

Review Article

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Cite this article: Yurchenko V, Chistyakov DS, Akhmadishina LV, Lukashev AN, Sádlová J, Strelkova MV (2022). Revisiting epidemiology of leishmaniasis in central Asia: lessons learnt. *Parasitology* **150**, 129–136. <https://doi.org/10.1017/S0031182022001640>

Received: 15 September 2022

Revised: 21 November 2022

Accepted: 23 November 2022

First published online: 1 December 2022

Key words:

Animal reservoir; central Asia; coinfection; great gerbils; *Leishmania gerbilli*; *Leishmania major*; *Leishmania turanica*; *Leishmaniavirus*

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Revisiting epidemiology of leishmaniasis in central Asia: lessons learnt

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Abstract

In this work we reviewed historical and recent data on *Leishmania* spp. infection combining data collected in Turkmenistan, Uzbekistan, Kazakhstan, Kyrgyzstan, Iran, China and Mongolia. We specifically focused on a complex of co-existing species (*Leishmania major*, *Leishmania turanica* and *Leishmania gerbilli*) sharing the same animal reservoirs and vectors. In addition, we analysed the presence of dsRNA viruses in these species and discussed future research directions to identify species-specific traits, which may determine susceptibility of different *Leishmania* spp. to viral infection.

Introduction

Leishmaniasis is one of the neglected vector-borne tropical diseases endemic in almost 100 countries worldwide caused by *Leishmania* spp. (Euglenozoa: Trypanosomatidae) (Bruschi and Gradoni, 2018; Kostygov *et al.*, 2021b). Between 10 and 15 million people in the world are infected, and the annual rate of new infections is over 2 million cases (WHO, 2022). The mortality per year from leishmaniasis is second only to malaria among all parasitic diseases (Pace, 2014). Its clinical manifestations range from cutaneous ulcers to systemic multiorgan diseases in the cases of cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL), respectively (Bruschi and Gradoni, 2018).

In the Old World, the main areas of CL circulation are northern Africa, central Asia (hereafter, Kazakhstan, Kyrgyzstan, Mongolia, Turkmenistan and Uzbekistan) and the Middle East (Alvar *et al.*, 2012; Torres-Guerrero *et al.*, 2017). The most common *Leishmania* spp. documented in the Old World are *Leishmania aethiopica*, *Leishmania major*, *Leishmania tropica* and species of the *Leishmania donovani* complex (*L. donovani* and *Leishmania infantum*) (Lukeš *et al.*, 2007; Bruschi and Gradoni, 2018). The VL in humans is mainly caused by members of the *L. donovani* complex and may manifest in damages to the liver, spleen, lymph nodes and bone marrow often resulting in death of a patient, if not diagnosed and treated in a timely manner (Strelkova *et al.*, 2015; Mann *et al.*, 2021). Infection with these species may also present skin manifestations in the cases of post-kala-azar dermal leishmaniasis or atypical leishmaniasis (Guan *et al.*, 2013; Zhang *et al.*, 2014; Ben-Shimol *et al.*, 2016; Zijlstra, 2016). *Leishmania aethiopica*, *L. major* and *L. tropica* mostly cause CL, although some isolates of *L. major* and *L. tropica* were occasionally identified from patients with VL (Alborzi *et al.*, 2008; Bruschi and Gradoni, 2018; Charyyeva *et al.*, 2021). The CL can be further subdivided into anthroponotic (ACL) and zoonotic (ZCL) forms, which are predominantly caused by *L. tropica* and *L. major*, respectively (Akilov *et al.*, 2007; Ghatee *et al.*, 2020). Great gerbils (*Rhombomys opimus*) and fat sand rats (*Psammomys obesus*) serve as the main animal reservoirs for ZCL in central Asia and the Middle East, correspondingly (Elfari *et al.*, 2005; Akhavan *et al.*, 2010c), although other animal species – for example, Libyan jird (*Meriones libycus*), Shaw's jird (*Meriones shawi*), Indian gerbil (*Tatera indica*) or Indian desert gerbil (*Meriones hurrianae*) – may play this role in particular geographic regions (Yaghoobi-Ershadi *et al.*, 1996; Rassi *et al.*, 2001; Mohebbi *et al.*, 2004; Parvizi *et al.*, 2008; Ghawar *et al.*, 2011; Akhoundi *et al.*, 2013).

