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Zoonotic cutaneous leishmaniasis caused by *Leishmania major*: Do humans play a role in amplifying transmission?

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Abstract – Zoonotic cutaneous leishmaniasis (ZCL) caused by *Leishmania* (*L.*) *major* is the most widespread form of CL worldwide, with hundreds of thousands of cases annually. It is associated with significant morbidity and economic burden, particularly in North Africa and the Middle East. For over a century, the zoonotic transmission of ZCL, involving wild gerbils (Muridae: Gerbillinae) as the reservoir and *Phlebotomus* (*Ph.*) *papatasi* as the vector, has been considered an established fact, with no contradictory debate. However, the pronounced endophilic and anthropophilic behaviors of *Ph. papatasi*, the exposure of multiple and large lesions, although with relatively limited persistence, to sandflies during their seasonal activity, and the simultaneous detection of human and *L. major* DNA within the vector, suggest a contribution of humans to the parasite cycle. Conversely, the high incidence of the disease in anthropized foci and the high prevalence of family cases highlight the role of humans in amplifying transmission. The experiments carried out by Adler and Theodor in the 1920s in Palestine and the more recent studies done by Fatemi *et al.* (2018) in Iran that identified *L. major* infectious metacyclic forms in *Ph. papatasi* fed on ZCL lesions reinforce this hypothesis. Additional xenodiagnoses-based approaches could provide definitive answers and lead to better management and control of ZCL, leading to a recommendation of updated preventive measures at the household level. This review aims to report on what is currently known about the zoonotic transmission of *L. major*, and to develop arguments supporting the hypothesis that humans play a potential role as "reservoir host" of the parasite, albeit a complementary one.

Key words: Zoonotic Cutaneous Leishmaniasis, *Leishmania major*, *Phlebotomus papatasi*, Human, Transmission.

Résumé – Leishmaniose cutanée zoonotique due à *Leishmania major* : les humains jouent-t-ils un rôle dans l'amplification de la transmission ? La leishmaniose cutanée zoonotique (LCZ) due à *Leishmania (L.) major* est la forme de leishmaniose cutanée la plus répandue au monde, avec des centaines de milliers de cas par an. Elle est associée à une morbidité et un fardeau économique importants, notamment en Afrique du Nord et au Moyen-Orient. Pendant plus d'un siècle, la transmission zoonotique de la LCZ, impliquant la gerbille sauvage (Muridae : Gerbillinae) comme réservoir et *Phlebotomus (Ph.) papatasi* comme vecteur, a été considérée comme un fait établi, sans controverse. Cependant, les comportements endophiles et anthropophiles marqués de *Ph. papatasi*, l'exposition de lésions multiples et étendues, bien que de persistance relativement limitée, aux phlébotomes lors de leur activité saisonnière, et la détection simultanée d'ADN humain et de *L. major* chez le vecteur, suggèrent une contribution des humains au cycle parasitaire. D'autre part, la forte incidence de la maladie dans les foyers anthropisés et la prévalence élevée de cas familiaux soulignent le rôle des humains dans l'amplification de la transmission. Les expériences d'Adler et Theodor dans les années 1920 en Palestine et l'étude plus récente de Fatemi *et al.* (2018) en Iran, qui ont identifié des formes métacycliques infectieuses de *L. major* chez *Ph. papatasi* nourri de lésions de la LCZ, renforcent cette hypothèse. Des approches complémentaires basées sur le xénodiagnostic pourraient apporter des réponses définitives et permettre une meilleure prise en charge et un meilleur contrôle de la LCZ, ce qui pourrait conduire à recommander des mesures préventives actualisées au niveau des ménages. Cette revue vise à présenter l'état actuel des connaissances sur la transmission zoonotique de *L. major* et à développer des arguments suggérant que les humains pourrait jouer un rôle de réservoir pour le parasite, bien que complémentaire.

