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Possibility of *Leishmania* Transmission via *Lutzomyia* spp. Sand Flies Within the USA and Implications for Human and Canine Autochthonous Infection

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Abstract

Purpose of Review Leishmaniasis is a leading cause of parasitic death, with incidence rising from decreased resources to administer insecticide and anti-leishmanial treatments due to the COVID-19 pandemic. Leishmaniasis is nonendemic in the United States (U.S.), but enzootic canine populations and potentially competent vectors warrant monitoring of autochthonous disease as a fluctuating climate facilitates vector expansion. Recent studies concerning sand fly distribution and vector capacity were assessed for implications of autochthonous transmission within the U.S.

Recent Findings Climate change and insecticide resistance provide challenges in sand fly control. While most *Leishmania*-infected dogs in the U.S. were infected via vertical transmission or were imported, autochthonous vector-borne cases were reported. Autochthonous vector-borne human cases have been reported in four states. Further vaccine research could contribute to infection control.

Summary Both cutaneous and visceral leishmaniasis cases in the U.S. are increasingly reported. Prevention measures including vector control and responsible animal breeding are critical to halt this zoonotic disease.

Keywords *Leishmania* · Sand Fly · Vector · Zoonotic · One Health · Canine Leishmaniosis

Introduction

Leishmaniasis is a worldwide neglected tropical disease that affects between 700,000 and 1 million people per year [1]. In the Americas, the Pan American Health Organization (PAHO) reports an average of 53,387 cutaneous leishmaniasis (CL) cases per year and an average of 3400 visceral leishmaniasis (VL) cases per year, both largely occurring in Brazil [2]. While many CL cases were considered cured, VL had an approximate 8% case fatality rate in 2020, which varied by country [2]. The COVID-19 pandemic has decreased funding for leishmaniasis programs and negatively affected disease control, impacting surveillance, chemotherapy availability, and residual insecticide spraying programs [3, 4]. These impacts will likely prolong leishmaniasis control and elimination [3].

In endemic areas, *Phlebotomus* and *Lutzomyia* sand flies transmit *Leishmania* protozoal parasites. Dogs are the main reservoir for visceralizing leishmaniosis (CanL), and dogs from over 70 countries have this disease [5]. Other reservoirs for *Leishmania* spp. include rabbits, hares, rats, and mustelids [6••]. Although documented to occur in endemic areas, *Leishmania* spp. transmission via vertical transmission is a predominant means of CanL transmission in the United States (U.S.), especially in canine populations [7, 8••, 9]. Vector-borne transmission is the most reported mode of transmission worldwide, and the expanding distribution of *Lutzomyia* spp. in the Americas heightens risk for autochthonous leishmaniasis cases, in both humans and animals. Monitoring sand fly distributions and incidence of leishmaniasis within the U.S. will provide evidence to institute prevention

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measures, including effective insecticide treatments, vaccination, and educational campaigns. For nonendemic areas, such as the U.S., previous research emphasized imported cases, but expansion of sand fly distributions has increased autochthonous transmission. This review highlights recent findings concerning the ability of sand flies to vector *Leishmania* spp. in the U.S. as well as recent human and canine cases, both imported and autochthonous.

Sand Flies as *Leishmania* Vectors

Leishmaniasis is a vector-borne parasitic disease caused by 20 species of flagellated protozoans of the *Leishmania* genus [10]. The *Leishmania* parasite is transmitted between mammalian hosts by female sand flies of the genus *Phlebotomus* in the Old World and the genus *Lutzomyia* in the New World [11]. Currently, 93 of the 800 known sand fly species have been incriminated as competent vectors for *Leishmania* parasites [11]. Confirmed *Phlebotomus* vectors have been reported in Africa, Asia, the Mediterranean, and the Middle East [11]. Further, *Phlebotomus* spp. in the Old World can vector *Leishmania* spp. that cause VL, CL, and mucocutaneous leishmaniasis (MCL) [11]. In the U.S., experts estimate that three sand fly species of the *Lutzomyia* genus are competent vectors for CL: *Lutzomyia anthophora*, *Lutzomyia diabolica*, and *Lutzomyia shannoni* [12].

Sand Fly Species of Interest in the U.S.