The great gerbils may simultaneously host several species of *Leishmania*. In addition to pathogenic to humans *L. major*, they may also be infected by gerbil-restricted *Leishmania turanica* and *Leishmania gerbilli* (Strelkova *et al.*, 1990b, 2001; Akhavan *et al.*, 2010b). Here, we reviewed the literature on the mixed infections of *L. major*, *L. turanica* and *L. gerbilli* in central Asia and neighbouring countries with a focus on their natural animal reservoirs. As a second aim, we wanted to highlight some important papers on this topic published in Russian, and, as such, not well-known to the researchers in other countries.

Historical notes

Parasites of the genus *Leishmania* were first formally described by Leishman and Donovan in 1903 in patients infected with kala-azar in India (Donovan, 1903; Leishman, 1903).

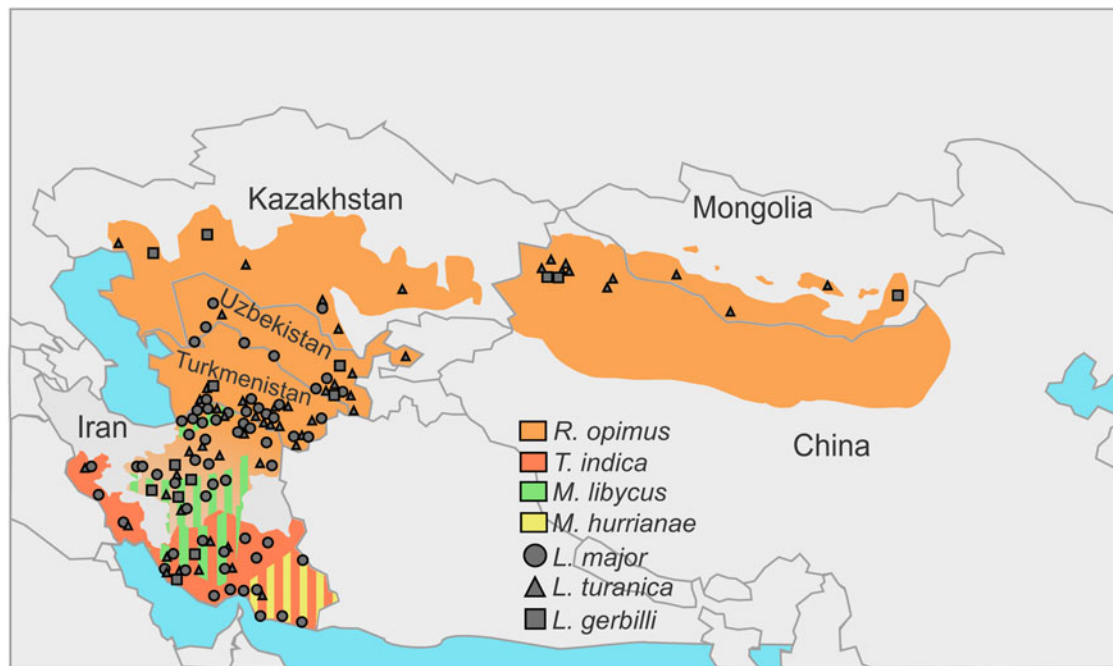


Fig. 1. Incidences of *Leishmania* spp. in the central Asia and Middle East over the distribution areas of their predominant animal reservoirs. Stripes indicate the presence of 2 species serving as animal reservoirs in the same territory.

