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Cutaneous leishmaniasis in Afghanistan

Bilal Ahmad Rahimi [a,*], Mohammad Amin Ghatee [b], Muhammad Naeem Habib [c], Khushhal Farooqi [a], Koert Ritmeijer [d], Huma Syed Hussain [e], M. Asim Beg [e], and Walter R. Taylor [f]

[a]Department of Pediatrics, Faculty of Medicine, Kandahar University, Kandahar 3801, Afghanistan; [b]Department of Medical Micriobiology, Professor Alborzi Clinical Microbiology Research Center, Shiraz University of Medical Sciences, Shiraz 71348-14336, Iran; [c]Department of Malaria, National Malaria & Other Vector Borne Diseases Program, Ministry of Public Health, Kabul 1001, Afghanistan; [d]Médecins Sans Frontières, Amsterdam 14 1018, the Netherlands; [e]Department of Pathology and Laboratory Medicine, Aga Khan University Hospital, Karachi 74800, Pakistan; [f]Mahidol Oxford Tropical Medicine Clinical Research Unit, Bangkok 10400, Thailand

*Corresponding author: Tel: +93 (0) 700309692; E-mail: drbilal77@yahoo.com

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Old World cutaneous leishmaniasis (OWCL) is a sand fly-transmitted skin infection caused by Leishmania species that extends from West Africa to China. Afghanistan probably has the highest burden of OWCL and is home chiefly to *Leishmania tropica* and *Leishmania major*, which cause anthroponotic and zoonotic CL, respectively. Although data on the species distribution in Afghanistan are patchy, *L. tropica* predominates over *L. major*, reflecting its concentration in large cities. CL prevalence in Afghanistan increases with increasing age to peak at 5–10 y, depending on the local epidemiology. Clinically, there is a spectrum of lesions common to both main species with nodules, ulcerated nodules and papules accounting for the majority (50–80%) of lesions at presentation. When healed, CL lesions leave pale scars that often have deleterious psychosocial effects. Leishmania control involves vector control and treating patients, but these are severely challenged by decades of war and disruption to the health system. In the public sector, only injectable antimonials, sodium stibogluconate or meglumine antimoniate, are available and, anecdotally, efficacy remains high. Few clinical trials have been conducted in Afghanistan and data support antimonial efficacy; small clinical series suggest good efficacy of oral miltefosine against the two main species. Herein, we focus our review on the epidemiological and clinical aspects of CL in Afghanistan and suggest avenues of future research.

Keywords: Afghanistan, cutaneous, Kandahar, leishmaniasis, treatment

Introduction

Leishmaniasis encompasses several sand fly-borne diseases that are caused by a protozoan of the Leishmania (L) genus and manifests as cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis or visceral leishmaniasis (VL). Based on their global distribution, leishmania parasites are traditionally divided into Old World cutaneous leishmaniasis (OWCL) and New World cutaneous leishmaniasis (NWCL).

In the Old World, the main leishmania-causing species are *Leishmania tropica*, *Leishmania major*, *Leishmania aethiopica*, *Leishmania infantum* and *Leishmania donovani*, which are prevalent mostly in the Mediterranean basin, Middle East, Horn of Africa, West Africa and the Indian subcontinent. Among these species, *L. infantum* and *L. donovani* are the main causes of VL in the Mediterranean, East Africa and South Asia and are less likely causes of CL.[1] The *L. tropica* to *L. major* ratio varies in different countries, but *L. tropica* predominates in Afghanistan, northern Syria, Pakistan and Turkey.[1,2,3]

The main CL species in the New World are either in the *Leishmania mexicana* (*L. mexicana*, *Leishmania amazonensis* and *Leishmania venezuelensis*) or *Leishmania* (*V.*) *braziliensis* species complex; the latter is also known as the Viannia subgenus (*L.* [*V.*] *braziliensis*, *Leishmania* [*V.*] *guyanensis*, *Leishmania* [*V.*] *panamensis* and *Leishmania* [*V.*] *peruviana*).[4] *Leishmania infantum* is the main cause of VL in Central and South America (i.e. the New World), where it is also known as *Leishmania chagasi*.

The sand fly vectors are Phlebotomus in the OW and Lutzomyia in the NW. Infected sand flies transmit the disease between humans and animals like dogs and rodents to cause zoonotic (Z) CL, or between humans to cause anthroponotic (A) CL.[1] Transmission of leishmaniasis is influenced by multiple factors, including socioeconomic status, poverty, access to healthcare and the immunogenic profile of the affected individual.[5] *Phlebotomus sergenti* is the predominant OW ACL vector[6,7] and *Phlebotomus papatasi*[8,9] is the main species for transmitting OW ZCL. Lutzomyia species in NWCL include *Lutzomyia wellcomei*,[10]

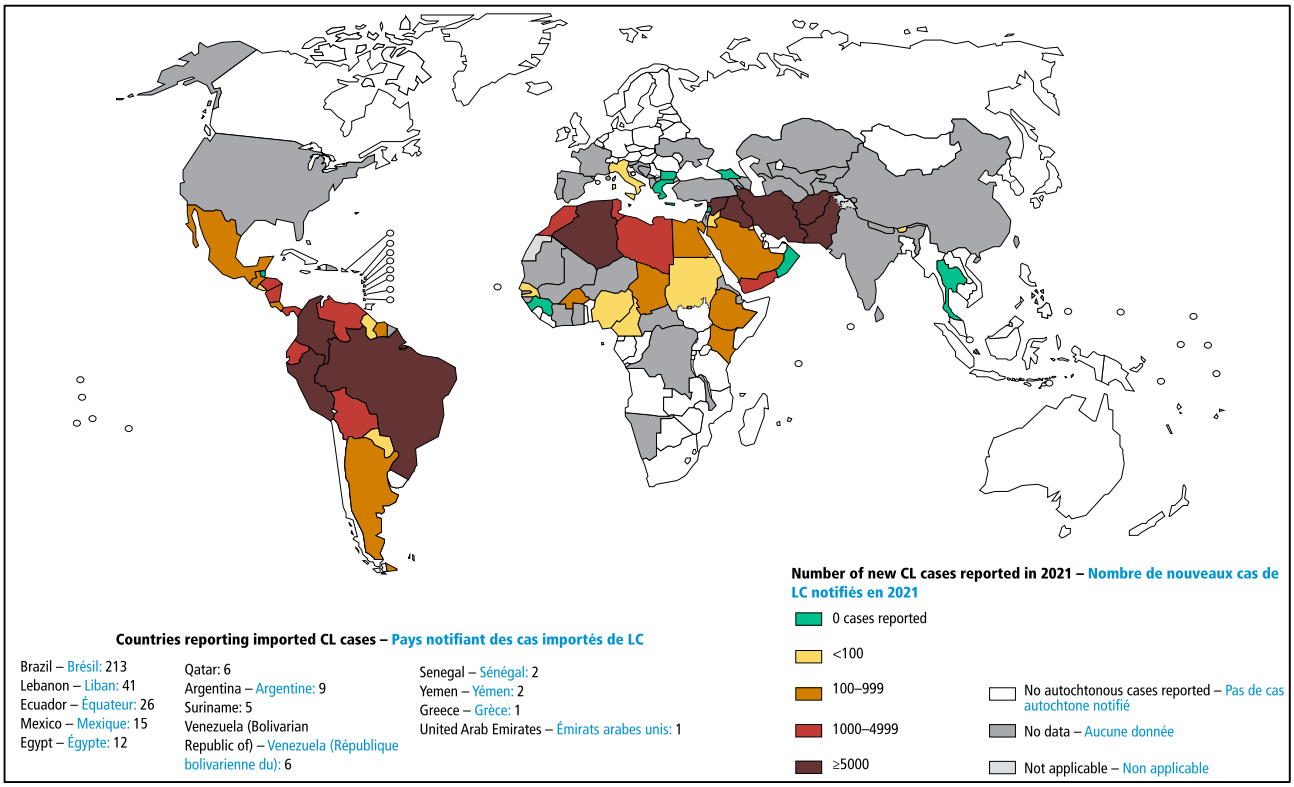

Figure 1. Global status of cutaneous leishmaniasis (World Health Organization, 2021).

