) for VL in the mid-2000s, requiring minimal equipment and training, and providing rapid results within 20 min, has made diagnosis simpler at primary healthcare facilities, although roll-out within national programmes were gradual. Other methods such as the direct agglutination test (DAT) and tissue aspiration are more appropriate for use in hospitals. The rK39-antigen-based RDTs are less sensitive in Africa than in Asia,[22 23] yet their advantages as point-of-care tests make them an essential tool for.the national control programmes.

VL diagnostics and medicines need to be continuously available, affordable and accessible to the health systems and all patients. A functioning supply chain is imperative, but it can be influenced by various factors at multiple levels.[24] Availability is determined by the manufacturing capacity of the single or few producers. Unfortunately, poor needs' assessment, sub-optimal stock planning and management, and complex procurement procedures often lead to shortages at health facility level.[25] Forecasting or quantification of needs relies mainly on past consumption data; but the VL caseload can vary considerably from year to year, such as when a VL outbreak occurred in South Sudan in 2012.[7] In some countries,

public and private not-for-profit entities, including non-governmental organisations (NGOs) coexist as procurers and, in the absence of coordination, may duplicate efforts. In eastern Africa, VL medicines and diagnostics are mostly provided for free to the patients in the public and non-profit sector yet remains expensive and limit availability for national programmes. Frequent stock-outs deter patients from seeking timely care and frustrate healthcare workers.[26 27]

Despite the increased awareness about the importance of access to essential medicines in general, NTDs, including leishmaniasis, are still neglected. Strengthening of commodity supply chains has often been limited to HIV, tuberculosis, malaria or other priority programmes.[28–30] For NTDs, studies on availability and access have mainly focused on those that are amenable to mass drug administration, and those mostly rely on large donation programmes.[31 32] In the era of universal health coverage, access to quality-assured medicines and diagnostics for VL must be enhanced, particularly for the eastern Africa region. We conducted this study to document key barriers to sufficient supply of VL diagnostics and medicines, from the perspective of stakeholders at global and national levels from Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda.

METHODS

Analytical framework

Access refers to people's ability to obtain and use quality health products or technology when they are needed. We interpreted access, not as a single event but as a continuous process involving a series of activities and actors over time. We adopted the access framework from Frost and Reich[33 34] which encompasses four key elements (affordability, availability, quality and adoption), and three overarching elements from the health system's perspective (coordination, financing and legislation).[35] We defined the supply chain as an ecosystem of organisations, people, technology, activities, information and resources that come together to ensure the most efficient delivery of the product from the point where it is manufactured to the end user, the patient.[36] We broke down the key steps of the supply chain into six main activities (figure 1).

Study design

The study consisted of two parts: first a policy analysis of the access landscape at global and country level through desk reviews, and second, mapping of supply barriers through in-depth interviews (IDIs) of key stakeholders at the global and national levels. The literature covered both peer-reviewed and grey literature, in the field of VL supply in eastern Africa (ie, Ethiopia, Kenya, South Sudan, Somalia, Sudan and Uganda). The online sources included PubMed, Web of Science, Eldis, Google and Google Scholar. Grey literature included national policy documents or guidelines, WHO published information, reports and meeting records. The desk review was conducted between November 2017 until April 2018.

For the second part, we employed a qualitative research method through IDIs with individual key informants. Purposive sampling was chosen to ensure maximum depth and variation of information and was furthered with snowball sampling. Participants for IDIs consisted of representatives of three categories: (1) global stakeholders, that is, multilateral organisations, non-governmental organizations (NGOs), donors and procurement or distribution agencies; (2) manufacturers of leishmaniasis medicines and (3) country stakeholders, consisting of civil servants of the Ministry of Health (MoH), national programmes or in-country implementing partners.

The purpose of the study was introduced to all participants by email or phone. Informed consent was obtained from all participants before the interviews began. The principal investigator (TS), who is trained in qualitative research methodology, conducted all IDIs. Interviews were done face-to-face, by telephone or Skype and conversations were, after the consent, recorded on a digital voice recorder. Semistructured topic guides were piloted and then used to guide the IDIs, and additional items were included as data collection progressed (see the online supplementary information 1a,b). The IDI lasted on average 60 min (range: 45–90 min). Data collection continued until saturation was reached and no new

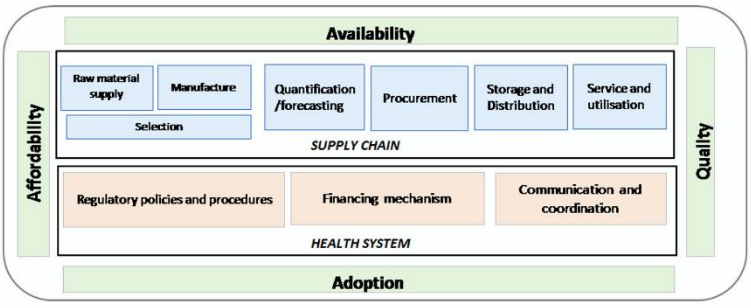

Figure 1 Conceptual framework of supply chain within access.

information emerged. All interviews were conducted in English.

Data management

Recordings from the interviews were transcribed verbatim by a professional transcriber, with quality supervision by TS. TS and JP independently reviewed and analysed the data using the framework method analysis.[37] This method is used to organise and manage research through the process of summarisation, resulting in a robust and flexible matrix output which allows the researcher to analyse data both by case and theme.[38] Following the thematic content analysis approach,[39 40] we identified themes through careful reading and re-reading of the data, and the emerging patterns and themes became the categories for analysis. Using the analytical framework displayed in figure 1, we applied a broad deductive approach using pre-defined codes but allowed some open coding to ensure the essential aspects of the data were not missed. We classified, compared and charted the data into a framework matrix (see the online supplementary information 2). The charting involved summarising the data by the profile and role of the stakeholder(s) from each transcript, which included the review and comparison of data, across and within matrices. We used NVivo V.12 software (QSR International, Melbourne, Australia) to facilitate data management during analysis.

Ethical statement

This study is part of a research project for which we obtained ethical approval from the Institutional Review Board of the Institute of Tropical Medicine-Antwerp 1209/17 5IRB/AB/AC/181). Participants in IDIs provided consent and confidentiality were guaranteed. Quoted information was anonymised during the analysis and reporting.

Patient and public involvement

This study is part of a larger research project on access to care for leishmaniasis in Africa (http://www.euroleish.net), and the research question was informed by the experience of patients' and healthcare workers' who often face the reality that the medicines and diagnostics are not available. Access barriers from patients' perceptions have been published previously,[26] but there is a critical gap in the barriers from the actors involved in providing care, therefore this stakeholders' study. The results will be shared with the study participants and policy-makers through communication and advocacy actions, in order to increase awareness and improve the effective supply of commodities for this fatal disease.

RESULTS

Key findings from the desk review are summarised in table 2, while the online supplementary information 3 shows a diagram of the VL pharmaceutical supply system in each country. The online supplementary information 4 provides a list of abbreviations. For the second part, we conducted a total of 29 IDIs (table 3). Respondents from the country represented Ethiopia, Kenya, Somalia, South Sudan, Sudan and Uganda.

Reported barriers along the supply chain in VL endemic countries in eastern Africa

Respondents opinions on the barriers within the supply chain activities framework (figure 1), which apply to both VL medicines and diagnostics unless stated otherwise, were documented.

Barriers in manufacturing VL medicines and diagnostics

The manufacturers of the finished pharmaceutical products (VL medicines in table 1) depend on outside suppliers of active pharmaceutical ingredients (API) (eg, Gland Pharma has to order API from Italy to make PM, and Knight's source of API is in Switzerland), which can affect the lead delivery time. In some cases, the same company that produces the finished product may also produce the API (eg, Albert David for SSG), reducing the delay. However, the manufacturers explained that lines of production have been designed to produce only certain quantities (ie, one batch, eg, 8000 vials for SSG, 70 000 vials for PM and 200 000 capsules for MF). This minimum order quantity may pose difficulties for procurers and prolong the delivery time.

> *"Access for us is volumes and forecasts. If we do not have a proper forecast, it is hard to schedule productions. It takes a lead time in between the moment we intend to produce, and the moment it is available for shipment. This time cannot be shortened with different requirements regarding the quality of the API, the active ingredient, and the rest of the chain."* (IDI, manufacturer)

The development of all current VL medicines (AmBisome, SSG, PM and MF) was based on partnerships between industry and the public sector, at least for part of their development history. Although this has created a certain 'familiarity' between stakeholders and each manufacturer, it was felt insufficient to bridge the gap between the commercial mindset and public health needs. The diversity in company profiles and policies resulted in different 'access' strategies: donation in the case of AmBisome or tiered pricing in the case of MF. Respondents expressed concern that the shrinking market due to the declining caseload in South Asia may lead companies to halt production. VL medicines constitute a relatively small segment in the companies' portfolio, and without market incentives, ceasing production is a plausible scenario. Nevertheless, all industry representatives expressed their commitment to continue producing VL medicines, as an expression of corporate social responsibility or from an altruistic motive. Similarly, for diagnostic tools, respondents considered the limited number of sources for purchase of rK39 RDT to be especially problematic given that these RDTs are in the front line of every country's diagnostic algorithm.

Table 2 Dashboard of the visceral leishmaniasis pharmaceutical management in endemic countries in eastern Africa

	Ethiopia	Kenya	Somalia	South Sudan	Sudan	Uganda
Endemic areas	6 out of 9 Regions	6 out of 47 counties	14 out of 90 districts	28 out of 86 counties	27 out of 187 localities (in 12 states)	52 out of 146 counties
Population at risk in 2015*	3 168 835	3 268 626	2 337 787	2 034 944	8 696 636	No data
VL cases per year (estimate)†	3700–7400	610–1200	1400–2700	15 700–30 300	7400–14 200	350–520
VL cases reported in 2016‡	1593	692	911	4175	3810	35
National VL guidelines (last update)	Yes (2013)	Yes (2017)	Yes (2012)	Yes (2011)	Yes (2016)	Yes (2019)
First-line medicines for VL§	SSG, PM	SSG, PM, MA	SSG, PM	SSG, PM	SSG, PM	SSG, PM
Second-line medicines for VL¶	LAMB, MF, PM	LAMB, Amph B	LAMB	LAMB	LAMB, Amph B, MF	Amph B, LAMB, MF
VL medicines for special groups**	LAMB	LAMB	LAMB	LAMB	LAMB	LAMB
Diagnostics for VL in the guidelines††	rK39 RDT, DAT, microscopy	rK39 RDT, DAT, microscopy	rK39 RDT, DAT, microscopy	rK39 RDT, DAT, microscopy	rK39 RDT, DAT, microscopy	rK39 RDT, DAT, microscopy
VL medicines in National Essential Medicine List	MA, SSG, LAMB, MF	None	SSG	SSG, PM, MF, Amph B	SSG, PM, MA, Amph B, LAMB, pentamidine	SSG, PM, Amph B
VL medicines registered in the country	PM, (SSG submitted)	SSG, PM	NA	NA	SSG, PM	SSG, PM
National leishmaniasis control programme	Yes, since 2006	Yes, since 2012	Not available	Not available	Yes, since 2012	Not standing alone
Health facilities with VL diagnosis and treatment provision (2016)	22 Facilities‡‡	18 Health facilities	3 Health facilities	38 Health facilities¶¶	44 Hospitals	1 Hospital
Treatment provided for free in public sector§§	Yes	Yes	Yes	Yes	Yes	Yes
National medicine regulatory authorities	FMHACA	PPB	NA	DFCA	NMPB	NDA
Procurement agencies involved in the supply of VL commodities	PFSA	KEMSA; CHMP	No centralised body but for VL through WHO	No centralised body, but for VL through WHO and international NGOs	NMSF, formerly CMS	NMS
NGOs involved in VL control	MSF, KalaCORE consortium (with implementing partners – Amigo da Silva)	DNDi	International SOS	MSF, KalaCORE (IMA World Health as implementing partner)	MSF, DNDi, KalaCORE (WHO as implementer)	DNDi

*Data from 2015 WHO Country Profile on leishmaniasis, available at http://www.who.int/neglected_diseases/news/New_leishmaniasis_country_profiles_based_on_routine_surveillance/en/.
†Estimate from Alvar *et al*, 2012 based on WHO data since 2008.
‡Data from WHO Global Surveillance of Leishmaniasis, available at http://www.who.int/leishmaniasis/resources/who_wer9340/en/.
§First-line for all the countries is combination regimen of SSG/PM for 17 days.
¶Second-line medicines are meant to treat patients not responsive to first-line treatment (eg, relapses).
**These special groups are listed as: pregnant women, children <2 years old, age >45 years, HIV-infected patients, or those contraindicated for first line.
††Diagnostic algorithm in the countries' guidelines is similar. Currently, a national essential diagnosis list not yet existed, similarly the regulatory pathways for diagnostics as 'medical device' are unclear.
‡‡Ethiopia has 22 facilities, including a refugee camp in Gambella where MSF is present. (source: MSF and KalaCORE).
§§Despite official free diagnosis and treatment, patients and household still have to pay other non-medical costs, notably transport, hospitalisation and food.
¶¶South Sudan has 38 facilities that are receiving full support (supplies, supervision and on-site mentorship) and another 8 that are receiving more indirect support (source: KalaCORE).
Amph B, conventional amphotericin B deoxycholate; CHMP, Centrale Humanitaire Medico – Pharmaceutique; DAT, direct agglutination test; DFCA, Drugs and Food Control Authorities; DNDi, drugs from neglected diseases initiative; FMHACA, Food, Medicine and Health Care Administration and Control Authority; KEMSA, Kenya Medical Supplies Authority; LAMB, liposomal amphotericin B; MA, meglumine antimoniate; MF, miltefosine; MSF, Médecins Sans Frontieres; NA, No information; NDA, National Drug Authority; NGO, non-governmental organisation; NMPB, National Medicine and Poisons Board; NMS, National Medical Stores; NTD, neglected tropical disease; PFSA, Pharmaceutical Fund and Supply Agency; PM, paromomycin; PPB, Pharmacy Poisons Board; RDT, rapid diagnostic tests; SSG, sodium stibogluconate; VL, visceral leishmaniasis.

Table 3 Overview of resource-persons interviewed

Level	Profile	Number
Global	Multilateral organisations	2
	Donor	2
	NGOs	4
	Distributor/procurement agencies	4
	Manufacturers	5
National/country	MoH/Leishmaniasis National Control Program	6
	Implementing NGOs	6
Total		29

MoH, Ministry of Health; NGO, non-governmental organisations.

"There are stock outs due to unexpected emergencies, but also due to the issue of the one-source suppliers. Either that they could not finish and get the batch in time, the production batch was later than promised and anticipated or that quality issues with a batch. That is the whole problem with the single supplier issue." (IDI, NGOs)

Barriers in medicine/diagnostics selection and forecasting

The list of VL commodities in eastern Africa is short with only a handful of manufacturers. The main repertoire of medicines consists of SSG, PM and AmBisome, whereas MF has been used only for VL/HIV co-infection (ie, in Ethiopia). The MF+PM combination is currently undergoing clinical trial (ClinicalTrials.gov NCT03129646). At the global level, the quality-assured sources of these drugs are scarce, and in most cases limited to a single source. For example, AmBisome (Gilead Sciences, Inc, San Dimas, CA) is the only lipid formulation of amphotericin B approved by a Stringent Regulatory Authority (SRA), the current regulatory standard to guarantee product quality. Generic SSG and PM are produced by two Indian companies (Albert David and Gland Pharma), both expressing their willingness to continue producing based on public health needs. For diagnostics, the DAT antigen is only available from two academic centres, ITM in Antwerp, Belgium and the Academic Medical Center of the University of Amsterdam, the Netherlands. For the rK39 RDT, the two widely used brands in eastern Africa are Kalazar Detect (InBios) and IT-Leish (previously DiaMed AG, now BioRad Laboratories). In Sudan, the import of some RDTs was restricted because of economic sanctions by the USA. Respondents expressed the need to improve on the suboptimal performance of rK39 RDTs in eastern Africa, acknowledging that this optimisation will take time, while other tests (rK16, rK28) are still under evaluation.

All stakeholders concurred that consolidating demand, in the form of forecasting, is the critical issue to ensure availability.

"The forecasting is done by people, not by the machine." (IDI, Multilateral organisation)

"Even the historical data is difficult to use in a situation like kala-azar." (IDI, Distributor)

Data on past consumption determine the quantities being ordered at the health facility level, with a centralised buffer stock deemed necessary to compensate for the fluctuating caseload. In the context of health system devolution such as in Kenya, coordination for a common country forecast is even more challenging.

"The health centre may see only 10 people because after 2 weeks of rupture in drugs, nobody came. But the next month they only ordered the same… inability to have a constant supply also limits their knowledge on the number of cases, because they don't record the case that they weren't able to treat." (IDI, NGO South Sudan)

Furthermore, reporting quality is considered as not yet satisfactory (eg, due to delay, lack of dedicated staff, weak stock management or unreliable data), despite increase support on surveillance and effective communication at different levels. A 'push' mechanism—sending medicines to hard-to-reach facilities or in anticipation of cut-off access in the rainy season—is done pragmatically, for example in Sudan and South Sudan.

From the manufacturers' perspective, the forecasted demand is welcome information, yet results in frustration when not all predictions are translated into real orders. A 'single entity' holding all actors in the supply chain accountable would be welcome.

Barriers in VL medicine/diagnostic procurement process

In all countries, a vertical commodity supply system for VL exists, that is parallel to and separate from the procurement and supply of essential medicines. Purchasers from the public sector and not-for-profit NGOs involved in VL control can place an order directly to the manufacturer or a procurement agency (see figure 2). A private market for these commodities is non-existent. The centralisation of orders can take place, meaning a 'leading' actor keeps an overview of needs, orders and stock at the country or regional level, but such coordination mechanisms depend on specific funding contexts.