The three *Lutzomyia* spp. found in multiple U.S. states (Fig. 1) are associated with autochthonous transmission of cutaneous *Leishmania* infections, principally *L. mexicana* (Table 1) [13–18]. Multiple *Lutzomyia* species are associated with *L. mexicana* transmission in North America [19], but transmission dynamics of *L. mexicana* within the U.S. is still not well understood. *Lu. diabolica* was considered the probable vector for CL in Texas due to its anthropophagic nature and wide distribution in the state [12]. *Lu. anthophora* typically prefers to feed on non-human hosts and has thus been disregarded as a vector for *Leishmania* spp. responsible for human infections [12]. However, a study in Texas found that 98% of the sand flies found within 100 m of the autochthonous CL patients were *Lu. anthophora* [20•]. Further, two of the 188 *Lu. anthophora* collected had human DNA within them [20•]. This finding suggests that *Lu. anthophora* was the most likely vector species for CL in the area and that the sand flies had actively fed on humans there [20•]. Recent surveillance efforts to identify local cases of human leishmaniasis identified the human blood that was PCR-positive for *L. mexicana* within *Lu. anthophora* specimens, which also suggests that *Lu. anthophora* is a *Leishmania* vector species in Texas [20•].

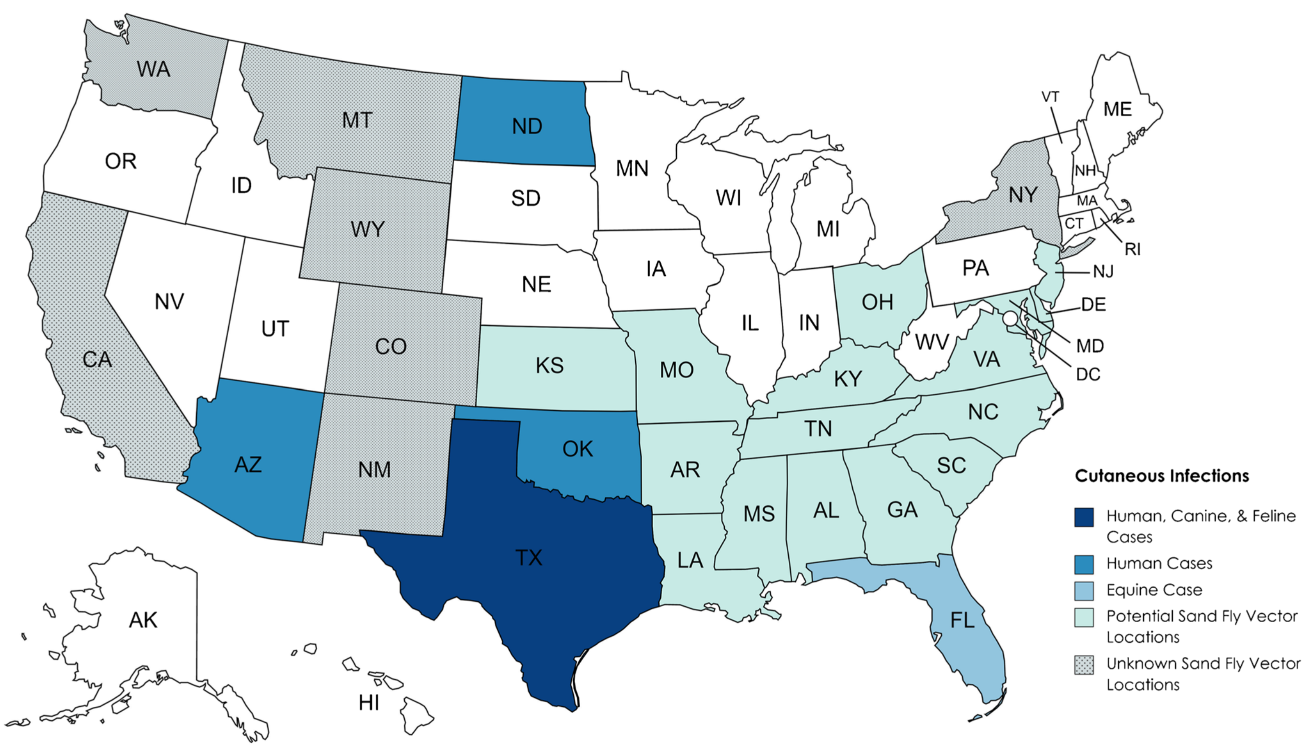

Fig. 1 Autochthonous cutaneous *Leishmania* infections reported in the U.S. and potential sand fly vector locations. [a]Texas, Oklahoma, and Florida also have found sand fly vectors