Lutzomyia almeca, *Lutzomyia flaviscutellata*,[11] *Lutzomyia peruensis*, *Lutzomyia verrucarum* and *Lutzomyia ayacuchensis*.[12]

Global epidemiology

According to the WHO, >1 billion people live in areas endemic for leishmaniasis (Figure 1) and are at risk of infection. Estimating the global burden of acute CL is challenging because of underreporting, but the WHO estimates that there are 600 000 to 1 million new CL cases annually (World Health Organization, 2025).[13] The burden of CL is far greater if a more inclusive definition incorporates healed scars, which are more prevalent than active CL, and the deleterious social and psychological effects.[14]

In 2021, >85% of new CL cases occurred in nine countries: Afghanistan, Algeria, Brazil, Colombia, Islamic Republic of Iran, Iraq, Pakistan, Peru and the Syrian Arab Republic.[15] In terms of disability adjusted life years (DALYs)/100 000 population that were reported for 2013, six OWCL and three NWCL countries had age-standardised DALYs/100 000 that exceeded the global mean: Afghanistan (87.0 DALYs/100 000), Sudan (20.2), Syria (9.2), Yemen (6.2), Iraq (6.0), Burkina Faso (4.8), Bolivia (4.6), Haiti (4.1) and Peru (4.0).

Regarding CL incidence rates/100 000 population in 2013, the four countries with the highest incidence rates were Palestine (616.2 for males and 222.1 for females), Afghanistan (566.4 for males and 623.9 for females), Syria (357.1 for males and 406.3 for females) and Nicaragua (354.8 for males and 180.8 for females).[16] War, poverty, population displacement, destruction of buildings and health system deterioration are great drivers of CL seen in Afghanistan,[17–20] as well as in Syria[21,22] and Yemen.[23]

Historically, OWCL has become known as the 'Oriental sore/boil' and been prefixed by the names of the towns and cities where OWCL was prevalent, such as Sart and Pendeh (towns in historical Turkistan encompassing present day Turkmenistan, Kazakhstan and Uzbekistan), where leishmaniasis was first identified by the Russian military surgeon, Borovsky[24]; other names include Delhi, Kandahar, Baghdad and Aleppo boil.[25–27]

Epidemiology of OWCL in Afghanistan

Overview

Cutaneous leishmaniasis is well known in Afghanistan and is referred to locally as 'saldana' or 'kaldana', meaning 'that which lasts one year' and 'Kandahar boil'; an early description of the 'Balkh sore', in northern Afghanistan (Figure 2), comes from the well-known physician-philosopher, Abū ʿAlī al-Ḥusayn ibn ʿAbd Allāh ibn Al-Hasan ibn Ali ibn Sīnā in the 10th century. His description of dry skin lesions is suggestive of *L. tropica*.[28]

CL is focally endemic within major cities such as Kabul, Herat and Kandahar, in areas such as Charikar, as well as the Panjsheer and Gorband valleys. Most cases are caused by *L. tropica* (mainly urban endemicity)[29,30] that is transmitted anthroponotically by *P. sergenti*,[6] while *P. papatasi*, the main ZCL vector,[9] is ecologically associated with *L. major* rodent reservoirs, namely, *Rhombomys opimus*, the great gerbil, and

Figure 2. Afghanistan's provinces.
*maps-of-the-world.net/maps/maps-of-asia/maps-of-afghanistan/large-administrative-divisions-map-of-afghanistan-2008.jpg (accessed May 2024).

Meriones libycus, the Libyan jird (Figure 3); the great gerbil prefers desert habitats while the Libyan jird also inhabits subtropical/tropical dry shrubland and rural gardens.[31,32] Rarely, OWCL may be caused by *L. donovani*, the species associated with VL.[33]

In the 1960s and 1970s, CL in Afghanistan was nearly eliminated thanks to an extensive DDT spraying campaign that significantly reduced the sand fly population. However, CL caused by *L. tropica* has resurged over the past decades as a significant public health concern due to factors such as war, mass migration, inadequate treatment and a lack of control measures, all within a background of a changing political landscape. Afghanistan now has one of the highest global CL burdens. According to the WHO Global Health Observatory of CL cases reported to the WHO,[34] the three highest burden countries are Syria, Afghanistan and Pakistan; over 5 y (2019–2022) the mean number of reported cases was 72 786, 47 326 and 24 277, respectively, followed by Brazil at 15 065. The WHO estimates that CL under-reporting is 2.8–4.6-fold in high-burden countries[35] and, given its very poor availability and access to CL treatment, it is likely that Afghanistan has a higher CL burden than Syria.

ACL is a very old and well-established disease in the big cities of Kandahar and Herat, but appears to have been virtually non-existent in Kabul and its neighbouring areas until the late 1940s/early 1950s.[36,37] Data from a 1977 epidemiological study of CL scarring found that a scar was observed in 6.8% (n=7648), 26.3% (n=1917) and 45.6% (n=1610) individuals from Panjsher (north of Kabul), Kandahar and Herat provinces, respectively.[36,38] Overall, *P. sergenti* was the dominant vector and together with the absence of rodents, the authors concluded that ACL was the main cause of CL.

There are limited data on the regional distribution, seasonality and public health impact of ZCL. *Leishmania major* is reported as the minority species in Herat, Badakhshan and Kandahar,[31,32,39] but is more commonly found in the northern plains of Afghanistan along the Amu Darya river, which extends from Herat to Balkh and Kunduz provinces along the border with Turkmenistan and Tajikistan and matches the distribution of the great gerbil, *R. opimus*.[31,32,40]

ACL transmission in Kabul occurs from April to October,[41] with clinical cases presenting in the winter and early spring months.[32] By contrast, in the northern cities of Balkh and Kunduz, there is an increase of ZCL cases over late summer, peaking in October then falling rapidly in November; in Faizabad, there is low perennial incidence, with two peaks in March and November.[32] Seasonal 2023 CL data for Afghanistan are shown in Figure 4.

The reporting system is weak in Afghanistan so cases are under-reported; moreover, most of the reported CL patients are diagnosed clinically when they visit the malaria and leishmania clinics in the major cities; however, many patients from remote

Figure 3. The two main rodent reservoirs of *Leishmania major*. The great gerbil, *Rhombomys opimus* (left), and the Libyan jird, *Meriones libycus* (right). File: Rhombomys opimus 2.jpg—Wikimedia Commons, accessed 18–3–23.
(Image—Meriones libycus (Libyan Jird) | BioLib.cz, accessed 18–3–23 'The resized photographs can be freely used on any pages for non commercial, scientific and educational purposes, if you let me know about it first.' Permission to publish obtained from K. Rudloff.)

Figure 4. The trends in clinically diagnosed anthroponotic and zoonotic cutaneous leishmaniasis reported through the national system in 2023 for the whole of Afghanistan.

areas have no access to treatment, while many others seek care in the informal private sector because of the lack of drugs in government clinics.[42]

CL is reported through the public health system from 24 of Afghanistan's 34 provinces, in which approximately 23.6 million individuals are at risk of CL, representing about two-thirds of the total population. From 2003 to 2016, a total of 351 945 new CL cases were reported; males and females were equally affected and 78 106 (22%) cases were children aged <5 y. Geographically, the provinces of Balkh, Kandahar and Kabul had particularly high CL rates (Figure 5). In more recent years, cases declined after 2019, but then rose sharply (Figure 6).