"Yes, we buy our own drugs and diagnostics, not to be dependent on vulnerable supply lines from the national system or from others." (IDI, Country NGO)

Centralised supply management by WHO is currently in place for the AmBisome donation programme in the six countries. WHO also manages the procurement of SSG and PM in all except Uganda (where this is taken care of by Drugs forNeglected Diseases *initiative* (DND*i*)). WHO supplies VL commodities to all NGOs working with VL in Kenya, Somalia, and South Sudan, except Médecins Sans Frontières (MSF) and DND*i*. The latter organisations procure independently for their projects in Ethiopia, Sudan, Kenya and Uganda, as there are no

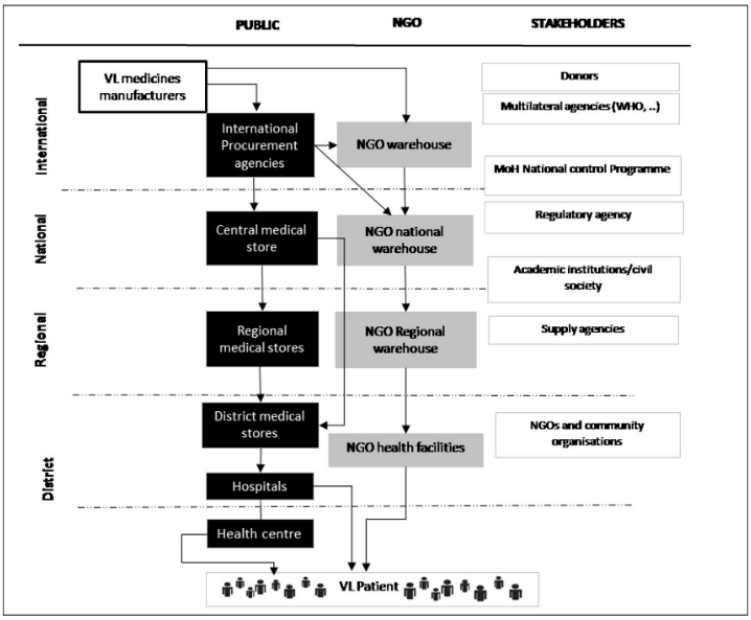

Figure 2 Procurement and distribution network of leishmaniasis diagnostics and medicines in the eastern Africa region. NGO, non-governmental organisation; VL, visceral leishmaniasis.

other NGOs involved in VL. A decentralised process was tried in 2017, in which WHO country offices, in coordination with National Control Programmes, managed the procurement. However, long delays ensued due to lack of awareness about the long lead time for SSG and PM delivery, especially as the orders were not submitted in time and the volumes were too small. Many respondents perceived the procurement process as frustrating:

> "*They are not able to change the situation very quickly; they say no, the drugs are in customs or waiting for customs clearance. Sometimes orders are blocked on the path from the health centre to the regional, or federal level. It is this procedure and the fact that the kala-azar drugs are not part of the normal procurement cycle.*" (IDI, donor)

VL diagnostics are usually procured together with the medicines, though national programmes or implementation agencies face more difficulties in identifying the right channels to contact the manufacturers. Certain specific issues were raised by the participants, such as the short shelf life of the RDT, which had impeded importation, as procedures require a certain remaining shelf life. Different country regulations regarding diagnostics could obstruct receiving a donation when there was a shortage, such as was the case in 2017/2018 in South Sudan. Registration of diagnostic tests in-country is often problematic, and some companies impose a minimum purchase order and require registration as a buyer.

Barriers to the distribution of VL medicines/diagnostics

Distribution and delivery of VL medicines are generally done separately through a vertical programme in the public sector (figure 2), without 'integration' into the general supply of essential medicines (Central Medical Store or equivalent mechanisms). However, a certain degree of logistic integration takes place, for example, distribution of VL commodities follows the national supply agency schedule in certain states in Sudan. Health-facility level stock-outs occur regularly and require impromptu solutions, for example, the dispatch from other VL centres nearby or from central facilities. Long lead or delivery times are reported frequently, though reasons given for this ranged from bureaucracy or lack of communication, for example, lower levels not knowing about existing stock at the regional level, or *vice versa*. Shortages have invariably been reported, with the notable example the big stock-out during the 2012–2014 outbreak in South Sudan.

> We do not get forward planning and predictions, and suddenly everybody starts saying: Oh, you are out of stock!(IDI, MoH)

Respondents considered the lack of stable funding for the management of medium and long-term stocks of VL medicines as the main factor that negatively affects availability. These barriers inevitably also applied to diagnostic devices, especially with regards to cold chain

requirements which complicate adherence to good distribution practices. Logistic challenges such as the rainy season, lack of roads and transport delays are common, especially in South Sudan where the infrastructure is extremely limited. The cost of distribution is high if the only options are small aircraft or airdrops. Respondents describe the management of transportation and storage as challenging, especially in tropical contexts where the temperature often exceeds 25°C (the limit for AmBisome) or 30°C, for RDTs.

Reported barriers in the health system affecting the VL commodities supply chain

Legislation: barriers in regulatory procedures and policies for VL medicines and diagnostics

The regulatory requirements for granting a marketing authorisation (or registration) to medicines varies from country to country, and not all VL medicines are yet registered where they are used. Also, the registration process can be inefficient; for instance, in Sudan and Ethiopia, the registration process for SSG and PM took years, and SSG registration is still pending in Ethiopia. Medicine registration involves a complex regulatory pathway and is the jurisdiction of the national medicines regulatory authorities (NMRAs). The manufacturers are responsible for submitting the registration dossier to the NMRAs; unfortunately, there are little or no commercial incentives to do so when there is no profitable private market.

> "*Registration comes at a cost, so if you do not have the commercial value, then you wonder why you want to invest that time and money into that.*" (IDI, Multilateral organisation)

> "*If the private market, for some reason, we are providing a decent number that could justify registration then we would look into it. But the truth is that that is not the case anywhere, because this disease is mainly in countries with low income.*" (IDI, Manufacturer)

The registration process may be costly and labour-intensive, further lessening the appeal. Technical and financial support from international agencies such as the IDA Foundation and DND*i* has been crucial in registering SSG and PM in Sudan and Ethiopia.

In reality, respondents reported that VL medicines that are listed in a country's Essential Medicine List and recommended in the national guidelines could be granted a special import authorisation, despite not (yet) being formally registered. In the long term, the respondents agree that registration is crucial, as it is the best way to guarantee that the quality of the product has been duly evaluated and approved by the National Regulatory Authority. Harmonisation of regulations across NMRAs in different countries is desirable as harmonised inspections and registration dossiers would mean a significantly reduced cost for meeting registration requirements. Different regulations in labelling and quality requirements had complicated importation in the past. The regulatory pathways for RDTs, which some consider as 'medical devices', are an area that is currently being overlooked, with unclear procedures on registration and utilisation. Some respondents raised the issue of the lack of a quality-assurance mechanism.

> "*Some countries tend to overshoot with the regulations…you have to balance the registrations against what is needed, there's a gap, and they [countries] don't have the capacity. Leishmaniasis is a very limited disease in fact, so it is easy to ask all of these requirements, but there's a mismatch about the time frame and the cost of the registration and what is immediately needed.*" (IDI, NGO)

Ensuring the quality of VL medicines was deemed to be a priority by the respondents. Currently, only AmBisome and Impavido (MF) have been authorised by an SRA, while neither generic SSG nor PM are prequalified by any SRA nor by the WHO Prequalification Programme (WHO PQP). In 2016, both generic manufacturers of SSG and PM obtained time-limited positive advice from WHO's Expert Review Panel (https://extranet.who.int/prequal/sites/default/files/documents/73_ERP_Feb2019.pdf), which is a mechanism designed to help identify quality products to meet urgent demands, based on a careful risk assessment. However, stringent approval or prequalification should be aimed for in the long term. Respondents stated that the limited awareness of these processes, including the recent WHO Collaborative Registration Process across various stakeholders, is a barrier. The respondents expressed the need for these mechanisms to be more widely shared, advertised and communicated. More efforts to engage with VL medicines manufacturers, for example, in responding to invitations for expression of interest on the WHO PQP website, are recommended by study respondents. SSG and PM were included in the 2015 call, and LAMB and MF were added in 2017.

Barriers to the financing of VL supplies

All respondents stressed the fact that VL is still neglected at the country level, despite the creation of national working groups or task forces, such as in Kenya or Sudan. Political commitment beyond MoH lacks in all the VL endemic countries, especially when it comes to financing or budget allocation. The responsibility of the MoH for these NTDs is not fully realised when external partners bring in the medicines and diagnostics. None of the countries is currently procuring VL commodities by themselves independently.

Moreover, the respondents pointed out that as VL usually clusters in a few and generally remote regions of a country, policy-makers in the capital lack awareness of the disease. Clinical and diagnostic skills are equally concentrated in towns and not freely available in the VL-affected areas. Capacity strengthening is jeopardised by the high turnover of health staff, both in clinical duties and in control programmes. For most of the respondents, the unsustainable funding mechanisms, even for the medium term, limits the reach and scope of VL control

Table 4 Price per visceral leishmaniasis treatment per course

Current treatment regimen used in eastern Africa	Treatment duration (days)	Medicine cost in US$* for 35kg patient¶
SSG 20 mg /kg/day + PM 15 mg/kg/day	17	42–51
SSG 20 mg/kg/day†	28–30	61
PM 15 mg/kg/day†	21	19
Other regimen used elsewhere‡	**Treatment duration in days**	**Medicine cost in US$* for 35kg patient¶**
LAMB 10 mg/kg	1	113
MF 100 mg/day	28	114–160§
LAMB 5 mg/kg+MF 100 mg/day	8	103
LAMB 5 mg/kg+PM 15 mg/kg/day	11	67
MF 100 mg/day+PM 15 mg/kg/day	10	73

*Exchange rate through http://www.xe.com on 05 December 2018; an Estimated average weight of an African VL patient.
†Monotherapy not used any more, here provided for comparison.
‡Price of LAMB is based on access price US$16.25 per 50 mg vial. In reality, AmBisome is now provided by donation which started in 2011 through WHO until 2021.
§Price quoted by Knight Therapeutics for purchase by non-profit organisations MSF.
¶ Estimated average weight of a VL patient from Africa
LAMB, liposomal amphotericin B; MF, miltefosine; MSF, Médecins Sans Frontières; PM, paromomycin; SSG, sodium stibogluconate.

programmes as they depend on external grants and donor's performance requirements.

The price of VL medicines and diagnostics was stated as one of the principal barriers to ensuring access for all those in need. WHO has established a Long-Term Agreement with most of the manufacturers, essentially an 'advanced commitment' to purchase for an agreed time frame and price. These dialogue between supplier and purchaser includes negotiations to ensure that the price for public health needs remains reasonable; for instance, with Gilead for the access price of AmBisome (table 1) and also with Albert David for SSG. The price of VL medicines, in general, has been increasing and there are no other binding agreements to make sure that these medicines remain affordable. Respondents from MoH voiced concern over the substantial cost borne by the national programme for the provision of VL diagnostics and treatments without external support (see tables 4 and 5). Eastern Africa needs US$750 000 to ensure first-line treatment for 15 000 patients per year (average US$50 per patient).

Communication and coordination barriers to ensuring the supply of VL commodities

Improvement in coordination, collaboration and communication has been reported by participants,

Table 5 Overview of rapid diagnostic tests for visceral leishmaniasis in eastern Africa

Product	Manufacturer	Type	Lateral flow format	Shelf life	Accuracy in eastern Africa*	Cost
Tests currently in use						
Kalazar Detect	InBios International, Inc	RDT rK39	Dipstick	24 mo	Se 67.6%; Sp 90.8%	~3 Eur
DiaMed-IT LEISH	BioRad Laboratories	RDT rK39	Cassette	16 mo	Se 87.2%; Sp 96.4%	57.24 Eur for 24 kits
Other tests						
Crystal KA	Span Diagnostics, India	RDT rKE16	Dipstick	18 mo	Se 36.8%; Sp 98%	NA
Signal KA	Span Diagnostics, India	RDT rKE16	Cassette	12 mo	Se 73.2%; Sp 96.4%	NA
Onsite Leishmania Ab Rapid Test	CTK Biotech, USA	RDT rKE16	Dipstick	18 mo	NA	NA
rK28	CTK Biotech, USA	RDT rK28	Cassette	NA	Se 92.5%; Sp 100%†	US$3‡

*Source: Cunningham *et al*.[22]
†Source: Mukhtar *et al*[62]
‡Price quoted for RUO without negotiation.
NA, not available; RDT, rapid diagnostic test; RUO, research use only; Se, sensitivity; Sp, specificity.

despite examples of misunderstandings and conflicting internal requirements across stakeholders. The small network of individuals and organisations working with VL in the endemic countries enables communication and quick fixes to arising supply issue; borrowing and lending to stopgap stock rupture. The respondents stated that communication is essential to an effective supply chain management and thus should be prioritised.

> "*You have all kinds of matters influencing the solution of what, again in my eyes, is very simple as we are talking only about a few drugs. We are talking about a disease that is being well-monitored so you could react quite quickly if you had a centralised approach. So the moment you chose not to do that, that is the core issue. You fragment the demand, and you fragment the supply, and that makes it very difficult, and again, it is something we cause ourselves. If for some reason we're not wise enough to step out of whatever problem we have and look for a solution. Again, I'm not naive, but in this case, I find it very difficult to accept that you cannot find a supply solution.*"(IDI, Implementing NGOs).

Perceived remedies to supply chain barriers

Most respondents mentioned the concept of 'pooled procurement' as an obvious solution, in which countries or purchasers within countries share their needs and make a consolidated forecast for VL procurement.

> A pooled procurement with one party responsible for contact, supply and procure the products, keep them in stock and that everybody buys from them would be ideal (IDI, Procurement agency).

However, beyond 'pooling the needs', there are few concrete suggestions from the respondents as to how to move beyond that, for example, combining purchases or negotiations with manufacturers. However, due to the small VL market size, economies of scale would not lead to better prices. For stock management, the web-based District Health Information System 2 is recognised by most stakeholders as a prominent tool, currently being rolled out in all VL endemic countries in eastern Africa by WHO and also for the global emergency stock to which some 50 users worldwide have been granted access. Initially designed as a surveillance tool, this digital platform enables the addition of a leishmaniasis supply dashboard. If filled in correctly it would allow an accurate follow-up of the stock level of medicines and diagnostics at each VL health facility. There is a healthy cautionary attitude towards it, with some respondents endorsing the idea and the tool but questioning the capacity in-country and efforts required to reach the standard. In addition to VL national guidelines, 'standard operating procedures' for the VL supply chain were proposed as guidance for stakeholders, which would be of particular use when personnel change.

Respondents described several current initiatives and commitment to improving access to VL commodities. A global security stock of VL medicines and diagnostics, in essence, a rotating buffer stock, was re-established in 2017 by WHO through an agreement with one of MSF procurement agencies (MSF Logistics in Bordeaux, France). The KalaCORE consortium programme in Africa also implemented a security stock, stored by one of the procurement agencies, IDA Foundation, in 2015–2016. VL endemic countries may use the WHO emergency stock to cover the treatment of 1000 patients immediately. However, with a limited 5-year funding guarantee for the WHO leishmaniasis programme, there is an uncertainty about this approach in the long run, despite a clear consensus among stakeholders on its purpose, benefits and scope. The IDA Foundation in Amsterdam has committed to ensuring the continued availability of SSG and PM; through working with the manufacturers on quality assurance and control, keeping stocks in Amsterdam for immediate shipment, and taking responsibility for the registration of both drugs in East African countries, while DND*i* facilitated their registration financially. These collaborations need to be fostered and maintained—the AmBisome donation programme through WHO is a positive development, although the sustainability beyond 2021 is not ensured.

> "*WHO is getting the donations and there's a contract they signed with the manufacturer. Unfortunately, it's very short-sighted and without condition to the manufacturers, such to engage in registration, affordable price…it needs to happen. It's one thing to have the donation, but we often see that the donation is not enough or that the donation needs to pave the way for the future.*" (IDI, NGOs).

In this regard, all respondents emphasised that long-term solutions can only be achieved if they come from the country itself and are not (wholly driven) by external partners. A regional approach to this common problem was an attractive idea for most of the stakeholders, mirroring the commitment for VL elimination in the Indian subcontinent. Nevertheless, the respondents also noted that the context in each country needs to be considered; South Sudan and Somalia are still in armed conflict, whereas Sudan, Ethiopia, Kenya and Uganda also differ regarding capacity and resources that are available for VL and NTDs in general. Securing political commitment seems crucial for securing the resources needed to maintain progress. Integration with the in-country supply of essential medicines is heavily questioned by the study respondents, mostly in terms of justification and feasibility. To some, the low number of commodities and the low quantities involved are good reasons for integrating VL supply, whereas those convinced that the neglect of this disease will persist, argue that a dedicated and separate supply channel is still the only way to go. The integration of small amounts of donated drugs into the regular supply chain was not deemed even necessary.

DISCUSSION

This study expounds on barriers identified by the representatives of the primary stakeholders at the global and

national levels in the VL supply chain in eastern Africa that need to be addressed to increase access to diagnosis and treatment. These barriers were grouped into supply chain activities and health system, while fully recognising that they are inter-related and interdependent. The bottlenecks affect medicines and diagnostics, whose availability and access are imperative for VL case detection and management. For the patients, these medicines and diagnostics are life-saving; and from the public health perspective, VL control is impossible without them. Physicians, other field health staff and overall health system certainly benefit from an uninterrupted supply of VL medicines and diagnostics.

The eastern Africa region bears the highest burden of VL cases worldwide, yet VL supply chain management is still based mainly on parallel and externally supported efforts. The short list of VL medicines and diagnostics do not mean that their availability and access are secured. The barriers described by study respondents demonstrate a range of issues at global, national and subnational levels. There is no real 'selection' or competition of sources of VL medicines and diagnostics for supply, as for most items a single manufacturer only produces the product, that is, generic SSG, PM, MF and AmBisome. Another antimonial, MA (Glucantime), has never been used widely in eastern Africa except as a substitute when SSG is not available. Therefore, the default choice remains SSG/PM as recommended in the six countries as first-line treatment. The fact that the supplier pool has not expanded puts a real critical risk if production ceases. Though all VL medicines are included in the WHO Model of Essential Medicines List, there is a lack of WHO prequalified sources. This problem has been mitigated through the WHO Expert Review Panel assessments of SSG and PM, but manufacturers should be more engaged in adequate procedures to ease procurement in the future (eg, properly registered, aiming for pre-qualification), and purchasers could join forces to jointly require that manufacturers implement stringent quality assurance (ie, WHO PreQualification Programme).

