Visceral leishmaniasis: a global overview

Richard G. Wamai, Jorja Kahn, Jamie McGloin, Galen Ziaggi

Department of Cultures, Societies and Global Studies, Northeastern University, College of Social Sciences and Humanities, Integrated Initiative for Global Health, 360 Huntington Ave., Boston, MA 02115, USA.

E-mail: r.wamai@northeastern.edu

© 2020 Korean Society of Global Health. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID IDs
Richard G. Wamai
https://orcid.org/0000-0001-6566-5159
Jorja Kahn
https://orcid.org/0000-0001-8658-7890
Jamie McGloin
https://orcid.org/0000-0003-1577-1601
Galen Ziaggi
https://orcid.org/0000-0001-6858-0886

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Wamai RG; Formal analysis: Wamai RG, Kahn J, McGloin J, Ziaggi G; Investigation: Wamai RG, Kahn J; Methodology: Wamai RG; Resources: Wamai RG

Visceral leishmaniasis: a global overview

ABSTRACT

The leishmaniases are protozoan infections that are among the neglected tropical diseases (NTDs). Over one billion people are at risk of these diseases in virtually all continents. These diseases debilitate large numbers of people, keeping them from full, productive lives. Visceral leishmaniasis (VL) is the most severe form of these diseases, killing more people than any other parasitic disease except malaria. About 90% of the global burden for VL is found in just 7 countries, 4 of which are in Eastern Africa (Sudan, South Sudan, Ethiopia and Kenya), 2 in Southeast Asia (India, Bangladesh) and Brazil, which carries nearly all of cases in South America. In 2005 the World Health Organization launched a strategy to eliminate VL in the Indian subcontinent resulting in significant progress there. The London Declaration on NTDs in 2012, with targets to 2020, heightened attention to VL, and NTDs were formerly adopted into the Sustainable Development agenda for 2015–2030. However, there has been limited progress in most regions and especially in Eastern Africa. Challenges remain as instability, population movements and environmental changes test programming and political commitments. We review disease transmission and management dynamics, epidemiology, policy interventions, and identify outstanding issue towards elimination concluding with the call that, at the start of another decade, there is need to redouble efforts to control this deadly disease as part of the push towards the Sustainable Development Goals.

Keywords: Visceral leishmaniasis; Review; Global; East Africa; Southeast Asia; Neglected tropical diseases

INTRODUCTION

A group of enzootic and zoonotic protozoan infections, the leishmaniases constitute among the most severely neglected tropical diseases (NTDs) and are found in all continents except Oceania. Representing the most common infectious diseases, NTDs comprise an opened list of some 20 parasitic, bacterial, viral, protozoan and helminthic infections. Called “diseases of the poor,” because of their characteristic prevalence in poor populations regardless of a country’s income status, they infect over one billion people in over 140 countries, with about 90% of the global burden in Africa. While NTDs do not contribute significantly to global deaths, they are debilitating and remain the most common infections...
A global review of visceral leishmaniasis

RG, Kahn J, McGloin J; Supervision: Wamai RG; Validation: Wamai RG; Visualization: Wamai RG, Kahn J; Writing - original draft: Wamai RG, Writing - review & editing: Wamai RG, Kahn J, McGloin J, Ziaggi G.

Among the poor worldwide, preventing them from escaping poverty by impacting livelihoods such as agriculture and livestock, and affecting cognitive, developmental and education outcomes.8,12,13

At the turn of the century in 2000, the UN Millennium Declaration galvanized significant attention to infectious diseases in the developing world with the 2000–2015 Millennium Development Goals (MDGs). However, NTDs were overshadowed by other diseases, causing them to remain neglected in research, funding and global health implementation,14-18 receiving only 0.6% of development aid during the MDGs period.15,17 Unprecedented mobilization of resources saw significant progress on the major diseases (namely, HIV/AIDS, malaria and tuberculosis), but not for NTDs.20,21 This galvanized calls for the inclusion of NTDs in the post-2015 Sustainable Development Goals (SDGs) agenda.17,22-24 NTDs are now recognized in the SDGs for health with target 3.3 articulated as “the end of NTDs” by 2030, to be measured by “number of people requiring interventions against” these diseases among which leishmaniasis is included.25

Following its first report on NTDs in 2010,26 on January 30, 2012 the World Health Organization (WHO) launched an implementation roadmap for accelerating work on NTDs27 during a gathering in London, resulting in the London Declaration on NTDs.28 The “Uniting to Combat NTDs – Ending the Neglect and Reaching 2020 Goals” campaign generated an unprecedented renewed focus on these diseases. This roadmap targets 10 diseases, including visceral leishmaniasis (VL), for elimination by year 2020 and the WHO has been rallying regional processes for strategic and integrated activities towards the goal with notable progress to date.29 In 2013, the Commission on Investing in Health estimated that spending US $300–400 million annually up until around 2020 could virtually eliminate the leading NTDs, representing a good value for money.30 While there was strong optimism that several NTDs could be eliminated within this timeframe and there is notable progress, various gaps persist for key diseases such as VL especially in sub-Saharan Africa and the Americas.29 For this reason, the WHO has launched a new goal for 2030, aligned with the SDG framework, aiming at “90% reduction in the number of people requiring interventions against NTDs.”31

Among the leishmaniases, 4 types are prevalent, namely VL, cutaneous leishmaniasis (CL), mucosal (or mucocutaneous) leishmaniasis (MCL), and post-kala-azar dermal leishmaniasis (PKDL).32,33 PKDL, which is subcutaneous, often occurs after treatment of VL34,35 and thus has been known as an intermediate disease state before full recovery from VL.36,37 On the other hand, CL is the most widespread type of leishmaniasis.38,39 Using the common measure of disease burden, the disability adjusted life years (DALYs),40 NTDs were responsible for over 26 million DALYs in the 2010 Global Burden of Disease Study, with leishmaniasis ranked second among NTDs with 3.3 million DALYs.20 The more recent 2017 Global Burden of Disease Study estimated NTDs were responsible for 62 million DALYs, with 774,000 DALYs from leishmaniasis.41 In 2015 VL contributed 97% of the total DALYs for the leishmaniases,42 ranking it as the second leading cause of parasitic deaths after malaria.43

Given that 90% contribution of the DALYs for VL are due to years of life lost due to premature mortality, the disease is almost always fatal without treatment,20 with fatality varying by factors such as age, gender and residence in countries like Brazil44 and India.45 Furthermore, VL contributes significantly to household economic loss, as shown by individual studies across countries46-50 and systematic reviews.51,52 The high risk of fatality and impoverishing effect of VL would be expected to draw heightened attention. Consequently, in 2005 the
WHO launched an elimination strategy for VL with a focus on Southeast Asia, requiring detection and treatment of all cases. As a result, there is evidence of significant progress on VL in Southeast Asia whereas increased incidence is reported in the Americas and there is no reliable data from Africa to indicate trends. Furthermore, despite having a high research intensity relative to its burden among other infectious diseases, attention in the African region is still inadequate. As we enter the next decade for VL (and other NTDs) programming with eyes on 2030, it is timely to review the global problem of VL. Here we review disease transmission and management dynamics, epidemiology, policy interventions in Southeast Asia and Africa, and identify outstanding issue towards elimination. This review serves to update the global evidence base for VL, highlighting significant issues in science and policy. An understanding of the current status of VL will help to inform the next decade of NTD control.

ETIOLOGY AND TRANSMISSION OF VL

The 2010 WHO Technical Report Series 949, “Control of the Leishmaniasis,” provides a detailed account of the transmission dynamics of VL. The human infection of leishmania parasites occurs through the bite of the female Phlebotomus sandfly in the Old World and Lutzomyia in the New World. Comprising 500–800 species, only about 90 are known to transmit leishmania despite being distributed over large tropical and subtropical climate around the world. Female sandflies feed on blood from humans and animals to fertilize their eggs and male sandflies have no role in transmission. Sandfly vectors are only those that carry and can transmit parasites capable of infecting man or other hosts, i.e., are competent. Entomological studies that collect sandflies to determine vector competency often identify few relevant vectors. Leishmania donovani and Leishmania infantum, also known as L. chagasi) are the primary parasites in the Old World whereas L. infantum is the dominant one in the New World.

Identifying which parasites infect which species and their role in transmission to animal reservoirs and man is difficult due to the variety of the Phlebotomos species, leishmanial species and foci-specificity of these. For example, L. donovani is mostly anthroponotic and L. infantum is mostly zoonotic both being indistinguishable morphologically. On the other hand, geographical variation of the VL vector and parasites are fairly well understood. In the Latin American region, the main established cause is the L. infantum (L. chagasi) transmitted by Lutzomyia (L. longipalpis) as the main sandfly species with the main reservoir host in urban areas being the domesticated dog (Canis familiaris). For the European region, a WHO manual on leishmaniasis management and surveillance notes that L. infantum is the only agent for VL in the region, domestic dogs are the primary reservoir host, and transmission is by several Phlebotomus (Larroussius) sandfly species. Both L. donovani and L. infantum have been reported in Asia, the Middle East and Mediterranean basin in one extensive review of geographic locations with dogs, jackals, foxes, wolves and goats reported as predominant reservoir host. In Eastern Africa, the main infectious agent for VL is L. donovani transmitted by 2 principle vectors (P. orientalis and P. martini). In this region, other than humans, dogs are also known to be among the important reservoir host.