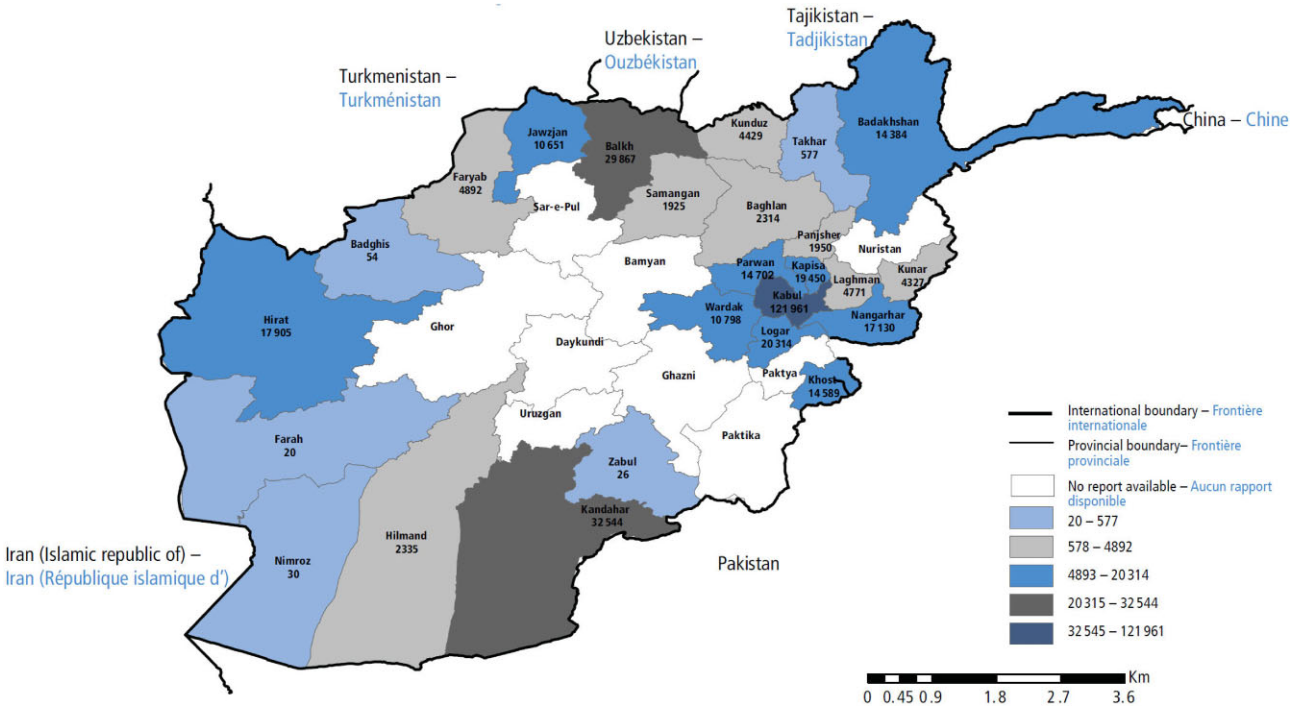

Figure 5. Reported cases of cutaneous leishmaniasis in the provinces of Afghanistan, 2003–2016*.
*Control of cutaneous leishmaniasis in Afghanistan: achievements and challenges 2018. https://www.who.int/publications/i/item/who-wer9317.

Historically, war and political instability have conspired to maintain a significant human reservoir through low coverage of treatment, the breakdown of health infrastructure and the influx of refugees and internally displaced individuals. Cases increase when infected populations introduce CL in a new area where a competent vector is already present and when those with limited CL exposure settle in endemic areas and become infected.[17,30,41,43,44]

Data on the species distribution in Afghanistan and their genetic relationships with other *Leishmania* species in neighbouring countries are limited. In Herat province, *L. tropica* accounts for 96–98% of diagnosed CL[45,46] and shares genetic characteristics with South-East Iranian strains.[29,46] The species in Badakhshan and Kandahar provinces are probably similar to the bordering Pakistani provinces of Khyber Pakhtunkhwa (KPP; formerly North West Frontier Province) and Baluchistan, respectively. KPP has predominantly *L. tropica*,[2,47] where high prevalence rates of up to approximately 9% of active lesions and approximately 6% of scars were reported in the late 1990s in the Afghan refugee camps.[19] Balochistan province has both *L. tropica*, found mostly in mountainous regions bordering Afghanistan, and *L. major*, which is a disease of the plains.[48]

A survey of Afghan refugee camps and local villages in Balochistan and KPP in the late 1990s indicated that 38% of the camp's population compared with 17% the year before, indicating that the outbreak likely originated within the camp; *L. tropica* was detected in a subset of those affected[44] and a PCR study showed a single homogeneous schizodeme clone.[49] The prevalence of CL was seen to increase with age to peak at 5–6 y in the villages and 10 y in the refugee camps, declining thereafter, with consistently lower prevalence rates in the villages. These data suggest that the outbreak started within the camp, following the introduction of this clone from Afghanistan, and spread to the villages in an area in Pakistan where *L. tropica* was not present before[50] but where a potent vector was present. There was also significant household clustering and no evidence of spatial structuring between villages, underscoring the highly focal distribution of ACL transmission in the villages.[43]

CL is also a growing health concern in Pakistan, affecting both locals and Afghan refugees, notably along the Durand line, the border between east Afghanistan and the Pakistani provinces of Gilgit Baltistan, Khyber Pakhtunkhwa and Balochistan; for example, a consistent rise in the number of CL patients seeking medical care has been observed in clinics across Baluchistan province, especially in Quetta and Killa Saifullah.[51] Moreover, being landlocked, Afghanistan exports a large quantity of fruits such as pomegranates, apricots and peaches, and vegetables in wooden crates, particularly from highly endemic areas like Kandahar, bringing competent vectors and a human reservoir that probably contribute to transmission within Pakistan.

Kabul

The earliest reported study of CL appears to be in the early 1960s when Eliseev and Kellina reported human ZCL and infections in the great gerbil, *R. opimus*, in the northern provinces.[52] Their report mentions CL in Herat and Kandahar but apparently no CL in towns of eastern Afghanistan, notably, Kabul, Gazni, Saroobi and Jalalabad. There were several individuals in Kabul with scars, but

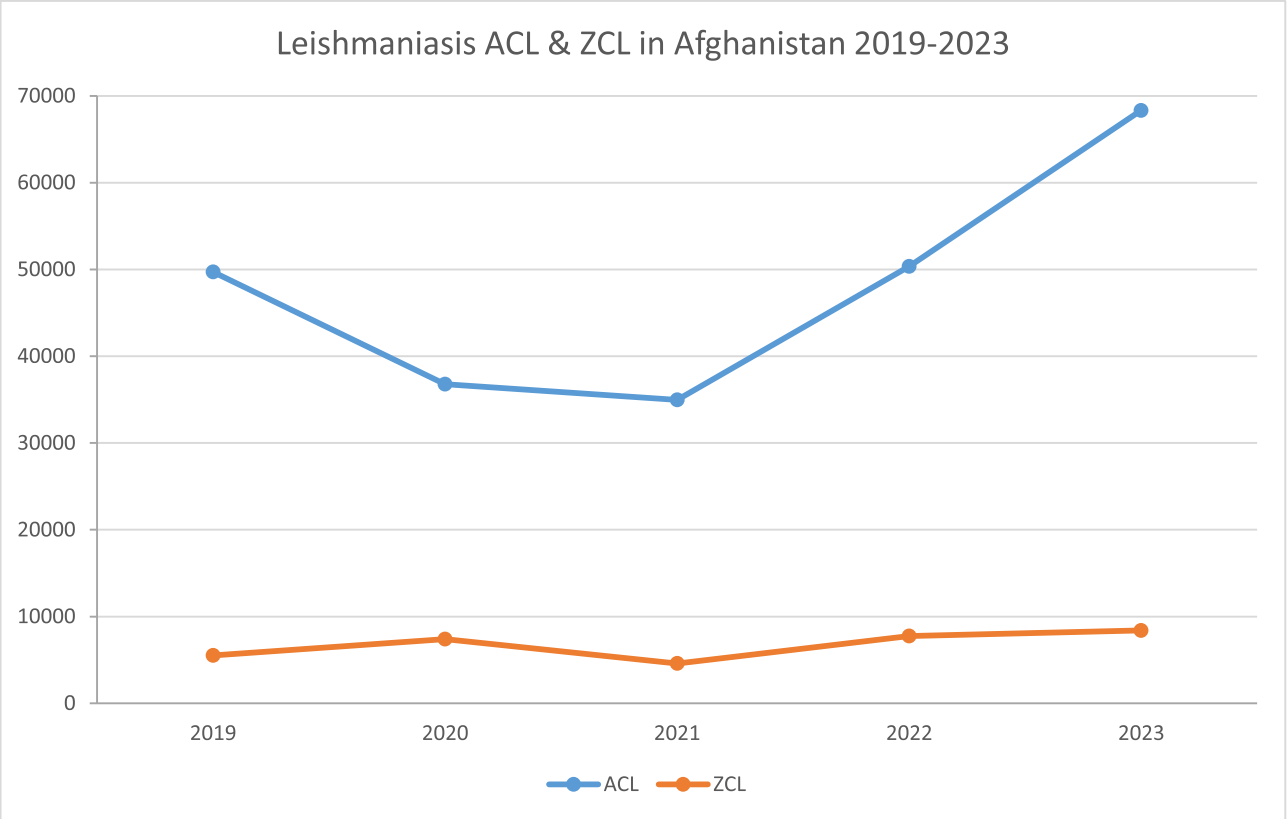

Figure 6. Trend of anthroponotic and zoonotic cutaneous leishmaniasis in Afghanistan reported through the national system from 2019 to 2023.