Affordability is still a significant issue: VL medicines and diagnostics are still relatively expensive from the national perspective, despite price reductions negotiated by WHO or at cost price with a negligible profit margin.[41 42] Companies do not always register medicines with preferential prices where they are needed, as there is no profitable market.[43] Not all medicines in the national treatment protocols are available in endemic countries, even though they are included in the national essential drug lists.[44] VL medicines, except AmBisome, have no other substantial indication outside leishmaniasis and significant global case reduction in the Indian subcontinent have shrunk the market volume for VL,[45] whereas cutaneous leishmaniasis (CL) now represents a larger market for these drugs, as well as HIV/VL co-infection and post-kala-azar dermal leishmaniasis. In reality, despite the designation of VL medicines for patients with VL, patients with CL also are being treated and contribute to increased demand, for example, in Sudan or Ethiopia.[45] As these drugs are mainly procured through public or non-for-profit channels, competition from new producers is unlikely in the short term.[46] The current preferential pricing (for MF and PM) and donation programme (for AmBisome)[47] are not long-term solutions, although they are acceptable for VL (no multisource production capacity and small market size).[48–50] Alternate strategies are needed to achieve the lowest sustainable price, that is, a price that fulfils the criteria of affordability aligning with public health needs while keeping production a viable option before new drugs enter the market.[12]

Our findings indicatethat the importance of diagnostics has been underestimated. All barriers related to the VL medicines supply chain inevitably affect VL diagnostics, mainly rK39 RDTs. Despite the suboptimal performance of RDT and worse for patients with VL/HIV,[22 51–53] RDTs remain valuable for eastern Africa contexts, where delays in diagnosis remain an unaddressed needs.[27 54] Unfortunately, in eastern Africa, not all brands of rK39 RDTs perform equally well and improved field-adjusted diagnostic tool is urgently needed.[22 55]

Recent collaborative efforts across stakeholders groups have led to improved coordination and consensus to address access issues better, creating a window of opportunity.[56] Taking stocks on what has been tried and learnt in the last decade and proposing ways forward has implications at various levels. A common platform of VL drug supply monitoring could facilitate better forecasting and needs' estimation. The establishment of rotating buffer stock and centralisation of procurements were seen as low hanging fruits.[57] Centralised procurement reduces cost,[58] and consolidating demand in a 'pooled procurement' process appears attractive especially as the number of products is few.[57] Nevertheless, there are central design issues to be considered, such as ownership (governments or regional/international quasi-government organisations) and mechanisms. Several 'models' exist and could provide insights into similar schemes for VL in eastern Africa, for example, the centralised supply mechanism for the human African trypanosomiasis medicine donation programme, the International Crisis Group (for vaccines), the Drug Revolving Fund of the WHO American Region (Pan American Health Organization), the Tuberculosis Global Drug Facility and the Gulf Cooperation Council Group Purchasing Program.[57 59] Each has advantages and limitations. Therefore, in-depth scrutiny of these mechanisms in a feasibility study is needed. The regional approach, however, is desirable.

At the global level, although advocacy efforts have increased VL awareness nationally and internationally, the sustainability remains compromised. Respondents liken the current situation to plastering over the cracks rather than addressing the root causes, which would require a real political commitment and allocation of domestic resources. VL programmes could benefit from cross-cutting health system strengthening efforts, such as financing mechanisms, information system and legislation,[36] but

Table 6 Summary of barriers and action recommendations for the visceral leishmaniasis supply chain in eastern Africa

Area	Barriers	Recommended actions with level of actions required (global, regional or national)
Specific areas		
Production/selection	► Single quality-assured source(s) ► Minimum order quantity	► Ensure sustained production (SSG, PM) – *global* ► Expedite research for better diagnostic and treatment – *global*
Forecast/procurement	► Lack of adequate stock management ► Difficulty in forecasting	► Accelerate use and roll out of common tool (DHIS2) – *regional, national* ► Engage in defining and using 'pooled forecast and procurement' alongside existing mechanisms – *regional* ► Clarify and harmonise in-country procurement procedures – *regional and national*
Distribution	► Logistical challenges ► Parallel vertical channels	► Maintain the WHO-led 'emergency stock' and explore alternatives for medium and long-term – *global and regional* ► Examine the feasibility of integration with essential medicine supply – *all*
Cross-cutting		
Regulatory	► Registration in all endemic countries ► Pathways for RDT registration and use	► Harmonisation of regulatory standards, including for RDTs – *all* ► Support and (market) incentives for WHO PQP for VL products – *global* ► Share and communicate between regulatory authority, control programmes, partners, manufacturers and other stakeholders – *global*
Financing	► Still relatively expensive ► Sustainability	► Safeguard public health price through negotiations and binding agreements - *global* ► Ensure VL care included in national budget and UHC benefit package – *national* ► Define strategy to ensure sustainability of VL supply with a regional approach – *regional*
Coordination	► *Ad hoc* solutions ► Lack of political commitment	► Improve advocacy (national and global) ► In-country capacity strengthening and empowerment through specific technical assistance – *regional and national* ► Strategic plan/SOP for the country and regional VL supply chain – *national* ► United front for better negotiation leverage – *global, regional*

DHIS2, District Health Information System; PQP, PreQualification Programme; RDT, rapid diagnostic test; SOP, standard operating procedure; UHC, universal health coverage; VL, visceral leishmaniasis.

also targeted projects on pharmaceutical supply management and access to medicines in general.[60 61] Empowering country staff is paramount to achieving country ownership and responsibility towards patients with VL in the long run. Table 6 summarises our recommended actions from the public health perspective.

What are the implications for policy and research?

Despite the gargantuan task of addressing these barriers, clear mapping can help prioritise actions and inform future activities and intervention. Policy-makers, programme managers, academics and suppliers should work better together to investigate which type of actions is relevant in which type of context, across the six VL endemic countries. A good level of communication across stakeholders needs to be nurtured and strengthened to develop a collective bargaining power in securing access. Unlike the case for HIV/AIDS or TB, patients with VL are less vocal in expressing their demands, and mostly do not influence international or national priority setting. Strategies for a wide dissemination of the study findings through policy brief and advocacy efforts are therefore requisite.

Future research should help better monitoring of access to quality-assured antileishmanial medicines and diagnostics, taking into account the specific context in these endemic countries. An efficient and effective supply

chain should not be seen as a merely technical and organisational challenge; the socioeconomic deprivation of the affected communities should be acknowledged as having a profound link. Simultaneous actions to strengthen health systems and to overcome these barriers are critical, considering the time required for new, better medicines and diagnostics for VL in eastern Africa to become a reality.

CONCLUSION

This study aimed to better understand the key barriers and enablers for an efficient, effective supply chain for VL medicinesand diagnostics in the eastern Africa region. Ensuring a reliable supply chain for VL has been chronically challenging due to the context and dependence on external support. This study provides clear documentation of key barriers along the supply chain for VL medicines and diagnostics. Addressing these barriers calls for a more unified approach among the stakeholders. Our findings indicate that despite the diversity in each country's context, simultaneous efforts and collaboration in policy and implementation are required. At the country level, national interagency technical working groups to drive the VL agenda appears to be needed. Regional coordination for forecasting and procurement is synchronised with global leadership through a partnership of stakeholders and funders on pricing and availability. Although perspectives may differ, the ultimate goal of increasing access to VL care should guide actions and collaborations in the future.

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Competing interests RR was a member of the EuroLeish Ethics Board and ITM IRB. As such, she participated in the ethics review of this project, before she became involved in the assessment and interpretation of these findings. MdB, JP and KR are affiliated with Médecins Sans Frontieres (MSF), which has been actively working in the field of leishmaniasis in Africa since decades. MSF is currently running VL projects in Ethiopia, Sudan, and South Sudan. FA is affiliated to DNDi, an organization dedicated to develop new treatment for neglected diseases, with VL as one of the focus. DNDi manages treatment centers in Sudan, Kenya and Uganda. JARP is affiliated to WHO Geneva in the Leishmaniasis program and have been involved in technical support to the countries for the VL control globally. WHO also hosted the WHO Working Group on Access to Leishmaniasis medicines where MSF and DNDi were active participants.

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SUPPLEMENTARY INFORMATION 1A

Information sheet

Access to visceral leishmaniasis (VL) drugs in Africa – barriers and facilitators

Background:

The Institute of Tropical Medicine, Antwerp (ITM) is conducting a study, partnering with MSF and others, to investigate access barriers to quality drugs to treat visceral leishmaniasis (VL) in eastern Africa region. This study aims to analyse the different factors affecting access to these life-saving medicines, from global and/or regional perspective, in order to enhance access to these drugs. Information will be collected for the following products:

1. Sodium stibogluconate (SSG) - generic
2. Paromomycin
3. Liposomal amphotericin B (AmBisome®)
4. Additional: meglumine antimoniate (Glucantime®), Pentostam® (SSG from GSK)
5. Additional: rK39 RDT

Interview description:

All partners or stakeholders involved in the access to VL drugs in countries in east Africa, including those providing support (financial or otherwise) to the procurement and distribution of VL medicines (and diagnostics). We have selected your organisation and approached you to assist in this assessment by providing information (and your expert opinion) on any of the above products.

With your consent, the interview will be recorded, and we will use a semi-structured questionnaire in which some information will be noted down. It should take 60 minutes of your time.

Confidentiality and information security

Participation in this study is completely voluntary and you may withdraw at any time without prejudice of negative consequences. All information will be kept secured and confidential. The study team will have access to the information arising from this interview. Information which could potentially identify participants will not be published without the participants' consent, nor disclosed outside of the study team.

If you need further information, please contact:

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Semi-structured questionnaire for interviews for global stakeholders: Mapping access barriers to quality VL drugs in Africa

Name of partner/organisation: _____

Person interviewed/ completed the questionnaire: _____

Contact: _____

Position: _____

Date: _____

Name of interviewer: _____

Question guides

1. Can you explain what is the role of your organisation related to VL in Africa?
   - Financial support
   - Procurement
   - Implementation/Technical support (define)
   - _____
   - _____

2. Which among the VL medicines (and diagnostics) that your organisation support?

	Yes/No	Amount of support in previous year (US$)	Year foreseen to end support	Countries	Type of support (financial -including loan, donation, technical, others)
SSG					
PM					
LAMB					
Others					

3. What do you think are the access challenges for VL drugs in Africa? (prompt: selection of products, quality, procurement, distribution, capacity…)

   _____

   Follow up questions/to elaborate more on what is mentioned):
   3 a. Why is it so difficult? (e.g. forecasting the demand, ……*as per the answer)*

   _____

4. What do you think are barriers to access at global level? What are the reasons for that?

   _____

5. What do you think are barriers to access at country level? What are the reasons for that?

   _____

6. How are the situation of access now in 2017? Do you think it was improved/not from 10 years ago? Why is that?

   _____

7. Have you heard/experienced stock-outs of one of the VL medicines? What are the reasons for that?

   _____

8. What do you think is particular for VL drugs access as compared to other NTDs, or even to other essential medicines?

   _____

9. What are your thoughts on integrating VL supply with the public procurement system? (What are your views on the parallel procurement channels for specific disease such as VL? Agree or disagree…why?)

   _____

10. Research suggest different supply improvement such as technology use, different distribution systems, outsourcing – what are your thoughts about the different options?

    _____

11. What do you think are the critical actions that need to be taken at global (and/or regional level)?

    _____

12. What do you think are the most important actions to be taken at national level (can give example of specific VL endemic countries)? Something that only the country should take the actions?

    _____

13. Specifically, for rK39 RDT, in your opinion, what are the most important access barriers?

    _____

14. Is there any examples of good practices that you thought might be applicable for VL?

    _____

15. Is there an area of research or further studies on this topic? What would you suggest?

    _____

SUPPLEMENTARY INFORMATION 1B

Information sheet

Access to visceral leishmaniasis (VL) drugs in Africa – barriers and facilitators

Background:

The Institute of Tropical Medicine, Antwerp (ITM) is conducting a study, partnering with MSF and others, to investigate access barriers to quality drugs to treat visceral leishmaniasis (VL) in eastern Africa region. This study aims to analyse the different factors affecting access to these life-saving medicines, from global and/or regional perspective, in order to enhance access to these drugs. Information will be collected for the following products:

1. Sodium stibogluconate (SSG) - generic
2. Paromomycin
3. Liposomal amphotericin B (AmBisome®)
4. Additional: meglumine antimoniate (Glucantime®), Pentostam® (SSG from GSK)
5. Additional: rK39 RDT

Interview description:

All partners or stakeholders involved in the access to VL drugs in countries in east Africa, including those providing support (financial or otherwise) to the procurement and distribution of VL medicines (and diagnostics). We have selected your organisation and approached you to assist in this assessment by providing information (and your expert opinion) on any of the above products.

With your consent, the interview will be recorded, and we will use a semi-structured questionnaire in which some information will be noted down. It should take 60 minutes of your time.

Confidentiality and information security

Participation in this study is completely voluntary and you may withdraw at any time without prejudice of negative consequences. All information will be kept secured and confidential. The study team will have access to the information arising from this interview. Information which could potentially identify participants will not be published without the participants' consent, nor disclosed outside of the study team.

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Semi-structured questionnaire for interviews

Barriers to effective supply of quality VL drugs and diagnostics in Africa

Name of partner/organisation: _____

Name of country: _____

Person interviewed/ completed the questionnaire: _____

Contact: _____

Position: _____

Date: _____

Name of interviewer: _____

Question guides

1. Is health care in the public sector officially provided free of charge to patients in case of leishmaniasis?
   Yes/No

2. Who supplies the medicines used to treat VL ?
   - National programme
   - Donor _____
   - Organisation_____
   - _____
   - _____

3. Which among the VL medicines (and diagnostics) below that are available in your country?

	Yes/No	Registered (Yes/No/Don't know)	Imported/Produced	Supplier	Remarks
Conventional amphotericin B					
Liposomal amphotericin B					
Meglumine antimoniate					
Sodium stibogluconate					
Miltefosine 50 mg/tablet					
Miltefosine 10 mg/tablet					

Paromomycin					
Pentamidine					
Other.....					
Other.....					

4. Were there donations of drugs for leishmaniasis in 2015 or 2016 (by WHO, pharmaceutical industry or aid agencies)?

   Yes/No

5. If yes, please specify the donor and which medicine and its quantities if possible by giving the numbers in the smallest unit (vials, tablets):

Donor	**Name of drug + manufacturer**	**Quantity (vials, tablets)**

6. Are drugs for leishmaniasis sold in the private sector?
   In regulated pharmacies:
   Yes/No/Don't know
   In unregulated drug markets/by drug vendors:
   Yes/No/Don't know

7. What is the process to procure VL medicines? (prompt: together with other essential medicines…)

   _____

   Follow up questions/to elaborate more on what is mentioned):
   4 a. Why is so difficult? (e.g. forecasting the demand, ……*as per the answer)*

   _____

8. What is the process to procure VL diagnostic (rK39 RDT)?

   _____

9. What do you think are the difficulties to effective supply of VL drugs and diagnostics? What are the reasons for that?

   _____

   Prompt (tick if appropriate)
   □ No treatment is offered in the public sector.
   □There is no leishmaniasis control programme.
   □Treatment is only offered at advanced health care levels and not at primary care level.
   □There is no money to roll out the existing leishmaniasis control programme.
   □ There is no continuous supply of drugs at public health facilities.

Comments: _____

□ Drugs/diagnosis offered in public health facilities are not effective.

Reason: _____

□ Patients are too poor to pay for treatment which is not offered for free in public health facilities.

□ There is a lack of trained human resources for treating leishmaniasis.

□ Patients live in very remote areas with no health facilities and no transport.

□ Transport to health facilities exists but patients can't afford it.

□ Patients suffer economical catastrophe due to days of missed work when they spend time away from home in order to receive treatment.

□ Patients do not seek treatment in time due to certain cultural beliefs or a lack of awareness of the serious nature of the disease.

□ There is gender inequality in seeking treatment.

□ Patients seek substandard private care or care from traditional healers before reporting to health facilities.

Comments: _____

□ Certain groups of patients have no access to the public health system (refugees, returnee camps, tribal regions).

Comments: _____

□ Other:_____

10. In your opinion, have there been changes in the supply mechanisms of VL drugs and rK39 RDT?

_____

11. Have you heard/experienced stock-outs of one of the VL medicines? What are the reasons for that?

_____

12. What do you think is particular for VL drugs access as compared to other NTDs, or even to other essential medicines?

_____

13. What are your thoughts on integrating VL supply with the public procurement system? (What are your views on the parallel procurement channels for specific disease such as VL? Agree or disagree…why?)

_____

14. Research suggest different supply improvement such as technology use, different distribution systems, outsourcing – what are your thoughts about the different options?