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Introduction

Cutaneous leishmaniasis (CL) is one of the most common vector-borne diseases worldwide with approximately 600,000 to 1,000,000 new cases per year [10, 31, 84]. It is currently endemic in 89 countries where constantly increasing incidence and morbidity have been observed over the past 40 years due to environmental changes favorable to transmission and spread [14, 84]. The Middle East (ME), North Africa (NA), Central Asia, and South America [10, 14, 84], and more recently West Africa [41], are the most affected regions with a high incidence of cases exceeding 1 per 100 inhabitants in some areas [14]. Unfortunately, CL remains a neglected disease that primarily affects regions and countries with limited resources and scarce means for management and control [84]. In the Old World, *Leishmania* (*L.*) *major* (Yakimoff and Schokhor, 1914) and *L. tropica* (Wright, 1903) are by far the most prevalent causative species [10, 14, 84]. Transmission of *L. major* is considered rural and zoonotic, while transmission of *L. tropica* is mainly described as urban and anthroponotic [14, 72], although recent findings have suggested the possible involvement of dogs [7]. *Leishmania major* is associated with the highest incidence and the widest geographical distribution [10, 14, 84]. It is the main species involved in *Leishmania* transmission in the Maghreb countries (NA) where zoonotic CL (ZCL) is considered to be a major health threat [14, 25].

The first descriptions of ZCL in NA were reported towards the end of the 19th century by Hamel and Dépéret and Boinet who documented regional cases in the oases of Biskra (Algeria) and Gafsa (Tunisia) in 1860 and 1884, respectively [46]. Since then, the number of cases has remained relatively stable and low, until sudden outbreaks occurred in the 1980s [14, 23]. ZCL then spread rapidly through the central and southern regions of all the Maghreb countries [14, 25, 56, 75]. This was likely favored by the construction of dams and hill lakes and the promotion of irrigation and agriculture, which may have contributed to increased densities of reservoir hosts and vectors [21, 22, 24, 51]. Moreover, concomitant, rapid, and uncontrolled urbanization have likely led to increased human exposure to the parasite [14, 77]. Currently, ZCL is the cause of significant physical and psychological morbidity as well as considerable economic losses [14, 33, 72, 84]. Its incidence exceeds thousands of cases per year in Algeria, Morocco, Libya, and Tunisia, with a peak that reached 25,000 cases in Algeria in 2005 [14, 25].

Despite its high incidence and morbidity and its tendency to emerge and expand [14, 25, 84], relatively few studies have focused on ZCL's risk factors. Studies depicting the modalities of parasite circulation, particularly those concerning the precise roles played by hosts and vectors, remain rare. The same applies to studies on prevention and control options. The historic eco-epidemiologic knowledge developed in the first half of the 20th century, a period when case incidence was significantly lower, is often treated as unquestionable "dogma" and is still cited in most publications. Therefore, it is widely assumed that *L. major* is a zoonotic parasite whose reservoirs are exclusively wild rodents belonging to the Gerbillinae subfamily [5, 18, 20, 50, 53, 73], and that its life cycle occurs in suitable biotopes between gerbils and the sandfly vectors *Phlebotomus (Ph.) papatasi* in NA and the ME [24, 45, 76, 79, 85], and *Ph. duboscqi* in West Africa [41]. Humans are considered accidental and dead-end hosts contracting the infection through the bite of a sandfly that has acquired the parasite from a wild rodent reservoir [64]. However, besides the principal role of rodents as reservoirs, several entomological data as well as recent eco-epidemiologic observations argue in favor of a secondary or complementary role of humans. The reports presented by Adler and Theodor in the 1920s [3, 4], and recently the studies carried out by Fatemi *et al.* [49], can also be interpreted as experimental proof of this hypothesis. The objective of this review was to discuss the "paradigm" of the strict zoonotic nature of ZCL and to question a potential "reservoir role" of humans.

Current knowledge on the components and dynamics of the *L. major* transmission cycle

Phlebotomus papatasi

Phlebotomus papatasi (Scopoli, 1786) is the confirmed vector of *L. major* in NA and the ME and the first sandfly species described of the 1,026 sandfly species reported to date [24, 52, 56, 58, 63, 79, 82, 85]. It is widely distributed across the Old World, extending from East to West from Morocco to Central Asia, passing through the Maghreb, the Mediterranean Basin, and the ME countries [6, 45, 48, 65], where it is abundant in semi-arid and arid zones [24, 42, 55]. In the Maghreb and ME, *Ph. papatasi* is seasonally active from May to October [37, 43, 55, 62], and even November in some warmer regions [38]; a diapause at the fourth larval stage allows it to survive the cold winter months [71]. Only females are hematophagous and bite during the evening and early morning [42, 76]. It is noteworthy that surveys have shown high density and abundance of *Ph. papatasi* in ZCL endemic areas and a strong correlation with disease transmission [19, 25, 35, 55, 63].