The leishmania parasite develops in 2 morphological life cycle stages, as amastigotes and promastigotes in mammalian and sandfly host respectively, propagating in the human host through 8 stages (Fig. 1) from the US Centers for Diseases Control and Prevention.)

https://e-jghs.org
https://doi.org/10.35500/jghs.2020.2.e3
Infection in humans presents in the liver, spleen, bone marrow and lymph nodes leading to classic characteristic features of enlarged spleen and weight loss.\(^{33,74}\) Although the incubation period ranges from 10 days to 34 months, most infected individuals develop symptoms after 3 to 8 months.\(^{33,75}\) Fatality of untreated cases, usually within 2 years, results from organ failure, anaemia or secondary infections.\(^{33,76-78}\) Perhaps the highest case fatality rates (50%) are those reported from the Sudan wars in the 1980s.\(^{79,80}\)

**DETECTION, DIAGNOSIS AND TREATMENT**

WHO’s “Control of the Leishmaniasis”\(^ {33}\) provides a comprehensive account on the leishmaniasis across the world including detection, diagnosis and treatment. According to the report, presentation of a prolonged fever, splenomegaly and weight loss are typical signs for case detection. Clinical diagnosis then needs to be confirmed using a range of serological, parasitological and PCR techniques.\(^ {33}\) Due to the sophistication, cost, and limited availability of tests, test specificity primarily depends on the level of health system at which it is administered. Rapid diagnostic tests (RDTs), notably the rK39 antigen immunochromatographic blood test, is widely used and recommended as a first line test with microscopy of bone marrow or spleen aspirates as the second-level test followed by polymerase chain reaction (PCR).\(^ {66,77,81,82}\) The performance of RTDs is known to differ by region and country.\(^ {83,84}\) A Cochrane review of RDTs found that the rK39 worked better in correctly diagnosing VL in India and Nepal (97% correct results) but was less effective in East Africa (85% correct results).\(^ {85}\) This RDT was also better than a urine-based latex agglutination test. Clinical trials of multiple RDTs in countries like Bangladesh,\(^ {86}\) Brazil,\(^ {87}\) Ethiopia,\(^ {88}\) India,\(^ {89}\) Kenya,\(^ {90}\) Uganda\(^ {91}\) and Sudan and South Sudan\(^ {92}\) have also confirmed the
better performance of rK39 and variation between tests and regions. Real-time PCR assays have been shown to improve diagnosis and measure treatment outcomes in VL, PKDL and relapsed VL cases that are more difficult to test.93

Several drugs to treat VL are currently in use around the world. WHO’s “Control of the Leishmaniases” also contains comprehensive and region-specific recommendations for these including dosage by weight and age.33 These include: *pentavalent antimonials* (e.g., sodium stibogluconate [SSG], given through intramuscular injections for 28–30 days); *paromomycin* (PM, injection for 21 days), approved in 2006; *liposomal Amphotericin B* (L-AmB, 15–20 doses intravenously, daily or on alternate days), approved in 1996; and *Miltifosine* (pill for 28 days), approved in 2004. The reported efficacy (cure rate) of these, respectively, is above 90%, 93%–95% (in India) and 85% (East Africa), 99% (in India), 94% (India) and 90% (Ethiopia).33 Country-specific studies for drug used and effectiveness have been summarized elsewhere.84

A recent systematic review and meta-analysis of studies of comparative effect of L-AmB found this drug was effective in achieving definitive cure.94 L-AmB is the recommended and research confirmed drug for VL-HIV coinfected persons and pregnant women.33,95,96 While there are currently no vaccines, research is ongoing towards these.97-99

In practice, and based on studies, countries have either developed their own diagnostic and treatment protocols or are using the guidelines presented in this WHO report. For the European region, a manual on management and surveillance was recently developed.66 The 3 southeast Asian countries endemic for VL (Bangladesh, India and Nepal) have individual guidelines100-102 as do the East African countries.103 For example, in the East African region combination of SSG and PM is commonly given as it shortens the treatment period to 17 days33,84,103 and has also been shown to have better treatment outcomes than SSG alone in the largest systematic review and meta-analysis of treatment outcomes in East Africa, conducted in Ethiopia during 2001–2017.104 According to the study success rates at end of treatment and after 6 months of follow up (the time final cure rate is determined) were, respectively, 81.5% and 80.7% for SSG alone, 96.7% and 71%–100% for L-AMB and 90.1% for SSG (at 6 months). Overall, the development of VL treatments globally has had successes but also many pitfalls.105,106

**GLOBAL VL EPIDEMIOLOGY**

While endemic in specific geographic regions, the global occurrence of VL is widely dispersed in all continents but Oceania.4 However, assessing its worldwide burden is challenging due to various factors such as diverse clinical and epidemiological manifestations, focality, and reliability of data.80 Three recent key studies have attempted to examine the worldwide distribution39,107,108 and are summarized here. Table 1 contains country-specific data that was captured in 2 of these reports.107,108 The third study did not include country-level case data. Fig. 2, from the WHO,109 shows the latest global distribution map.

The first of these is a global update by the Leishmaniasis Control Program of the WHO’s NTDs Department of the of the empirical evidence for the leishmaniases by Alvar and colleagues.107 The team organized regional meetings between 2007–2010 in 98 countries and 3 territories. Country representatives and scientists provided local health data on VL/CL for at least the previous 5 years and contributed to epidemiological questionnaires focused on treatment and control. Authors also conducted a comprehensive literature review examining
Table 1. Country-specific VL data\textsuperscript{107,108}

| Region/country       | Years of report | Alvar et al.\textsuperscript{107} (reported VL cases/year) | Estimated VL incidence (min) | Estimated VL incidence (max) | WHO\textsuperscript{108} (reported VL cases, 2016) |
|----------------------|-----------------|---------------------------------------------------------------|------------------------------|-------------------------------|---------------------------------------------------|
| African              |                 |                                                               |                              |                               |                                                   |
| Algeria              | 2004–2008       | 111                                                           | 130                          | 200                           | 74                                                |
| Eritrea              | 2008            | 100                                                           | 200                          | 400                           | ND                                                |
| Ethiopia             | 2004–2008       | 1,860                                                         | 3,700                        | 7,400                         | 1,593                                             |
| Kenya                | 2004–2008       | 145                                                           | 610                          | 1,200                         | 692                                               |
| Nigeria              | 2004–2008       | 1                                                             |                              |                               | ND                                                |
| South Sudan          | 2004–2008       | 1,756                                                         | 7,400                        | 14,200                        | 4,775                                             |
| Uganda               | 2004–2008       | 288                                                           | 350                          | 520                           | 35                                                |
| South-East Asia      |                 |                                                               |                              |                               |                                                   |
| Bangladesh           | 2004–2008       | 6,224                                                         | 12,400                       | 24,900                        | 255                                               |
| Bhutan               | 2005–2009       | 2                                                             | 10                           | 20                            | ND                                                |
| India                | 2004–2008       | 39,918                                                        | 146,700                      | 282,800                       | 6,249                                             |
| Nepal                | 2004–2008       | 1,477                                                         | 3,000                        | 5,900                         | 242                                               |
| Thailand             | 2006–2010       | 2                                                             | 5                            | 10                            | 0                                                 |
| Americas             |                 |                                                               |                              |                               |                                                   |
| Argentina            | 2004–2008       | 8                                                             | 20                           | 30                            | 11                                                |
| Brazil               | 2003–2007       | 3,481                                                         | 4,200                        | 6,300                         | 3,200                                             |
| Colombia             | 2004–2008       | 60                                                            | 70                           | 110                           | 37                                                |
| Guatemala            | 2004–2008       | 15                                                            | 20                           | 30                            | 2                                                 |
| Honduras             | 2004–2008       | 6                                                             | 7                            | 10                            | 7                                                 |
| Mexico               | 2004–2008       | 7                                                             | 8                            | 12                            | 0                                                 |
| Nicaragua            | 2004–2007       | 3                                                             | 3                            | 5                             | 0                                                 |
| Paraguay             | 2004–2008       | 48                                                            | 100                          | 200                           | 64                                                |
| Venezuela            | 2004–2008       | 40                                                            | 50                           | 70                            | 33                                                |
| Eastern Mediterranean|                 |                                                               |                              |                               |                                                   |
| Afghanistan          |                 | ND                                                            |                              |                               | 9                                                 |
| Egypt                | 2008            | 1                                                             | 1                            | 2                             | 0                                                 |
| Iran                 | 2004–2008       | 149                                                           | 300                          | 600                           | ND                                                |
| Iraq                 | 2004–2008       | 1,711                                                         | 3,400                        | 6,800                         | ND                                                |
| Libya                | 2004–2008       | 3                                                             | 5                            | 10                            | 10                                                |
| Morocco              | 2004–2008       | 152                                                           | 300                          | 610                           | 92                                                |
| Oman                 | 2004–2008       | 1                                                             | 2                            | 4                             | ND                                                |
| Palestine            | 2004–2008       | 5                                                             | 10                           | 20                            | 3                                                 |
| Saudi Arabia         | 2004–2008       | 34                                                            | 40                           | 60                            | 4                                                 |
| Somalia              | 2009            | 679                                                           | 1,400                        | 2,700                         |                                                   |
| Sudan                | 2005–2009       | 3,742                                                         | 15,700                       | 30,300                        | 3,810                                             |
| Syria                | 2004–2008       | 14                                                            | 30                           | 60                            | 25                                                |
| Tunisia              | 2004–2008       | 89                                                            | 110                          | 160                           | 17                                                |
| Yemen                | 2004–2008       | 0                                                             | 20                           | 50                            | ND                                                |
| European             |                 |                                                               |                              |                               |                                                   |
| Albania              | 2004–2008       | 114                                                           | 140                          | 210                           | 15                                                |
| Armenia              | 2004–2008       | 7                                                             | 10                           | 30                            | 17                                                |
| Azerbaijan           | 2004–2008       | 28                                                            | 60                           | 110                           | 44                                                |
| Bosnia and Herzegovia| 2002–2005       | 2                                                             | 2                            | 3                             | 0                                                 |
| Bulgaria             | 2004–2008       | 7                                                             | 8                            | 12                            | 3                                                 |
| Croatia              | 2004–2008       | 5                                                             | 6                            | 8                             | 0                                                 |
| Cyprus               | 2008            | 2                                                             | 2                            | 4                             | ND                                                |
| France               | 2004–2008       | 18                                                            | 20                           | 30                            | 8                                                 |
| Georgia              | 2004–2008       | 164                                                           | 330                          | 660                           | 60                                                |
| Greece               | 2004–2008       | 42                                                            | 50                           | 80                            | 57                                                |
| Israel               | 2003–2007       | 2                                                             | 3                            | 4                             | 1                                                 |
| Italy                | 2003–2007       | 134                                                           | 160                          | 240                           | 49                                                |
| Kazakhstan           | 2004–2008       | 1                                                             | 2                            | 4                             | 0                                                 |
| Macedonia            | 2005–2009       | 7                                                             | 9                            | 13                            | 5                                                 |
| Malta                | 2002–2005       | 2                                                             | 3                            | 4                             | ND                                                |
| Montenegro           | 2004–2008       | 3                                                             | 4                            | 5                             | 6                                                 |
| Portugal             | 2003–2007       | 15                                                            | 20                           | 30                            | ND                                                |
| Spain                | 2004–2008       | 117                                                           | 140                          | 210                           | ND                                                |