The parasite causing tropical ulcer was described as *Helcosoma tropicum* by Wright in the same year (Wright, 1903) and renamed as *Leishmania tropica* in 1906 by Lühe (1906). Yet, the first scientist documented the presence of a parasite now known as *L. tropica* was Cunningham in 1885 (Cunningham, 1885). Its protistan nature ('class of protozoa') was discovered by Borovsky (1898), but remained unrecognized until much later (Hoare, 1938). In 1914, Yakimov identified 2 variants of *Leishmania* sp., based on the size of amastigotes in the macrophages of patients and named them *L. tropica minor* and *L. tropica major* (Yakimov and Schokhor, 1914). Later studies revealed that *L. t. minor* causes dry ulcers usually lasting for over a year and it is more commonly spread in the cities. In contrast, *L. t. major* manifests in wet ulcers, the course of the disease is shorter and it is more commonly spread in rural areas (Latshev and Krukova, 1941; Kozevnikov, 1963; Schnur, 1987). In 1973, summarizing the accumulated data, Bray proposed to reclassify parasites as *L. tropica* for the causative agent of ACL and *L. major* for the causative agent of ZCL (Bray et al., 1973).

It is important to note that for about 50 years all isolates of *Leishmania* coming from animals and people in central Asia and neighbouring countries with a characteristic clinical picture were classified as *L. major*, with the only exception being a description of another *Leishmania* sp., *L. gerbilli*, from *R. opimus* in 1964 in China (Wang et al., 1964). In line with that, *in vitro* experiments in animals demonstrated that different isolates have different levels of virulence. The highly virulent (HV) strains were invariably isolated from humans. They caused a progressive disease with obligatory ulceration in golden hamsters and domestic mice. Conversely, the strains with virulence ranging from low (low virulent strains, LV) to high could be isolated from gerbils. The LV strains caused a slow course of the disease that was limited to infiltrates and never led to ulceration. The strains with intermediate virulence caused a prolonged disease manifesting in small abortive ulcers in the later stages (Kellina, 1965; Lavrova et al., 1973; Kellina et al., 1981). Experimental infection of different animal species (in which *Leishmania* presence was documented in nature) with clonal cultures or strains of

Leishmania with different virulence (HV and LV) revealed that HV parasites infected all the tested animals – great gerbils, Libyan jirds, Severtzov's jerboa (*Allactaga severtzovi*), long-eared hedgehogs (*Hemiechinus auritus*), domestic mice (*Mus musculus*) and golden hamsters (*Mesocricetus auratus*). In contrast, only the great gerbils, some Libyan jirds and golden hamsters could be infected by the LV clones or strains (Eliseev et al., 1980; Strelkova et al., 1980).

The mystery of strains with different virulence was solved only with an advent of molecular techniques in the late 1980s. The isoenzyme analysis revealed that the strains previously identified as *L. major* include 3 independent species – *L. major sensu stricto*, *L. turanica* and *L. gerbilli* (Strelkova, 1990; Strelkova et al., 1990b). These experiments also confirmed that HV and LV strains belonged to *L. major* and *L. turanica/L. gerbilli*, respectively. Notably, all strains isolated from humans were *L. major*, implying that *L. turanica* and *L. gerbilli* are restricted to gerbils. To sum up, all 3 abovementioned species can infect great gerbils, golden hamsters and Libyan jirds, but only *L. major* (neither *L. turanica* nor *L. gerbilli*) can infect Severtzov's jerboa, long-eared hedgehogs and domestic outbred mice.

Communal epidemiology and ecology of *L. gerbilli*, *L. major* and *L. turanica*

Central Asia

Ecology

In the natural foci of the ZCL on the territory of Turkmenistan, Uzbekistan, Kazakhstan, Kyrgyzstan and Mongolia great gerbils are the main natural hosts of *Leishmania* spp. discussed above (Eliseev and Kellina, 1963; Dubrovsky, 1978; Eliseev and Neronov, 1997; Bruschi and Gradoni, 2018) (Fig. 1, Table 1). Parasites' life cycle not involving *R. opimus* was shown in some rare cases (e.g. in the lower reaches of the Surkhandarya river it involves *M. libycus*) (Strelkova et al., 1980). Great gerbils form topical and, as a result, trophic relationships with sand flies (Abai et al., 2010; Akhavan et al., 2010c). They dig large and

