

## Review Article



# Visceral leishmaniasis: a global overview

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## ABSTRACT

The leishmaniasis 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 leishmaniasis constitute among the most severely neglected tropical diseases (NTDs) and are found in all continents except Oceania.<sup>1-5</sup> Representing the most common infectious diseases, NTDs comprise an open-ended list of some 20 parasitic, bacterial, viral, protozoan and helminthic infections.<sup>6,7</sup> Called “diseases of the poor,”<sup>8</sup> because of their characteristic prevalence in poor populations regardless of a country's income status,<sup>9</sup> they infect over one billion people in over 140 countries, with about 90% of the global burden in Africa<sup>10,11</sup> While NTDs do not contribute significantly to global deaths, they are debilitating and remain the most common infections

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

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,<sup>14–18</sup> receiving only 0.6% of development aid during the MDGs period.<sup>15,19</sup> Unprecedented mobilization of resources saw significant progress on the major diseases (namely, HIV/AIDS, malaria and tuberculosis), but not for NTDs.<sup>20,21</sup> This galvanized calls for the inclusion of NTDs in the post-2015 Sustainable Development Goals (SDGs) agenda.<sup>17,22–24</sup> 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.<sup>25</sup>

Following its first report on NTDs in 2010,<sup>26</sup> on January 30, 2012 the World Health Organization (WHO) launched an implementation roadmap for accelerating work on NTDs<sup>27</sup> during a gathering in London, resulting in the London Declaration on NTDs.<sup>28</sup> 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.<sup>29</sup> 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.<sup>30</sup> 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.<sup>29</sup> 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.”<sup>31</sup>

Among the leishmaniases, 4 types are prevalent, namely VL, cutaneous leishmaniasis (CL), mucosal (or mucocutaneous) leishmaniasis (MCL), and post-kala-azar dermal leishmaniasis (PKDL).<sup>32,33</sup> PKDL, which is subcutaneous, often occurs after treatment of VL<sup>34,35</sup> and thus has been known as an intermediate disease state before full recovery from VL.<sup>36,37</sup> On the other hand, CL is the most widespread type of leishmaniasis.<sup>38,39</sup> Using the common measure of disease burden, the disability adjusted life years (DALYs),<sup>40</sup> 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.<sup>20</sup> The more recent 2017 Global Burden of Disease Study estimated NTDs were responsible for 62 million DALYs, with 774,000 DALYs from leishmaniasis.<sup>41</sup> In 2015 VL contributed 97% of the total DALYs for the leishmaniases,<sup>42</sup> ranking it as the second leading cause of parasitic deaths after malaria.<sup>43</sup>

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,<sup>20</sup> with fatality varying by factors such as age, gender and residence in countries like Brazil<sup>44</sup> and India.<sup>45</sup> Furthermore, VL contributes significantly to household economic loss, as shown by individual studies across countries<sup>46–50</sup> and systematic reviews.<sup>51,52</sup> 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.<sup>53,54</sup> As a result, there is evidence of significant progress on VL in Southeast Asia<sup>55-57</sup> whereas increased incidence is reported in the Americas<sup>58</sup> 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,<sup>18</sup> attention in the African region is still inadequate.<sup>59</sup> 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.<sup>33</sup> 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.<sup>33,60</sup> Comprising 500–800 species, only about 90 are known to transmit leishmania despite being distributed over large tropical and subtropical climate around the world.<sup>33,60,61</sup> Female sandflies feed on blood from humans and animals to fertilize their eggs and male sandflies have no role in transmission.<sup>33,62</sup> Sandfly vectors are only those that carry and can transmit parasites capable of infecting man or other hosts, i.e., are competent.<sup>3,62</sup> Entomological studies that collect sandflies to determine vector competency often identify few relevant vectors.<sup>61</sup> *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.<sup>33,61,63</sup>

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.<sup>33,61</sup> For example, *L. donovani* is mostly anthroponotic and *L. infantum* is mostly zoonotic both being indistinguishable morphologically.<sup>64</sup> 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*).<sup>65</sup> 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.<sup>66</sup> 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.<sup>1</sup> In Eastern Africa, the main infectious agent for VL is *L. donovani* transmitted by 2 principle vectors (*P. orientalis* and *P. martini*).<sup>67,68</sup> In this region, other than humans, dogs are also known to be among the important reservoir host.<sup>69,71</sup>