(continued to the next page)
global incidence, distribution, surveillance and trends, with additional consideration for potential under-reporting. Mapping technology (GIS) used the compiled epidemiological data to develop final incidence estimates. The official incidence totaled 58,000 annual cases of VL. However, there were significant gaps in surveillance, with only two-thirds of endemic countries reporting incidence data. Final analysis produced a range of incidence estimates: 202,000–389,100 cases per year for VL. While case fatality rate differs from 1.5% in Bangladesh to 20% in peacetime South Sudan, based on an estimated 10% overall case fatality rate, annual deaths were 20,000–40,000. Over 90% of VL cases were found within 6 countries (India, Bangladesh, Sudan, South Sudan, Brazil, and Ethiopia). Authors also

Table 1. (Continued) Country-specific VL data

| Region/country | Years of report | Alvar et al. (reported VL cases/year) | Estimated VL incidence (min) | Estimated VL incidence (max) | WHO (reported VL cases, 2016) |
|----------------|-----------------|--------------------------------------|-----------------------------|-----------------------------|-------------------------------|
| Tajikistan     | 2004–2008       | 15                                   | 30                          | 60                          | 25                            |
| Turkey         | 2003–2007       | 29                                   | 60                          | 120                         | 23                            |
| Turkmenistan   | 2004–2008       | 0                                    | 10                          | 30                          | 1                             |
| Ukraine        |                 |                                      |                             |                             | 1                             |
| Uzbekistan     | 2004–2008       | 7                                    | 10                          | 30                          | 38                            |
| Western Pacific|                 | 378                                  | 760                         | 1,500                       |                               |
| China          | 2004–2008       | 378                                  | 760                         | 1,500                       |                               |

Excludes countries with zero cases reported and/or those without reported data (in both reports). Blank cell indicates data missing from report. ND = “No Data” listed in report; VL = visceral leishmaniasis; WHO = World Health Organization.

Fig. 2. Status of endemicity of visceral leishmaniasis worldwide, 2016. VL = visceral leishmaniasis.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2018. All rights reserved

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD) World Health Organization

https://e-jghs.org https://doi.org/10.35500/jghs.2020.2.e3
created country profiles with further specifications regarding their leishmaniasis situation. This is the first comprehensive overview of the leishmaniasis burden.

More recently, the WHO World Epidemiological Record (WER) provides an overview of global leishmaniasis surveillance with time trends from 1998–2016 covering all WHO regions with differing data years.\textsuperscript{108} The Global Health Observatory provides publicly available data for VL on the following indicators: status of endemicity of VL; number of VL cases reported; number of imported VL cases. This last indicator was added in 2013 to distinguish between the number of autochthonous and imported cases of leishmaniasis. The global leishmaniasis program issued standardized tools for data collection in 2014, which have also been used to publish country profiles. High-burden countries also have the capability of reporting data online via the WHO Integrated Data Platform (WIDP) launched in 2016. Of the 200 countries or territories that report to WHO in 2016, 75 were considered endemic for VL. In 2016 alone, 22,233 new VL cases were reported to WHO. The Eastern Mediterranean Region (EMR) reported the highest proportion of countries (54 of 75) endemic for VL but accounted for 22% of the global burden in 2016. Southeast Asia (SEAR) and Africa (AFR) regions reported 30% each of the 2016 global cases with the Americas (AMR), European (EUR) and Western Pacific (WPR) regions reporting 15%, 2% and 1% of cases, respectively. This report establishes that East Africa, the Indian subcontinent, and Brazil continue to be epidemiological hotspots for VL.

There are several limitations to the VL data reported by these studies. Alvar and colleagues\textsuperscript{107} noted limitations due to gaps in surveillance and unknown underreporting. In particular, many countries, particularly in sub-Saharan Africa, had no data available and thus did not produce estimates. Additionally, the mortality estimate range is particularly uncertain. Since VL occurs mainly in rural and remote populations,\textsuperscript{39} most deaths from the disease occur outside of medical facilities. In addition, there are significant regional differences regarding the reporting rate for VL. The African region had a reporting rate at 38%, and the Eastern Mediterranean region had 78%, while both the Americas and European regions had 100%.\textsuperscript{108} However, WER highlights underreporting and poor timeliness by countries to report data to WHO so that this limitation can be considered in global reports and updates. In some years, this could result in what appears to be a surge of leishmaniasis cases as detection and surveillance improve. Ultimately, however, relying on expert opinion, rather than actual confirmed cases, cannot reliably predict the true status of disease.\textsuperscript{110,111}

In a 2014 study Pigott et al.\textsuperscript{39} attempt to address such limitations in global leishmaniasis data by providing global distribution maps.\textsuperscript{69} The researchers used a boosted regression tree modeling framework to create what we think is the most comprehensive database of both CL and VL occurrences worldwide. This regression model utilized 4 areas: a map of the global extent of leishmaniasis, global data sets on geographical occurrence of leishmaniasis, global gridded data on environmental correlates of leishmaniasis, and pseudodata to supplement occurrence records. Information from each state and province around the globe was gathered and recorded on whether or not leishmaniasis was reported. The researchers concluded that 1.69 billion people live in areas susceptible to VL transmission. Six countries (Brazil, Ethiopia, Sudan, South Sudan, India, and Bangladesh) make up 90% of all VL cases. Ultimately, this study highlights areas and countries requiring more leishmaniasis treatment and prevention methods.

More than the other 2 studies, Pigott et al.’s study\textsuperscript{39} identifies the focality of the distribution of cases and risk maps at small scale (polygon) level. For example, in the Eastern African
countries with high burden of disease, Ethiopia and Sudan seem to have the wide distribution by geographical extent. Other studies show that in Ethiopia, VL is prevalent in 6 of the country’s eleven regions, in both lowlands in the south and southwest as well as the plains and highlands in the northeast. In Sudan and South Sudan, the disease is spread out from the Sudan-Ethiopian border in the east and South Sudan-Kenya border all the way to the west and north of the White Nile. In the Indian subcontinent comprising 3 countries (Bangladesh, India and Nepal) with approximately 30% of the global VL burden, nearly 40% of cases occur in the cross-border areas. In the Americas VL endemicity occurs in 12 countries that reported a total of 59,769 new cases during a 17-year time period (2001–2017). However, the cases are concentrated in a single country, with Brazil reporting 96% of these.

These reports collectively indicate 3 global endemic foci, or hotspots, for VL: in East Africa (Ethiopia, Kenya, Somalia, South Sudan, Sudan, and Uganda), in the Indian subcontinent (Bangladesh, India, and Nepal), and in Brazil. The first report, published in 2012 by Alvar and colleagues, specified 6 countries representing 90% of VL burden: Bangladesh, Brazil, Ethiopia, India, South Sudan, and Sudan. However, the more recent WER report, which used data from 2016, found increased VL burden in countries such as Kenya and Somalia, and relatively lowered burden in Bangladesh and India. The WER highlighted 4 countries found to have greater than 3,000 cases in 2016: Brazil (3,200), India (6,249), South Sudan (4,175), and Sudan (3,810). Table 1 reflects the changing trends of VL burden between these 2 reports. The global distribution of VL has notably shifted over time, according to the WER. For example, the proportion of global VL burden from East Africa rose from 40% to 50% between 2015 and 2016. On the other hand, the proportion of global burden from the Indian subcontinent decreased from 39% to 30% within the same time frame. Brazil, however, did not change and consistently represented 14% of global VL burden.

**ELIMINATION OF VL IN ASIA AND CONTROL IN EASTERN AFRICA**

Elimination of a disease is a hallmark of global public health and requires the confluence of biological, political and socioeconomic factors. In 2005, the WHO determined that several of these factors were conducive for launching a VL elimination campaign in southeast Asia, specifically in the countries of Bangladesh, India, and Nepal, which comprise Southeast Asia or the Indian subcontinent as used in different reports. For example, it was known that the disease was focalized in a 109 borderline districts (45 Bangladesh, 52 India and 12 Nepal) and there were clear intercountry collaboration and availability of highly effective diagnostics and treatments. The VL elimination target was defined as the reduction to less than one case for 10,000 inhabitants in these districts by 2015. Furthermore, this goal requires 100% detection and treatment of all VL cases. Achieving this milestone would ensure that the disease would no longer be a public health problem.