Table 1. ZCL in central Asia, Iran and China (data summarized for field studies)

	Reservoir host	Main vectors	<i>Leishmania</i> sp.	Mixed infections
Uzbekistan	<i>Rhombomys opimus</i>	<i>Phlebotomus papatasi</i> <i>Phlebotomus caucasicus</i> <i>Phlebotomus andrejevi</i> <i>Phlebotomus alexandri</i> <i>Phlebotomus mongolensis</i>	<i>Leishmania major</i> <i>Leishmania turanica</i> <i>Leishmania gerbilli</i>	<i>L. major</i> + <i>L. turanica</i> rarely <i>L. major</i> + <i>L. turanica</i> + <i>L. gerbilli</i>
Turkmenistan	<i>R. opimus</i>	<i>P. papatasi</i> <i>P. caucasicus</i> <i>P. andrejevi</i>	<i>L. major</i> <i>L. turanica</i> <i>L. gerbilli</i>	<i>L. major</i> + <i>L. turanica</i>
Kazakhstan South of 43°N	<i>R. opimus</i>	<i>P. papatasi</i> <i>P. caucasicus</i>	<i>L. major</i> <i>L. turanica</i>	<i>L. major</i> + <i>L. turanica</i>
Kazakhstan North of 43°N	<i>R. opimus</i>	<i>P. mongolensis</i>	<i>L. turanica</i> <i>L. gerbilli</i>	Not detected
Mongolia	<i>R. opimus</i>	<i>P. andrejevi</i> <i>P. caucasicus</i>	<i>L. turanica</i> <i>L. gerbilli</i>	Not detected
Iran	<i>R. opimus</i> <i>Meriones libycus</i> <i>Tatera indica</i> <i>Meriones hurrianae</i>	<i>P. papatasi</i> <i>Phlebotomus salehi</i> <i>P. caucasicus</i> / <i>mongolensis</i> <i>Phlebotomus ansari</i> ^a	<i>L. major</i> <i>L. turanica</i> <i>L. gerbilli</i>	<i>L. major</i> + <i>L. turanica</i> <i>L. major</i> + <i>L. gerbilli</i> <i>L. turanica</i> + <i>L. gerbilli</i> <i>L. major</i> + <i>L. turanica</i> + <i>L. gerbilli</i>
China	<i>R. opimus</i>	<i>P. mongolensis</i> <i>P. andrejevi</i>	<i>L. turanica</i> <i>L. gerbilli</i>	Not detected

^aSuspected vector.

Note: *Leishmania infantum* may also manifest skin symptoms, main reservoir hosts are dogs, vectors are *Phlebotomus wui*, *Phlebotomus longiductus*, *Phlebotomus alexandri*, *Phlebotomus chinensis*, *Phlebotomus sichuanensis* and *Phlebotomus smirnovi* in China; *P. alexandri*, *Phlebotomus transcaucasicus*, *Phlebotomus kandelakii*, *P. chinensis* and *P. major* s. l. in Iran; *P. longiductus* and *P. smirnovi* in Kazakhstan and Uzbekistan; *Phlebotomus turanicus* in Turkmenistan.

complex burrows (colonies), ideal for hatching and feeding of sand flies. Other animals [such as *M. libycus*, midday jird *Meriones meridianus*, *H. auritus* or *M. musculus* (Dubrovsky, 1978)] may cohabitate with the greater gerbils for some time usually occupying the outer parts of the colony. This significantly reduces the likelihood and intensity of sand flies' feeding on them.