_____

15. What do you think should be the strategies to improve supply of VL commodities?

_____

	Supply chain side (manufacturing, selection/forecasting, procurement, distribution and delivery)	Health system side (legislation, coordination, communication, financing)
Multilateral organisation	- Supply is not the role of WHO, but when there is nobody else - the Ministry doesn't do something or does not procure those medicines and there is no any other partner. Without countries' request though, the HQ cannot do much. - The role of WHO is actually to make the programmes in the countries to speak to each other and coordinate their needs. - There is a gap between policy and reality, which can be frustrated to all sides - "My opinion is that the word 'integrated' does not have a room here. Because what we need to do is to stop the neglect of those diseases. See, a national medicine system in a country, is the national essential medicine list, right? So, this by itself is to cover the essential needs of that given country. So, integrated, well it's the national system, but my point is why do those countries have deliberately excluded NTDs from that service? So, who decided to exclude our medicines, the leishmaniasis medicines, from the list? Because if it's not in the national medicine list, then everything gets impossible or difficult, because it's not that we should integrate. We should be in the place where we must be, so the abnormal thing is to have it excluded. Because then it's in a corner, nobody orders, nobody follows and so on."	- WHO depends on external funding, while trying not to duplicate or compete with others. Fund use is not very flexible and WHO ready to chip in the supply chain when neither MoH nor other agencies can take over. - There are some people in WHO who are field-oriented, there should be more trust to WHO - Country should step up and not neglect their VL patients - Capacity in-country should be strengthened as much as possible so dependence on external people can be reduced - Partnership is crucial among all the involved stakeholders - The higher level politicians need to commit, just like in Asia - Not all the countries have funding for VL because it's not a priority disease, and affect neglected population so no provisions to give as such. - Level of commitment of people is important, and this is not the case for NTDs - There are only very limited resources, and this is linked to the neglect, the focal geography plays a role as well
Donor	- There have been stock outs of all drugs, over time PM and SSG and also some rapid diagnostic test. In Ethiopia in 2017, there had been a problem with a manufacturer of rK39. - Stock out problem can be due to manufacturing problems, or other bottlenecks such as forecasting the needs, which obviously a problem with supply. - There are stock outs due to unexpected emergencies, but also due to the issue of the one-source suppliers. Either that they could not finish and get the batch in time, the production batch was later than promised and anticipated or that quality issues with a batch. That is the whole problem with the single supplier issue. -	- Lack of transparency and logic behind funder (e.g. UK-Aid) decisions, e.g. how to utilise the pot of money for VL or NTD in general, operating in Sudan, etc. - Various donors involved in supply chain strengthening (e.g. Ethiopia) and requires streamlining and consolidation, clear strategy going forwards - Vertical approached by NGOs like MSF may be best for patients, but it means their presence is needed forever, there is a need for more country level capacity building - "WHO is not natural leader everywhere' – country office can hire many staff but inefficient and there has been some disappointment over specific activities performance. - Stock out can be due to communication problem where the drugs were actually in the country already, but the Ministry of Health had not released them or no communications

		- A regional programme for leishmaniasis with regional strategy at a ministerial level, like the Asian agreement on elimination. - Sometimes things depend very much on the people involved - There are sometimes in-country dynamics between institutions and/or between people which can complicate this smooth functioning of supply chain of VL medicines and diagnostics
NGOs	- Timely reports are crucial, because procurement is done at the beginning of the project and updated regularly, estimate is based on, for example, the number of people tested last year and the year before. There was a shortage once (in Turkana), due to the lack of communication at the beginning - When there is shortage, the buffer stock was not quick enough to cover that, but also due to the rainy season it was impossible to land planes in the targeted areas - "Yes. So those are the stock outs due to unexpected emergencies, but we've also had real problems with the issue of the one-source suppliers that have problems. Either that they could not finish and get the batch in time, the production batch was later than promised and anticipated or that quality issues with a batch. That is the whole problem with the single supplier issue." - Who will take the risk of keeping a stock when no one wants to order? The problem also is about the bill, who is going to pay the bill? - "Now what we see is that WHO has to do their own procurement, they cannot rely on IDA, they have to go directly to the manufactures because they have the rule apparently internally that will not allow them to go to a distributer. So, this is already removing a major stakeholder in the procurement, but if we could maybe better plan our orders that should not be so much of an issue. Both manufactures should be able to see what has been the order of WHO for the last couple of years. Then you have IDA, IDA was or is doing the procurement for DND*i*. At some point these two were supposed to join and again the exact reasons why we didn't join at the time I'm not sure about. I know that we are a little bit like WHO, we like to procure directly from the manufacturer. We don't have to rely on IDA as such. Even though I think that we're now ready to get back to the table, because clearly with a decision we took in 2014 or 2015 was not the best one, because we lost a lot of money and we lost a lot of stock that we couldn't use. " (MSF)	- KalaCORE programme will end in March 2019 and there has been progress, but discussions still ongoing on what needs to be done by the national programmes. The fear is that without external funding, control will collapse and go back to how it was. - Very unclear situation once the KalaCORE ends, who will buy the medicines? Sustainability is clearly a major issue, between actors we can coordinate but it is far from ideal - Lack of awareness and varied capacity between counties endemic of VL - NGOs need to coordinate always, like in Kenya, (FIND) has strategy to improve access to diagnosis, through an agreement with the DND*i* and with WHO or whoever take the responsibility of making drugs accessible in these counties, whenever they are necessary. - "The main countries where we have activities are Sudan, Ethiopia, Kenya and Uganda and for each of these countries we have partners who are the ones implementing the research, but in order for us to be able to implement the research we have also a component of capacity building and even when we don't have clinical trial going on, we have to maintain minimal structure in this clinical trial site. This means that we are also supporting sides for the routine treatment of viscera leishmaniasis in the region." (DND*i*) - Changing regulations are not easy to follow and there is no real interests from the manufacturers to do registration - "For diagnostic tests for leishmaniasis, the total shelf life is 14 months and according to the regulation of FMHACA when they arrive at port of entrance, they should have at least 50% remaining shelf life." (Ethiopia) - "I think that Gilead, did not do it for patients with kala-azar, but more because they see the market opportunities with HIV-patients with

	- Agreement with manufacturers and also in regard to donation needs to be more correct, with condition to guarantee access in the long term, for example by engaging in registration… the agreement should not be shortsighted. - It's 1 thing to have the donation, but we often see that the donation is not enough or that the donation needs to pave the way for the future. I don't know if this donation, I mean at the end of the day the NTD department is funded by Gilead at the moment. I don't think that they have that their hands are so tight. I'm not saying that, but I just ... I'm not saying it's that easy, I'm just saying to the contrary, but as we are more and more asked to sign this kind of agreements with manufactures, if we are not more careful, they are going to put a lot of constraints on us and it would really shrink our activities.	Cryptococcus meningitis but still, it could benefit so we need to sell that wave and benefit from as much as we can from that. And then we need to push countries that are affected by kala-azar to join this collaborative registration procedure so that they can also register faster. - It was a great initiative to have ERP mechanism in order to have a quality access to a quality product, but there remains no market incentive behind it, so manufactures will not be inclined to continue to provide information and update their manufacturing standards and also it wasn't really advertised or shared or communicated - Without coordination, money and time are lost - Unclear responsibility in the health facility regarding reporting of cases
Distributor or procurement agency	- It's difficult without forward planning nor predictions and there is stock rupture. Pooled procurement is ideal but sometimes people are not completely open about that. There are issues of trust and communication. -Each drug is challenging, and people need strategy to deal with them. "Gilead is difficult, but in the end, we will manage but for me, Gland Pharma is much more unclear on what is going to happen. Albert David isn't such a difficult manufacturer " -Definitely, IDA has been busy with these manufacturers from the beginning of the 90s, and there's no other organisation with so much experience with SSG. - "For NTD, it's the same system, only then we do more strategic meetings on what products we keep in our stock. It's an effort we do especially for the regulatory affairs, then I come in and interfere a little bit to get it in the right direction… And of course, we have a policy internal about what kind of focus areas and which type of neglected diseases we would like to give some extra attention" - There is not a better preparedness in case of a large outbreak as in 2014, "When quite quickly all our stock were depleted, and MSF had to buy large quantities directly from the manufacturer and Gland Pharma, being in that day, a very unreliable partner and made it very difficult." - Costs are increasing, because there are so many regulatory requirements every time so there, or a change like in Kenya, suddenly "Oh, now registration is not needed anymore". But still there is a need of country representative to navigate through different things, and there are regulations that you can only find out when you start a registration. Sometimes they are easy,	-"The problem then and all the time is to try to establish who's going to be doing what … I feel like people always try to do something, but it's not very coordinated. It's not in the open and clear, and that's what I'm still missing a little bit." - All the parties and stakeholders need to do it better than this, even if they have specific purposes like research, because we are there to serve the people and to get better access if everyone put the experience in that. - "Relations between organisations isn't always easy, but there are possible solution. Better to have one party doing whole stock keeping, who has a more global view on the situation. IDA, for years, has been the leading supplier with good contacts with the current manufacturers. For me, again with the experience I have with IDA, they're always willing to negotiate and come to a very good solution. They take action. I think, you should sort this out instead of wanting to do it yourself. But again, our experience with IDA is positive and I can't say that the French or MSF Logistique think that way. So, if you look at the role of WHO, which of course is difficult, because I know that in the past WHO and IDA used to cooperate and now because... As I understood, the administrative system of WHO with regard to procurement has changed and they're not allowed to work in the same way with IDA, so you have all kinds of matters influencing the solution of what, again in my eyes, is a very simple .... I mean, we're talking only about a few drugs. We're talking about a disease that is being well-monitored, so

	but sometimes they can be very difficult, and they can get a little bit annoyed if they want all kind of things, leaflets and changes. - If there are contradictions between all these countries for the requirements of one product, then it becomes very difficult. - Harmonisation of the regulation is needed. Of course, every country differs, but…	you could react quite quickly if you had a centralised approach. And the moment you chose not to do that, that's the core issue. You fragment the demand and you fragment the supply and that makes it very difficult, and again, it's something we cause ourselves. If for some reason we're not wise enough to step out of whatever problem we have and look for a solution. Again, I'm not naive, but in this case, I find it very difficult to accept that you cannot find a supply solution here." - "For registration, somebody has to be the owner of the dossier, add the stability data and pay for new updates stabilising and continue the stability. Then you can out contract it to any manufacturer, that is not the problem. The formula of the contract, that's possible of course, but then you should have somebody who owns the intellectual property of the manufacturing process and update a dossier every time and do the registration, the submissions … And that's also still quite costly, these kinds of things. IDA very often has people telling them: "Oh do the registration". And then they don't realise that there's quite some effort and capacity needed for that." -
Manufacturer	- Availability and accessibility is critical, especially the capacity of the different partners to provide the forecasts. - « Now the major problem they have, talking about the WHO, PAHO, and others, is that they provide this to governments. Governments... The Ministry of Health its intentions to buy is in terms of volumes, but those who give the forecasts of intentions to buy in terms of volumes, are not the financial guys. A lot of intentions to buy do not materialise, because they don't have the money when they go back to double check. So, whenever we have a tentative forecast, we know it's not going to be correct and the production takes a lot of time and is costly so it's hard to keep a big amount and it expires gradually because the orders are not coming. So, that is our main challenge at our level. » - SSG has a dedicated facility, so it will be there as long as needed - For PM the amount is 65-70,000 ampoules per batch, and the company is not making any profit to that, this is cost to produce, with very negligible margin, that has been fixed since 10 years... and since then everything has gone up and they take it as CSR (Corporate Social Responsibility) initiative - Production will continue as long as there is order, and capacity can even be increased	- "Pre-qualifications process is sometimes seen as looking into destination in the European market nowadays. For SSG, they asked a lot, a lot of data, on identification of all kind of product, because there is perception it is not a very well characterised product and you have to investigate further, and the whole thing is just process, I don't see AD as culpability, but I don't know if they'd do it if they know the product is good." - "Registration of the drugs in the different countries may have lapsed, because the last owners really pursue this, as they never get orders from the private sector and when the orders are coming from the public sector there's always an agreement from the government to get it in. So, a registration process, for example in Brazil, for a normal drug takes 5 years. In many countries it takes 3 years. It's costly in terms of work, because you have to follow up on it permanently, you have to add new documents and you have to do this and then the other. So even us at this point in time, because we never have all private orders, we are not even looking into re-establishing the registration. "

	- It is simple: 60,000 ampoules, 1,5 $ each so total is 100,000 so not that much. So, anyone can do this and buy supply for one batch and then distribute to whoever will buy from them. Irregularity of the order is a problem. The low margin also an issue as it means keeping stock is like blocking money, resources. - Sustained demand is the key issue - Price is agreed before, and Knight has policy of different prices when it is a full batch or more than a full batch. What happens when we do a full batch, because of the regulation we have to do regular analysis on the quality of the product. You rate the time and date of expiry. Those analyses are very expensive. It increases the cost of the product if we sell a batch over a long period of time. Now, if we sell this batch immediately, we only have to do the regulatory control of the quality for the time that we have it. If we sell it within 6 months, then … Because we don't have it anymore, we can't do this testing. It's already in usage, so that way we can offer a different price when the batch is sold full. Those prices are already been communicated to WHO, DND*i*. - "That agreement says also that the price has to be covering the costs plus a margin. That agreement was signed, I don't know how many years ago, but before 2000. And since then there has been an increase in costs everywhere. That particular agreement never took that specifically in consideration. Now, we were not the signatories of this agreement, but it has come to us with the acquisition of the product and what we look at is how much it cost us to make and you very well know, regulations on pharmaceutical drugs have not reduced the number of controls and checks and quality this and quality that and reporting this and reporting that. All the opposites, everything is increasing every day, you know. So, considering that the price that was valid 20 years ago is today is counter intuitive" - Expanding indication is not easy and requires all the trials - Donation as a policy is not universally possible for all manufacturers as it is not seen as economically sound. - "Consistently right now, with the trends we have, the trends are more for producing the orders than increasing them. We're caught into this particular situation."	- Regular meeting between Gilead and WHO - For this kind of disease with no private market, there definitely a need for collaboration - The price is about quality, with assumption that lower price is lower quality, an analogy made: " there is already generic manufacturers in India, it's like 18K gold versus 24 K gold. If you don't have money for 24K gold, you should be happy with 22 K gold." - Technology transfer is done but nobody is able to make the medicines

MoH	- WHO emergency stock is in Geneva, for all the world. "Few years ago, 2014 we had shortage for long period for PM, even this time we have problem with PM... that is internal logistic in WHO, people who received is not the one responsible, one month nobody knows where it is… they say IDA sent it, the logistic received it and keep them in the stock not knowing that people are waiting... we are asking for the drug and we don't get them, there was an outcry and somebody remembers oh I received that some time ago can you check... and that was three months later.. - "Before KalaCORE, there was sometimes no drugs in the country, a national shortage" (Sudan) - "The health centre may saw only 10 people because after 2 weeks rupture in drugs, so nobody came, but the next month they only ordered the same ... that ability to have a constant supply also limits their knowledge on the number of cases, because they don't record the case that they weren't able to treat" (South Sudan) - Microplanning at the health facility level - There might be infrastructure and connectivity issues with the platform (DHIS2)	- Complexity of the disease, with treatment regimens vary for both visceral and cutaneous leishmaniasis and at country level, we lack capacity to manage them, these compounds being also neglected, unlike malaria - Elimination target brings donor attention, but for country in Africa this is still very far thus less attractive for funding - "Regional approach I think indeed it can be easier and the drug can be closer, we do this with WHO emergency stock the drugs go to Somalia, South Sudan, where forecast is difficult. So perhaps regional approach makes sense. However, agreement between countries are needed, a kind of MoU similar like what they did in the elimination in India, at least in the region." - Training and supervision of the staff is important - There is not enough budget to cover leishmaniasis as one, not separating VL and CL. So, there is not enough budget because of the CL challenge.
Implementing actors (local NGOs)	- Transporting sample can be a problem, for example for DAT samples, adding delays of 3 weeks, 1 month. Other places they told the patients to wait after checking for malaria, but unclear if or whether they were coming back - Geographical access to the areas can be difficult, borrowing from MSF until the consignment arrives - "Whenever there is a stock amount below the threshold, we run and try to avoid any rapture. There are sometimes issue with the expiry or customs, but total rapture is rare" - "In 2016, we had that very shortage, especially SSG was out of stock. WHO supply was not available; so, we tried to get from Nairobi, but it was very costly and can't be sustained by us' (local NGO in Somalia) - "Yes, there were several stock outs perhaps every 2 or 3 months. Main reason again, because it's not integrated in the system, if it was integrated it was only PFSA who distribute it to the health facilities, and would have been better… but the problem was it's kind of orphan drug, it goes through the programme, due to lack of integration, the	- Capacity of the health facility varies (cold chain, drug administration) - Procurement always by external agent, e.g. AmBisome is just with WHO. - Referrals very difficult. - "Pool procurement, including to align the ordering schedule is something that needs to be done, but it's not simple because everybody needs to agree ... I do think that what happened a couple of years ago is that MSF needed urgently some products and could not wait for this pool procurement to be set up and that's the reason why they decided to go ahead: they had a big need and they just went." - Training is difficult because people changing all the time; the poor functioning of the health system definitely is a barrier - "Having the integrated system, I do think that was the way forward but then you just need to get the people that buy in and get the training and actually do it. You need to have a health centre, a health post who has a champion.

	estimation or quantification is done separately at national task force, we did quantification for three years, we made distribution lists based on treatment sites, or needs that we thought per site based on case load, and after for every compound, antimonial, PM, the tests and this was distributed by the ministry every three months. In collaboration with the Regional Health Bureau. So, it means it is not fully integrated in the PFSA so sometimes you have the drugs in the Regional Health Bureau, but at the health facilities there are no communication and the stock of PFSA at regional level was not properly communicated to the programme." (Ethiopia) - Especially like, considered the diagnosis tests for leishmaniasis. This data in total shelf life is 14 months and according to the regulation of FMHACA when they arrive at port of entrance, they should have at least 50% remaining shelf life. -	If you have one strong person who is willing to drive it, willing to push these processes through then I think you can have success, but often that's what missing. You have people who don't show up to work, there's a super high turnover, they're always being shifted to different locations, so there's very little consistency." -

CHAPTER 5
GENERAL DISCUSSION

Ensuring access to quality care in eastern Africa is challenging. Children often bear the brunt of infectious diseases, as in Bor , Jonglei state in South Sudan. Photo by T. Sunyoto

This thesis aims to improve our understanding on access to leishmaniasis care in the sub-Saharan African (SSA) region, by documenting availability, affordability, and accessibility of care; exploring novel ways of enhancing such care; and providing insights for policy formulation.

THE BURDEN OF LEISHMANIASIS IN EASTERN AFRICA: IMPACT OF CONFLICT AND KNOWLEDGE GAPS

Over the past decades, leishmaniasis has obtained unprecedented attention from the international community, much in relation to the 2005 regional elimination initiative of visceral leishmaniasis (VL) -or kala-azar- in the Indian subcontinent[126]. Since 2005, global VL cases have declined dramatically, but this is not the case in eastern Africa. Countries in this region, namely Sudan, South Sudan, Ethiopia, Kenya, Uganda, and Somalia are one of the geographic areas hardest hit by VL. Conflicts, displacements, drought and dysfunctional health system are some of the determinants of VL in eastern Africa countries.

Somalia, the country of focus of **Article 1**, is the archetypal example of leishmaniasis in a 'fragile state,' whereby availability and accessibility of care face extra challenges. Our work is the first published paper about VL in Somalia after a 10-year gap since the last one by Raguenaud et al. (2007)[127], providing a comprehensive update. Somalia has replaced Bangladesh in the top seven high-burden VL countries since 2015[1,128], with 1400-2700 VL cases estimated per year[2]. A significant number of patients, however, may not reach health centres due to access issues. There is limited coverage and quality of leishmaniasis care in the country, with only three centres located in the militia-controlled areas. The country depends entirely on WHO for its supply of VL drugs and diagnostics.

VL in Somalia is not well documented, with only two reports on VL cohorts from endemic areas: the first one the above-mentioned study by Raguenaud et al about the MSF centre in Huddur (1671 cases in 2004-2006)[127] and a 2017 report from three WHO-supported centres in Baidoa, Tijeglow and Huddur (3112 cases in 2013-2015)[129]. These studies reported that more than half of the VL patients were children under 5, whose susceptibility was often aggravated by poor nutritional status[130]. Monotherapy with SSG alone continues, as the supply of PM relies on DND*i*[129]. The prolonged hospitalisation for treatment affects service uptake, as families have to cover travel and food expenses. Nevertheless, there has been progress on several fronts, e.g., on surveillance with mapping village level data, implementation of DHIS2[129] and intention to assess the feasibility of AmBisome® use in 2018[131].