As one researcher posed, is elimination of kala-azar feasible by 2017? As this author notes, the goal had originally been set for 2015 then extended to 2017, and currently to 2020. Evidence shows that the program resulted in major progress with Nepal and Bangladesh achieving elimination status in 2013 and 2016, respectively. While India is progressing towards VL elimination, in 2015 the country reported 8,500 cases to the WHO. Provisional cases in 2019 from India's National Vector Borne Disease Control Programme (NVBDCP) were 3,122 in 4 states (Bihar, Jharkhand, Uttar Pradesh, and West Bengal) with Bihar and
Jharkhand carrying 77.4% and 17.3%, respectively.120 Through the NVBDCP, the Ministry of Health’s VL elimination strategy is laid out in the 2017 Accelerated Plan for Kala-azar Elimination.121 The challenges to reach elimination in India need to be overcome. At the same time, sustaining the elimination status in Bangladesh and Nepal will require much effort in surveillance, pharmacovigilance and continued policy engagement.56,122,123

One notable example of a successful VL elimination campaign is seen with China. Between 1951–1972, VL was endemic to at least 16 provinces, primarily concentrated in the North China Plain and Central Shaanxi Plain.124 Following the People’s Republic of China establishment in 1949, epidemiological surveys were conducted throughout the country; a 1951 survey estimated 530,000 people throughout China were infected with VL during that year. Starting in the 1950s, the Chinese government created specific VL institutions and developed a national VL control plan. Importantly, VL treatment (primarily SSG) was provided at no cost to Chinese citizens, and government coordination with pharmaceutical factories improved the production and availability of SSG treatment. Furthermore, the Chinese government aimed for comprehensive control measures, including improved surveillance and vector control strategies, such as widespread insecticide spraying.124 In 2012, China reported only 378 cases, demonstrating significant improvement.107

Outside Southeast Asia, the America’s have implemented the Leishmaniasis Plan of Action and in Brazil the Visceral Leishmaniasis Control and Surveillance Program (VLCSP). Overall, these show some progress in reducing case fatality rate but increased incidence of 26.4% in 2017 from 2016.58 Previous research in Brazil has reported increasing mortality and variation by geographical region mainly in the Northeastern part of the country.44 In 2014, the WHO developed a framework for controlling leishmaniasis in the WHO European Region with a target to eliminate VL mortality by 2020.125 However, a recent WHO assessment of the control efforts in the Eastern Mediterranean, African and European regions indicates there is limited vector control activities in these regions.126

In East Africa on the other hand, the status of VL programming has been inadequate.43,79 For a long time, most work to address the problem was done by Médecins Sans Frontières (MSF) which began work in the Sudan in 1989.127 In 2003 the Drugs for Neglected Disease Initiative (DNDi) organized a network of stakeholders bringing together Ethiopia, Kenya, Sudan and Uganda together to create the Leishmaniasis East Africa Platform (LEAP).128 The main work of the group has been, in furtherance of DNDi’s mission which is, as the name suggests, to develop better treatment for NTDs,106,129 mainly focused on clinical trials for VL including development of standards. Another regional initiative for VL programming implemented in the region during 2014–2019 is KalaCORE, a consortium for the Control and Elimination of VL formed by the UK Department for International Development, the London School of Hygiene and Tropical Medicine, the Mott McDonald Foundation and MSF.130 KalaCORE operated in Ethiopia, South Sudan and Sudan and also in 3 Indian subcontinent countries (Bangladesh, India and Nepal) providing training, case management, education, surveillance and operations research131 In Somalia, interventions by WHO in partnership with the local Ministry of Health and several non-governmental organizations have achieved successful diagnosis and treatment outcomes.132

A powerful approach to address VL, especially in the sub-Saharan Africa region with highest burden of infectious diseases, is to use integrated interventions. One study has assessed the integration landscape in 25 countries from all NTDs endemic region.133 The study finds
multiple models for administrative integration through ministries of health. An example is where the same personnel are involved in implementing VL and other NTD programming in India.\textsuperscript{133} VL especially has a natural reason for integrated interventions with programs targeting HIV. Since most funding for infectious diseases in the Africa region target HIV,\textsuperscript{19,59} health system structures developed for this has potential to benefit VL thus increasing funding for the disease.

Recently, an NTD Modelling Consortium has been formed by several academic entities with a goal to generate evidence base aligned with the goals set out for 2020 by the 2012 London Declaration.\textsuperscript{134} Based on several studies from the group, elimination of VL will require multiple approaches. Mathematical modeling on elimination has determined varied outcomes of multiple transmission and control models and in different levels of VL endemicity.\textsuperscript{118,135-137} In settings with asymptomatic infections, possible reactivation of initial infection and PKDL, these researchers show that optimal indoor residual spraying (IRS) could be effective in settings with low and medium endemicity. Poor community acceptance and health seeking behavior can severely hinder programming and WHO and other studies underscore community engagement as part of an evaluation component for VL elimination.\textsuperscript{54,138}

**OUTSTANDING ISSUES ON VL ELIMINATION**

There are several important issues that should influence efforts for VL elimination and control. Primarily these have to do with co-morbidities, drug resistance/treatment failure, and the population-ecology nexus.

**Comorbidities**

Studies have well established immunosuppression as a risk-factor for VL infection. The most significant of these is HIV, initially reported from southern Europe, notably Spain in the 1980s.\textsuperscript{139,140} In the year 2000, nearly 2000 cases of VL-HIV co-infections had been reported.\textsuperscript{141} Evidence of *L. infantum* anthroponotic transmission through injection drug-use was documented. Infection of HIV has been noted to increase risk of developing VL by 100 times and mortality by 5 times in endemic areas.\textsuperscript{142} According to the WHO 35 countries have reported cases of VL-HIV co-infection.\textsuperscript{143}

In the Americas, VL-HIV co-infections have been reported since the early 2000s in Brazil. One study covering the period 2001–2010 reported a rise in cases from 0.01 to 0.07 per 100,000 inhabitants but a decrease in case fatality from 27.3\% to 23.2\% during the same period.\textsuperscript{144} More recent data from 2017 indicates that approximately 8\% of VL cases from Latin America were co-infected with HIV, with Brazil reporting 95.3\% of these co-infections.\textsuperscript{58} These are concerning especially in Brazil, where they are mostly in urban areas both in the south and northeast mapping concentration of HIV populations.\textsuperscript{144,145} Currently, endemicity of VL-HIV is most predominant in Eastern Africa\textsuperscript{146,147} corresponding to the high HIV prevalence in these regions.\textsuperscript{148} For this reason, in 2011, MSF released an urgent call for HIV programs in Eastern African countries to wake up to VL.\textsuperscript{149} While the WHO Technical Report Series 949 of 2010 included recommendations for VL-HIV management,\textsuperscript{33} the US Centers for Diseases Control and Prevention does not list HIV as an opportunistic infection, which hinders monitoring.\textsuperscript{141} Presently, due to continued treatment challenge, coinfection and mortality of VL-HIV the WHO has undertaken a process to revise its recommendations (Dr. Abate Mulugeta, WHO Regional Office for Africa; personal communication, January 28, 2020).
Co-infections have also been reported for non-HIV-related immunosuppressive states, mainly in the areas of rheumatology, oncology, transplantation medicine, and haematology. The overall implication of co-morbidities is on VL diagnosis and treatment. HIV positive VL patients are more difficult to diagnose and treat. Additionally, because of the lower performance of current RDTs in Eastern Africa, negative results from these does not rule out possibility of infection.

**Asymptomatic carriers and resistance**

Studies showing large asymptomatic carriers of VL parasites including in dogs have called for better identification of disease agents to target interventions. For example, several studies using DNA techniques in Northeastern Brazil, where VL is concentrated in that country, found concerning levels of leishmania infection among asymptomatic blood donors. Other studies of blood donors have been conducted in many countries including France, Greece, Spain and Italy. A cohort study of asymptomatic cases from Bihar, India has recommended no treatment but careful follow up of these as they develop VL earlier.

Although not reportedly a widespread problem, resistance of the parasite to antimonials as well Miltefosine and AmB has been reported in parts of India reducing treatment outcomes. Such a concern led to a call for development of a policy to monitor drug resistance, and needs for pharmacovigilance as well as continued drug development.

**Population migration and conflict**

The complexity of VL transmission is exacerbated by population factors such as migration and conflicts. Human population factors include demographic patterns such as migration, household density, type of shelter, livelihood patterns and migration. In particular, migration and cross-border movements are known to play a significant role in transmission and dispersal of VL foci in every endemic region. Because of the high concentration of disease in the Indian subcontinent, the reported high cross-border transmission of 40% of all cases remains a major hindrance to elimination, especially in India. In Ethiopia, of note is the phenomenon where farm laborers from highland areas seasonally migrate to work in lowland VL endemic areas and then return back to their homelands with infection.

Conflicts, on the other hand, disrupt health systems and programming and uproot people from stable environments to new areas where they come into contact with vectors or are endemic of the disease. While the conflicts in the Middle East pose a danger to VL control, nowhere is this more evident for VL than in the Eastern African countries of Sudan and South Sudan. Notably, the civil wars in Sudan during 1983–2005 sparked devastating epidemics of VL reported to cause 100,000 deaths due to complicated interventions and exacerbated mortality. In Sudan, case fatality rate of 50% in areas without interventions have been reported. In Somalia, continuing civil war, conflict and instability complicates assessment of disease epidemiology as well as population needs and availability of care. Continued violent conflicts could derail achievement of the agenda for NTDs.

**Global climate change**

The complexity of VL transmission is also exacerbated by environmental factors. Ecological factors include rainfall patterns, temperature, soil types, and vegetation. Like other vector-borne infections, leishmaniasis is in the frontlines of the global climate change phenomenon.
Studies have shown that distribution of vectors including sandfly vectors is expanding due to global climate change including in specific regions such as Europe and the Americas. In the southeast Asian region, for example, vector competency has been observed at 15–38 degrees Celsius range meaning increasing temperature variation alters vegetation, rainfall patterns and vector-human behavior. Concerned with the effects of climate change and population movement and urbanization on vector-borne diseases, the WHO has developed the “Global Vector Control Response 2017–2030” to tackle these.

CONCLUSIONS

This review shows that VL is a major disease to be contended with. Nearly a quarter of the world’s population is at risk of infection and the worldwide risk has been increasing. While progress has been made towards elimination in southeast Asia, it is a growing threat in Brazil and eastern Africa. Much of the call made about a decade ago to target the disease as a development issue has not yet been answered. As one example, treatments such as Miltefosine licensed nearly 2 decades ago and widely used in the Indian subcontinent is not yet available treatment in much of Eastern African countries. Additionally, most of studies on the effectiveness of drugs like AmB have been done in the Indian subcontinent so trials in other areas are needed. Continued development of new drugs and ultimately a vaccine is needed.