Hosts and vectors

In central Asian countries, the spectra of documented hosts and vectors vary for different *Leishmania* spp.: *L. major* has been isolated from humans, great gerbils, Libyan jirds, *Phlebotomus papatasi* and *Phlebotomus andrejevi*, while *L. turanica* and *L. gerbilli* have been found in great gerbils, *P. papatasi*, *P. andrejevi*, *Phlebotomus caucasicus*, *Phlebotomus mongolensis*, *Phlebotomus alexandri*, *Sergentomyia clydei*, and great gerbils and *P. mongolensis*, respectively (Strelkova, 1996). Out of all the identified sand fly species, only *P. papatasi* and *P. mongolensis* are anthropophilic (Killick-Kendrick, 1990; Guan *et al.*, 1995). Notably, experimental coinfections of *L. major* and *L. turanica* in *P. papatasi* revealed that 2 parasite species do not outcompete each other and develop in parallel (Chajbullinova *et al.*, 2012). In addition to (albeit, loose) vector specificity and host specificity, different *Leishmania* spp. inhabit somewhat different geographic areas. While *L. turanica* was found infecting *R. opimus* throughout its distribution areas (see Fig. 1 in Strelkova, 1996), *L. major* parasitizes great gerbils and Libyan jirds in more southern parts of their distribution areas predominantly in river valleys, oases, areas adjacent to the oases and foothill plains (Neronov *et al.*, 1987; Strelkova *et al.*, 1990a). Conversely, in the southern and southwestern areas of Iran not populated by great gerbils, the circulation of CL is unstable confirming the role of these animals as the main reservoirs (Neronov and Farang-Azad, 1973) (Table 1, see below). *Leishmania gerbilli* is not as widespread as the other 2 species discussed above and epizootics caused by this parasite are limited to the local populations of *R. opimus* in several regions

of China, Iran, Kazakhstan, Turkmenistan and Uzbekistan (Strelkova, 1996; Strelkova *et al.*, 2003).

Infection prevalence and seasonal dynamics

The prevalence of *L. turanica* infection in *R. opimus* is high (over 50%, sometimes achieving 100% in certain populations) and fairly stable over the years. The transmission season lasts from late April to mid-October and from late May to early September for southern and northern parts of the area, respectively; it usually peaks around late June–early July and remains stable until the end of transmission period. The prevalence of *L. major* in *R. opimus* is lower than that of *L. turanica*; it peaks in July–August achieving 10–50% in different years and places. The prevalence of this parasite in *M. libycus* (usually, within the *R. opimus* distribution range) does not exceed 3–4%. The prevalence of *L. gerbilli* infection in *R. opimus* is even lower than that of *L. major* (Strelkova, 1996).

Coinfections, sympatric and allopatric populations

A remarkably high proportion of great gerbils in central Asia is infected by more than 1 *Leishmania* spp.; occasionally, all 3 species have been documented in the same animal (Strelkova, 1990; Strelkova *et al.*, 1990a) (Fig. 1, Table 1). Populations of *L. gerbilli*, *L. major* and *L. turanica* are sympatric in some areas of *R. opimus* distribution (Strelkova *et al.*, 2003). The human ZCL caused by *L. major* in these areas always occurs on the background of *L. turanica* or, more rarely, *L. gerbilli* infection. It has been demonstrated that coinfection with *L. turanica* facilitates *L. major* perseverance in rodents during the 6–10 months break in the sand flies-mediated transmission of these parasites in central Asia (Strelkova *et al.*, 2001). In contrast, the populations of *L. turanica* in northern Kazakhstan and Mongolia are allopatric, as the Iran–Turanian part of the ZCL range is geographically isolated from the central Asian one (Shurkhal *et al.*, 1985; Neronov *et al.*, 1987).

The dynamics of parasite presence in sympatric populations was investigated in the cases of predominant *L. turanica* and subsidiary *L. major* in great gerbils in central Asia (Eliseev *et al.*,

1991; Strelkova et al., 1993, 2003). Three main types of natural foci are described in *R. opimus* (Lysenko and Beljaev, 1987). The hypoendemic foci are characterized by the very low-density circulation of *L. major*; here *L. turanica* predominates throughout the year, often for several years in a row. As a consequence, human ZCL in these foci is rare. In the hyperendemic foci, the proportion of *L. major* goes up during the transmission period (May–September), in some cases achieving 50% by the end of the season. This results in a substantially higher incidence of human ZCL. *Leishmania major* in the mesoendemic foci may accumulate up to 50% prevalence in *R. opimus* for several years, while being virtually absent in certain years in-between (Eliseev et al., 1991; Strelkova, 1996).