Our review shows that leishmaniasis remains a neglected disease in Somalia, competing with other health priorities and impending catastrophes such as famine threats and cholera outbreak[132]. Would the prolonged conflict setting in Somalia increase the risk of an outbreak in the future? We cannot provide a definite answer to that question, but in any case, the mechanisms by which conflict exerts an impact on disease outbreaks are challenging to pinpoint. Spiegel et al. analysed the overlap between the 30 biggest natural disasters, complex emergencies and epidemics over 1995-2004 and concluded that lethal epidemics occur more frequently during large-scale complex emergencies[133]. For leishmaniasis, its association with conflict has been demonstrated through a series of factors: people moving to areas with active transmission, the weak nutrition status following the displacement, and the lack of access to health services. Based on 1995-2010 data, a significant dose-response relationship for leishmaniasis (cutaneous/CL and visceral/VL) incidence on increasing levels of conflict and terror was reported[134]. The odds ratio

for CL and VL in country-years with very high levels of conflict-terror were 2.38 (95%CI 1.40-4.05), and 6.02 (95%CI 2.39-15.15), respectively. The stronger risk for VL is linked to its anthroponotic transmission, which corresponds with displacement, crowding, poor housing, immune-compromised health status, and increased human-vector interactions. Health system deterioration also plays an important role in exacerbating the impact of conflicts.

The impact of access breakdown due to conflict is best illustrated during the 1984-1994 VL outbreak in Western Upper Nile, South Sudan[3]. Between 1999-2002, only 55% of people can access care and close to 91% of deaths were unseen[135]. Treatment was only started in 1989 in Khartoum for the refugees, while aid agencies could only access the epicentre of the outbreak two years later. Another epidemic recurred in 2009-2012 with more than 76,000 cases and only in 2010 the 17 days SSG/PM is rolled out beyond MSF sites[4]. Responding to the outbreak was difficult as most areas are cut-off during the rainy season and the number of people who died because they could not reach a treatment centre is unknown. Unfortunately, the conflict continues; following a clash in December 2013, tens of thousands of people fled to VL endemic areas during the high transmission period (February-May). More than 6000 VL patients were treated at MSF-H site in Lankien during a nine-month period, amongst whom 23% were categorised as severe[136,137].

The cyclical epidemic patterns of VL, combined with population displacement and lack of access to diagnosis and treatment, create the 'perfect storm' conditions for a VL epidemic[36]. Our review on Somalia, therefore, underlines the need for improved preparedness, especially as conflict and unrest remain rampant in almost all the endemic countries. In South Sudan, ethnic and political tensions persist, and sporadic fighting continues in the areas known to be VL endemic such as Greater Upper Nile, the Equatorial provinces and parts of Greater Bahr el Ghazal. Despite efforts to revitalise a fragile 2015 peace deal, more than 4 million people have been forced to flee their homes, half of whom took refuge in United Nations compounds or neighbouring countries[138]. In Somalia, though the civil war between rival clan warlords is already decades-long, the situation remains volatile with flare-ups against the Mogadishu-based federal government and ensuing military offensives. The al-Shabaab militants continue to carry out deadly attacks in (e.g., Mogadishu bombing that killed 512 people in 2017 and several others in 2019) and outside the country (Uganda was attacked in 2010 and Kenya in 2013, 2015 and 2019)[139]. In 2017, the UN estimates 1 million people were newly displaced, bringing the total internally displaced persons (IDP) population to 2.1 million. Access to the southern areas remains a challenge along with disruptions to supply chains because of insecurity.

Other countries in the region are relatively stable, yet with their own woes. Ethiopia only lifted its state of emergency in April 2018, after years of widespread protests against government policies. In Sudan, low-intensity armed conflicts continue between government forces and armed opposition groups in Darfur, Southern Kordofan and Blue Nile states. Recently, Sudan was predicted to be on a trajectory towards a health and humanitarian crisis because of the near total collapse in governance[140]. The civil unrest, triggered by high prices of food and essential medicines, started in December 2018 in the town of Atbara, located in the high VL burden state of Gadarif[141]. Hospitals have reportedly been attacked and doctors arrested[142]. Despite the eventual Bashir regime fall, the situation is still tense and not fully stabilised as consensus between civil society and the military has yet to be reached.

Conflict could derail health programme and services, including and perhaps, more precariously, NTDs control programmes[143]. Maintaining access to health care in a precarious

situation is very difficult. Some lessons have been learned. Decentralisation of care, in the form of 'mobile clinics' in which trained local teams provide VL care, have shown to work in South Sudan[4]. With cross-border population movement, provision of VL diagnosis and care in the refugee camps in Uganda and Ethiopia may be justified, including efforts to increase awareness of the health workers in areas receiving an influx of people. Based on our findings on Somalia, innovative approaches adjusted to the context appear to be important, such as working with the community including clan elders and utilise the widespread mobile phone network in rural Somalia to encourage care-seeking. Parallelly, efforts to improve coordination in health assistance, ensure sufficient funding and reduce the silo-approach of the federal government structure are important[144]. Rejuvenating the country's capacity, including in research, is imperative in the long run and has recently started through Swedish and Somalia universities collaboration[145].

Our review of Somalia serves as a reminder that tackling leishmaniasis in highly insecure context need bold actions. NTD should not be excluded for the health prioritisation and continued as moral imperative[146]. The lack of appropriate diagnostic tools and medicines for the kind of field settings in eastern Africa, therefore, needs to be addressed and shall be of note in the advocacy.

KNOWLEDGE GAPS: EPIDEMIOLOGY OF CL AND LEISHMANIASIS SOCIO-ECONOMIC ASPECTS

Knowing the magnitude of the problem is the first step in addressing it, although assessing the real burden of leishmaniasis remains complex[56]. **Article 2** and **Article 3** focused on areas where considerable knowledge gaps existed. In both papers, we adopted the methodological approach of a systematic review of the evidence.

Cutaneous leishmaniasis or CL has been given lesser priority by countries and the international community due to its non-fatal nature[147]. Nevertheless, CL occurs across vast geographical areas, and the psychosocial burden it entails has recently gained recognition[148]. With the ongoing war in Syria, an increased number of cases have been reported[149,150], not to mention other conflict-related CL outbreaks in Afghanistan, Iraq, and Pakistan in the last decade[151,152]. Epidemics of CL has also been reported following a major earthquake in Bam, Iran, due to activation of several risk factors[153,154]. *L. tropica*, with its anthroponotic transmission, flourishes in urban settings, while the zoonotic *L. major* is considered the main cause in the rural areas of Africa. Some VL high burden countries in eastern Africa are also prevalent for CL, most notably Sudan. The intriguing *L. aethiopica*, confined to the Ethiopian highlands and a pocket in Kenya, causes up to 50,000 cases per year. The lesions commonly evolve to diffuse CL or mucocutaneous forms and are notoriously difficult to treat[155,156]. Several countries in western Africa are known to be endemic for CL, but with less intensity and as a consequence, the problem is less documented. In summary, the epidemiological burden in sub-Saharan Africa (SSA) was largely unknown.

Our systematic review covered all published evidence on CL since the colonial times and included 54 papers. These papers showed high methodological variability, so caution is needed when comparing results. A number of studies evaluated infection prevalence. The Leishmanin Skin Test (LST) was used in community surveys to explore reported foci in Senegal, Guinea, and Mali in the 1980s, with prevalence rates ranging from 5-61%. While LST can only prove exposure to the parasite, other studies use hospital records or active screening to report CL prevalence/incidence of active lesions and the scars. One-third of the studies were case series

and therefore do not reflect the true burden, though they do provide some insight on the clinical features and co-infection with HIV, an emerging threat[157,158]. Passive surveillance at facility level further reflects data paucity at country level, and only during outbreak settings (such as reported from Ethiopia, Sudan, Ghana, and Burkina Faso) that leishmaniasis gained attention. Studies reported the causative species poorly.

CL is generally treated using the same medicines as VL. Therefore, a high number of CL cases stresses the supply lines for both diseases. The current lack of appropriate diagnostic and treatment tools for CL seems to contribute to the lack of quality data from SSA. Underreporting of CL cases is very common as diagnostic methods are not widely available. Moreover, the lack of effective treatment of active lesions and scars leads patients to rely on self-treatment, traditional and folk remedies, which are not captured by the surveillance systems. Evidence are scarce: the 2017 Cochrane review on interventions for Old World Leishmaniasis concluded that there were insufficient studies to be included and eventually could only reported the certainty of evidence for two identified comparison (oral itraconazole and paromomycin ointment) for *L. tropica,* which was very low[71]. Guidance on standardisation of methods for the conduct and analysis of clinical trials of CL have been proposed[159,160], but a new breakthrough for CL is currently not foreseeable in the near future.

We proposed in our study to improve surveillance, at the very least to mitigate outbreak risks. One emerging policy approach is to integrate CL with other NTDs affecting the skin such as Buruli ulcer, leprosy, mycetoma, yaws, lymphatic filariasis, and onchocerciasis. With adequate training, local health workers can identify multiple conditions in a single visit, either at the community level or in schools[161]. An integrated approach to skin NTDs is expected to increase the coverage and cost-effectiveness of interventions[162]. Advocacy to obtain political support as well as resources from stakeholders for this approach is important. Acknowledging the importance of each of these conditions in terms of burden, and the limited resources available to tackle each vertically, the integrated approach may have the potential to advance the control efforts of this diverse group of diseases.

A second knowledge gap that we attempted to address is the socio-economic burden of leishmaniasis (in **Article 3**). Leishmaniasis is intricately linked with poverty[163], but its economic impact on the patients and their households is more difficult to ascertain. Our study systematically identified and reviewed all cost-of-illness (COI) studies on leishmaniasis across the world. From the 14 included studies, there is only one from eastern Africa (Sudan), while a majority (n=11) are from India, Nepal, and Bangladesh. All included papers focused on VL except one (PKDL) and no COI studies were found for CL or MCL. Costing studies from a health system perspective are even more rare and as shown by Brazil, mainly used the top-down approach based on national insurance data, which are non-existent in VL endemic countries in Asia and Africa to date.

We reported a substantial socioeconomic burden due to a visceral leishmaniasis episode (ranging between 11-57% annual households' income), a burden even more pronounced when there is household clustering with more than one VL patient per family. The patients' pathways to eventually reach care varied according to context, but all studies demonstrated that patient and doctor delay clearly augmented the costs incurred. While standardizing the costs to US$2016 for ease of comparison, the direct cost of a VL episode was $760 in Sudan[70] , $189 in India[85] and $76 in Nepal[19]. Although the VL diagnosis and treatment are provided for free in the public sector, other important expenses are not covered and this 'non-medical' cost is particularly important in

Sudan, where transport and food costs remain substantial. This is probably similar in other rural contexts in eastern Africa. Indirect costs in terms of productivity loss are detrimental in the long run and coping strategies to avoid catastrophic health expenditure are commonly reported. This profound impact on household wealth was one of the main arguments WHO used to plead for investment in control efforts for leishmaniasis[116].

Nonetheless, the data on the economic dimension of VL and its control are scanty. Only when all economic evidence is put together can we see the gaps: firstly, from the methodological point of view – COI studies are cross-sectional in nature and may use different category of costs, making comparisons difficult. The current cost evidence for leishmaniasis also is outdated as treatment regimens changed, such as the shift to single-dose AmBisome® in the Indian subcontinent and a shorter duration (17 days) regimen of PM and SSG in Africa. Only one study reported a relatively recent data on economic impact of CL patients (2013-2016) from Sri Lanka[164] . Certainly, there should be more economic evaluations to better inform policymakers. But perhaps the main recommendation we can make on the basis of current findings is that removing access barriers during the care-seeking process and reducing patient and doctor delay will have a major mitigating effect on the vicious cycle of poverty that VL induces.

UPSTREAM DIMENSION OF ACCESS: BARRIERS IN THE R&D FOR LEISHMANIASIS AS NTD

As the previous section demonstrates, the lack of appropriate tools is one of the vital barriers to tackle leishmaniasis in eastern Africa. Optimising the existing diagnostic tests and medicines is important, as the outcome of the current R&D pipeline is still uncertain[165]. All countries in eastern Africa base their national guidelines on the same therapeutic arsenal: SSG, PM and LAMB (AmBisome®); unfortunately, without different drug effectiveness as in the Indian subcontinent. Innovation is therefore critical, also in the light of the HIV-VL co-infection problem in the region; where the therapeutic needs are even more pressing.

In Article 4 of this thesis, we made a case study of MF development and post-marketing access, as it illustrates well the challenges in the domain of R&D for NTDs. The lessons learned are undoubtedly important for the future products and also relevant for access to medicines in general.

Miltefosine (MF) as the only oral drug for leishmaniasis underpinned the big hope to overcome the limitation of injectable drugs. Though discovered serendipitously while being an anticancer drug candidate, MF (Impavido®) was expected to be the breakthrough in leishmaniasis therapy. Unfortunately, its potential was not fully realised due to various access issues. MF reached the milestone of registration in 2002, only 7 years after the public-private partnership (PPP) sponsoring it was created. The company signed an agreement with WHO/TDR motivated by the market opportunity offered by the high burden countries (e.g. India) aiming for elimination[166]. For a mid-sized company -like Zentaris at that time- the attractive features of being part of a PPP was the availability of public assistance, including substantial in-kind public input and expertise from WHO/TDR[167], and trials support from the Indian public research groups. Registration in India was promptly achieved, but negotiations for the WHO-agreed price (for the public/NGO market, aimed at US$60 per course) took longer than expected. As the public market was not accessible by the company, Impavido® was launched first in the Indian private market at the price of US $150 per treatment course—made it out of reach for the poorer patients who

need it. The partnership's failure in the rollout phase of the drug persisted, along with changes in the owners of MF and problematic procurement; resulting in shortages and continued use of already resistant antimonials some years beyond designation of MF as first-line regimen for VL[168].

In brief, the rights of MF was exchanged 4 times and the current company, Knights Therapeutics, registered the drug in the US and obtained the Priority Review Voucher (PRV) in 2014. The PRV is one of the 'pull' incentives designed to stimulate private companies to develop drugs for tropical diseases, awarded when the drug is approved by the U.S. Food and Drug Administration (FDA). The voucher can then be used to reduce FDA review time by about 4 months for another drug (thus gaining market advantage). This voucher can either be used by the same company or sold to a third-party. The PRV for MF was sold to the company Gilead for US$ 125 million, earning Knights a significant windfall – albeit for a product it never helped develop.

In summary, the patent-based, value-maximising model of drug discovery and development is not geared towards diseases of poverty, as we described. It has become increasingly accepted that the pharmaceutical industry, especially the big multinational pharma companies, will not invest on R&D for diseases without viable market, even if governments would make advance market commitments, as these markets are simply too small and not lucrative. Public intervention and regulation is therefore needed, and public-private development partnerships have proven their value. Based on our analysis we identified several key points worth noting for such product development partnership (PDP). One, more concrete and binding conditionality for access should be included in the PDP partners' agreement. Ensuring sufficient safeguards for affordable public access is crucial. Similar calls have also been advocated for donation from the pharmaceutical companies, which is a laudable gesture, but often left the public at the mercy of the donating company[169,170]. Access, including through donation or tiered pricing, and should be backed by enabling regulatory environment, and with sustainability in mind[98].

Since its creation, a PRV has been awarded to 8 drugs with tropical disease indication. The 2014 PRV for MF for leishmaniasis generated calls to the US Congress to amend the drawbacks of the scheme[171,172]. First, to truly reward novelty drugs, not old ones that have been used outside the US for some time (which was the case for MF and three other PRV drugs: artemether-lumefantrine and bedaquiline, and the 2019 awardee triclabendazole). Demonstration of the registering company's involvement in the drug development is also desirable. Second, the PRV awardee should do better in ensuring access[109,173]. Albeit no refinement has taken place for the PRV scheme so far, there has been an encouraging development. In 2017-2018, three drugs which received a PRV were registered or at least supported by a PDP: benznidazole for Chagas disease (Chemo Group/DnD*i*)[174], moxidectin for onchocerciasis (Medicine Development for Global Health, with WHO/TDR)[175] and tafenoquine for *P. vivax* malaria (Medicines-Malaria Venture and Glaxo Smith Kline)[176]. The real impact of the PRV in stimulating R&D for tropical disease is still inconclusive, especially with the decline in PRV value to currently US$80 million (from an average price in 2016 of US$200 million)[177].

Coming back to our last point on MF, we iterated the importance of safeguards for public affordability. High price of medicines has increasingly become a concern even in high-income countries, e.g. for cancer medicines[178]. From the industry perspective, the traditional justification of high drug pricing is to recoup the R&D cost or more recently the 'value-based pricing' (i.e. the costs inherent to the value of drugs for avoiding future cost of more complex, invasive therapy or procedures)[179]. However, analysis has suggested that it is difficult to accurately estimate the cost to make a medicine, ranging from $100 million to a staggering $2.6 billion, depending on the

methods used[180,181]. What we need to emphasise is the significance of public sector contributions to the R&D of medicines. These include funding of basic science research, physical research infrastructure, education of medical research workforces and even incentivizing R&D through tax credits or reductions. For NTDs, the 2017 G-Finder survey reported that public investment accounts to 30-65% of the global investment for R&D[182]. Such public-sector investment has led directly to the discovery and development of leishmaniasis medicines such as MF and PM. Therefore, a claim to recover the full costs of R&D by setting high prices for medicines developed with significant involvement of the public sector seems unfair. Medicines for NTDs should be developed with the public health commitment at the outset, as the patients should not be expected to pay.

In this regard, there have been considerable efforts to improve the R&D system in recent years in the interest of the public. With skyrocketing price of medicines, the attention on this issue is spreading beyond low (and middle) income countries. Initiatives aiming for better global governance on R&D were formed, including (but not limited to): the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) in 2012[183], the United Nations Secretary-General's High-Level Panel on Access to Medicines in 2015[184], and more recently, the WHO/TDR project on Health Product Research and Development Fund: a Proposal for Financing and Operation[185]. Other collaborative efforts are in place, mainly for mapping different facets of R&D, for example the G-FINDER survey and database that reports the global investment in R&D for neglected diseases[106], the new Global Observatory on Health R&D hosted by WHO and the TDR Portfolio-to-Impact R&D modelling tool to analyse the health product pipeline of the poverty-related neglected diseases[186]. Furthermore, there is evidence that the use of TRIPS (Trade-Related Aspects of Intellectual Property Rights) flexibilities as measures to ensure access to medicines for all was more frequent than previously thought[187]. A real convergence towards a global treaty and governance for R&D may still be a wishful thinking[188], but nevertheless the critical mass is forging[189].