The leishmania parasite develops in 2 morphological life cycle stages, as amastigotes and promastigotes in mammalian and sandfly host respectively,<sup>72</sup> propagating in the human host through 8 stages (Fig. 1) from the US Centers for Diseases Control and Prevention).<sup>69,73</sup>

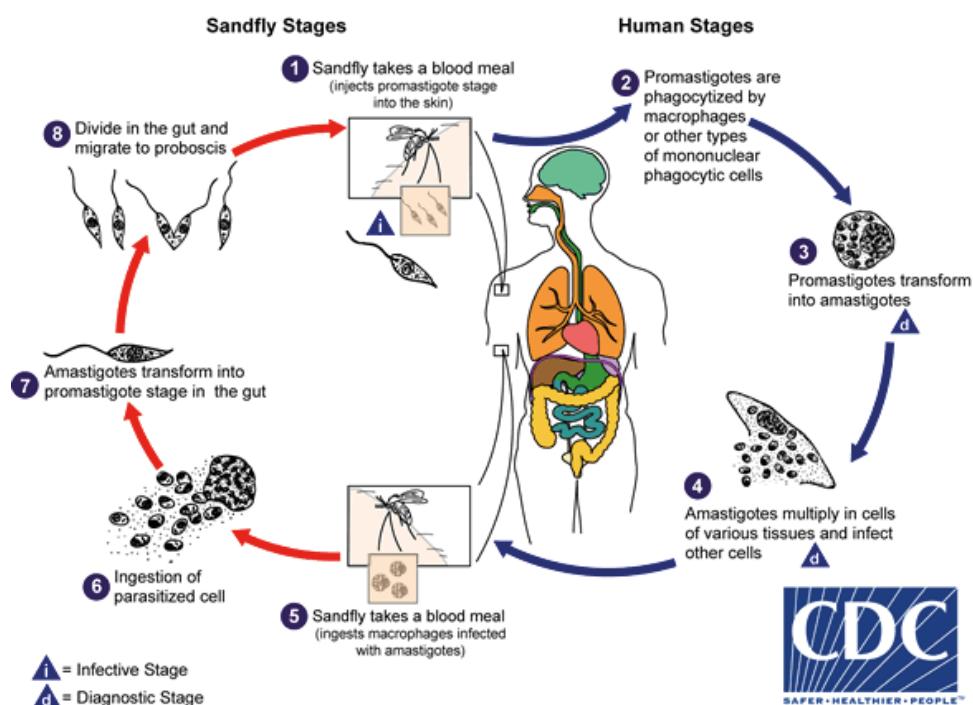


Fig. 1. Image from courtesy of DPDx, a website by the Centers for Disease Control and Prevention (CDC)'s Division of Parasitic Disease and Malaria.<sup>73</sup> The website provides open-access digital material, free of copyright.

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

## DETECTION, DIAGNOSIS AND TREATMENT

WHO's "Control of the Leishmaniasis"<sup>33</sup> 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.<sup>33</sup> 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).<sup>66,77,81,82</sup> The performance of RDTs is known to differ by region and country.<sup>83,84</sup> 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).<sup>85</sup> This RDT was also better than a urine-based latex agglutination test. Clinical trials of multiple RDTs in countries like Bangladesh,<sup>86</sup> Brazil,<sup>87</sup> Ethiopia,<sup>88</sup> India,<sup>89</sup> Kenya,<sup>90</sup> Uganda<sup>91</sup> and Sudan and South Sudan<sup>92</sup> 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.<sup>93</sup>

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.<sup>33</sup> 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 *Miltefosine* (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).<sup>33</sup> Country-specific studies for drug used and effectiveness have been summarized elsewhere.<sup>84</sup> A recent systematic review and meta-analysis of studies of comparative effect of L-AmB found this drug was effective in achieving definitive cure.<sup>94</sup> L-AmB is the recommended and research confirmed drug for VL-HIV coinfecting persons and pregnant women.<sup>33,95,96</sup> While there are currently no vaccines, research is ongoing towards these.<sup>97-99</sup>