they had reportedly caught the disease in northern Afghanistan, Kandahar or Herat.

In later work in 1967, Omar et al. studied CL in Kabul city and reported that autochthonous CL cases had been reported since 1947. The number of cases recorded in the city had been very low from 1947 to 1963, but, from 1964 to 1967, had increased and reached 334 in 1967.[36] They also reported approximately 1000 acute cases epidemiologically linked to areas of new construction, suggesting exposure of individuals in areas where competent vectors and mammal host reservoirs were breeding. In 1972, Nadim and Rostami investigated another CL outbreak in a new housing development project in Khair Khana, northwest Kabul.[37] They found prevalence rates of active sores and scars of approximately 12% and 4%, respectively, suggesting ongoing/recent infection; the age-specific attack rates were high across the age spectrum and were lowest in the under 1s (15%) and highest in adults (approximately 34%). No species diagnosis was made but the absence of gerbils in the area suggested this was an ACL outbreak.

Reyburn et al. documented the substantial increase in ACL from 1987 onwards that peaked in 1996 when they estimated that 12% of the population had active disease. Infants aged <2 y had the lowest prevalence that rose with increasing age, with adult females outnumbering adult males by approximately 50%. Approximately one-third had moved to Kabul, while another one-third were indigenous Kabul residents. Active disease in Kabul residents correlated significantly with that of the new immigrants, supporting the hypothesis that the steady arrival of susceptible immigrants fuelled the epidemic.[30]

These findings were consistent with another study conducted in 2002 in which approximately 22% of sampled Kabul residents had scars and just under 3% had active lesions, indicating long-standing transmission. Females were more affected than males, increasing age was associated with active lesions and the study reconfirmed the highly focal distribution of ACL.[41] A later study demonstrated again a high prevalence of active lesions and scars with an increasing prevalence with age, peaking at 6 y. Multivariable analysis identified a positive association between active ACL and age, ACL in the same household and dwellings made of brick or stone with wooden ceilings but a protective effect of screened windows.[53] A recent study in Kabul reports the continuing high CL burden with a total of 12 292 cases recorded in 2021 and 2022; the sexes were equally affected and approximately 50% were children aged <11 y.[54] In a diagnostic study in Kabul, *L. tropica* was confirmed in all 274 CL patients.[55]

Herat

Herat is an important focus of ACL and where ZCL is rare.[46] In a study of 3861 slide positive CL patients from 177 villages in Herat province (January 2012 to December 2013), 127 were selected for internal transcribed spacer (ITS) 1 PCR–RFLP analysis; 125

Table 1. Data for 2018 to 2023 in the Malaria and Leishmania clinic in Kandahar City. The increase in cases in 2022 and 2023 could be due to the establishment of a new government, with better security helping a better surveillance system

Year	CL cases	<5 y	<5 y (%)	≥5 y	≥5 y (%)
2018	2745	960	35	1785	65
2019	3069	958	31.2	2111	68.8
2020	2933	843	28.7	2090	71.3
2021	2988	926	31	2062	70
2022	5887	1903	32.3	3984	67.7
2023	7007	2165	30.9	4842	69.1
Grand total	24 629	7755	31.5	16 874	68.5

(>98%) were due to *L. tropica* and these strains were genetically related to isolates from Iran and India.

Kandahar

In one small series, six Canadian soldiers with ACL acquired in Kandahar (two with parasitologically diagnosed *L. tropica*) failed to improve with fluconazole but responded to miltefosine; the isolates demonstrated in vitro resistance to fluconazole but sensitivity to miltefosine.[56] Similarly, in another study, four Canadian soldiers with *L. tropica* responded to miltefosine.[39]

Data recorded from 2018 to 2023 in the Malaria and Leishmania clinic in Kandahar City show that there were a mix of slide and clinically diagnosed cases numbering 24 629, with a marked increase in 2022 and 2023 (Table 1). Routine data collection only classifies age as < or ≥5 y, with the under 5s accounting for approximately 30% of the burden.

Northern Afghanistan

Epidemiological studies have been conducted across the northern provinces with several centred on Mazar-e-Sharif. ZCL has been diagnosed clinically as wet lesions, some with sporotrichoid spread, and ACL as dry lesions, with few studies including a parasitological and species diagnosis.[31,32,40,57]

Early survey work in the mid-1970s in Mazar-e-Sharif, Aqcha (approximately 100 km to the north west), Pol-e-Khombri (approximately 200 km to the southeast) and Baghlan (approximately 30 km north of Pol-e-Khombri) detected slide positive leishmania-infected *R. opimus* and evidence that *P. papatasi* was probably the main vector of human CL, given its abundance in houses and burrows of *R. opimus*.[31] A human survey in a village close to Aqcha documented an overall high rate of scars, approximately 35%, with the highest rates in children aged 6–14 y (45%). The overall rate of active lesions was 30-fold lower at 1.5%, with ages up to 9 y having the highest rates of just over 4%.

In 2003, a survey was conducted in Faizabad (Faysabad) city, the capital of Badakhshan, Afghanistan's most northeastern province. In this survey, the rates of active CL lesions and scars were almost the same, around 8%, and younger individuals (age ≤15 y) had a twofold higher risk of CL than those aged >15 y. Collectively, these data suggested a recent introduction of CL into the city and the authors hypothesised this was *L. tropica*.[57]

Leishmania major (95%) was the overwhelming species (vs 5% for *L. tropica*) in 3782 CL cases diagnosed in Mazar-e-Sharif over 1 y.[40] In this study, ZCL cases were more commonly seen in late summer and autumn, falling by the end of December, while the number of ACL cases declined over the autumn and was highest in the winter and spring. The attack rates were similar in the <5, 5–14 and ≥15 y age groups. The Mazar-e Sharif area, especially around the airfield, is semidesert and has an exceptionally high density of burrows (3380/hectare) that house *R. opimus* in the sandy canal embankments that were formed as part of constructing irrigation canals.