Rodent reservoirs

The reservoir hosts of *L. major* are wild rodents belonging to the Gerbillinae subfamily [14, 72]. Dogs have occasionally been reported as infected by *L. major*, although without any evident role in transmission [8, 66]. Depending on the geographic region, the following genera of gerbils are involved: *Psammomys*, *Meriones*, *Rhombomys*, and *Mastomys* [5, 20, 26, 41, 47, 50, 53, 73].

Psammomys obesus (Cretzschmar, 1828), also known as the fat sand rat, is the main reservoir host of *L. major* in NA and the ME [18, 20, 26, 51, 53, 58]. It is particularly abundant in semi-desert areas, especially in the chott and sabkha regions, where halophytic vegetation (chenopods) grows abundantly and constitutes its almost exclusive food source [26, 44, 50]. *Psammomys* rodents are diurnal and relatively sedentary. Their burrows provide highly favorable conditions for sandfly survival and reproduction, offering darkness, coolness, humidity, organic matter, and blood meals [51, 81].

The *Meriones* gerbils, *Meriones (M.) shawi* (Duvernoy, 1842) and *M. libycus* (Lichtenstein, 1823) are known to be reservoirs of *L. major* in NA and the ME, respectively [47, 53, 70, 73, 74]. They are granivorous and inhabit agricultural fields, particularly wheat and corn, as well as vegetable plots. *Meriones* burrows are typically found at the edges of fields, often on raised earth or clay embankments "touabis" that separate them. They are also commonly encountered along riverbanks and dry wadis, in oases and, increasingly, in peri-domestic areas, where they inhabit animal shelters, abandoned constructions, and even dwellings [20, 49]; these sites also provide favorable habitats for *Phlebotomus* [51, 55, 76].

Rhombomys opimus (Lichtenstein, 1823) and *Mastomys natalensis* (Smith, 1834) are also murids closely related to *Meriones* and serve as reservoirs for *L. major* in Central Asia and West Africa, respectively [5, 41].

Depending on the region, all these gerbils are highly abundant in active ZCL foci, with *Leishmania* infection rates sometimes exceeding 50% [5, 50]. Infections mainly affect their ears and nose but do not appear to impair their vitality [26, 47, 50, 51]. Additionally, nearly 30% of infected gerbils remain clinically asymptomatic yet are still capable of transmitting the parasite to sandflies [5, 26, 50]. Their ability to survive for over a year makes them ideal reservoirs for maintaining the parasite during the winter, when sandflies are inactive and transmission ceases.

Key components of the *L. major* epidemiological cycle

It has been widely accepted that *L. major* circulates in the wild between its vector, *Ph. papatasi*, and rodent reservoirs. Transmission primarily occurs inside rodent burrows, but also around animal shelters and rural dwellings [2, 14, 53, 73]. Humans are considered accidental hosts and acquire the infection through the bite of an infected female sandfly. This is made possible by the proximity of humans to rodent and *Ph. papatasi* habitats. The high prevalence of ZCL in hyperendemic foci is therefore explained by the high densities of both sandflies and rodents in these areas [35, 50, 53, 55].

The rodent species *P. obesus* is traditionally responsible for most parasite circulation, particularly in and around chotts and sabkhas [14, 18, 50]. It is thought to play a key role in amplifying local parasite transmission [51]. This was evident during the ZCL epidemics in Algeria and Tunisia in the 1980s. The epidemics occurred around the Chott Hodna in Biskra and M'sila, Algeria, and the sabkhas of central Tunisia, particularly in Kairouan and Sidi Bouzid, before spreading to other parts of the two countries [14, 25, 26]. Conversely, the *Meriones* species, which are more prevalent in agricultural and peri-domestic areas, are believed to be responsible for spreading the parasite and disseminating it into new areas, thanks to their low dietary requirements and greater mobility [14, 51, 54].

In addition to ecological changes, the ZCL epidemic in the 1980s was also the result of social and behavioral factors that have significantly increased human exposure to the parasite. Rapid population growth and uncontrolled urbanization led to higher population densities and to the encroachment of human settlements into areas of high *L. major* transmission, particularly around chotts, sabkhas, and oases [14, 25, 49]. Furthermore, the intensive use of water resources, coupled with the promotion of irrigation and agriculture in arid and even desert regions, has led to migration of susceptible non-immunized agricultural workers and their families to these areas alongside a proliferation of sandflies and *Meriones* [14, 22, 34].