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.<sup>66</sup> The 3 southeast Asian countries endemic for VL (Bangladesh, India and Nepal) have individual guidelines<sup>100-102</sup> as do the East African countries.<sup>103</sup> For example, in the East African region combination of SSG and PM is commonly given as it shortens the treatment period to 17 days<sup>33,84,103</sup> 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.<sup>104</sup> 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.<sup>105,106</sup>

## GLOBAL VL EPIDEMIOLOGY

While endemic in specific geographic regions, the global occurrence of VL is widely dispersed in all continents but Oceania.<sup>4</sup> However, assessing its worldwide burden is challenging due to various factors such as diverse clinical and epidemiological manifestations, focality, and reliability of data.<sup>80</sup> Three recent key studies have attempted to examine the worldwide distribution<sup>39,107,108</sup> and are summarized here. **Table 1** contains country-specific data that was captured in 2 of these reports.<sup>107,108</sup> The third study did not include country-level case data. **Fig. 2**, from the WHO,<sup>109</sup> 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 empirical evidence for the leishmaniases by Alvar and colleagues.<sup>107</sup> 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

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**Table 1.** Country-specific VL data<sup>107,108</sup>

Region/country	Years of report	Alvar et al. <sup>107</sup> (reported VL cases/year)	Estimated VL incidence (min)	Estimated VL incidence (max)	WHO <sup>108</sup> (reported VL cases, 2016)
<b>African</b>					
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	4,175
Uganda	2004–2008	288	350	520	35
<b>South-East Asia</b>					
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
<b>Americas</b>					
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
<b>Eastern Mediterranean</b>					
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
<b>European</b>					
Albania	2004–2008	114	140	210	15
Armenia	2004–2008	7	10	30	17
Azerbaijan	2004–2008	28	60	110	44
Bosnia and Herzegovina	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

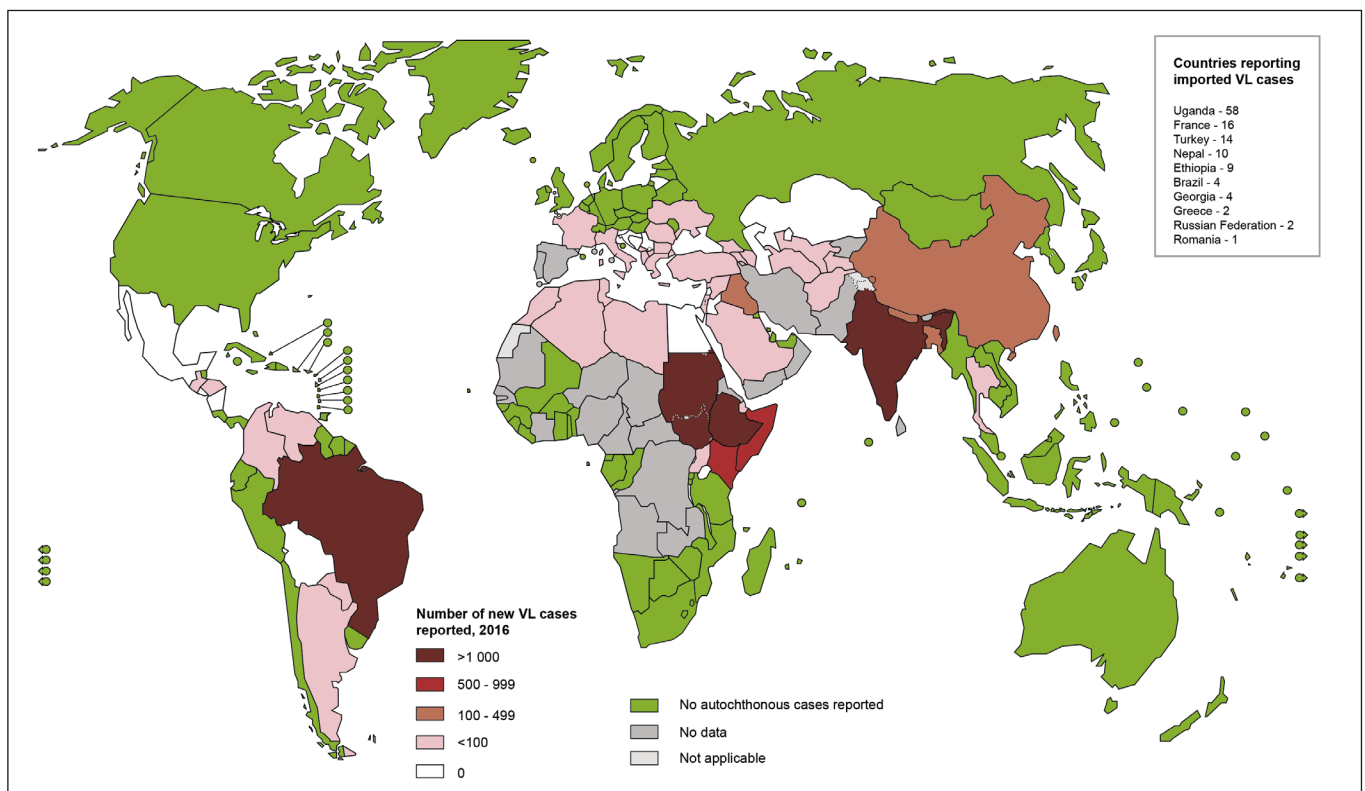
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**Table 1.** (Continued) Country-specific VL data<sup>107,108</sup>