A critical component in reducing the disease burden and averting fatalities is early detection and treatment. However, these remain a challenge notably in poor, remote, rural settings and areas with conflict, instability, climate change impacts, and population movements. At the same time methods to control and prevent the disease need to be implemented and studied as few trials to guide programming in this area exist. Researchers have also called for a data sharing platform for VL clinical trials to allow informative analysis of developments and outcomes in case management for better disease control. Ultimately, focusing on VL and other NTDs is necessary to achieving specific SDGs including the goal for universal healthcare coverage (UHC) by 2030 and therefore demands accelerate efforts in funding to meet that call.

Furthermore, as the world heads into the 2020 timeline for the WHO Roadmap for NTDs it is necessary to evaluate current state of knowledge, progress and interventions for VL especially with a view to supporting the Eastern Africa region. It is encouraging to note that the world has marked the first NTDs Day ever on January 30, 2020 which promises hope and good things to come for VL and these other diseases to one day remove the “neglected” from the term (World NTDs Day, https://worldntdday.org/).

REFERENCES

1. Esch KJ, Petersen CA. Transmission and epidemiology of zoonotic protozoal diseases of companion animals. Clin Microbiol Rev 2013;26(1):58-85.
2. Desjeux P. Worldwide increasing risk factors for leishmaniasis. Med Microbiol Immunol 2001;190(1-2):77-9.
3. Taylor LH, Latham SM, Woolhouse ME. Risk factors for human disease emergence. Philos Trans R Soc Lond B Biol Sci 2001;356(1411):983-9.
4. Torres-Guerrero E, Quintanilla-Cedillo MR, Ruiz-Esmenjaud J, Arenas R. Leishmaniasis: a review. F1000 Res 2017;6:750.
PUBMED | CROSSREF

5. Santos SS, de Araújo RV, Giarolla J, Seoud OE, Ferreira El. Searching drugs for Chagas disease, leishmaniasis and schistosomiasis: a brief review. Int J Antimicrob Agents 2020;105906.
PUBMED | CROSSREF

6. Neglected tropical diseases. https://www.who.int/neglected_diseases/en/. Updated 2020. Accessed December 10, 2019.
PUBMED | CROSSREF

7. Mitra AK, Mawson AR. Neglected tropical diseases: epidemiology and global burden. Trop Med Infect Dis 2017;2(3):E36.
PUBMED | CROSSREF

8. Global report for research on infectious diseases of poverty 2012. https://apps.who.int/iris/handle/10665/44850. Updated 2012. Accessed January 5, 2020.
PUBMED | CROSSREF

9. Hotez PJ. Blue Marble Health: an Innovative Plan to Fight Diseases of the Poor amid Wealth. Baltimore, MD: Johns Hopkins University Press; 2016.
PUBMED | CROSSREF

10. Neglected tropical diseases: overview. https://www.afro.who.int/health-topics/neglected-tropical-diseases. Updated 2020. Accessed December 10, 2019.
PUBMED | CROSSREF

11. Hotez PJ, Kamath A. Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 2009;3(8):e412.
PUBMED | CROSSREF

12. Molyneux D. Neglected tropical diseases. Community Eye Health 2013;26(82):21-4.
PUBMED

13. Manderson L, Aagaard-Hansen J, Allotey P, Gyapong M, Sommerfeld J. Social research on neglected diseases of poverty: continuing and emerging themes. PLoS Negl Trop Dis 2009;3(2):e332.
PUBMED | CROSSREF

14. Molyneux DH. “Neglected” diseases but unrecognised successes—challenges and opportunities for infectious disease control. Lancet 2004;364(9431):380-3.
PUBMED | CROSSREF

15. Liese BH, Schubert L. Official development assistance for health—how neglected are neglected tropical diseases? An analysis of health financing. Int Health 2009;1(2):141-7.
PUBMED | CROSSREF

16. Molyneux DH, Malecela MN. Neglected tropical diseases and the millennium development goals: why the “other diseases” matter: reality versus rhetoric. Parasit Vectors 2011;4(1):234.
PUBMED | CROSSREF

17. Smith J, Taylor EM. MDGs and NTDs: reshaping the global health agenda. PLoS Negl Trop Dis 2013;7(12):e2529.
PUBMED | CROSSREF

18. Furuse Y. Analysis of research intensity on infectious disease by disease burden reveals which infectious diseases are neglected by researchers. Proc Natl Acad Sci U S A 2019;116(2):478-83.
PUBMED | CROSSREF

19. Liese BH, Houghton N, Teplitskaya L. Development assistance for neglected tropical diseases: progress since 2009. Int Health 2014;6(3):162-71.
PUBMED | CROSSREF

20. Hotez PJ, Alvarado M, Basáñez MG, Bolliger I, Bourne R, Boussinesq M, et al. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Negl Trop Dis 2014;8(7):e2865.
PUBMED | CROSSREF

21. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392(10159):1736-88.
PUBMED | CROSSREF

22. Raviglione M, Maherb D. Ending infectious diseases in the era of the Sustainable Development Goals. Porto Biomed J 2017;2(5):340-2.
CROSSREF

23. Vanderslott S. Moving from outsider to insider status through metrics: the inclusion of “neglected tropical diseases” into the Sustainable Development Goals. J Human Dev Capabil 2019;20(4):418-35.
CROSSREF

24. Addisu A, Adriaensen W, Balew A, Asfaw M, Diro E, Garba DJirmay A, et al. Neglected tropical diseases and the sustainable development goals: an urgent call for action from the front line. BMJ Glob Health 2019;4(1):e001334.
25. Sustainable Development Goal 3. https://sustainabledevelopment.un.org/sdg3. Updated January 31, 2020.

26. World Health Organization. Working to Overcome the Global Impact of Neglected Tropical Diseases: First WHO Report on Neglected Tropical Diseases. Geneva: World Health Organization; 2010.

27. World Health Organization. Accelerating Work to Overcome the Global Impact of Neglected Tropical Diseases: A Roadmap for Implementation. Geneva: World Health Organization; 2012.

28. London Declaration on neglected tropical diseases. https://unitingtocombatntds.org/london-declaration-neglected-tropical-diseases/. Updated 2012. Accessed January 31, 2019.

29. Reaching a billion: ending neglected tropical diseases: a gateway to universal health coverage: fifth progress report on the London Declaration on NTDs. https://unitingtocombatntds.org/reports/5th-report/. Updated 2020. Accessed January 31, 2019.

30. Jamison DT, Summers LH, Alleyne G, Arrow KJ, Berkley S, Binagwaho A, et al. Global health 2035: a world convergeing within a generation. *Lancet* 2013;382(9908):1898-955.

31. NTD roadmap 2021–2030. https://www.who.int/neglected_diseases/news/NTD-Roadmap-targets-2021-2030.pdf?ua=1. Updated 2020. Accessed January 5, 2020.

32. Murray HW, Berman JD, Davies CR, Saravia NG. Advances in leishmaniasis. *Lancet* 2005;366(9496):1561-77.

33. Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniasis, Geneva, 22–26 March 2010 (WHO technical report series: No. 949). Geneva: World Health Organization; 2010.

34. Desjeux P, Ghosh RS, Dhalaria P, Strub-Wourgaft N, Zijlstra EE. Report of the Post-Kala-azar Dermal Leishmaniasis (PKDL) Consortium Meeting, New Delhi, India, 27–29 June 2012. *Parasit Vectors* 2013;6:196.

35. Mukhopadhyay D, Dalton JE, Kaye PM, Chatterjee M. Post kala-azar dermal leishmaniasis: an unresolved mystery. *Trends Parasitol* 2014;30(2):65-74.

36. Zijlstra EE. The immunology of post-kala-azar dermal leishmaniasis (PKDL). *Parasit Vectors* 2016;9:464.

37. Zijlstra EE, Musa AM, Khalil EA, el-Hassan IM, el-Hassan AM. Post-Kala-azar dermal leishmaniasis. *Lancet Infect Dis* 2003;3(2):87-98.

38. Karimkhani C, Wanga V, Coffeng LE, Naghavi P, Dellavalle RP, Naghavi M. Global burden of cutaneous leishmaniasis: a cross-sectional analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis* 2016;16(5):584-91.

39. Pigott DM, Bhatt S, Golding N, Duda KA, Battle KE, Brady OJ, et al. Global distribution maps of the leishmaniases. *Elife* 2014;3:e02851.

40. Murray CJ, Acharya AK. Understanding DALYs (disability-adjusted life years). *J Health Econ* 1997;16(6):703-30.

41. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1859-922.

42. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388(10053):1603-58.

43. Burki T. East African countries struggle with visceral leishmaniasis. *Lancet* 2009;374(9687):371-2.

44. Martins-Melo FR, Lima MS, Ramos AN Jr, Alencar CH, Heukelbach J. Mortality and case fatality due to visceral leishmaniasis in Brazil: a nationwide analysis of epidemiology, trends and spatial patterns. *PLoS ONE* 2014;9(4):e93770.

45. Jervis S, Chapman LA, Dwivedi S, Karthick M, Das A, Le Rutte EA, et al. Variations in visceral leishmaniasis burden, mortality and the pathway to care within Bihar, India. *Parasit Vectors* 2017;10(1):601.
46. Anoop Sharma D, Bern C, Varghese B, Chowdhury R, Haque R, Ali M, et al. The economic impact of visceral leishmaniasis on households in Bangladesh. *Trop Med Int Health* 2006;11(5):757-64.

47. Meheus F, Abuzaid AA, Baltussen R, Younis BM, Balasegaram M, Khalil EA, et al. The economic burden of visceral leishmaniasis in Sudan: an assessment of provider and household costs. *Am J Trop Med Hyg* 2013;89(6):1146-53.