In the last decade, leishmaniasis R&D benefitted from steady global funding, with an annual average around $40m per year[182], with almost two-thirds for basic research. High-income countries and multilateral donors made up the most budget (69%), followed by philanthropy (20%) and industry (11%). Leishmaniasis control is in dire need of a vaccine, as well as more effective, oral drug formulations and better diagnostics that can detect early-stage disease. At least one vaccine candidate in clinical development is undergoing evaluation for prophylactic and therapeutic indications[190]. A topical formulation of an existing drug (amphotericin B) is currently in clinical trials for the treatment of cutaneous leishmaniasis[191]. A phase III trial for combination therapy MF/PM for VL is also underway in Ethiopia, Kenya, Sudan and Uganda[192]. Several projects to improve diagnostics for resource-limited settings include optimizing an antigen test (urine-based),, a LAMP-based test for VL and CL[193], and validation of rK28 RDT in the frame of AfriKADIA[194]. In terms of new molecules, there are two pre-clinical compounds that enter clinical development this year (DND*i* 6148 oxaborole and 01690 nitroimidazole class)[9].

With the rapidly changing landscape for R&D for NTDs, our work should serve as compelling evidence on the importance of post-marketing access. The MF case study demonstrated the complexity of ensuring such access, but also that this is indispensable for the patients affected by leishmaniasis. Developing new tools for the disease will be useless if its affordability, availability, and quality is not optimal.

ACCESS DOWNSTREAM: BARRIERS AT HEALTH SYSTEM AND COMMUNITY LEVELS

Once the products are defined, next phase of access begins. When access is translated to timely use of necessary health product/technology, what comes to mind is the process through which the products finally reach the patients. We have approached the issue by focusing on the access barriers occurring at two levels: the supply chain (within the national health system) and the community. Understanding what these barriers were is critical in proving our hypothesis of the access inadequacy. We showed that, while adequate access implies an uninterrupted supply of diagnostics and medicine, in reality many barriers exist, and they may deter care-seeking process by the patients.

In both works (**Article 5 and Article 6**), we employed qualitative research methods to gain a rich in-depth understanding regarding the actual barriers in the field to diagnosis and treatment of VL. **Article 5** highlights that the robustness of the health system and health service organisation in each country is paramount. The country capacity serves , as mediator between challenges at international (see access upstream section) and national level in ensuring effective supply of commodities for health. In **Article 6**, we engaged with the community living in Gadarif state of Sudan, which has been a hotspot of VL since decades. How exactly do former patients perceive the care they received, and what are the opinions of community members and leaders or the health care workers? What stood in the way to utilise the available health services, and have these barriers changed? **Article 5 and 6** are interrelated and provide insights into a complexity of access in Sudan and beyond.

Disruption of supply is common in eastern Africa countries. One example is the unprecedented demand related to VL outbreaks in South Sudan in 2012-2014 causing ruptures of PM, and procurement difficulties of RDTs necessitating lending and borrowing among health actors. Causes of shortages are complex and involve both supply and demand factors, and existing data on these issues are not robust. Therefore, we explored the views of purposively selected key informants, representing both the demand side (i.e. national programme or ministry of health, implementing NGOs and international organisation) and the supply side (procurement agencies and manufacturers). This is the first comprehensive study involving key stakeholders- focusing on leishmaniasis commodities supply in eastern Africa.

The key barriers to effective supply of leishmaniasis medicines and diagnostics that they identified were related to 1) selection and manufacture (issues of single producer, quality concern, …) 2) poor forecasting (issues of unreliable data, fluctuation, ...); 3) procurement (complex process, parallel system) and 4) distribution and delivery (logistical challenges,). These were directly influenced by the gaps in the related health system building blocks – coordination and communication, financing mechanisms and regulatory environment. The manufacturers' perspective was evidently informed by their economic considerations (questioning why the burden estimates of VL do not translate linearly to orders and a general reluctance to register their products in endemic countries without private market), while on the users' side there is a sense of frustration that things are not changing fast enough in the last decade, despite increased momentum currently spearheaded by WHO[195]. The current available mechanisms for enhancing access to VL drugs each have their drawbacks as discussed below.

Donation - In December 2011, Gilead Sciences agreed to donate 445,000 vials of AmBisome® (LAMB), managed by the WHO, for the treatment of ~50,000 VL patients. This agreement as extended in 2016 for another 380,000 vials[48,49]. Initially, the scope of this donation

was limited and strict. Though donations programmes are usually seen positively, they have their downsides. Companies may be motivated to donate because of the related tax reductions . In the specific case of LAMB, this large donation could discourage other companies to enter the market of alternative or generic LAMB formulations[197]. Extending the donation would only be a solution if it sustainably covered the needs of all leishmaniasis patients in developing countries who need LAMB. Donation of drug for NTD health programme is therefore laudable, yet sustainability and its unintended consequences must be mitigated[114,198]. The importance of drug donations in terms of cost-saving and reaching an elimination goal does not absolve the public health sector to develop the necessary long term vision.

Preferential pricing or tiered pricing. Amongst the leishmaniasis medicines, SSG and PM are currently sold at-cost or with negligible profit. AmBisome®, prior to the donation programme, was also available at a lower price for the public sector in VL endemic countries (US$20 per vial in 2006, and US$18 per vial in 2008). This tiered pricing may have increased access to LAMB in the Indian subcontinent, but was probably still too high for many health systems in developing countries (based on a cost-effectiveness study, this price has been called to be further reduced to US$10 per vial[47]). Knights also set up preferential pricing for MF for the non-profit sector, tied to the minimum order requirement to fulfil a batch production. This has proven to be quite a barrier for small procurers, and even more so since this price has been increasing over the years[199]. Tiered pricing is not advantageous when not pushed by a strong competitive environment, but rather by arbitrary divisions between markets and/or countries by the company, i.e. concentrating more decision-making power in the hands of sellers vis-à-vis consumers[200].

Competition with generic producers – Currently, this does not exist for any of the leishmaniasis medicines. For antimonials, the generic SSG is produced by Albert David, India (there are also branded formulations, namely Pentostam® and Glucantime® but they are not used in Africa). Only perhaps for MF and LAMB there will be interest from other manufacturers as there exist lucrative potential sales for the other indications of LAMB than in occasional small-scale public procurement for national leishmaniasis programmes[201]. For MF, with potential expansion of indication, including the Free Living Amoeba, or for possible higher demand for leishmaniasis in Latin America, there has been several expressions of interest, including generic producers in India and other. Despite the fact that more producers are welcome, the necessity to respect the quality requirements is also of utmost importance, and more engagement with schemes such as WHO Pre-Qualification Program (PQP), Expert Review Panel (ERP) and Collaborative Registration Procedure (CRP) is needed.

Coming back to our work, we laid out as well the perceived progress and actions moving forward. Several have been in place, yet need further refinement, e.g. a pooled procurement approach and establishment of a rotating stock for eastern Africa. Pooled procurement refers to arrangement where financial and non-financial resources are combined across various purchasing authorities to create a single entity for purchasing on behalf of the individual purchasing authorities[202]. Pooled procurement has been used at subnational, national and international levels such as for Human African Trypanosomiasis and to some extent as well in the Global Fund mechanism, but for leishmaniasis it has been largely underused. A regional approach towards tackling leishmaniasis in eastern Africa is already starting through annual exchange of information, but more efforts are needed to realise more concrete collaboration. New funding

injections through collaborative platforms such as KalaCORE could contribute to improving the supply chain and alternative strategies should be explored for eastern Africa.

In our view, the main stakeholders must come together in a more united front, define paths and mechanisms to strengthen the supply chain for leishmaniasis commodities, especially since no private market is involved.

As the diagnostics and medicines are delivered to the health facilities, now as the last phase of access, the patients should utilise them. It is important to reiterate from the outset that suboptimal access to leishmaniasis medicines is only one of the many challenges relating to people's access to appropriate care. Patient access to adequate care depends on a range of factors such as financial resources, availability and skill set of health workforce, health care infrastructure and physical access to health services. As these factors are inextricably linked, many problems and challenges related to the provision of VL medicines are likely to be common across other parts of the health care system.

Our work in **Article 5** explored the barriers faced by the community in Gadarif state in Sudan, using the Andersen's health utilisation conceptual framework, complemented with the three delays model by Thaddeus&Maine[203]. A diverse population with large farming livelihood that attracts migrant workers even from the bordering north-west Ethiopia, Gadarif provides the mosaic needed to understand what the 'suffering' is all about when we speak of NTDs.

There has been relatively less evidence focusing on the worldview of patients' and their families. Even if Gadarif has known leishmaniasis since the 1990s when an outbreak occurred in Barbar el Fugara village and has attracted scientific attention since, the interventions have focused on expanding the number of hospitals that provide VL care. Meanwhile, delay to seek care was attributed to low knowledge and financial barriers[88]. VL has its vernacular name in many contexts, including in the two river basins in Gadarif, and our work demonstrated that even if knowledge has increased, some misconceptions persisted.

The multiple trajectories in seeking care is also constrained by the various symptoms of VL (fever, splenomegaly, wasting – each requires its own remedy) and the difficulties in getting positive diagnosis. Multiple visits to health care providers were consistently needed to access VL diagnosis. The symbolic '*Alhamdulillah*' or *Praise be for Allah* (God Bless) reflects the relief when finally, VL is diagnosed and treatment could be commenced. Furthermore, the RDT which remains positive for some years for VL patients appears not to be fully trusted by health providers in this endemic area. A paying, private lab in the Gadarif city has become the '*de facto'* referent diagnostic laboratory. The use of RDTs use in VL endemic countries in eastern Africa is still not optimal and requires further study[73].

The costs involved in VL care remain a significant barrier to seek care for the household, moreover during the rainy season when transport costs increase substantially. Lower priority when female family members are affected–a long-suspected gender bias–may also have financial aspects in it[123]. Access has also become inequitably distributed between and within localities, as the quality of care in hospitals varies, including level of free-of-charge service that differs between NGO-supported hospitals and non-supported. Unavailability of trained staff and diagnostic/treatment demotivate people to seek care earlier.

Our study was conducted in concurrence with another qualitative study on migrant workers in the bordering Ethiopia[204]. Essentially, both studies provide a comparison of the

vulnerability to VL among the two populations, where the borders are illusory as in Sudan there are also residents engaging in transitory work. For the migrant workers in Ethiopia, the labour condition further complicates access, e.g. workers unable to receive salary advances, compensation for partial work, sick leave or simply permission to seek care when they fall ill. Decentralisation of diagnostic tests to primary healthcare facilities was called for.

Contrary to what is prescribed by national policy and guidelines, our study participants in Sudan reported poor access to diagnosis and, consequently, significantly delayed access to treatment. To reduce health disparities and the VL burden, interventions needs to be tailored to address the barriers at individual, society and health system levels outlined in our paper. Only when the complexities of individuals and households in relations to VL are really understood (and measured) are the needs of affected population likely to be prioritised and addresses.

POLICY IMPLICATION, FUTURE RESEARCH AND PERSPECTIVES

An increased awareness towards NTDs has resulted in several milestones, including increased resources (such as pharmaceutical donations) and a more effective partnerships and governance[205]. Several milestones that are specific to (visceral) leishmaniasis is depicted in **Figure 10** below. As we can see, the Indian sub-continent Kala-Azar Elimination programme has amassed significant political, financial and scientific commitments, while the endgame for eastern Africa is clearly still far.

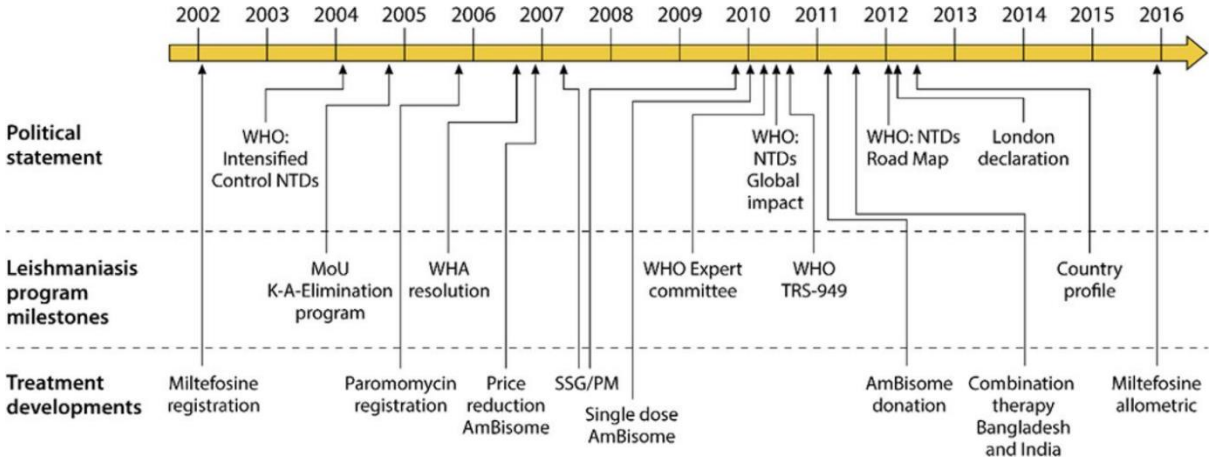

Figure 10. Chronogram of benchmarks in visceral leishmaniasis (adapted from Alves et al, 2018 and WHO Leishmaniasis timelines of fact: https://www.who.int/leishmaniasis/disease/Leishmaniasis-interactive-timelines/en/).

The uptake of the policy recommendations issued in the seminal 2010 WHO technical guideline "Control of Leishmaniasis" was generally slow, and until date, no real breakthrough in novel control options has been seen in eastern Africa. Despite continued support and involvement from donors and international agencies, the disease remain hidden in remote rural areas and also largely silent, as the people affected or at risk have little political voice. NTDs traditionally rank low in national or international agenda, and leishmaniasis has been dubbed 'neglect within neglect' as it is not attributed the same level of resources or attention than other NTDs amenable to mass preventive chemotherapy. For all these reasons, leishmaniasis control needs to consider the full spectrum of access in the interventions. Whether a greater return on investment would

be gained from improving access to preventative interventions (e.g. vector control or others), than from access to newer, field-friendly medicines, remains to be seen.

Designation of 'neglect' stops being useful when nothing happens (CL is also considered as a 'neglected' leishmaniasis as compared to the fatal or severe forms), and as we can see in leishmaniasis R&D landscape, there are quite several positive developments whether specific or rather global (funding stream and flows, impacts of PPP and PDPs, advocacy towards fairer R&D system, etc). We described the importance of partnerships and collaborations (through which leishmaniasis has benefited), and nevertheless, a cautionary attitude is warranted, as MF case study has shown. Our work on access, both upstream and downstream, underlines the vital role of the governments (and public sector at large) to step up in owning up their responsibilities towards leishmaniasis patients.

Through our work we contend the following concluding messages; one, despite progress in NTDs response worldwide, for leishmaniasis there are inequalities in different parts of the word and eastern Africa has suffered the brunt of neglect. Access to care in this region urgently needs to be addressed in a more comprehensive way. Second, a promising pipeline of new chemical entities (NCEs) and repurposed therapies for leishmaniasis is not sufficient. The next decade should also do better in ensuring that new tools are accessible, affordable and available for the people who need them. Access is a multifaceted spectrum, and this should guide the efforts to tackle leishmaniasis. Political support is pivotal and continued advocacy will remain a necessity.

Our findings highlighted several further research priorities spelled out in each article. Several unanswered questions should be followed up with quantification approaches (such as for burden, or effectiveness of supply chain); while at the same time the view to understand the lived experiences and challenges that affect patients and their families need to be bolstered. Lastly, we propose to develop a better measure of progress in improving access to care for leishmaniasis in Africa based on components described in this thesis. Current monitoring efforts only focus on measurement of availability of medicines in health facilities, separate from measures of affordability which relied on information from stakeholders. Quality (of care, including the diagnosis and treatment) currently is difficult to assess due to absence of data. Improving access needs target measurements, a robust monitoring and accountability system – framework that has been called by Paul Hunt, former UN Special Rapporteur on the Right to Health[206]. The three steps include appropriate collection of data, independent review, and the necessary corrective action; these certainly can be adapted for leishmaniasis context in eastern Africa.

The table below summarises options and recommendations of actions that might enhance access to leishmaniasis medicines and diagnostics in eastern Africa.

Recommendations	Level of action requred		Time of action			Proposed actions taken by			
	Local/National	International	Short	Medium	Long	Government	Industry	Health workers	Patients
Improving adoption									
Registration of all leishmaniasis medicines in endemic countries	●	○				◊	□		
Regulatory pathways for diagnostics/medical devices	●	○				□			
All leishmaniasis drugs are Pre-Qualified		●					□		
WHO treatment guidelines recommendations are adopted	●					□		◊	
Regulatory harmonisation accross region		●				□			
Advocacy for leishmanaisis from national budget	●					□		◊	◊
Improving availability									
Drugs included in the National Medicine List are registered	●					□			
Implementation of forecasting/quantification platform, eg DHIS2	●	○				□		◊	
Improve coordination and communication	●	○				□	□	□	□
Pooled procurement mechanisms for eastern Africa	○	●				□	◊		
Assess feasibility of integration of supply with essential medicines	●					□		◊	
Increase coverage of care in endemic areas	●					◊		□	
Improving quality									
All leishmaniasis drugs undergo Pre-Qualification		●					□		
Adherence to the national clinical guidelines	●							□	◊
Increase capacity and skills in-country in clinical and pharmaecutical management	●					□			
Continued engagement with community to reduce delay in seeking care	●							□	□
Improving affordability									
Policy to de-link price and cost of R&D, along with improved tranparency	○	●				□			
Access plan included in the PDPs portfolio		●					□		
Realign R&D incentives such as PRV to the public health needs and impact		●				□	□		
Prepare sustainability plan after donation	○	●				□	◊		
More united front accross stakeholders when negotiating for better price	○	●				□	◊	□	
Leishmaniasis care included in the UHC package	●					□			◊
Mechanisms to reduce non medical costs of leishmaniasis	●					□			◊

Key:
Time frame for action*Short term: within 1-5 year; medium term: 5–10 years; long term: more than 10 years.
Proposed actions taken by: Government Industry :
Primary level of action ●; Complementary level of action ○
Primary actor □; Complementary actors ◊

CHAPTER 6
CONCLUSIONS

The current efforts to control visceral leishmaniasis (VL) in eastern Africa need to deal first and foremost with access to care, which sadly remains inadequate. Conflict-affected areas require innovative strategies. Developing improved diagnostic and treatment control tools is crucial, and so is ensuring that these tools reach the patients who need them the most.