A larger study in Mazar-e Sharif (n=3971) and two other northern provinces, Kundoz (n=3362) and Faizabad (n=2726), essentially reconfirmed the epidemiological findings of the 2006 study but also found a high *L. major* positivity rate (28%) in *P. papatasi* sand flies in the sandy canal embankments housing the *Rhombomys* burrows.[58]

Dutch troops stationed in Mazar-e-Sharif experienced a high attack rate (18%) of *L. major*[59] and there was an impression that, compared with a small number of *L. major*-infected soldiers acquired in southern Afghanistan, the clinical features in the northern infected soldiers were more severe.[60] Another *L. major* confirmed CL outbreak with unusually severe clinical features, for example, sporotrichoid lymphatic spread, large ulcerations and satellite papules around healing sores, was reported in British and Fijian soldiers also camped outside Mazar-e-Sharif.[20]

Geography, climate and CL distribution

Several GIS/RS (Geographical Information System/Remote Sensing) studies have shed light on the climatic and geographical factors that affect the CL burden, namely, altitude, humidity, soil type and soil moisture. In Herat province, ACL incidence was associated with areas near the Harirud river, intensively and irrigated farmland, and altitudes between 700 and 1200 m; these climatic conditions favour the breeding of *P. sergenti*.[29]

Using clinic data from 20 sites throughout the country, Adegboye et al. reported several CL hot spots: Kabul, the eastern provinces of Lahman, Nangarhar and Kunar, as well as the northwestern province of Jowzjan, while malaria was concentrated in Lahman and Nangarhar provinces. Overall, CL cases were highest in the summer and autumn. CL risk factors were antecedent malaria, altitude and temperature.[61] Although they did not find a significant effect of rainfall, ZCL vectors are known to flourish in areas of high rainfall.[62]

In KPP, bordering eastern Afghanistan, elevation was identified as the main factor determining the distribution of *Leishmania* vectors; *P. sergenti* thrived better at higher altitudes while *P. papatasi* preferred lower altitudes.[63] These data support the roles of higher altitudes in ACL, also reported by Fakhar et al. from Herat,[29] and lower altitudes in ZCL, reported from the lowlands of Iran[64] and Libya.[62]

Historically, urban areas have been important centres of ACL. Data from South Khorasan province, a desert region of eastern Iran that borders western Afghanistan where the main species is *L. tropica*, showed that there was a 52-fold increase in the probability of CL in urban dwellers.[65]

Clinical features of CL

Clinically, CL lesions are painless, unless secondarily infected, and manifest a wide variety of morphologies that are shared across the two main species.[2,48,66] They are usually present on exposed areas of skin and a significant proportion (up to approximately 40–60%) of patients have multiple lesions.[45,59,67]

CL commonly starts as a small erythematous papule that may develop into a nodule that often breaks down to form an ulcer. In one large (n=1000+), *L. major* clinical series from Iran, ulcerated nodules (approximately 25%) and papules (approximately 25%) accounted for about 50% of lesions at presentation,[67] while *L. major*-infected Dutch soldiers in Afghanistan presented with nodules (approximately 40%), ulcerated nodules (approximately 40%) and mixed lesions (approximately 20%).[59] A *L. tropica* series from Herat (n=4127) reported nodules in two-thirds, ulcers in almost one-quarter and papules in <10%.[68] Other described morphological features include plaques, ulcerated plaques, impetiginised lesions, sporotrichoid lymphatic spread, satellite papules, milia formation around healing lesions and annular lesions as part of healing.[20,67,69,70]

In the Dutch soldier series, clinical features suggested aggressive *L. major*. The majority (approximately 60%) had multiple lesions, including approximately 20% with ≥4 lesions; approximately 40% had nodules, approximately 40% had ulcers and the rest were mixed; and approximately 20% had local lymphadenopathy, approximately 15% satellite lesions and approximately 5% lymphangitis.[59] These clinical features were consistent with another group of vulnerable foreign soldiers from the UK and Fiji[20] and Afghan migrants new to Isfahan in Iran who tended to have more severe disease with more lesions and signs of acute inflammation compared with the local Isfahanis.[67] More florid disease may be related to no/low immunity and/or greater vector exposure in areas infested by *R. opimus*.

Lupoid cutaneous leishmaniasis (leishmania recidivans) is an uncommon form of chronic CL and is a recurrence of *L. tropica* and *L. braziliensis* around the edge of a previously healed lesion. It was observed in 4.2% of the 4189 CL patients in Herat province who had these lesions for 2–4 y and approximately 40% of patients were children aged <10 y.[71] Another rare manifestation of *L. tropica* and *L. major* CL is oropharyngeal and upper airways ulceration.[72–74] Mucocutaneous CL is more commonly associated with *L. aethiopica*[75] and NWCL with *L. braziliensis*, *L. amazonensis*, *L. guyanensis* and *L. panamensis*.[76–78]

Sand flies bite in the evening and at night and this explains the preponderance of lesions on exposed areas, independent of infecting species. The face is the most affected area with reported proportions varying from approximately 40%[67,79] to approximately 90%,[71] followed by the upper arms/hands and lower legs at varying proportions in different studies. In Kabul, the face (43.4%) was affected most, followed by the hands (38.2%), legs (15.9%) and arms (2.4%),[80] similar to CL studies in Sweden (travellers and migrants)[81] and France (travellers),[82] in whom about one-third of lesions were on the legs and feet and may, in part, be explained by wearing shorts.

Without treatment, lesions tend to self-heal but time to healing varies considerably between species. Healing is defined as complete epithelialisation with flattening of skin for ulcerated lesions and a return to normal skin contour for non-ulcerated lesions. Self-healing occurs at a faster rate in *L. major* (2–8 mo) compared with *L. tropica* (≥1 y), and at 3 mo, a time point suggested for assessing 'initial cure' in trials,[83] 70% of *L. major* lesions self-cure[84] compared with 1% for *L. tropica*,[70] 22% for *L. braziliensis* and 88% for *L. mexicana*.[69]

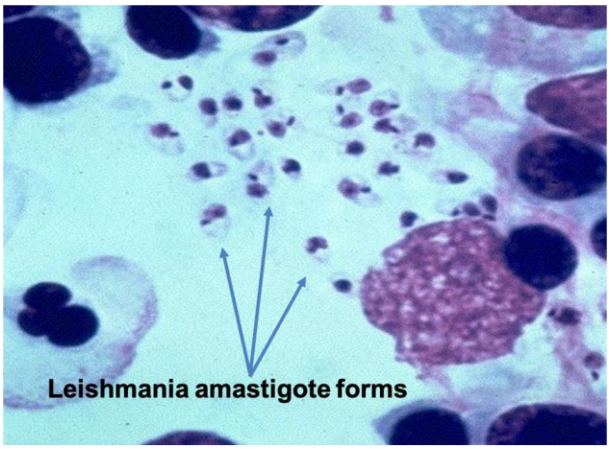

Figure 7. A positive leishmaniasis microscopy slide from an Afghan patient.

Leishmania tropica-related visceral leishmaniasis

Several countries, such as India, Iraq and Iran, report visceralisation of *L. tropica*.[85–87] VL appears to be rare in Afghanistan, but in the absence of sound diagnostics and reporting, the VL burden cannot be estimated accurately. Cases are reported from the central and northern provinces of Bamyan, Baghlan, Faryab, Balkh and Jawzjan and are often referred to the tertiary care hospitals of Kabul (Rahimi, personal communication). VL in Afghanistan is assumed to be caused by *L. infantum*.[88]

Diagnosis of CL in Afghanistan

Diagnostic tools in Afghanistan are limited to microscopy. Histopathology, culture, serology and molecular methods are not available in the public sector but, as of early 2025, plans are afoot to establish a molecular laboratory in the Ministry of Public Health that will include leishmania diagnosis.

Skin scraping and microscopy

In Afghanistan, CL is mostly diagnosed on clinical suspicion (World Health Organization, 2011) but microscopy is usually available in all government malaria and leishmaniasis clinics.[89] Giemsa-stained smears are obtained by scraping the edge of skin lesions and examining the slide under x1000 magnification. The WHO recommends an examination time of 20 min, which may be challenging in busy clinics, to detect amastigotes (Figure 7).

One study in Kabul demonstrated a slide sensitivity and specificity of 79.0% (95% CI 73.74 to 84.20%) and 77.3% (95% CI 57.49 to 97.06%), respectively.[90] In a small Lebanese study, a thick smear detected leishmania amastigotes in 64% (21/33) of slides compared with 85% (28/33) for PCR detection[91] and

broadly similar results were reported from Iran in 219 patients: approximately 77% and 94% were detected by microscopy and PCR, respectively.[92]

Two studies from Iran[93] and Pakistan[94] have shown that samples obtained by fine needle aspiration of lesions results in higher sensitivities of 89% in both studies with 100% specificity; moreover, this was a less painful procedure than a skin scrape.

Rapid diagnostic test

The CL Detect Rapid Test (Inbios International, USA), a qualitative, immunochromatographic test designed to detect the peroxidoxin amastigote antigen, was originally developed to detect *L. major* but showed promise in areas where other CL species exist. It is now approved by the United States Food and Drug Administration.