Region/country	Years of report	Alvar et al. <sup>107</sup> (reported VL cases/year)	Estimated VL incidence (min)	Estimated VL incidence (max)	WHO <sup>108</sup> (reported VL cases, 2016)
Tajikistan	2004–2008	15	30	60	25
Turkey	2003–2007	29	60	120	23
Turkmenistan	2004–2008	0			1
Ukraine					1
Uzbekistan	2004–2008	7	10	30	38
Western Pacific					
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.

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



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



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

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.<sup>108</sup> 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<sup>107</sup> 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,<sup>39</sup> 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%.<sup>108</sup> 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.<sup>110,111</sup>

In a 2014 study Pigott et al.<sup>39</sup> attempt to address such limitations in global leishmaniasis data by providing global distribution maps.<sup>69</sup> 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<sup>39</sup> 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.<sup>69,112,113</sup> 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.<sup>68,114</sup> In the Indian subcontinent comprising 3 countries (Bangladesh, India and Nepal) with approximately 30% of the global VL burden,<sup>108</sup> nearly 40% of cases occur in the cross-border areas.<sup>53,57</sup> 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).<sup>58</sup> 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.<sup>39,107,108</sup> The first report, published in 2012 by Alvar and colleagues,<sup>107</sup> 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.<sup>108</sup> 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).<sup>108</sup> **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.<sup>108</sup> 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.<sup>115,117</sup> 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.<sup>53,55</sup> 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.<sup>53,118</sup> Achieving this milestone would ensure that the disease would no longer be a public health problem.

As one researcher<sup>119</sup> 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.<sup>53</sup> Evidence shows that the program resulted in major progress with Nepal and Bangladesh achieving elimination status in 2013 and 2016, respectively.<sup>56,57</sup> While India is progressing towards VL elimination, in 2015 the country reported 8,500 cases to the WHO.<sup>108</sup> 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.<sup>120</sup> Through the NVBDCP, the Ministry of Health's VL elimination strategy is laid out in the 2017 Accelerated Plan for Kala-azar Elimination.<sup>121</sup> 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.<sup>56,122,123</sup>

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.<sup>124</sup> 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.<sup>124</sup> In 2012, China reported only 378 cases, demonstrating significant improvement.<sup>107</sup>

Outside Southeast Asia, the Americas 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.<sup>58</sup> Previous research in Brazil has reported increasing mortality and variation by geographical region mainly in the Northeastern part of the country.<sup>44</sup> In 2014, the WHO developed a framework for controlling leishmaniasis in the WHO European Region with a target to eliminate VL mortality by 2020.<sup>125</sup> 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.<sup>126</sup>