Our work provides these conclusions:

1. Access to care in Somalia is limited due to its fragile context and more appropriate tools for such conflict-affected settings are urgently needed.
2. Cutaneous leishmaniasis in sub-Saharan Africa has been overlooked and critical knowledge gaps remain.
3. In endemic setting, the economic burden of leishmaniasis is still significant, and should be part of universal health care agenda.
4. In current R&D landscape, the role of public private partnerships are important for leishmaniasis product development. However, the case study of miltefosine, the only oral drug, reminds us on the importance in ensuring access once a product receives market authorisation.
5. In VL endemic area in Sudan, the community perspectives on access to care is far from satisfactory, and these insights should guide future intervention(s).
6. Effective supply chain for leishmaniasis diagnostic and medicines in eastern Africa possesses potentials to be improved, which requires more collaboration amongst stakeholders.

CHAPTER 7
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Tell me, what is it you plan to do

with your one wild and precious life?

—Mary Oliver

ANNEXES

1. ADDITIONAL ARTICLE

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Field safety and effectiveness of new visceral leishmaniasis treatment regimens within public health facilities in Bihar, India

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Abstract

Background

In 2010, WHO recommended the use of new short-course treatment regimens in kala-azar elimination efforts for the Indian subcontinent. Although phase 3 studies have shown excellent results, there remains a lack of evidence on a wider treatment population and the safety and effectiveness of these regimens under field conditions.

Methods

This was an open label, prospective, non-randomized, non-comparative, multi-centric trial conducted within public health facilities in two highly endemic districts and a specialist referral centre in Bihar, India. Three treatment regimens were tested: single dose AmBisome (SDA), concomitant miltefosine and paromomycin (Milt+PM), and concomitant AmBisome and miltefosine (AmB+Milt). Patients with complicated disease or significant co-morbidities were treated in the SDA arm. Sample sizes were set at a minimum of 300 per arm, taking into account inter-site variation and an estimated failure risk of 5% with 5% precision. Outcomes of drug effectiveness and safety were measured at 6 months. The trial was prospectively registered with the Clinical Trials Registry India: CTRI/2012/08/002891.

Results

Out of 1,761 patients recruited, 50.6% (n = 891) received SDA, 20.3% (n = 358) AmB+Milt and 29.1% (n = 512) Milt+PM. In the ITT analysis, the final cure rates were SDA 91.4% (95% CI 89.3–93.1), AmB+Milt 88.8% (95% CI 85.1–91.9) and Milt+PM 96.9% (95% CI

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95.0–98.2). In the complete case analysis, cure rates were SDA 95.5% (95% CI 93.9–96.8), AmB+Milt 95.5% (95% CI 92.7–97.5) and Milt+PM 99.6% (95% CI 98.6–99.9). All three regimens were safe, with 5 severe adverse events in the SDA arm, two of which were considered to be drug related.

Conclusion

All regimens showed acceptable outcomes and safety profiles in a range of patients under field conditions. Phase IV field-based studies, although extremely rare for neglected tropical diseases, are good practice and an important step in validating the results of more restrictive hospital-based studies before widespread implementation, and in this case contributed to national level policy change in India.

Trial registration

Clinical trial is registered at Clinical trial registry of India (CTRI/2012/08/002891, Registered on 16/08/2012, Trial Registered Prospectively).

Author summary

Treatment is one of key strategies for visceral leishmaniasis control and elimination. Historically a number of monotherapy drugs for VL treatment were used in India including pentavalent antimonials, amphotericin B deoxycholate (AmB), and miltefosine (MF). With the limited number of drugs available there was a need to preserve existing drugs and to develop shorter and safer treatment regimens. Three short-course combination regimen including AmBisome, miltefosine and paromomycin have been evaluated in a phase III clinical trial conducted in India (2008–2010). All showed an excellent safety profile and an efficacy of at least 97% in controlled conditions. In 2010, WHO recommended the use of new short-course treatment regimens in kala-azar elimination efforts for the Indian subcontinent. Although phase 3 studies have shown excellent results, there remains a lack of evidence on a wider treatment population and the safety and effectiveness of these regimens under field conditions within national program settings. This study was implemented in field conditions with treatment provided by government doctors, providing further evidence for scaling up new regimens in national program contexts within the public health sector and contributing to national policy change in India.

Introduction

Visceral leishmaniasis (VL, also known as kala-azar) is an ultimately fatal disease with 10,311 reported cases in the Indian subcontinent in 2014 [1], although under-reporting means that the real number is likely to be higher [2]. The number of reported cases in India has progressively declined in recent years from 33,187 in 2011 to 6245 in 2016, an approximate annual reduction of 30–35% [3]; this may be due to a number of factors, including the VL elimination initiative in South-East Asia, the natural incidence cycles of the disease, and improvements in social conditions.

Early and effective treatment is one of the pillars of the VL elimination strategy. Historically, a number of drugs have been used in India in monotherapy, including pentavalent

antimonials, amphotericin B deoxycholate, miltefosine, paromomycin, and liposomal or lipid formulations of amphotericin B [4,5]. Pentavalent antimonials, the only available treatment for VL for decades, are no longer recommended in the most endemic state of Bihar due to development of resistance, with treatment failure reaching more than 60% in some villages [6].

Miltefosine was introduced into the national program as an orally administered 28-day monotherapy in 2005, with very satisfactory cure rates. However, its efficacy decreased from 96% to 90% within a decade of use in India [7,8], with higher reported failure rates in children, likely to be related to the inappropriate linear dosage which was used [9].

In Nepal, a 10% failure rate for miltefosine at 6 months doubled to 20% at 12 months follow-up. With limited drugs available, there was a need to preserve the existing drugs and to develop shorter and safer treatment regimens [10]. Amphotericin B deoxycholate is a highly efficacious drug with a cure rate of 97%, but requires in-patient treatment for up to a month, which, coupled with infusion and drug-related adverse effects, has limited its utility [11].

AmBisome (Gilead Pharmaceuticals, Foster City, CA, USA) is a brand name for liposomal amphotericin B (AmB). It has been studied extensively at a range of doses and shows excellent safety and efficacy. In a study carried out by Sundar *et al*., a single 10 mg/kg dose of AmB had 95.7% efficacy and was safer than conventional amphotericin B deoxycholate [11].

An earlier phase III non-inferiority clinical trial in India comparing conventional amphotericin B deoxycholate with three different low-dose combinations (AmBisome 5 mg/kg plus 7 days of miltefosine; AmBisome 5 mg/kg plus 10 days of paromomycin; miltefosine plus paromomycin both for 10 days) found all three to be non-inferior with final cure rates of $\geq$97% at 6 months [12]. In 2010, the WHO recommended these combination regimens along with a single dose of 10mg/kg AmBisome (known as Single Dose AmBisome/SDA) as first line treatments in South Asia [13] based on economic, safety, and efficacy considerations [14–16].

However, these hospital-based studies were restricted in sample size, conducted under very controlled conditions, and mostly excluded unwell or patients from more vulnerable groups (e.g. pregnant women or the very young/old). As such, the Drugs for Neglected Diseases *initiative* (DND*i*), in collaboration with Rajendra Memorial Research Institute of Medical Science (RMRIMS), State Health Society Bihar, and Médecins Sans Frontières (MSF), conducted this field effectiveness study to better determine the safety and feasibility of these treatment regimens under field conditions within public healthcare facilities in Bihar, India.

Methods

Ethics statement

The protocol was approved by the Institutional Ethics Committee of RMRI Patna, Ethics Review Board of Mèdecins Sans Frontières, London School of Hygiene & Tropical Medicine (Ref 6046), Indian Council of Medical Research, Drug Controller General of India and National Vector Borne Disease Control Programme. Written informed consent was obtained by a treating physician. For children, consent of parents or of a legal representative was obtained.

Trial design

This study was an open label, prospective, non-randomized, non-comparative multicenter phase IV clinical trial conducted through government hospitals and primary health clinics (PHCs) in Bihar state, India. The study was conducted from August 2012 to September 2015 in two districts (Vaishali and Saran) and at the Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), a government research institute specializing in VL located in Patna.

Inclusion and exclusion criteria

All patients meeting a case definition of VL defined as fever for more than 2 weeks, splenomegaly, and confirmed with a positive rK-39 rapid diagnostic test (InBios, USA) were included in the study. Relapse cases with a confirmatory parasitological diagnosis were also eligible. Patients with concurrent PKDL, HIV and those reporting a history of hypersensitivity to the investigational drugs were excluded.

Upon confirmation of VL, written informed consent was obtained by a treating physician. For children, consent of parents or of a legal representative was obtained. Prior to treatment, blood was taken for haemoglobin, alanine aminotransferase (ALT), aspartate aminostransferase (AST), and serum creatinine. Other tests were performed when medically indicated. For women aged 12–55 years, a urinary pregnancy test was also conducted, with all pregnant women being referred for SDA treatment. Due to the teratogenicity of miltefosine, women with child-bearing potential unwilling to use long-acting injectable contraception during and for three months after treatment were also referred for SDA treatment.

Height and weight were measured for all patients at admission. Anthropometric indicators appropriate for patient age were calculated using the latest World Health Organization (WHO) Multicentre Growth Reference [17]. Severe wasting was defined based on WHO criteria (weight for height Z-score <-3 for children <5 years; BMI-for-age Z-score <-3 for those 5–19 years; and BMI <16.0 for adults). Severe anaemia was defined as haemoglobin <7 g/dL for children <5 years; <8 g/dL for 5 years and older; moderate anaemia defined as <11 g/dL but above the cut-off for severe anaemia [18].

Patients with haemoglobin <4 g/dl, serious concomitant infection (e.g. severe pneumonia), complicated severe malnutrition, TB/VL co-infection, or children <2 years of age were referred to the MSF VL treatment unit within Hajipur district hospital or RMRIMS for further specialist management. These patients were treated with SDA as per physician decision and included in the study.

Treatments

The three regimens evaluated were: a 10 mg/kg single intravenous dose of AmBisome (SDA); a 5 mg/kg single intravenous dose of AmBisome plus 7 days of linear dosage oral miltefosine (AmB+Milt); and 11 mg/kg intramuscular base paromomycin plus linear dosage oral miltefosine for 10 days (Milt+PM). Linear dosage of miltefosine was 2 doses of 50 mg (morning and evening) for patients ≥12 years weighing more than 25 kg, or a single morning dose of 50 mg for those weighing less than 25 kg. Children of 2–11 years were given miltefosine at a dose of 2.5 mg/kg/day orally divided into two daily doses.

The SDA regimen was administered in 5% dextrose over approximately 2 hours after completion of a test dose of 1 mg to check for hypersensitivity over 30 minutes; patients were discharged the following day from the district hospital where clinical conditions allowed a safe return home. The AmB+Milt regimen consisted of AmBisome 5 mg/kg, administered as above on day 1, with oral miltefosine on days 2 to 8 to be taken at home with advice to return in case of any adverse event. The Milt+PM regimen consisted of the oral miltefosine dose plus intramuscular paromomycin (11 mg/kg/day in a single daily dose) given concomitantly daily for 10 days. Patients treated at the district hospital were admitted to a VL ward for the 10 days of treatment, whereas patients enrolled at PHC level were managed on an outpatient basis, returning each day for the injection. Patients who failed to return for ambulatory treatment were actively traced by telephone and, if necessary, in person to ensure maximum compliance.

Following national regulatory recommendation as part of the study approval process, children were only treated at the district hospitals under the supervision of a paediatrician. At the specialist

RMRI facility, all three modalities were used, based on clinician decision. Patients that relapsed with any of the three treatment regimens were given rescue treatment as per physician decision.

Follow-Up

Patients were asked to return for two post-treatment follow-up visits. The first was scheduled 7–20 days after treatment onset to assess initial cure. A second follow-up visit was planned at 6 months (with a 5–10 month window period) after treatment onset, to assess final cure. Patients were actively traced if they did not attend follow-up visits.

Outcomes

Treatment stopped was defined as treatment stopped early by the attending clinician for any reason.

Default was defined as failure to finish treatment against medical advice.

Relapse was defined as recurrence of clinical symptoms and visualization of parasites in spleen or bone marrow aspirate before the 6 month follow up period.

Death was reported if it occurred from any cause up to 6-months post-treatment.

Lost to follow-up was defined as a patient who was unable to be traced at the 6 months follow up window.

For effectiveness analyses, the primary outcome was final cure defined as a negative test of cure at the end of treatment, absence of clinical signs and symptoms of VL and no relapse up to 6 months follow-up.

Data analysis and statistical methods

Sample size. Since the objective of the study was to evaluate the effectiveness and safety of each new treatment modality, the sample size requirement was based around the precision with which effectiveness and safety could be estimated. Assuming a risk of failure of 5% at 6-months follow-up, a sample size of 225 patients per arm would allow for an effectiveness estimation with 3% precision. Since treatment modality allocation was planned to be different between sites, and the patient population might not be homogeneous (referral hospital vs PHC in different districts), an adjustment was applied using a conservative design effect of 4 to account for between-centre variability. In this case, a failure risk of 5% could be estimated at around 5% precision with 300 patients per arm.

Statistical analysis. Two effectiveness analyses were performed. In the intention-to-treat (ITT) analysis, all patients who received at least one drug dose were included; those with treatment stopped, treatment default, or lost to follow-up at 6 months were considered as treatment failures. In the complete case analysis, those with treatment stopped, default, or lost to follow-up at 6 months were excluded. A single patient with post-kala-azar dermal leishmaniasis (PKDL) treated before the 6-month follow-up was considered a treatment failure for the ITT analysis, but was excluded from the complete case analysis. Analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC, USA). Statistical differences were tested in univariate analyses using Chi Square test, Fisher Exact test, Wilcoxon Rank Sum, or Kruskal-Wallis tests as appropriate. Multivariable logistic regression models were constructed, and model fit tested using the Hosmer and Lemeshow Goodness-of-Fit Test. Inclusion of candidate variables was based on measures of clinical history and severity that were judged to potentially influence disease response; no automated variable selection was used for inclusion. Drug regimen variables were maintained in the model; other variables were eliminated at $p>0.05$ using a stepwise backwards elimination procedure, in order to construct a model for treatment failure that explored the role of potential risk factors and confounders. Confounding was ruled out for all covariates tested (sex, liver and renal function tests, wasting, severe anemia).

Safety. The adverse events reporting period for this trial lasted from the administration of the first dose of study medication until the initial outcome assessment. All adverse events (related or not related to medication) that occurred during the adverse event reporting period specified in the protocol were evaluated by a physician and reported in the register. Each adverse event was classified by the investigator as serious or non-serious. An adverse event was defined as serious if it is either fatal or life-threatening, or requires or prolong hospitalization, or resulting in persistent or significant disability or a congenital anomaly/birth defect. Serious adverse events were recorded from screening until 6-months follow-up and classified by severity, seriousness, relationship to study drug, and resolution.

Results

A total of 1,761 patients were recruited, 534 (30.3%) children (≤12 years) and 1,227 (69.7%) adults (>12 years). Male predominance was more marked for adults than for children (769/1227 [62.7%] vs 299/534 [56.0%]; p = 0.008). 891 (50.6%) of patients were treated with the SDA regimen, 358 (20.3%) patients were treated with the AmB+Milt regimen and 512 (29.1%) patients were treated with the Milt+PM regimen in the study (Table 1). Milt+PM was used predominantly in Chapra district hospital (Saran District) and Saran PHCs; AmB+Milt in Hajipur District Hospital (Vaishali District) and Vaishali PHCs and SDA almost exclusively in Hajipur District Hospital (Vaishali District). Chapra district hospital treated 378 patients (21.5%), Vaishali district hospital treated 1,052 patients (59.7%), 96 patients (5.5%) were treated in a tertiary referral centre (RMRI), and 235 patients (13.3%) were treated at primary health care centres in both districts (120 in Saran PHCs and 115 in Vaishali PHCs) (S1 Table). Specific regimens were assigned by treatment site, leading to collinearity between regimen and site. (Table 1 and S1 Table).

Although not significantly consistent, patients treated with SDA and Milt+PM (a majority of whom were treated at district hospitals) were younger, more likely to be female, and to present with severe wasting than those treated with AmB+Milt. The minority of patients treated at the RMRIMS had a significantly longer reported duration of illness (median of 8 weeks as compared to 4 weeks in other sites).

Severe anaemia was more common in the SDA treatment arm. ALT levels were higher in the AmB+Milt arm, whereas AST levels were higher in the SDA and AmB+Milt arms than in the Milt+PM arm (Table 1).

Overall, 1,684 patients (95.6%) completed the 6-month follow-up visit. Thirteen (0.7%) patients did not complete treatment or had their treatment stopped by a study physician, and 64 patients (3.6%) were lost to follow-up at 6 months. Baseline characteristics of patients lost to follow-up at 6 months (n = 64) differed from those who returned (n = 1697) for their follow-up visits (S2 Table).

6-month effectiveness analysis

In the ITT analysis, the final cure rate for SDA was 91.4% (95% CI 89.3–93.1), AmB+Milt 88.8% (95% CI 85.1–91.9), and Milt+PM 96.9% (95% CI 95.0–98.2). In the complete case analysis, cure rates were SDA 95.5% (95% CI 93.9–96.8), AmB+Milt 95.5% (95% CI 92.7–97.5) and Milt+PM 99.6% (95% CI 98.6–99.9) (Table 2).

Factors associated with relapse at 6 months

Relapse rates varied by drug regimen and were higher for children than for those older than 12 years (Tables 3 and 4). Those with illness that had lasted 8 weeks or less were also more likely to have relapse at 6 months.

Table 1. Baseline patient characteristics and completeness of follow-up by treatment arm.