Table 1 Potential *Leishmania* sand fly vectors by location and pathogen

Sand fly species	U.S. geographic locations	Incriminated vector	*Leishmania* spp.	Citations
Lu. anthophora	AR, OK, TX	Confirmed	*L. mexicana*	[21]
Lu. cruciata	FL, GA	Not confirmed	*L. mexicana*	[17]
Lu. diabolica	TX	Confirmed	*L. mexicana*	[22]
Lu. shannoni	AL, AR, DE, FL, GA, KY, KS, LA, MD MO, MS, NC, NJ, OH SC, TN, TX	Confirmed Confirmed	*L. mexicana* *L. infantum*	[14, 16, 18] [23, 24]
Lu. vexator	AL, AR, CA, CO, FL, GA, KS, LA, MD, MO, MT, NM, NY, OH, OK, TN, TX, VA, WA, WY	Not confirmed	Unknown	[14, 16, 25, 26, 27]

Several studies have determined the prevalence of *Leishmania* infection in sand flies in the U.S. A study published in 2001 found natural *Leishmania* infection in one of 347 *Lu. anthophora* sand flies collected from south-central Texas [28], while a 1993 study in San Antonio, Texas identified *Leishmania* parasites in three of 27 female *Lu. anthophora* sand flies collected [29]. These studies suggest that there is variability regarding *Leishmania* burden in *Lu. anthophora* in Texas. Similar variability in parasitic burden has been documented in Mexico [30, 31]. Research examining the potential role of sand fly vectors in the U.S. has highlighted the abundance of habitable territory for *Lu. cruciata*, *Lu. diabolica*, and *Lu. shannoni* [32–34]. Studies in Ossabaw Island, Georgia, found that *Lu. shannoni* was established in the area and survived seasonal variability [33, 34]. In addition, studies on U.S. Army bases have indicated risk of leishmaniasis incidence due to compounding factors of competent sand fly vectors, expanding sand fly habitats, and imported leishmaniasis cases in military personnel [32, 35].

Beyond the observations of sand fly habitats in the U.S., research has shown a clear potential for these sand flies to locally transmit *Leishmania* parasites. For example, Lawyer et al. (1987) established the development of *L. mexicana* parasites within *Lu. diabolica* and *Lu. shannoni* and incriminated both species as potential vectors for *L. mexicana* [36]. Further, Schaut et al. (2015) found that *L. infantum* from hunting dogs remained infectious in sand flies, which provided evidence of the risk for human exposure within areas where infected hunting dogs and sand fly populations overlap [23].

In addition to *Lu. diabolica* and *Lu. shannoni*, *Lu. cruciata* has been identified as an important vector for *Leishmania* transmission. Studies in Mexico have supported the role of *Lu. cruciata* as an important vector for *Leishmania* spp. both experimentally and naturally in the environment [30, 37, 38]. Interestingly, although *Lu. cruciata* is found in Texas, it is more commonly reported in Florida [17]. Increased surveillance is needed to improve our understanding of the distribution and transmission dynamics of *Lu. anthophora*, *Lu. diabolica*, *Lu. shannoni*, and *Lu. cruciata* to prevent and monitor the increased transmission of *Leishmania* in the U.S.

Insecticides and Sand Flies

Insecticide resistance remains a significant challenge to the success of sand fly control. For example, a recent study by Denlinger et al. (2015) evaluated the insecticide susceptibility of *Lu. longipalpis* and *P. papatasi* in a laboratory setting [39]. The authors found that *Lu. longipalpis* and *P. papatasi* were most susceptible to carbamates bendiocarb and propoxur as well as the organophosphate fenitrothion [39], but *Lu. longipalpis* and *P. papatasi* were least susceptible to DDT [39].

Notably, while using a CDC bottle bioassay, Denlinger et al. (2016) established diagnostic doses and times for the phlebotomine sand flies [40]. Both *Lu. longipalpis* and *P. papatasi* were highly susceptible to carbamates and more resistant to DDT's insecticide effects [39]. However, little is known about how carbamates and DDT-based insecticides would impact sand fly species in the U.S.