48. Ozaki M, Islam S, Rahman KM, Rahman A, Luby SP, Bern C. Economic consequences of post-Kala-azar dermal leishmaniasis in a rural Bangladeshi community. *Am J Trop Med Hyg* 2011;85(3):528-34.

49. Sundar S, Arora R, Singh SP, Boelaert M, Varghese B. Household cost-of-illness of visceral leishmaniasis in Bihar, India. *Trop Med Int Health* 2010;15 Suppl 2:50-4.

50. Uranw S, Meheus F, Baltussen R, Rijal S, Boelaert M. The household costs of visceral leishmaniasis care in south-eastern Nepal. *PLoS Negl Trop Dis* 2013;7(2):e2062.

51. Sunyoto T, Boelaert M, Meheus F. Understanding the economic impact of leishmaniasis on households in endemic countries: a systematic review. *Expert Rev Anti Infect Ther* 2019;17(1):57-69.

52. Marinho DS, Casas CN, Pereira CC, Leite IC. Health economic evaluations of visceral leishmaniasis treatments: a systematic review. *PLoS Negl Trop Dis* 2015;9(2):e0003527.

53. World Health Organization, Regional Office for South-East Asia. *Regional Strategic Framework for Elimination of Kala Azar from the South-East Asia Region (2005–2015)*. Geneva: World Health Organization; 2005.

54. World Health Organization, Special Programme for Research and Training in Tropical Diseases. *Indicators for Monitoring and Evaluation of the Kala-Azar Elimination Programme: Bangladesh, India and Nepal*. Geneva: World Health Organization; 2010.

55. Singh OP, Hasker E, Boelaert M, Sundar S. Elimination of visceral leishmaniasis on the Indian subcontinent. *Lancet Infect Dis* 2016;16(12):e304-9.

56. Rijal S, Sundar S, Mondal D, Das P, Alvar J, Boelaert M. Eliminating visceral leishmaniasis in South Asia: the road ahead. *BMJ* 2019;364:k5224.

57. Bhattacharyya SK, Dash AP. Elimination of kala-azar from the Southeast Asia region. *Am J Trop Med Hyg* 2017;96(4):802-4.

58. Leishmaniases: epidemiological report of the Americas Nº 7 - 2019, March. https://iris.paho.org/bitstream/handle/10665.2/50505/Leishreport2019_eng.pdf?ua=1. Updated 2019. Accessed November 1, 2019.

59. Olesen OF, Parker MI. Health research in Africa: getting priorities right. *Trop Med Int Health* 2012;17(9):1048-52.

60. Lewis DJ. Phlebotomid sandflies. *Bull World Health Organ* 1971;44(4):535-51.

61. Young DG, Lawyer PG. New world vectors of the leishmaniases. In: Harris KF, editor. *Current Topics in Vector Research*, Vol. 4. New York, NY: Springer; 1987, 29-71.

62. Yared S, Gebresilassie A, Abbasi I, Aklilu E, Kirstein OD, Balkew M, et al. A molecular analysis of sand fly blood meals in a visceral leishmaniasis endemic region of northwestern Ethiopia reveals a complex host-vector system. *Heliyon* 2019;5(7):e02132.

63. Michel G, Pomares C, Ferrua B, Marty P. Importance of worldwide asymptomatic carriers of *Leishmania infantum* (*L. chagasi*) in human. *Acta Trop* 2011;119(2-3):69-79.

64. Mahdy MA, Al-Mekhlafi AM, Abdul-Ghani R, Saif-Ali R, Al-Mekhlafi HM, Al-Eryani SM, et al. First molecular characterization of sand fly species causing visceral leishmaniasis among children in Yemen. *PLoS One* 2016;11(3):e0151265.

65. Romero GA, Boelaert M. Control of visceral leishmaniasis in Latin America-a systematic review. *PLoS Negl Trop Dis* 2010;4(1):e584.
66. World Health Organization. *Manual for Case Management of Cutaneous Leishmaniasis in the WHO Eastern Mediterranean Region*. Geneva: World Health Organization; 2014.

67. Jamjoom MB, Ashford RW, Bates PA, Chance ML, Kemp SJ, Watts PC, et al. *Leishmania donovani* is the only cause of visceral leishmaniasis in East Africa; previous descriptions of *L. infantum* and "*L. archibaldi" from this region are a consequence of convergent evolution in the isoenzyme data. *Parasitology* 2004;129(Pt 4):399-409. PUBMED CROSSREF

68. ElNaieem DE. Ecology and control of the sand fly vectors of *Leishmania donovani* in East Africa, with special emphasis on *Phlebotomus orientalis*. *J Vector Ecol* 2011;36 Suppl 1:S23-31. PUBMED CROSSREF

69. Leta S, Dao TH, Mesele F, Alemayehu G. Visceral leishmaniasis in Ethiopia: an evolving disease. *PLoS Negl Trop Dis* 2014;8(9):e3131. PUBMED CROSSREF

70. Mutungu MJ, Basimike M, Kamau CC, Mutero CM. Epidemiology of leishmaniasis in Kenya. Natural host preference of wild caught phlebotomine sandflies in Baringo District, Kenya. *East Afr Med J* 1990;67(5):319-27. PUBMED

71. Tonui WK. Situational analysis of leishmaniasis research in Kenya. *Afr J Health Sci* 2006;13(1-2):7-21. PUBMED

72. Wheeler RJ, Gluenz E, Gull K. The cell cycle of leishmania: morphogenetic events and their implications for parasite biology. *Mol Microbiol* 2011;79(3):647-62. PUBMED CROSSREF

73. Parasites-leishmaniasis-biology. https://www.cdc.gov/parasites/leishmaniasis/biology.html. Updated 2019. Accessed January 31, 2020.

74. Siddig M, Ghaleb H, Shillington DC, Petersen EA, Khidir S. Visceral leishmaniasis in Sudan. Clinical features. *Trop Geogr Med* 1990;42(2):107-12. PUBMED

75. Piscopo TV, Mallia Azzopardi C. Leishmaniasis. *Postgrad Med J* 2007;83(976):649-57. PUBMED CROSSREF

76. Desjeux P. Leishmaniasis. Public health aspects and control. *Clin Dermatol* 1996;14(5):417-23. PUBMED CROSSREF

77. Chappuis F, Sundar S, Hailu A, Ghaleb H, Rijal S, Peeling RW, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? *Nat Rev Microbiol* 2007;5(11):873-82. PUBMED CROSSREF

78. Sharma U, Singh S. Insect vectors of leishmania: distribution, physiology and their control. *J Vector Borne Dis* 2008;45(4):255-72. PUBMED

79. Reithinger R, Brooker S, Kolaczinski JH. Visceral leishmaniasis in eastern Africa--current status. *Trans R Soc Trop Med Hyg* 2007;101(12):1169-70. PUBMED CROSSREF

80. Bern C, Maguire JH, Alvar J. Complexities of assessing the disease burden attributable to leishmaniasis. *PLoS Negl Trop Dis* 2008;2(10):e313. PUBMED CROSSREF

81. de Ruiter CM, van der Veer C, Leeflang MM, Deborggraeve S, Lucas C, Adams ER. Molecular tools for diagnosis of visceral leishmaniasis: systematic review and meta-analysis of diagnostic test accuracy. *J Clin Microbiol* 2014;52(9):3147-55. PUBMED CROSSREF

82. Kühne V, Rezaei Z, Pitzinger P, Büscher P. Systematic review on antigens for serodiagnosis of visceral leishmaniasis, with a focus on East Africa. *PLoS Negl Trop Dis* 2019;13(8):e0007658. PUBMED CROSSREF

83. Cunningham J, Hasker E, Das P, El Safi S, Goto H, Mondal D, et al. A global comparative evaluation of commercial immunochromatographic rapid diagnostic tests for visceral leishmaniasis. *Clin Infect Dis* 2012;55(10):1312-9. PUBMED CROSSREF

84. Mondal S, Bhattacharya P, Ali N. Current diagnosis and treatment of visceral leishmaniasis. *Expert Rev Anti Infect Ther* 2010;8(8):919-44. PUBMED CROSSREF

85. Boelaert M, Verdonck K, Menten J, Sunyoto T, van Griensven I, Chappuis F, et al. Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. *Cochrane Database Syst Rev* 2014;(6):CD009135. PUBMED CROSSREF
86. Ghosh P, Hasnain MG, Ghosh D, Hossain F, Baker J, Boelaert M, et al. A comparative evaluation of the performance of commercially available rapid immunochromatographic tests for the diagnosis of visceral leishmaniasis in Bangladesh. *Parasit Vectors* 2015;8:331.

87. Molinet FJ, Ampuero JS, Costa RD, Noronha EF, Romero GA. Specificity of the rapid rK39 antigen-based immunochromatographic test Kalazar Detect(r) in patients with cutaneous leishmaniasis in Brazil. *Mem Inst Oswaldo Cruz* 2013;108(3):293-6.

88. Diro E, Lynen L, Assefa M, Takele Y, Mengesha B, Adem E, et al. Impact of the use of a rapid diagnostic test for visceral leishmaniasis on clinical practice in Ethiopia: a retrospective study. *PLoS Negl Trop Dis* 2015;9(5):e0003738.

89. Singh D, Pandey K, Das VN, Das S, Verma N, Ranjan A, et al. Evaluation of rK-39 strip test using urine for diagnosis of visceral leishmaniasis in an endemic region of India. *Am J Trop Med Hyg* 2013;88(2):222-6.

90. Mbui I, Wasunna M, Balasegaram M, Laussermayer A, Juma R, Njenga SN, et al. Validation of two rapid diagnostic tests for visceral leishmaniasis in Kenya. *PLoS Negl Trop Dis* 2013;7(9):e2441.