Using a skin scrape sample, CL Detect was assessed in Kabul in 274 patients with clinically suspected CL; all PCR-proven positives were due to *L. tropica*. Nodules (73%) and ulcers (25%) accounted for most lesions and had been present for a median of 2 (range <2–6, IQR 2–3) mo. The sensitivity was low, 65%, and appeared higher for nodules vs ulcers: 69% vs approximately 55% (95% CIs overlapped) and there was a trend of decreasing sensitivity with increasing lesion duration. Specificity in the 17 true negatives was 100%. Loopamp performed in Kabul and the reference laboratory in Holland achieved respective sensitivities of approximately 88% and 92% and specificities of approximately 71% and 94%, while microscopy had a high sensitivity of 97.5% but a very low specificity of approximately 25%[55]; the low microscopy specificity suggests difficulties in distinguishing artefacts from amastigotes.

CL Detect also had high specificities and broadly comparable sensitivities for *L. tropica* (73%) and *L. major* (59%) in Morocco,[95] but in Ethiopia the sensitivity was very low, approximately 31%.[96]

Molecular diagnosis of CL

Although molecular diagnosis of CL is unavailable currently in Afghanistan, a brief overview of the main techniques is presented below. Several molecular diagnostic tests have been developed as they offer high sensitivity and specificity compared with a skin scrape.[97] Skin swabs have been the main sample used, a simple and less invasive technique than a skin scrape or biopsy.[98] As there are no generally accepted protocols, most laboratories use in-house methods.

PCR

PCR has been used to amplify the ribosomal ITS-1 region, which separates the genes coding for the ssu rRNA and L5.8S rRNA, using the primers LITSR and L5.8S for PCR-ITS1[99,100]; the ITS-1 has also been used in the phylogenetic studies (described below). The kinetoplast DNA (kDNA) is another PCR target for amplification and has been used to speciate CL[101] and characterise genetic relationships in phylogenetic studies.[87]

Marfurt et al.[102,103] have developed a typing technology composed of a PCR assay amplifying all the mini-exon sequences in a single reaction using universal primers, which allows for the preliminary discrimination between the major complexes (i.e. OWL, NWL and NW Viannia complexes) based on the different sizes of the amplification products. This mini-exon PCR-RFLP genotyping approach has been validated against cultured WHO reference strains of leishmania and cultured isolates from patients. Accordingly, this method is widely used as a high-resolution, sensitive and specific tool that can identify all clinically relevant leishmania species.[104–107]

Microsatellites are becoming one of the principal genetic marker systems in phylogenetic, population genetic and molecular epidemiological studies. The leishmanial genome is relatively rich in microsatellite sequences, approximately 600 (CA)n loci per haploid genome. Multilocus microsatellite typing based on >10 different microsatellite markers has been used successfully to characterise and detect genetic variation in *L. infantum*,[108] *L. tropica*[109] and *L. major*.[110] Other molecular techniques include multilocus enzyme electrophoresis and cytochrome b gene analysis, which have been used for identifying the genetic diversity of *L. major* and *L. tropica* from biopsy[111] and filter paper samples.[2]

Isothermal platforms

PCR requires adequate infrastructure and technically skilled operators, making tests based on this platform less suitable for resource-poor laboratories in CL-endemic countries. To overcome this challenge, isothermal diagnostic platforms have been developed. Nucleic acid sequence-based amplification is an isothermal reaction targeting parasite RNA, and oligochromatography for post-amplification analysis further circumvents the use of complex equipment while achieving high sensitivity and specificity.[112,113] A further development in isothermal molecular diagnostics is loop-mediated isothermal reaction (LAMP). Specificity of this reaction is high because it uses six primers and the end products can be visualised directly using simple detection methods[114]; a specificity of 94% was seen in an assessment of CL in Kabul.[55]

Phylogenetic studies of OWCL

There are limited phylogenetic studies of OWCL in general with a small number from Afghanistan.

Using ITS1-rDNA sequence analysis, Fakhar et al. showed that *L. tropica* strains from rural areas of Herat province fell into four sequence types (ST 1–4). They were genetically similar to isolates from India and Southeast, East and Central Iran (Cluster A) and formed two genetic subpopulations; the main subpopulation was closest to isolates from Birjand (eastern Iranian province of south Khorasan) and the other was related to isolates from East and South-East Iran. The Herat ST1 isolates were identical to those from Birjand province and, given that CL is relatively new in Birjand, this raised the question of whether CL there originated from Herat province.[46] In a related study, the distribution of CL in Herat was investigated and ST 1–4 were associated with irrigated and intensely cultivated land, altitudes of 700 and 1200 m and three soil types, namely, haplocalcids, torriorthents and torrifluvents.[29]

Khan et al. showed a high degree of similarity of *L. tropica* population from KPP and the adjoining areas of eastern Afghanistan. They also showed that this Pakistani–Afghan cluster had the least genetic diversity compared with those of other countries in the Middle East,[115] adding further evidence that CL may have been imported from Afghanistan. In Kandahar, Plourde et al. showed

high genetic heterogeneity in four isolates of *L. tropica*,[39] and gene sequencing of the kinetoplastid cytochrome B gene of one isolate was identical to the 175 *L. tropica* strains isolated from a patient from Mashhad in North-East Iran who was sensitive to meglumine antimonial.[116] These genetic data suggest different epidemiological dynamics between eastern and southern Afghanistan; more generic research would shed more light on CL transmission within Afghanistan and its neighbouring countries.

Treatment of OWCL in Afghanistan

Most forms of OWCL are self-healing (see above); so, the aim of treatment is to reduce the time to healing, thereby preventing secondary infections and increasing the chances of a good cosmetic result. Making a species diagnosis enables tailored treatment as well as second-line options, if first-line treatment fails. Importantly, patients can be informed what to expect from their treatment. In Afghanistan, a species diagnosis is unavailable in the public sector and treatment of CL is only available in public health clinics, which are located mostly in urban areas and frequently run out of drugs.

The pentavalent antimonials sodium stibogluconate (SSG) and meglumine antimonial (MA) are the main treatments in Afghanistan and are obtained from the WHO or are imported mainly from India. Antimonials are administered as intramuscular (IM), intravenous (IV) or intralesional (IL) injections, a very painful procedure for patients, especially young children.

Parenteral antimonials are given in cases of multiple lesions, disfiguring facial lesions, or lesions at sites that make IL injections less desirable or too challenging, such as on the face, nose, lips, ears or near the eyes, also on joints. The dose of IM/IV antimonial is 20 mg/kg once daily for 21 d[117] and may be associated with severe toxicity, for example, pancreatitis, hepatitis, cardiotoxicity and nephrotoxicity, which may result in early discontinuation of treatment and even death.

An outbreak of fatal cardiotoxicity occurred in 23 Nepali VL patients who were treated with a recently introduced batch of generic SSG; eight (36%) died and five (23%) deaths were attributed to SSG-induced ventricular tachycardia or fibrillation.[118] SSG is well known to cause dose-related prolongation of the QTc interval[119] and this may have explained the deaths in Nepal. Cardiotoxicity in otherwise well patients with CL is likely to be less severe compared with VL patients; one study in healthy soldiers given 10 mg/kg/d of SSG for 10 d did not result in a significant change in mean QTc intervals and, in those who did have an increase in the QTc vs baseline, the median increase was only 5%.[120] In at risk-groups (e.g. older patients, those on other QT prolonging drugs), it is recommended to do an ECG before deciding to treat with systemic antimonials.