Arguments supporting the potential role of humans in *L. major* transmission

Behavior of *Ph. papatasi*

Endophily

Phlebotomus papatasi is the most abundant species found inside dwellings in ZCL endemic areas [35, 55, 78]. It is recognized as a peri-domestic species exhibiting strong endophilic behavior [1, 42]. It thrives in anthropized rural environments where females find optimal conditions and all the resources needed during their lifespan [1, 2, 42, 55, 63]. Poorly maintained dwellings with cracks in walls, crevices, and hay deposits provide suitable resting places and breeding sites for gravid females [2, 32, 37, 78, 81]. Furthermore, sandflies are weak fliers and are usually sedentary, staying not far from their breeding sites, which explains their close association with human dwellings [76]. This aligns with the fact that ZCL is mainly attributed to indoor transmission, particularly given that *Ph. papatasi* bite at the end of the night when most inhabitants are indoors and asleep [42].

Anthropophily

Although sandflies are essentially opportunistic and their feeding preferences are conditioned by their habitat and blood source availability [76], the attraction of *Ph. papatasi* to humans, particularly in peri-domestic environments has been well documented [1, 37, 42, 55]. Most surveys in ZCL endemic areas reported that blood meals from captured females are mostly of human origin, sometimes exceeding 70% of all blood sources [19, 61, 68, 85].

Both endophily and anthropophily of *Ph. papatasi* point to the high probability of this species becoming infected through an infective human bite and raise the question of the possibility of human-to-human transmission.

Epidemiologic features of ZCL

Rapid and sudden increase in incidence

The relatively recent increase in ZCL incidence has been attributed by almost all authors, quite rightly, to environmental changes that have brought humans into closer contact with the vector and that have exposed them to the zoonotic cycle of *L. major*. The sudden onset and extensive epidemic scale of this increase, from a few dozen cases to thousands in some regions [14, 25, 84], are reminiscent of vector-borne diseases that involve humans as reservoirs, such as malaria, African trypanosomiasis, and dengue fever [57]. This observation suggests that the potential role of humans in amplifying transmission as secondary reservoirs should be considered in epidemiologic assessments.

Frequency of cases among household members and close contacts

Several studies have reported a higher prevalence of ZCL cases among household members. In their respective studies in Gafsa, Tunisia, and M'sila, Algeria, Bellali and Benikhlef found that around half of the cases occurred within family clusters [21, 25]. Some authors have explicitly identified the family environment as a risk factor for the disease [21, 59]. Bellali's study in Gafsa, as well as certain WHO reports, have also suggested a positive correlation between ZCL incidence and household occupancy. This makes overcrowding another indoor risk factor for ZCL [21, 60, 84]. Although household members of confirmed cases are exposed to the same environmental conditions (infected sandflies and rodents in the area), and therefore share similar exposure risks, these findings highlight the fact that infected individuals may play a role in amplifying parasite transmission.

Higher ZCL incidence among children and women

Most studies show that children and women are the most affected by ZCL [25, 27, 40]. These incidence rates could suggest intra-domiciliary contamination involving humans in amplifying transmission. Of note, in socially traditional and conservative rural areas, women as well as children under five years of age rarely leave their homes in the evening when sandflies are active. The location of lesions on women's limbs also supports the indoor transmission hypothesis since, for social reasons, their arms and legs are usually covered outdoors [13, 59]. Overall, it is worth noting that the high incidence among children is also related to their lower immunity to the parasite, which is gradually acquired with age [34].

ZCL outbreaks without identified rodent reservoirs

ZCL cases in NA and the ME are typically recorded in areas where *Meriones* and/or *P. obesus* are nearby. However, some outbreaks, sometimes quite active, such as those in Bordj Bou Arreridj in northern Algeria and Métlaoui in central-western Tunisia [12, 14, 25], do not offer these conditions and the parasite reservoir remains hypothetical [49]. Therefore, the rather urban outbreak in Métlaoui, where dozens of indigenous cases of ZCL are reported annually, has always raised questions. The involvement of synanthropic rodents as a secondary reservoir, such as *Ctenodactylus gondii*, even though its biotopes are quite far from the city, or *Rattus rattus*, the only rodent in the vicinity, has been suggested as they have been reported to be mildly infected with *L. major* [28, 80]. In such situations, the possibility of a human role in amplifying the transmission and acting as a "secondary reservoir" created locally from imported cases from neighboring endemic villages cannot be entirely ruled out. However, the possibility of the epidemiologic cycle being maintained solely by humans in the absence of rodent animal reservoirs remains questionable.