91. Chappuis F, Mueller Y, Nguiimfack A, Rwakimari JB, Couffignal S, Boelaert M, et al. Diagnostic accuracy of two rK39 antigen-based dipsticks and the formol gel test for rapid diagnosis of visceral leishmaniasis in northeastern Uganda. *J Clin Microbiol* 2005;43(12):5973-7.

92. Amany JK, Peng HJ. Visceral leishmaniasis: evaluation of diagnostic tools, therapeutic regimens, and associated risk factors in areas with frequent outbreaks in South Sudan and Sudan: case reports and review of literature. *J Trop Dis* 2018;7(1):293.

93. Hossain F, Ghosh P, Khan MA, Duthie MS, Vallur AC, Picone A, et al. Real-time PCR in detection and quantitation of *Leishmania donovani* for the diagnosis of Visceral Leishmaniasis patients and the monitoring of their response to treatment. *PLoS One* 2017;12(9):e0185606.

94. Rodrigo C, Weeratunga P, Fernando SD, Rajapakse S. Amphotericin B for treatment of visceral leishmaniasis: systematic review and meta-analysis of prospective comparative clinical studies including dose-ranging studies. *Clin Microbiol Infect* 2018;24(6):591-8.

95. Monge-Mailllo B, López-Vélez R. Treatment options for visceral leishmaniasis and HIV coinfection. *AIDS Rev* 2016;18(1):32-43.

96. Mahajan R, Das P, Isaakidis P, Sunyoto T, Sagili KD, Lima MA, et al. Combination treatment for visceral leishmaniasis patients coinfected with human immunodeficiency virus in India. *Clin Infect Dis* 2015;61(8):1255-62.

97. Gillespie PM, Beaumier CM, Strych U, Hayward T, Hotze PJ, Bottazzi ME. Status of vaccine research and development of vaccines for leishmaniasis. *Vaccine* 2016;34(26):2992-5.

98. Ghorbani M, Farhoudi R. Leishmaniasis in humans: drug or vaccine therapy? *Drug Des Devel Ther* 2017;12:25-40.

99. Selvapandian A, Croft SL, Rijal S, Nakhasi HL, Ganguly NK. Innovations for the elimination and control of visceral leishmaniasis. *PLoS Negl Trop Dis* 2019;13(9):e0007616.

100. Directorate General of Health Services (BD); Ministry of Health and Family Welfare (BD); Government of the People’s Republic of Bangladesh. *National Guideline for Kala-azar Case Management. 3rd Edition*. Dhaka: Government of the People’s Republic of Bangladesh; 2016.

101. National Vector Borne Disease Control Programme, Ministry of Health & Family Welfare (ID). *Operational Guidelines on Kala-azar (Visceral Leishmaniasis) Elimination in India - 2015*. New Delhi: Ministry of Health & Family Welfare; 2015.

102. Ministry of Health and Population (NP). *National Strategic Guideline on Kala-azar Elimination Program in Nepal: 2014*. Kathmandu: Ministry of Health and Population; 2014.

103. World Health Organization. *WHO Bi-Regional Consultation on the Status of Leishmaniasis Control and Surveillance in East Africa*. Geneva: World Health Organization; 2018.
104. Gebreyohannes EA, Bhagvathula AS, Abegaz TM, Seid MA. Treatment outcomes of visceral leishmaniasis in Ethiopia from 2001 to 2017: a systematic review and meta-analysis. *Infect Dis Poverty* 2018;7(1):108.

105. Marty P, Rosenthal E. Treatment of visceral leishmaniasis: a review of current treatment practices. *Expert Opin Pharmacother* 2002;3(8):1101-8.

106. Abes F, Bille G, Blesson S, Goyal V, Monnerat S, Mowbray C, et al. Recent development of visceral leishmaniasis treatments: successes, pitfalls, and perspectives. *Clin Microbiol Rev* 2018;31(4):e00048-18.

107. Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, et al. Leishmaniasis worldwide and global estimates of its incidence. *PLoS One* 2012;7(5):e35671.

108. World Health Organization. Surveillance of leishmaniasis in the WHO European Region, 1998–2016. *Wkly Epidemiol Rec* 2018;40(93):521-40.

109. Global Health Observatory (GHO) data: map gallery. https://www.who.int/gho/map_gallery/en/. Updated 2020. Accessed January 31, 2020.

110. Chan M. From new estimates to better data. *Lancet* 2012;380(9859):2054.

111. Annan K. Data can help to end malnutrition across Africa. *Nature* 2018;555(7694):7.

112. Hailu A, Balkew M, Berhe N, Meredith SE, Gemetchu T. Is *Phlebotomus (Larroussius) orientalis* a vector of visceral leishmaniasis in south-west Ethiopia? *Acta Trop* 1995;60(1):15-20.

113. Gebre-Michael T, Malone JB, Balkew M, Ali A, Berhe N, Hailu A, et al. Mapping the potential distribution of *Phlebotomus martini* and *P. orientalis* (*Diptera: Psychodidae*), vectors of kala-azar in East Africa by use of geographic information systems. *Acta Trop* 2004;90(1):73-86.

114. Elnaiem DE, Schorscher J, Bendall A, Obsomer V, Osman ME, Mekkawi AM, et al. Risk mapping of visceral leishmaniasis: the role of local variation in rainfall and altitude on the presence and incidence of kala-azar in eastern Sudan. *Am J Trop Med Hyg* 2003;68(1):10-7.

115. Dowdle WR. The principles of disease elimination and eradication. *Bull World Health Organ* 1998;76 Suppl 2:22-5.

116. Arita I, Wickett J, Nakane M. Eradication of infectious diseases: its concept, then and now. *Jpn J Infect Dis* 2004;57(1):1-6.

117. Enserink M. Global public health. Scientists' new eradication target: a word in their lexicon. *Science* 2010;330(6012):1738-9.

118. Le Rutte EA, Coffeng LE, Ronije DM, Harker EC, Postigo JA, Argaw D, et al. Feasibility of eliminating visceral leishmaniasis from the Indian subcontinent: explorations with a set of deterministic age-structured transmission models. *Parasit Vectors* 2016;9:24.

119. Thakur CP. Is elimination of kala-azar feasible by 2017? *Indian J Med Res* 2016;144(6):799-802.

120. Kala-azar situation in India. https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=467&lid=3750. Updated 2020. Accessed January 30, 2020.

121. World Health Organization; Ministry of Health & Family Welfare, Government of India. *Accelerated Plan for Kala-azar Elimination 2017*. Geneva: World Health Organization; 2017.

122. Fitzpatrick A, Al-Kobaisi NS, Beitan Maya J, Ren Chung Y, Duan S, Elbegdorj E, et al. Sustaining visceral leishmaniasis elimination in Bangladesh - Could a policy brief help? *PLoS Negl Trop Dis* 2017;11(12):e0006081.

123. Olliaro PL, Shamsuzzaman TA, Marasini B, Dharwal AC, Be-Nazir A, Mondal D, et al. Investments in research and surveillance are needed to go beyond elimination and stop transmission of leishmania in the Indian subcontinent. *PLoS Negl Trop Dis* 2017;11(1):e0005190.
124. Guan LR, Wu ZX. Historical experience in the elimination of visceral leishmaniasis in the plain region of Eastern and Central China. *Infect Dis Poverty* 2014;3(1):10.

125. WHO Regional Office for Europe. *Strategic Framework for Leishmaniasis Control in the WHO European Region, 2014–2020*. Copenhagen: WHO Regional Office for Europe; 2014.

126. WHO Regional Office for the Eastern Mediterranean. *Summary Report on the Interregional Meeting on Leishmaniasis among Neighbouring Endemic Countries in the Eastern Mediterranean, African and European Regions: Amman, Jordan, 23–25 September 2019*. Cairo: WHO Regional Office for the Eastern Mediterranean; 2019.

127. Ritmeijer K, Davidson RN. Royal Society of Tropical Medicine and Hygiene joint meeting with Médecins Sans Frontières at Manson House, London, 20 March 2003: field research in humanitarian medical programmes. Médecins Sans Frontières interventions against kala-azar in the Sudan, 1989–2003. *Trans R Soc Trop Med Hyg* 2003;97(6):609-13.

128. Wasunna M, Musa A, Hailu A, Khalil EA, Olobo J, Juma R, et al. The Leishmaniasis East Africa Platform (LEAP): strengthening clinical trial capacity in resource-limited countries to deliver new treatments for visceral leishmaniasis. *Trans R Soc Trop Med Hyg* 2016;110(6):321-3.

129. Chatelain E, Ioset JR. Drug discovery and development for neglected diseases: the DNDi model. *Drug Des Devel Ther* 2011;5:175-81.

130. Al-Salem W, Herricks JR, Hotez PJ. A review of visceral leishmaniasis during the conflict in South Sudan and the consequences for East African countries. *Parasit Vectors* 2016;9(1):460.

131. Control and elimination of visceral leishmaniasis. [http://www.kalacore.org/](http://www.kalacore.org/). Updated 2020. Accessed December 10, 2019.

132. World Health Organization. Control of visceral leishmaniasis in Somalia: achievements in a challenging scenario, 2013–2015. *Wldl Epidemil Rec* 2017;92(38):566-72.

133. Standley C, Boyer MR, Klineberg A, Essis G, Katz R. Organization of oversight for integrated control of neglected tropical diseases within Ministries of Health. *PLoS Negl Trop Dis* 2018;12(11):e0006929.

134. NTD Modelling Consortium. [https://www.ntdmodelling.org/](https://www.ntdmodelling.org/). Updated 2020. Accessed December 5, 2019.

135. Le Rutte EA, Chapman LA, Coffeng LE, Jervis S, Hasker EC, Dwiweedi S, et al. Elimination of visceral leishmaniasis in the Indian subcontinent: a comparison of predictions from three transmission models. *Epidemics* 2017;18:67-80.

136. Rock KS, le Rutte EA, de Vlas SJ, Adams ER, Medley GF, Hollingsworth TD. Uniting mathematics and biology for control of visceral leishmaniasis. *Trends Parasitol* 2015;31(6):251-9.