Pancreatitis appears common following SSG or MA for CL. In one series of 49 patients, 48 had raised lipase and amylase and just under one-half were symptomatic.[121] In a Brazilian CL study, raised lipase, approximately 55% (34/62), was more common than raised amylase (approximately 20%); one-half of the patients had gastrointestinal symptoms consistent with pancreatitis, but only one-half of these had increases in either enzyme; higher lipase concentrations were seen with higher MA doses.[122]

Liver toxicity is well described and is usually transient despite continuing with SSG or MA. In a small study, seven British soldiers with CL were treated with 20-d SSG (20 mg/kg/d). A transient increase in alanine aminotransferase (ALT) was observed in all soldiers and three experienced increases of approximately 2.5–7-fold higher than the upper limit of normal (ULN).[123] Similarly, 10- or 20-d SSG (20 mg/kg) resulted in transient increases in ALT and aspartate aminotransferase (AST), peaking at 3 wk; mean peak ALT was approximately 4x ULN and mean peak ALT close to 2x ULN.[124] In 12 travellers, four had transiently raised liver function tests of 1.5 to 10x ULN; one stopped SSG and another had an interruption of treatment but then went on to complete SSG.[125]

The antimonials are renally excreted but nephrotoxicity appears rare in CL, with only a handful of case reports, including one death in a 50-y-old Brazilian male with generalised CL who was treated with MA and developed acute tubular necrosis (creatinine 5.6 mg/dL and BUN 71 mg/dL).[126] In VL-treated patients, other abnormal findings include renal cell casts, proteinuria, renal tubular acidosis and acute interstitial nephritis.[127]

IL drug administration is safer, and may be more effective due to a higher drug concentration in the lesion, and, therefore, promote faster action. As per WHO guidance, IL antimony is preferred in patients who have <4 lesions,[117] whereas guidance for travellers suggests <5 lesions.[106] The IL regimen recommended in Afghanistan is one weekly injection for 4 wk, extending for 2–4 more weeks if the lesion is not healed. There are no second-line treatments available in the public sector.

OWCL treatment studies in Afghanistan

There has been a smattering of CL treatment studies and small case series in foreign soldiers from 2004 to 2014. A brief overview is outlined below.

In Kabul, from 2004 to 2008, a comparatively small two-arm, randomised, double-blind trial compared bipolar high-frequency electrocauterization (EC) plus daily wound dressings (polyacrylate hydrogel) with (group [gp] I) or without (gp II) sodium chlorite in patients with proven *L. tropica*.[128] Skin biopsies were taken prior to EC (first), after wound closure (second) and after 6 mo (third). The mean time to wound closure was essentially the same (p=0.83) in both groups: 43.1 (gp 1) vs 42 d (gp II), but in patients with Leishmania-positive second biopsies, there was a strong trend of more rapid wound epithelialisation in the sodium chlorite recipients: 37.2 vs 58.3 d (p=0.08).

In another randomised trial conducted in Kabul, thermotherapy with radiofrequency-generated heat in a single application was compared with IM or IL SSG in CL patients with a single lesion (median size 1.2 [IQR 0.7–2] cm); cure was defined as complete re-epithelialisation at 100 d.[80] Cure was observed in approximately 70% of the thermotherapy recipients, approximately 75% of the IL patients and approximately 45% of patients who received IM SSG. Both thermotherapy (OR 2.80; 95% CI 1.45 to 5.41) and IL SSG (OR 3.75; 95% CI 1.86 to 7.54) were significantly more efficacious than IM SSG; IL SSG vs thermotherapy cure rates were not significantly different. In another similar study in Kabul in 382 CL patients, single localised thermotherapy or once-weekly IL MA for 5 wk were associated with respective cure rates at 6 mo of 82.5% and 74%.[129] Compared with IL SSG, thermotherapy was of shorter duration, associated with fewer

side effects and was deemed a promising alternative to antimonials.

At the time of writing, a small open trial (TCTR 20180710007) of oral miltefosine (aged ≥1 y, target dose 2.5 mg/kg/d x 28 d with allometric scaling) and IL or IM SSG (≥5 y, 20 mg/kg/d x 21 d) is being conducted. Results to date show that the crude 3-mo cure rates, after excluding patients lost to follow-up, were low for miltefosine, 9/29 (approximately 31%), but higher for IM SSG, 10/11 (approximately 91%), with four relapses (three and one, respectively). Ongoing analysis of miltefosine pharmacokinetics will shed light on patent adherence and possible pharmacokinetic pharmacodynamic relationships.

Several small series of CL in soldiers acquired in Afghanistan suggest the effectiveness of oral miltefosine. In six Canadian soldiers, two with confirmed *L. tropica*, four responded well to 28-d miltefosine, one was stopped early because of abdominal pain and the sixth soldier responded to IV SSG over 28 d.[56] Van Thiel et al. also reported good responses to miltefosine in Dutch soldiers with CL acquired in Mazar-e-Sharif; 27/34 had confirmed *L. major*.[130] At 6 mo, 28 were cured (30 by 12 mo), but three patients also received IL SSG and one with extensive lesions needed IV SSG to achieve cure.

Deployed to Mazar-e-Sharif in northern Afghanistan, 20/120 (17%) British soldiers developed *L. major*, some with disseminated disease.[20] Five received 200 mg of daily fluconazole, a regimen used previously with success in *L. major* in Saudi Arabia,[131] but this was stopped as lesions increased in size despite treatment. Different SSG regimens were used in 15 soldiers, ranging from 10 mg/kg for 14 d to 20 mg/kg for 20 d. One required a repeat course of 20 mg/kg x 20 d to achieve cure. Weekly IL SSG given to seven soldiers resulted in four cures and three cases of relapse post re-epithelialisation.

Psychosocial and economic challenges of CL in Afghanistan

Social stigma

Disfigurement caused by CL often leads to CL patients experiencing social stigmatisation, exclusion and psychological problems. Afghanistan is a male-dominated society and the social consequences of CL are more severe for women, who are often considered unfit for marriage and child-rearing.[132] In addition, women with CL often report their shame, embarrassment and low self-esteem. CL in Afghanistan[133] and other societies[134] is seen as denoting low social status and poverty, which further enhances stigma, especially among females. There is also the belief that CL is infectious, resulting in social exclusion from families and schooling.[133]

Economic aspects

Antimonial treatment of CL in Afghanistan is expensive. One vial of MA in 2018 cost US$5–6 in local pharmacies and the national cost is estimated at approximately US$0.5 million/year to treat 30 000 patients.[135] This high cost discourages donors from financing CL control programmes, compounded by the view of countries and donors that CL is not considered a priority disease. Moreover, donors are less interested in investing in diseases where control/elimination is very difficult/less feasible. However, in 2015, the WHO started to provide support for anti-leishmania medicines, and, in 2017, the Afghan Ministry of Public Health agreed to include leishmaniasis in the basic package of health services and to list SSG and MA as essential drugs. However, both drugs are bought on the open market. This is a boon for CL patients as many are poor and now have access to treatment. However, when there is a shortage of SSG and MA in government clinics, most patients go without treatment because they cannot afford to buy the drugs from private pharmacies.

A 2003 study in Kabul estimated that the cost of curing an SSG-treated patient (either IL or IM) was US$26.7 (95% CI 19.9 to 35.9), and the cost per DALY averted was estimated at US$1180.5 (95% CI 760.6 to 1826.9).[136] This cost per patient was considerably lower than the US$280 in Guatemala,[137] US$300 in Peru[138] and US$412.5 in Iran.[139] These differences in cost may be due to differences in drug prices, including the use of branded vs non-branded SSG or MA, treatment regimens (IL vs IM SSG or MA) and higher staff costs compared with Afghanistan.

Discussion

Historically, Afghanistan has one of the highest burdens of CL in the world and over the past 40 y much of that burden is related to political instability and wars with a consequential undermining of the health system. In a spatiotemporal analysis, Berry and Berrang-Ford found that CL incidence was 2.38 (95% CI 1.40 to 4.05)-fold higher in country-years with high levels of conflict/terror.[140] Research output from Afghanistan has been limited, conducted, in the main, by a small number of groups, and much of the recent research is approaching 20 y old. The situation in Afghanistan contrasts with the rich research output of other countries like Iran (OWCL) and those in Latin America (NWCL). Herein, we discuss principally issues surrounding diagnosis and treatment.