Coinfections with *L. turanica* and *L. major* in great gerbils appear to be evolutionarily beneficial over the single-species infections. Indeed, while individual experimental infections with *L. major*, *L. turanica* and *L. gerbilli* lasted for 7, 15 and 18 months, respectively, the coinfection of *L. major* and *L. turanica* lasted for over 25 months (Strelkova, 1991), indirectly confirming an early observation that duration of *Leishmania* spp. infection may be comparable with the life time of a host, *R. opimus* (Shishliaeva-Matova et al., 1966). While infections with *L. major* alone were mostly self-healing, those with *L. gerbilli*, *L. turanica*, or coinfections with *L. major* and *L. turanica* led to chronic diseases in vast majority of cases (Strelkova, 1991).

The situation in neighbouring countries (particularly, Iran and China) is somewhat different and deserves special discussion.

Iran

Hosts and vectors

The animal hosts of *L. major* are *R. opimus* in the north-eastern and central Iran, *M. libycus* in the south-western and central regions, *T. indica* in the south-west, west and south of the country and *M. hurrianae* in the south-east (Mohebbali et al., 2004; Akhouni et al., 2013). The presence of *L. turanica* was documented in great gerbils from the central and north-eastern Iran (Mohebbali et al., 2004; Mirzaei et al., 2011), *M. libycus* from Fars and Esfahan provinces (Akhouni et al., 2013; Asl et al., 2022), *Rattus norvegicus* and *T. indica* in Bushehr province (Yaghoobi-Ershadi et al., 2013), and short-tailed bandicoot rats (*Nesokia indica*) in the western province of Kermanshah (Hajjaran et al., 2009) (Fig. 1, Table 1).

Infection prevalence, seasonal dynamics and coinfections

The reported prevalence of single infections and coinfections with *L. major* and *L. turanica* in great gerbils varied greatly between different studies (Akhavan et al., 2010b, 2010c; Akhouni et al., 2013; Hajjaran et al., 2013; Mirzaei et al., 2014; Asl et al., 2022), indicating that more studies are needed to address this question. *Leishmania gerbilli* was previously detected only in the Esfahan and Bushehr provinces in single infections and coinfections with *L. major*, *L. turanica* or both, but usually in a small fraction of animals (Mirzaei et al., 2011; Yaghoobi-Ershadi et al., 2013). A recent study reported a higher frequency of *L. gerbilli* in the central Iran: out of 162 *R. opimus* and *M. libycus* analysed, 28 and 43 were infected by *L. gerbilli* alone and *L. gerbilli* with *L. turanica*, respectively (Asl et al., 2022). The seasonal dynamics of *R. opimus* infection in Iran also differs from that described for the former USSR: while single *L. major* infections were observed in autumn and winter, and coinfections with *L. major* and *L. turanica* in all seasons except for summer, the single *L. turanica* infections were present throughout the year (Akhavan et al., 2010a, 2010c). The proven vectors of *L. major* in this country include *P. papatasi*, *Phlebotomus salehi*, *P. caucasicus* and (suspected) *Phlebotomus ansari* (Azizi et al., 2012; Yaghoobi-Ershadi, 2012;

Maroli et al., 2013; Rafizadeh et al., 2016). The presence of *L. major*, *L. turanica*, and *L. gerbilli* in Iranian sand flies (*P. papatasi*, *P. caucasicus*, *P. mongolensis*, *P. salehi*, *Phlebotomus sergenti*, *P. ansari*, *P. alexandri* and *Sergentomyia sintoni*) was reported mostly from north-eastern and central regions (Parvizi and Ready, 2008; Bakhshi et al., 2013; Bordbar and Parvizi, 2014a; Sharbatkhori et al., 2014; Rafizadeh et al., 2016). Coinfections with *L. major* and *L. turanica* were rare and documented only in *P. papatasi* (Parvizi and Ready, 2008; Darvishi et al., 2015; Rafizadeh et al., 2016). Coinfections with *L. turanica* and *L. gerbilli* were seen in *P. papatasi* and *P. caucasicus* (Bakhshi et al., 2013; Darvishi et al., 2015). Overall, *P. papatasi* is the species, in which *L. turanica* has been found most frequently in Iran, both in single and coinfections with *L. major* or *L. gerbilli*. As its competence to support the development of *L. turanica* has also been demonstrated in the laboratory (Chajbullinova et al., 2012), *P. papatasi* is probably the main vector of *L. turanica* in Iran. Its vector competence for *L. gerbilli* has yet to be established.