	SDA[1] (N = 891)	AmB+Milt[2] (N = 358)	Milt+PM[3] (N = 512)
Demographic characteristics			
Mean age (years [SD])	24.8 (16.9)	30.4 (17.6)	23.1 (17.8)
Age range (years)	2–80	3–75	2–70
Age ≤ 12 years N (%)	271 (30.4)	74 (20.7)	189 (36.9)
Age > 12 years N (%)	620 (69.6)	284 (79.3)	323 (63.1)
Male N (%)	510 (57.2)	247 (69.0)	311 (60.7)
Recruitment site			
Chapra District Hospital (Saran)	4 (0.5)	0	374 (73.1)
Hajipur District Hospital (Vaishali)	828 (92.9)	218 (60.9)	6 (1.2)
RMRI (Patna)	59 (6.6)	25 (7.0)	12 (2.3)
Saran district PHCs	0	0	120 (23.4)
Vaishali PHCs	0	115 (32.1)	0
Clinical characteristics			
Weeks of illness			
Mean [SD]	7.3 (8.4)	6.7 (6.2)	7.0 (6.0)
Median [IQR]	4 (3–8)	4(3–8)	4 (4–8)
Severe wasting N (%)[4]	143 (16.0)	39 (10.9)	88 (17.2)
Weight (mean [SD] in kg)	36.6 (15.2)	40.9 (14.0)	34.6 (15.5)
Hemoglobin (mean [SD] in g/dL)	8.5 (2.0)	9.1 (2.0)	9.3 (1.8)
Anemia[5]			
Mild or none	103 (11.6)	66 (18.4)	91 (17.8)
Moderate	427 (47.9)	189 (52.8)	307 (60.0)
Severe	361 (40.5)	103 (28.8)	114 (22.3)
Creatinine (mean [SD] in μmol/L)	0.7 (0.3)	0.8 (0.3)	0.8 (0.3)
Alanine aminotransferase			
Moderate elevation (49–199) N (%)	251 (28.2)	128 (35.8)	152 (29.7)
Marked elevation (≥200) N (%)	32 (3.6)	17 (4.8)	11 (2.2)
Aspartate aminotransferase			
Moderate elevation (49–199) N (%)	444 (49.8)	189 (52.8)	220 (43.0)
Marked elevation (≥200) N (%)	90 (10.1)	44 (12.3)	33 (6.5)
Completeness of follow-up			
Initial follow-up N (%)	885 (99.3)	355 (99.2)	508 (99.2)
6-month follow-up N (%)	853 (95.7)	333 (93.0)	498 (97.3)
Time until 6-month follow-up Median (IQR)	195 (191–209)	194 (190–206)	203 (190–238)

[1]Single dose AmBisome

[2]AmBisome + miltefosine

[3]Miltefosine + paromomycin

[4]Severe wasting defined as weight-for-height Z-score <-3 for children <5 years; BMI-for-age Z-score < -3 for those 5–19 years; and BMI <16.0 for adults

[5]Severe anemia defined as hemoglobin <7 g/dL for children < 5 years; <8 g/dL for 5 years and older; moderate anemia defined as falling above the cutoff for severe anemia and <11 g/dL.

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Table 2. Cure at 6 months, by treatment regimen and age group.

	SDA[1]	AmB+Milt[2]	Milt+PM[3]
All ages			
Intention-to-treat (N = 1761 patients)			
Cured[4] / total	814/891	318/358	496/512
Cure rate % (95% CI)	91.4 (89.3–93.1)	88.8 (85.1–91.9)	96.9 (95.0–98.2)
Complete case (N = 1683)[5]			
Cured / total	814/852	318/333	496/498
Cure rate % (95% CI)	95.5 (93.9–96.8)	95.5 (92.7–97.5)	99.6 (98.6–99.9)
Age ≤12 years			
Intention-to-treat (N = 534 patients)			
Cured / total	250/271	67/74	184/189
Cure rate % (95% CI)	92.3 (88.4–95.1)	90.5 (81.5–96.1)	97.4 (93.9–99.1)
Complete case (N = 527)[6]			
Cured / total	250/268	67/73	184/186
Cure rate % (95% CI)	93.3 (89.6–96.0)	91.8 (83.0–96.9)	98.9 (96.2–99.9)
Age >12 years			
Intention-to-treat (N = 1227)			
Cured / total	564/620	251/284	312/323
Cure rate % (95% CI)	91.0 (88.4–93.1)	88.4 (84.1–91.9)	96.6 (94.0–98.3)
Complete case (N = 1156)[7]			
Cured / total	564/584	251/260	312/312
Cure rate % (95% CI)	96.6 (94.8–97.9)	96.5 (93.5–98.4)	100 (98.8–100)

[1]Single dose AmBisome

[2]AmBisome + miltefosine

[3]Miltefosine + paromomycin

[4]Cured defined as initial cure and no VL relapse at 6 month follow-up; treatment interruption, default, loss to follow-up and one patient treated for PKDL 2 months after VL treatment considered as treatment failures in the intention-to-treat analysis.

[5]Excludes 13 patients with treatment interruption or default, one patient treated for PKDL 2 months after VL treatment and 64 patients lost to follow-up

[6]Excludes 1 patient with treatment interruption or default and 6 patients lost to follow-up

[7]Excludes 12 patients with treatment interruption or default, one patient treated for PKDL 2 months after VL treatment and 58 patients lost to follow-up

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Safety analysis

Serious adverse events were infrequent in all study arms. There were 5 serious adverse events (SAE) in the SDA arm. Anaphylactic reaction occurred during treatment in one patient and was related to the study drug AmBisome. There were four SAEs after completion of treatment and discharge from hospital: one asymptomatic atrial ectopic possibly related to AmBisome and three other SAEs that were unrelated to the study drugs: TB empyema, hospitalization due to dehydration and elevated creatinine, and lower respiratory tract infection. All SAEs resolved completely with no sequela.

The most common adverse events were gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain) and back pain (Table 5). Adverse events leading to treatment interruption were rare (<1% for all three drug regimens).

Discussion

Previous phase-3 randomized controlled trials have shown these regimens were non-inferior to treatment with standard amphotericin B deoxycholate with ITT final cure of 93·0% for SDA (95% CI 87.5–96.3), AmB+Milt 97·5% (95% CI 93.3–99.2), and Milt+PM 98·7% (95% CI 95.1–99.8) [12]. Cure rates by ITT in this study, while not quite as high, still achieved acceptable levels with the differences largely due to loss to follow-up. Earlier DND*i* conducted a phase-3

Table 3. Univariate analyses of factors associated with VL relapse by 6 months, complete case population (N = 1683)[1].

Factor	Relapse (N = 55)	No relapse (N = 1628)	Odds ratio	p value
	n (row %)	n (row %)	(95% CI)	
Regimen				
SDA[2]	38 (4.5)	814 (95.5)	Referent	
AmB+Milt[3]	15 (4.5)	318 (95.5)	1.01 (0.55, 1.86)	0.974
Milt+PM[4]	2 (0.4)	496 (99.6)	0.09 (0.02, 0.36)	0.0008
Sex				
Male	36 (3.6)	977 (96.4)	1.26 (0.72, 2.22)	0.418
Female	19 (2.8)	651 (97.2)	Referent	
Age				
2–12 years	26 (4.9)	501 (95.1)	2.02 (1.18, 3.46)	0.011
>12 years	29 (2.5)	1127 (97.5)	Referent	
Reported length of illness				
< = 8 weeks	52 (3.9)	1277 (96.1)	4.76 (1.48, 15.35)	0.0089
>8 weeks	3 (0.9)	351 (99.1)	Referent	
Severe anemia[5]				
Yes	15 (2.7)	535 (97.3)	0.77 (0.42, 1.40)	0.39
No	40 (3.5)	1093 (96.5)	Referent	
Severe wasting[6]				
Yes	13 (5.0)	249 (95.0)	1.71 (0.91, 3.24)	0.097
No	42 (3.0)	1379 (97.0)	Referent	
ALT ≥200				
Yes	1 (1.7)	59 (98.3)	0.49 (0.07, 3.62)	0.487
No	54 (3.3)	1569 (96.7)	Referent	
AST ≥200				
Yes	4 (2.5)	158 (97.5)	0.73 (0.26, 2.05)	0.550
No	51 (3.4)	1470 (96.6)	Referent	
Creatinine ≥1.5				
Yes	1 (2.5)	39 (97.5)	0.76 (0.10, 5.59)	0.783
No	54 (3.3)	1589 (96.7)	Referent	
Patient category				
Primary kala-azar	50 (3.1)	1540 (96.9)	Referent	
Previously treated kala-azar	3 (4.6)	62 (95.4)	1.49 (0.45, 4.91)	0.512
Transferred	2 (7.1)	26 (92.9)	2.37 (0.55, 10.26)	0.249

[1]Excludes 13 patients with treatment interruption or default, one patient treated for PKDL 2 months after VL treatment and 64 patients lost to follow-up at 6 months

[2]Single dose AmBisome

[3]AmBisome + miltefosine

[4]Miltefosine + paromomycin

[5]Severe anemia defined as hemoglobin <7 g/dL for children < 5 years; <8 g/dL for 5 years and older; moderate anemia defined as falling above the cutoff for severe anemia and <11 g/dL.

[6]Severe wasting defined as weight-for-height Z-score <-3 for children <5 years; BMI-for-age Z-score < -3 for those 5–19 years; and BMI <16.0 for adults

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Table 4. Multivariable logistic regression model of factors associated with VL relapse by 6 months, complete case population (N = 1683)[1].

Factor	Adjusted Odds ratio (95% CI)	p value
Regimen		
SDA[2]	Referent	
AmB+Milt[3]	1.08 (0.58, 2.00)	0.818
Milt+PM[4]	0.08 (0.02, 0.35)	0.0007
Age		
2–12 years	2.07 (1.20, 3.59)	0.0096
>12 years	Referent	
Reported length of illness		
< = 8 weeks	4.28 (1.32, 13.88)	0.0154
>8 weeks	Referent	

[1]Excludes 13 patients with treatment interruption or default, one patient treated for PKDL 2 months after VL treatment and 64 patients lost to follow-up at 6 months

[2]Single dose AmBisome

[3]AmBisome + miltefosine

[4]Miltefosine + paromomycin

https://doi.org/10.1371/journal.pntd.0006830.t004

Table 5. Adverse events by treatment arm, intention-to-treat population (N = 1761).

	SDA[1] (N = 891)	AmB+Milt[2] (N = 358)	Milt+PM[3] (N = 512)
Adverse events	**n (%)**	**n (%)**	**n (%)**
At least one AE reported	134 (15.0)	91 (25.4)	92 (18.0)
AEs leading to treatment interruption	4 (0.4)	2 (0.6)	1 (0.2)
Hypersensitivity reaction	2 (0.2)	1 (0.3)	0 (0)
Dermatitis	1 (0.1)	0 (0)	0 (0)
Severe Vomiting	0 (0)	1 (0.3)	1 (0.2)
Severe Abdominal pain	1 (0.1)	0 (0)	0 (0)
Serious AE diagnosed after end of treatment			
Asymptomatic atrial ectopic	1 (0.1)	0 (0)	0 (0)
Serious AE judged unrelated to treatment			
TB empyema	1 (0.1)	0 (0)	0 (0)
Dehydration and elevated creatinine	1 (0.1)	0 (0)	0 (0)
Lower respiratory tract infection	1 (0.1)	0 (0)	0 (0)
Non-serious AEs			
Abdominal pain or dyspepsia	13 (1.5)	20 (5.6)	19 (3.7)
Vomiting	43 (4.8)	61 (17.0)	45 (8.8)
Injection site pain or swelling	0 (0)	1 (0.3)	15 (2.9)
Back pain	42 (4.7)	9 (2.5)	0 (0)
Cough	14 (1.6)	9 (2.5)	4 (0.8)

[1]Single dose AmBisome

[2]AmBisome + miltefosine

[3]Miltefosine + paromomycin

https://doi.org/10.1371/journal.pntd.0006830.t005

clinical trial in Bangladesh to assess safety and efficacy of short course combination regimens in field conditions at Upazila level that provided excellent efficacy outcome (≥95%) and very good safety profile [19].

The demographic characteristics of the population enrolled in the study correspond to those defined for this area, roughly 70% patients older than 12 years, 30% of them women of child-bearing age. The effectiveness in complete case analysis in this study was slightly higher in the Milt+PM arm than in the other two arms, which may partly be due to the higher number of clinically unwell patients being allocated to the SDA treatment arm.

Despite a range of clinical severity, presentations, and patient demographics, all of the treatments showed excellent safety profiles. This study was non-comparative, both SDA and combination of Milt+PM had satisfactory effectiveness of >90% which corroborates the decision by the Indian control program to use these treatments in the elimination program. No complications were seen in pregnant (treated with SDA) or extremely young patients. Generally, the treatments were easily prepared and administered by health care providers, and appeared to be well accepted by patients.

When elimination was first envisioned, oral miltefosine was proposed to be used primarily in the attack phase due to its acceptability. In parallel to the provisional results of this study, the WHO included India in the AmBisome donation programme, resulting in India adopting these new treatment modalities within the national elimination programme, replacing miltefosine monotherapy. To date, this has proved to be a very effective strategy, with over 12,000 patients having been treated in the attack phase with SDA within the public health sector across the Indian subcontinent with excellent safety and efficacy [14]. Although widely implemented, SDA is not without its limitations–complex storage and preparatory requirements mean that its safe use is contingent on logistical support that is not required for Milt+PM, for example. The unintended consequence of this has been the neglect of alternative drug combinations, which has resulted in a lack of stock and awareness of these regimens in the national programme.

Considering the limited number of therapeutic options available, it is critical to ensure that procurement and availability of all three drugs is ensured within the elimination framework. Currently, all three WHO supported formulations of these drugs are produced by single source manufacturers AmBisome (Gilead Sci., USA), miltefosine (Knight Therapeutic Inc., Canada), and paromomycin sulphate (Gland Pharma, India) [16], making the supply chain sensitive to factory and quality issues should they arise.

This reflects the urgent need for investment in bio-equivalence studies, technology transfer, and alternative production, which may potentially need to be centralized and pooled to ensure adequate market conditions. Moreover, all these limitations justify strengthening the development of new chemical entities (NCEs) that are needed in the form of short-course oral combinations, to replace the existing drugs in the Indian subcontinent and worldwide [20].

Although resistance to amphotericin B has yet to be demonstrated *in vivo* despite decades of use, prolonged use of monotherapies such as miltefosine and paromomycin have resulted in reduced drug susceptibility, and potential mechanisms of amphotericin B resistance have been described [21]. Reduced drug susceptibility for SSG and Milt were only determined well after they had progressed to unacceptable levels; as such it is critical that the national programme develops sentinel surveillance for drug susceptibility monitoring of VL drugs so that early signals can be generated that can guide more rational use of existing therapeutic options. Such initiatives are underway in India [22] but are yet to be developed in Bangladesh or Nepal. There are also a number of challenges that need to be considered for the Milt+PM and AmB +Milt regimens. Although compliance was very high in this study (>99%), this was based on patients being actively traced to complete treatment and a large proportion being managed as inpatients for the duration of treatment. The PHC system in Bihar remains weak and

overburdened with long waiting times and irregular timings–thus returning daily for treatment for a period of 10 days becomes an additional economic burden for patients and caregivers and is likely to result in reduced treatment compliance. Additionally, for Milt containing regimens, there is a requirement for women of reproductive age to take a pregnancy test, and, if negative, to comply with contraceptive cover during treatment and for 3 months afterwards, something that has generally been poorly followed under programmatic conditions. Given that the most common adverse event related to Milt is vomiting, contraceptive injections remain the most suitable option, recently been made available in India within the public health sector [23]. As such, clear coordination and preparation on safety messaging for all treatments evaluated in this study is required.

There are a number of limitations to this study. Although it was originally planned that each site would use a particular regimen, there was a degree of mixing of treatments between sites. Additionally, children were under-represented due to regulatory demands, while the majority of patients receiving the Milt+PM arm received treatment as in-patients, reducing the validity of the feasibility interpretation of this arm in normative settings. Finally, the majority of patients in two of the treatment arms were treated by MSF doctors, supporting activities at Hajipur hospital.

This is the largest prospective study conducted using the revised WHO recommended VL treatment regimens for the Indian subcontinent, and to the authors' knowledge, the first NTD based phase 4 study within the Indian subcontinent. The results were used by the Indian national programme to support policy change, introducing SDA and the different combinations as treatment options in the elimination strategy.

Supporting information

S1 Table. Allocation of drug regimens and baseline characteristics by recruitment site.
(DOC)

S2 Table. Characteristics of patients with and without 6m follow-up data.
(DOC)

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2. CURRICULUM VITAE

Temmy Sunyoto (born in Tulungagung, Indonesia on 25 November 1978) graduated with distinction as a Medical Doctor from University of Indonesia in 2003. Since then, she has worked extensively with Médecins sans Frontières (MSF), both in Indonesia and abroad. After being front-line physician in the Aceh tsunami in 2004 and HIV/TB doctor in Papua and the Moluccas, she joined ITM's Postgraduate Course in Tropical Medicine and Hygiene in 2006, before embarking on humanitarian assignments in various contexts. These include missions in South Sudan, India, Sudan (Darfur), Somalia, Ethiopia, and Kenya (2006-2009).

In 2010, she obtained the degree of Master in Public Health, orientation Disease Control at ITM with her thesis ''Visceral Leishmaniasis (VL) Control in an Unstable Context: Evaluation of an MSF Programme in Somalia, 2000-2008". The master thesis was awarded the Prize of Development Cooperation of the Province of Antwerp in 2010. One of the winners of Emerging Voice competition in its first year, she then took strategic position in MSF as Medical Coordinator in Somalia (2011-2012) and later for India (2013-2015). She was selected as Junior Public Health Professional in the Vector Borned Disease unit in the Communicable Disease department at WHO's South East Asia Regional Office in New Delhi, India (2012-2013). Keen on research, policy analysis and overall improving quality of programmes, she seized the opportunity to be in academia: in 2015 she was chosen as one of the PhD fellows in the Euroleish network, an EU funded Marie-Sklodowska Curie Innovative Training Network, based at ITM.

She has completed various courses and trainings in Epidemiology and Statistics (ITM and HardvardX), Qualitative and Mixed Methods Research (ITM), Global Health From a Biosocial Perspective (edX) Operational Research (SORT-IT), Fundamentals of Clinical Trials (ITM), Population in Precarious Situation (MSF), Project Coordination and Leadership/Management Course (MSF), SCART (ITM) and many others.

She remains committed to the field of Neglected Tropical Diseases and continues to expand her horizon post PhD training.

3. LIST OF PUBLICATIONS

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