137. Stauch A, Sarkar RR, Picado A, Ostyn B, Sundar S, Rijal S, et al. Visceral leishmaniasis in the Indian subcontinent: modelling epidemiology and control. *PLoS Negl Trop Dis* 2011;5(11):e1405.

138. DebRoy S, Prosper O, Mishoe A, Mubayi A. Challenges in modeling complexity of neglected tropical diseases: a review of dynamics of visceral leishmaniasis in resource limited settings. *Emerg Themes Epidemiol* 2017;14:10.

139. Montalban C, Martinez-Fernandez R, Calleja JL, Garcia-Diaz JD, Rubio R, Dronda F, et al. Visceral leishmaniasis (kala-azar) as an opportunistic infection in patients infected with the human immunodeficiency virus in Spain. *Rev Infect Dis* 1989;11(4):655-60.

140. Medrano FJ, Hernández-Quero J, Jiménez E, Pineda JA, Rivero A, Sánchez-Quijano A, et al. Visceral leishmaniasis in HIV-1-infected individuals: a common opportunistic infection in Spain? *AIDS* 1992;6(12):1499-503.

141. Desjeux P, Alvar J. Leishmania/HIV co-infections: epidemiology in Europe. *Ann Trop Med Parasitol* 2003;97 Suppl 1:3-15.

142. Daher EF, Fonseca PP, Gerhard ES, Leitão TM, Silva Júnior GR. Clinical and epidemiological features of visceral leishmaniasis and HIV co-infection in fifteen patients from Brazil. *J Parasitol* 2009;95(3):652-5.
143. Leishmaniasis and HIV coinfection. https://www.who.int/leishmaniasis/burden/hiv_coinfection/burden_hiv_coinfection/en/. Updated 2020. Accessed January 30, 2020.

144. Leite de Sousa-Gomes M, Romero GA, Werneck GL. Visceral leishmaniasis and HIV/AIDS in Brazil: Are we aware enough? PLoS Negl Trop Dis 2017;11(9):e0005772.

145. Nascimento ET, Moura ML, Queiroz JW, Barroso AW, Araujo AF, Rego EF, et al. The emergence of concurrent HIV/AIDS and visceral leishmaniasis in Northeast Brazil. Trans R Soc Trop Med Hyg 2011;105(5):298-300.

146. Alvar J, Aparicio P, Aseffa A, Den Boer M, Cañavate C, Dedet JP, et al. The relationship between leishmaniasis and AIDS: the second 10 years. Clin Microbiol Rev 2008;21(2):334-59.

147. Diro E, Lynen L, Ritmeijer K, Boelaert M, Hailu A, van Griensven J. Visceral Leishmaniasis and HIV coinfection in East Africa. PLoS Negl Trop Dis 2014;8(6):e2869.

148. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, et al. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature 2019;570(7760):189-93.

149. East African HIV programmes must wake up to visceral leishmaniasis. https://www.msf.org/east-african-hiv-programmes-must-wake-visceral-leishmaniasis. Updated 2011. Accessed January 31, 2020.

150. van Griensven J, Carrillo E, López-Vélez R, Lynen L, Moreno J. Leishmaniasis in immunosuppressed individuals. Clin Microbiol Infect 2014;20(4):286-99.

151. Diro E, Edwards T, Ritmeijer K, Fikre H, Abongomera C, Kibret A, et al. Long term outcomes and prognostics of visceral leishmaniasis in HIV infected patients with use of pentamidine as secondary prophylaxis based on CD4 level: a prospective cohort study in Ethiopia. PLoS Negl Trop Dis 2019;13(2):e0007132.

152. Bañuls AL, Bastien P, Pomares C, Arevalo J, Fisa R, Hide M. Clinical pleiomorphism in human leishmaniases, with special mention of asymptomatic infection. Clin Microbiol Infect 2011;17(10):1451-61.

153. Zhao GH, Yin K, Zhong WX, Xiao T, Wei QK, Cui Y, et al. Epidemiological investigation of asymptomatic dogs with Leishmania infection in Southwestern China where visceral leishmaniasis is intractable. Korean J Parasitol 2016;54(6):797-801.

154. Fukutani KF, Figueiredo V, Celes FS, Cristal JR, Barral A, Barral-Netto M, et al. Serological survey of leishmania infection in blood donors in Salvador, Northeastern Brazil. BMC Infect Dis 2014;14(1):422.

155. Monteiro DC, Sousa AQ, Lima DM, Fontes RM, Praciano CC, Frutuoso MS, et al. Leishmania infantum infection in blood donors, Northeastern Brazil. Emerg Infect Dis 2016;22(4):739-40.

156. França AO, Pomilio MA, Pontes ER, de Oliveira MP, Pereira LO, Lima RB, et al. Leishmania infection in blood donors: a new challenge in leishmaniasis transmission? PLoS One 2018;13(6):e0198199.

157. Chakravarty J, Hasker E, Kansal S, Singh OP, Malaviya P, Singh AK, et al. Determinants for progression from asymptomatic infection to symptomatic visceral leishmaniasis: A cohort study. PLoS Negl Trop Dis 2019;13(3):e0007216.

158. Hirve S, Boelaert M, Matlashewski G, Mondal D, Arana B, Kroeger A, et al. Transmission dynamics of visceral leishmaniasis in the Indian subcontinent - a systematic literature review. PLoS Negl Trop Dis 2016;10(8):e0004896.

159. Bryceson A. A policy for leishmaniasis with respect to the prevention and control of drug resistance. Top Med Int Health 2001;6(11):928-34.

160. Lemma W, Tekie H, Yared S, Balkew M, Gebre-Michael T, Warburg A, et al. Sero-prevalence of Leishmania donovani infection in labour migrants and entomological risk factors in extra-domestic habitats of Kafa-Humera lowlands - kala-azar endemic areas in the northwest Ethiopia. BMC Infect Dis 2015;15:99.
161. Beyrer C, Villar JC, Suwanvanichkij V, Singh S, Baral SD, Mills EJ. Neglected diseases, civil conflicts, and the right to health. Lancet 2007;370(9587):619-27.

162. Jacobson RL. Leishmaniasis in an era of conflict in the Middle East. Vector Borne Zoonotic Dis 2011;11(3):247-58.

163. Salam N, Al-Shaqha WM, Azzi A. Leishmaniasis in the middle East: incidence and epidemiology. PLoS Negl Trop Dis 2014;8(10):e3208.

164. Tabbabi A. Review of leishmaniasis in the Middle East and North Africa. Afr Health Sci 2019;19(1):1329-37.

165. Sunyoto T, Poterj J, Boelaert M. Visceral leishmaniasis in Somalia: A review of epidemiology and access to care. PLoS Negl Trop Dis 2017;11(3):e0005231.

166. Kolaczinski JH, Reithinger R, Worku DT, Ocheng A, Kasimiro J, Kabateereine N, et al. Risk factors of visceral leishmaniasis in East Africa: a case-control study in Pokot territory of Kenya and Uganda. Int J Epidem 2008;37(2):344-52.

167. Du RY, Stanaway JD, Hotez PJ. Could violent conflict derail the London Declaration on NTDs? PLoS Negl Trop Dis 2018;12(4):e0006136.

168. Githeko AK, Lindsay SW, Confalonieri UE, Patz JA. Climate change and vector-borne diseases: a regional analysis. Bull World Health Organ 2000;78(9):1136-47.

169. Peel GT, Araújo MB, Bell JD, Blanchard J, Bonebrake TC, Chen IC, et al. Biodiversity redistribution under climate change: Impacts on ecosystems and human well-being. Science 2017;355(6332):eaai9214.

170. Watts N, Amann M, Arnell N, Ayeb-Karlsson S, Belesova K, Berry H, et al. The 2018 report of the Lancet Countdown on health and climate change: shaping the health of nations for centuries to come. Lancet 2018;392(10163):2479-514.

171. Haines A, Ebi K. The imperative for climate action to protect health. N Engl J Med 2019;380(3):263-73.

172. World Health Organization. Global Vector Control Response 2017-2030. Geneva: World Health Organization; 2017.

173. Koch LK, Kochmann J, Klimpel S, Cunze S. Modeling the climatic suitability of leishmaniasis vector species in Europe. Sci Rep 2017;7(1):13325.

174. Fischer D, Moeller P, Thomas SM, Naucke TJ, Beierkuhnlein C. Combining climatic projections and dispersal ability: a method for estimating the responses of sandfly vector species to climate change. PLoS Negl Trop Dis 2011;5(11):e1407.

175. Purse BV, Masante D, Golding N, Pigott D, Day JC, Ibañez-Bernal S, et al. How will climate change pathways and mitigation options alter incidence of vector-borne diseases? A framework for leishmaniasis in South and Meso-America. PLoS One 2017;12(10):e0183583.

176. Rosenberg R, Lindsey NP, Fischer M, Gregory CJ, Hinckley AF, Mead PS, et al. Vital signs: trends in reported vectorborne disease cases - United States and territories, 2004–2016. MMWR Morb Mortal Wkly Rep 2018;67(17):496-501.

177. Guerin PJ, Olliaro P, Sundar S, Boelaert M, Croft SL, Desjeux P, et al. Visceral leishmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. Lancet Infect Dis 2002;2(8):494-501.

178. González U, Pinart M, Sinclair D, Firooz A, Enk C, Vélez ID, et al. Vector and reservoir control for preventing leishmaniasis. Cochrane Database Syst Rev 2015;(8):CD008736.

179. Bush JT, Wasunna M, Alves F, Alvar J, Olliaro PL, Otieno M, et al. Systematic review of clinical trials assessing the therapeutic efficacy of visceral leishmaniasis treatments: A first step to assess the feasibility of establishing an individual patient data sharing platform. PLoS Negl Trop Dis 2017;11(9):e0005781.

https://doi.org/10.35500/jghs.2020.2.e3