China

In China, both VL and CL leishmaniasis are endemic in the western and north-western areas, with a predominance of VL and rather rare cases of CL (Wang et al., 2010). *Leishmania major* in these regions has not been documented in rodents or humans, and human CL is caused by *L. infantum* transmitted by *Phlebotomus major wui* (Guan et al., 2013). *Leishmania gerbilli* has been described from desert areas inhabited by *R. opimus* since the 1960s (Wang et al., 1964), and *L. turanica* was first identified in *R. opimus* in mid-1990s in Xinjiang (Guan et al., 1995). *Phlebotomus mongolensis* and *P. andrejevi* are considered the main vectors; both are ecologically connected to *R. opimus* (Table 1). While *P. andrejevi* is scarcely captured in residential quarters, *P. mongolensis* is anthropophilic and dominates in human baits. In theory, reptilian reservoirs could also be involved in the circulation of *L. turanica* in the arid desert areas of north-western China, as this parasite has been found in 4 and 2 species of the genera *Phrynocephalus* and *Eremias*, respectively (Zhang et al., 2019).

In summary, the division of previously recognized as a single-species *L. major* into 3 *Leishmania* spp., of which only 1 is pathogenic for humans, facilitated revision of the earlier concepts about the epidemiology and endemicity of *L. major* in the territory that was considered well-studied.

Pathogenicity of *L. turanica* infections for humans

In Iran, asymptomatic *Leishmania* infections prevail in the natural rodent hosts: approximately 90% of the infected *R. opimus* showed no cutaneous lesions on their earlobes (Akhavan et al., 2010b, 2010c; Akhouni et al., 2013). Notably, among symptomatic *R. opimus*, both *L. major* and *L. turanica* were detected but not scrutinized further (Hajjaran et al., 2013). In line with these, single infections with *L. turanica* can cause lesions in humans too, as was demonstrated in a single study in northern Iran (Bordbar and Parvizi, 2014b). Subcutaneous inoculation of human volunteers with 2 strains of *L. turanica* (1 from a Mongolian great gerbil and 1 from a sand fly from Uzbekistan) resulted in mild cutaneous manifestations. The Mongolian isolate infection manifested in a small nodule, which persisted for 2 weeks and resolved with no ulceration. Infection with a strain originated from a sand fly led to a prolonged incubation period and ulceration. The lesions persisted for about 2.5 months and healed spontaneously leaving small scars (Strelkova et al., 1990b). In China, 2 healthy volunteers injected with *L. turanica* also had mild cutaneous manifestations (Guan et al., 1995).

Collectively, *L. turanica*, a species of *Leishmania* might be categorized better as being low in pathogenicity, rather than being non-pathogenic in humans. Further studies are warranted to clarify this issue, as the number of volunteers involved in experimental infections was too small to generalize.

Conclusions and perspectives

Genomics

Genomes of all *Leishmania* spp. discussed above have been sequenced. The iconic one, *L. major* MHOM/IL/81/Friedlin had been sequenced earlier in 2005 (Ivens *et al.*, 2005) and since then was used as a reference in numerous comparative studies (El-Sayed *et al.*, 2005; Peacock *et al.*, 2007; Lukeš *et al.*, 2018; Zakharova *et al.*, 2022). The genomes of *L. turanica* MRHO/SU/65/VL (LEM423) and *L. gerbilli* MRHO/CN/60/GERBILLI (LEM452) are also available, but they have not been scrupulously analysed yet (Warren *et al.*, 2021). It goes without saying that more strains of these *Leishmania* spp. need to be sequenced and analysed in order to shed light on molecular mechanisms driving speciation in allopatric and sympatric populations of *Leishmania* spp., as well as the details defining hypoendemic, mesoendemic and hyperendemic foci of this parasite in central Asia.