In East Africa on the other hand, the status of VL programming has been inadequate.<sup>43,79</sup> 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.<sup>127</sup> 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).<sup>128</sup> 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,<sup>106,129</sup> 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.<sup>130</sup> 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 research<sup>131</sup> 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.<sup>132</sup>

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.<sup>133</sup> 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.<sup>133</sup> 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,<sup>19,59</sup> 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.<sup>134</sup> 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.<sup>118,135,137</sup> 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.<sup>54,138</sup>

## 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.<sup>139,140</sup> In the year 2000, nearly 2000 cases of VL-HIV co-infections had been reported.<sup>141</sup> 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.<sup>142</sup> According to the WHO 35 countries have reported cases of VL-HIV co-infection.<sup>143</sup>

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.<sup>144</sup> 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.<sup>58</sup> These are concerning especially in Brazil, where they are mostly in urban areas both in the south and northeast mapping concentration of HIV populations.<sup>144,145</sup> Currently, endemicity of VL-HIV is most predominant in Eastern Africa<sup>146,147</sup> corresponding to the high HIV prevalence in these regions.<sup>148</sup> For this reason, in 2011, MSF released an urgent call for HIV programs in Eastern African countries to wake up to VL.<sup>149</sup> While the WHO Technical Report Series 949 of 2010 included recommendations for VL-HIV management,<sup>33</sup> the US Centers for Diseases Control and Prevention does not list HIV as an opportunistic infection, which hinders monitoring.<sup>143</sup> 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.<sup>150</sup> The overall implication of co-morbidities is on VL diagnosis and treatment. HIV positive VL patients are more difficult to diagnose and treat.<sup>151</sup> Additionally, because of the lower performance of current RDTs in Eastern Africa, negative results from these does not rule out possibility of infection.<sup>85</sup>

### 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.<sup>63,152,153</sup> 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.<sup>154-156</sup> Other studies of blood donors have been conducted in many countries including France, Greece, Spain and Italy.<sup>152</sup> A cohort study of asymptomatic cases from Bihar, India has recommended no treatment but careful follow up of these as they develop VL earlier.<sup>157</sup>

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.<sup>4,158</sup> Such a concern led to a call for development of a policy to monitor drug resistance,<sup>159</sup> and needs for pharmacovigilance<sup>92,106</sup> as well as continued drug development.<sup>5,106,128</sup>

### 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.<sup>138</sup> 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.<sup>53,57,119</sup> 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.<sup>69,160</sup>

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.<sup>161</sup> While the conflicts in the Middle East pose a danger to VL control,<sup>162-164</sup> nowhere is this more evident for VL than in the Eastern African countries of Sudan and South Sudan.<sup>130</sup> 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.<sup>79</sup> In Sudan, case fatality rate of 50% in areas without interventions have been reported.<sup>80</sup> In Somalia, continuing civil war, conflict and instability complicates assessment of disease epidemiology as well as population needs and availability of care.<sup>132,165</sup> Conflicts also have implications for cross-border migration and transmission of VL even in non-conflict countries in Eastern Africa.<sup>130,166</sup> Continued violent conflicts could derail achievement of the agenda for NTDs.<sup>166</sup>

### Global climate change

The complexity of VL transmission is also exacerbated by environmental factors. Ecological factors include rainfall patterns, temperature, soil types, and vegetation.<sup>39</sup> 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<sup>166,172</sup> including in specific regions such as Europe<sup>173,174</sup> and the Americas.<sup>175,176</sup> In the southeast Asian region, for example, vector competency has been observed at 15–38 degrees Celsius range<sup>33</sup> meaning increasing temperature variation alters vegetation, rainfall patterns and vector-human behavior.<sup>39</sup> 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.<sup>172</sup>

## 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.<sup>2</sup> 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.<sup>177</sup> 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.<sup>94</sup> Continued development of new drugs<sup>5,106</sup> and ultimately a vaccine is needed.<sup>97-99</sup>

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.<sup>178</sup> 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.<sup>179</sup> 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.<sup>2-24</sup>

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/>).

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