The species diagnosis of CL is challenging and is the key missing element in defining accurately the CL epidemiology and tailoring treatment. In the absence of a species diagnosis, clinicians often diagnose wet lesions as *L. major* and dry lesions as *L. tropica*.[141] However, work now shows clearly an overlap in skin morphologies for these two species and, therefore, species differentiation based on clinical signs is not reliable.[2,48]

With clinical diagnosis, few patients will be tested by skin scraping and microscopy even although it is cheap and is associated with high specificity; however, there are concerns regarding its variable sensitivity, which ranges from 70 to 90%.[142] As diagnosis is often on clinical suspicion, we would recommend that clinicians only request microscopy confirmation for patients if the result will have clinical implications. This would apply to patients with a lower probability of disease who would only be treated if microscopy is positive, or patients with a doubtful probability of having CL in whom a negative test would convince the clinician not to treat.

If the microscopy result would not change the management, requesting microscopy for diagnostic purposes alone should not be done. This could limit the number of skin scrapings taken, significantly lowering patient discomfort and reducing the workload of lab technicians. Potential harm to the patients should

also be considered. For patients needing low-risk IL treatment of localised CL lesions, microscopy confirmation would not be required. However, for higher risk treatment with IM antimonials of patients with more complicated lesions suggestive of CL, laboratory confirmation is more important.

Rapid diagnostic tests could be a good alternative to microscopy and a clinical diagnosis in the leishmania clinics where microscopy is unavailable. The CL Detect Rapid Test has high specificity but suffers from modest sensitivity. Nevertheless, it represents a good start and more development is needed to improve its performance.

Tissue culture and PCR are methods that allow speciation but require greater expertise and a laboratory infrastructure, while histopathology can support a tissue diagnosis of CL and is useful where the clinical diagnosis is challenging in the face of a negative slide. Efforts are now afoot to set up a molecular laboratory in Kabul and, if adequately resourced, could play a central role in defining the *L. tropica*: *L. major* ratios in different parts of the country and aid treatment algorithms.

Two key areas of research are effective, including child-friendly, inexpensive treatments for CL and monitoring for drug resistance. These are not Afghanistan-specific issues but affect many countries with OWCL and NWCL. Research funding is limited and its WHO-designated neglected status is not going away any time soon.

Currently, only the antimonials are available in Afghanistan and appear to remain effective. By contrast, clinical failures have been reported in Iran and, more recently, in Quetta,[116,143,144] as well as in NWCL,[145] suggesting antimonial resistance as one cause. The underlying mechanisms are complex and include a failure to reduce parent SSG to its metabolically active trivalent form (Sb III) in the parasite and macrophages,[146] reduced cellular drug intake, increased drug efflux or sequestration, improved cellular mechanisms to counter SSG-induced cell damage and changes in the drug binding affinity of the primary therapeutic target.[147] It is likely that antimonial resistance will increase over time and, therefore, clinical, pharmacokinetic and molecular criteria need to be developed to define a treatment failure due to resistance for both IL and parenteral antimonials. Such a definition could then be incorporated in, for example, a future WHO-validated in vivo test that could be used in endemic countries to monitor therapeutic efficacy. With evidence of reduced miltefosine sensitivity in NWCL,[148] a system would also need to be developed for miltefosine, if resistance in CL becomes established.

Oral miltefosine has emerged in recent years as a potentially useful drug, using the same target dose as in VL, namely, 2.5 mg/kg/d x 28 d. Its tolerability profile makes it a good choice to avoid the well-documented and potentially severe systemic toxicity of the antimonials,[118–119,149] but gastrointestinal side effects are very common. Nausea and abdominal pain accounted for approximately 40% and 13%, respectively, of reported side effects in Pakistan,[144] while Machado et al. reported high proportions of patients with vomiting (approximately 42%), nausea (40%), abdominal pain (approximately 23%) and diarrhoea (10%).[145]

Reported efficacy rates in small clinical series are broadly similar across the two species. In the 34 Dutch soldiers with *L. major*, an 82% cure rate was achieved despite the wide differences in mg/kg dose (150 mg/d, 70–113 kg)[130]; this is comparable with *L. tropica* in Pakistan, a 3-mo cure rate of 77% (40/52),[144] *L. major* in Iran, approximately 82%,[150] and a small retrospective study from Israel reporting complete resolution of CL in eight out of 10 children (six *tropica*, two *major*).[151] In NWCL, high cure rates are reported from Colombia (30/32),[152] but lower rates for *L. braziliensis*, 75% (45/60)[145] and 53% (20/38),[153] underscoring the species-dependent response.

In two travellers with CL, 150 mg of daily miltefosine resulted in a decline of parasite load of *L. major* (Morocco) and *L. infantum* (Spain) of 1 $\log_{10}$/week and a time to cure of 7 wk (*L. major*) and 7 mo (*L. infantum*).[104] The decline in parasite load could be a useful pharmacodynamic marker for predicting cure in different leishmania species and defining the relationship between miltefosine pharmacokinetic and parasite load decline. More research is needed to ascertain the dose–response relationship of miltefosine in CL in several settings and the relationship between a 'good' pharmacodynamic response and cure to guide optimal dosing, especially in children in whom cure rates appeared lower compared with adults in mostly *L.* (*V.*) *panamensis* in Colombia. Given 2.5 mg/kg/d, children had lower median plasma (71%) and monocyte intracellular (73%) miltefosine exposures vs adults and a failure rate of 5/30 vs 0/30, suggesting lower miltefosine exposure was a causative factor.[154] Dorlo et al. have proposed an allometrically scaled dosing schedule (2.5 mg/kg target dose) based on sex, height and weight for VL[155] and this regimen is being used by Médecins Sans Frontières (MSF) in Pakistan for OWCL.[144] Dose optimisation studies of miltefosine in CL will be challenging, especially with the slow healing *L. tropica*, which will require a minimum of 6 mo of follow-up and be adequately powered. If a robust pharmacokinetic–pharmacodynamic model could be established, this might reduce the 6-mo follow-up.

Two disadvantages of miltefosine are its 28-d regimen and its long half-life of approximately 30 d. Treatment could be shortened by testing miltefosine in combination with other drugs or cryo- and thermotherapy.[156] For women wishing to become pregnant, a 5-mo gap is currently recommended before attempting pregnancy.[157,158] Cost is another issue. The cost-effectiveness of miltefosine in poor countries like Afghanistan needs additional research and should include the cost of diagnostics as well as patient willingness to pay. Antimonials are free in Afghanistan, so convincing poor patients to contribute to miltefosine or another better-tolerated treatment requires showing it is much better than SSG.

A promising alternative to the antimonials and miltefosine could be topical paromomycin (not commercially available at present), which has been used successfully against *L. major*.[159] The data against *L. tropica* are scant.[160] An adequately powered trial is needed to prove whether topical paromomycin is effective in *L. tropica*. If effective, this could provide a cheap means to easily treat both species, but a willing drug company remains needed to register paromomycin to international standards. Cryotherapy with liquid nitrogen is cheap, effective for individual lesions, with few side effects, and is a good option for children.[161] Thermotherapy is effective in some settings (K. Ritmeijer, unpublished) but involves the use of cumbersome hot water baths[162] and specialised equipment (e.g. laser therapy, ultrasound[163] and infrared light). These modalities are probably better suited at secondary levels of care.

Conclusion

To conclude, increased endemicity of CL in Afghanistan is mainly related to poverty, social and cultural barriers, war, poor access to health services, lack of vector control, destruction of the public health infrastructure and migration of people from non-endemic areas to endemic areas. Ascertaining the changing burden of disease is challenging because detailed epidemiological studies have not been conducted and CL is only reported via the system of malaria and leishmania clinics in the major cities. Species differentiation is unavailable outside the research setting.

CL research in Afghanistan is limited and although there are research gaps in every aspect of CL, our review has focused on epidemiology and treatment. More work is needed to evaluate currently available drugs and drug combinations. Clinical trials in CL have suffered from variable study designs, small sample sizes, different dosing regimens and a lack of speciation, resulting in poor-quality evidence.[164,165] It is important to adopt a standard approach to improve the quality of evidence[83] and be able to conduct adequately powered studies. Funding remains a substantial barrier.

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