Presence of leishmaniaviruses

Another interesting and very important topic of investigation is interaction between *Leishmania* spp. and their endosymbiotic viruses. The fact that viruses can infect *Leishmania* was established half-a-century ago (Molyneux, 1974), but the real breakthrough came only after about 40 years of active investigation (Tarr *et al.*, 1988; Stuart *et al.*, 1992; Widmer and Dooley, 1995; Grybchuk *et al.*, 2018a), when it was demonstrated that the presence of *Leishmania RNA virus 1* (*Leishmaniavirus 1*, LRV-1) in *Leishmania guyanensis* controls the severity of mucocutaneous leishmaniasis (Ives *et al.*, 2011). The LRV-1 and LRV-2 are restricted to the New and Old World *Leishmania* spp., respectively and generally co-evolve with their hosts (Scheffter *et al.*, 1995; Widmer and Dooley, 1995; Cantanhêde *et al.*, 2021; Kostygov *et al.*, 2021a). Interestingly, their elimination from *L. major* and *L. guyanensis* *in vitro* prompts different cellular responses (Saura *et al.*, 2022). Our previous analyses of the available central Asian strains of *L. gerbilli* ($n = 2$), *L. major* ($n = 14$) and *L. turanica* ($n = 12$) revealed the presence of LRV-2 only in *L. major* with the prevalence of about 65% (Kleschenko *et al.*, 2019; Kostygov *et al.*, 2021a) corroborating findings of LRV-2 in the same parasite species in Iran and Turkey (Hajjaran *et al.*, 2016; Kurt *et al.*, 2019; Nalçacı *et al.*, 2019; Saberi *et al.*, 2020, 2022; Farrokhi-Karibozorg *et al.*, 2022; Moin-Vaziri *et al.*, 2022). The prevalence of *L. major* infection by LRV-2 in these studies varied between 2 and 68% and the presence of LRV-2 was confirmed in 87 out of 221 isolates of *L. major* analysed (only 1 isolate of *L. turanica* was included and reported as negative and no isolates of *L. gerbilli* were analysed).

These findings also pose an intriguing question – why *L. turanica* and *L. gerbilli* (note that conclusion about *L. gerbilli* is based on analysis of a very few isolates) are not infected with LRV-2? This is unlikely to be a virus-related feature, as LRVs were shown to be able to cross species barriers and even infect trypanosomatids of other genera (Grybchuk *et al.*, 2018b). This is also unlikely to be determined by the vector, because all 3 *Leishmania* spp. are transmitted by the same or closely related species of sand flies (Strelkova, 1996). The most parsimonious explanation is that *L. gerbilli* and *L. turanica* are naturally resistant

against LRV-2. If this is really the case, analysis of additional strains of *L. gerbilli* and *L. turanica* will help us to discover genetic elements making them resilient to viral infections possibly providing new tools for treatment of leishmaniasis. It is also important to consider how LRVs are transmitted. While to the best of our knowledge no experimental studies were performed on LRV-2s, in the cases of LRV-1 and New World *Leishmania* spp. it has been shown that viruses are transmitted horizontally via extracellular vesicles (Atayde *et al.*, 2019; Olivier and Zamboni, 2020).

In conclusion, we are now on the verge of new and exciting findings fuelled by recent development in sequencing technologies that may dramatically expand our knowledge about parasites causing leishmaniasis and change the way this disease is diagnosed and treated.

Author's contributions

Writing and revision – all authors.

Financial support. This work was supported by the Russian Science Foundation (no. 19-15-00054) to D. S. C. (section Historical notes), L. V. A. (section Introduction) and M. V. S. (section Communal epidemiology and ecology of *L. gerbilli*, *L. major* and *L. turanica*) and the Grant Agency of Czech Republic (no. 20-22689) to V. Y. (section Presence of leishmaniaviruses).

Conflict of interest. None.

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