Clinical features of ZCL lesions

Short incubation period and sufficient duration of ZCL lesions

The incubation period of ZCL is the shortest of all CL forms prevalent in the Maghreb [13, 16]. It has recently been estimated to average 5 weeks in Tunisia, sometimes with a shorter duration of 2–3 weeks [15, 16]. Thus, following the peak density of *Ph. papatasi* in August [37, 43, 55], the first lesions appear in September [13, 16, 25]. These highly inflammatory and parasitized lesions could be potentially infectious to sandflies [17, 49]. Before self-healing, they persist for several months (average of 2 to 6 months) and coexist in September, October, and even November with sill active sandflies [14, 30, 35, 37, 39, 55, 72]. This provides sufficient opportunities to females to become infected from CL lesions and subsequently transmit mature parasites to other household members [49].

High exposure of ZCL lesions to sandflies

In more than 60–70% of cases, ZCL lesions are multiple, with an average of nearly three lesions per patient [9, 13, 25, 39, 59]. These lesions are often large and located on limbs which are frequently uncovered and exposed during the warm seasons when transmission occurs [11, 13]. The combination of these three lesion characteristics (number, size, and location) results in large, parasitized areas that are easily accessible to *Ph. papatasi*. In addition, several authors have reported that hosts infected with *Leishmania* are particularly attractive to sandflies, thereby amplifying transmission [36, 67, 69]. Although such reports concerned systemic leishmaniasis in dogs, these findings could question interactions between parasitized mammals and *Ph. papatasi* females.

Simultaneous detection of human blood and *L. major* DNA in *Ph. papatasi* and experimental evidence of human-to-human transmission

Several reports have detected both human blood and *L. major* DNA within the same *Ph. papatasi* female, which suggests that females of the species can feed on ZCL lesions and acquire the parasites [19]. This was recently demonstrated by Fatemi *et al.* in Iran, who detected, despite a low infectiousness rate (2 infected females out of 93 blood-fed), metacyclic promastigotes following a xenodiagnoses experiment on a ZCL lesion [49]. In this context, the experiments conducted by Adler and Theodor in Jericho in the 1920s are particularly noteworthy [3, 4]. They demonstrated vector-mediated human-to-human transmission of *L. major* via *Ph. papatasi*. Although the authors used "*L. tropica"* to refer to the species of the parasite in question, this is likely to correspond to *L. major*. The same misbelief was adopted by the Sergent brothers in Biskra, Algeria, the historical and exclusive focus of *L. major* [83]. This taxonomic confusion persisted until 1973, when Bray formally differentiated the two subspecies, establishing *L. major* and *L. tropica* as distinct species [29]. Therefore, the results of Adler and Theodor that were recently sustained by Fatemi *et al.* represent a further argument that justifies our questions about the possible role of humans as a source of infection for sandflies.

Conclusion

The biological cycle of *L. major* is still considered exclusively zoonotic. However, the high exposure of CL lesions, combined with the strongly endophilic and anthropophilic behavior of *Ph. papatasi*, raises legitimate questions regarding the potential role of humans as a secondary "parasite reservoir". Outbreaks occurring in urban areas, high proportions of family cases, and high incidence rates among children and women also suggest amplified local transmission in households, independently of rodent involvement. Moreover, the experiments by Adler and Theodor and Fatimi *et al.* provided evidence of potential anthroponotic parasite circulation. Nonetheless, this hypothesis has never been debated, investigated, or ruled out, highlighting the need for targeted research into *L. major* transmission. It is noteworthy that elucidating the role of humans in parasite transmission would enable a reassessment of the risk factors for the disease and lead to an update of the current recommendations for prevention, management, and control. In addition to medical treatment, simple household measures could be relevant, such as covering lesions and further promoting the use of repellents and bed-nets. These new measures could be beneficial, especially since all programs against ZCL, which rely primarily on rodent control, have proven ineffective.

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Conflicts of interest

The authors have no conflicts of interest to declare regarding this manuscript.

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