Novel topical insecticide formulations have proven effective for preventing sand fly bites and, in turn, canine *Leishmania* infections [41]. Deltamethrin-impregnated collars have an estimated maximum efficacy of 2 weeks [41]. Collars impregnated with fulmethrin and imidacloprid have effectively protected puppies in hyperendemic areas of southern Italy [41]. Spot-on topicals that use permethrin and imidacloprid in combination have been notably efficacious at protecting canine health by repelling sand flies [41]. Recently, topical treatments that use dinotefuran, permethrin, and pyriproxyfen in combination or permethrin and fipronil in combination were 96% efficacious at repelling and 88% efficacious at killing sand flies for 21 days [41]. Finally, insecticide lotions that use permethrin or pyriproxyfen provide effective sand fly protection [41]. Various insecticides are efficacious either in isolation or combination, although, more research is needed to identify the emergence of insecticide resistance among U.S. sand flies.

Potential Impact of Climate Change on Leishmaniasis in the USA

Sand fly development is significantly affected by ambient temperatures and subsequently changes in climate conditions [42]. As the climate changes, it is expected to impact vector distributions around the world. In turn, vector-borne disease distributions will change. Currently, scientists estimate that the world's temperature will increase by more than 1.5℃ between 2030 and 2052 [42–44]. Typically, sand fly vectors require temperatures as high as 20–26℃ to develop and sustain life [42, 44]. Thus, extreme freezing events may inhibit sand fly survival and distributions. Conversely, increased temperatures may allow sand fly vectors to move progressively northward [12]. Current ecological niche models focused on *Lu. anthophora* and *Lu. diabolica* in North America included risk factors such as habitat availability, dispersal ability, and the number of people at risk for leishmaniasis [17, 44]. These models predict that the risk of leishmaniasis will spread beyond the current range of the southern U.S. to as far north as Michigan [17]. The geographic distribution of *Lu. longipalpis* could spread beyond its current range of southern Mexico into southern Texas and Louisiana [45]. Therefore, it is essential to monitor the sand fly distribution as the climate continues to change.

Xenodiagnoses from Vertically Infected Dogs

The risk of *Lu. longipalpis* range expansion is just one of several plausible concerns for future *Leishmania* spp. transmission in the U.S. Schaut et al. (2015) demonstrated the ability of sand flies to become infected with the *Leishmania* parasite from vertically infected dogs in the U.S. [22], which suggests that *Leishmania* transmission from infected dogs is possible. More recently, Scorza et al. (2021) demonstrated that this population of hunting dogs has an abundant dermal parasite burden and that subclinical animals transmitted *Leishmania* parasites during xenodiagnoses to *Lu. longipalpis* [46••]. *Lu. longipalpis* ingested parasites from the skin of dogs with mild to moderate clinical disease [46••], which suggests that healthy-appearing, vertically infected dogs can transmit parasites to sand flies and propagate emergence of *L. infantum* in locations where *Lu. longipalpis* or other competent vector species were present [46••]. Therefore, clinicians, public health practitioners, and scientists must remain mindful of the impact of subclinical dogs on maintaining *Leishmania* parasites in the environment, particularly in non-endemic areas where *Lu. longipalpis* may gain an ecological foothold with a changing climate.

Interrupted Feeding Increases Burden of *Leishmania* Parasites

Given the potential propagation effect of sand flies feeding on infected hosts, preventing multiple blood meals could vastly decrease parasite burden for vectored transmission in the U.S. Researchers have found that sequential blood meals increased *Leishmania* parasite replication due to interrupted feeding within the sand fly vector [47]. During the time an interrupted sand fly seeks a second blood meal, it has rapidly expanding numbers of parasites within its midgut. Serafim et al. (2018) found that when sand flies took a second blood meal from an uninfected host, *Leishmania* parasite load was 125-fold greater than from sand flies that consumed just one blood meal [47]. Consequently, a sand fly that feeds on an infected human or canine host followed by a secondary non-infected host could significantly increase the parasitic burden within the sand fly. The likelihood of interrupted sand fly blood feeding in the wild is high. Therefore, while the burden of human leishmaniasis in the U.S. may remain low, the risk of parasite amplification could be much greater than previously understood based on single blood meal studies.

Disease Manifestations and Implications

Canine Vertical Transmission

Canine leishmaniosis (CanL), the visceral form of *Leishmania* spp. disease, is caused predominantly by *Leishmania infantum*. Notably, CanL is principally manifested as dermatopathies, especially in earlier stages of disease [48]. Canine cutaneous leishmaniosis can be caused by a variety of *Leishmania* spp. and vectored by different sand fly species depending on the geographic location. In the U.S., vertical transmission is the primary mode for transmission of autochthonous *L. infantum* CanL. In 2011, Boggiatto et al. found 10/12 naturally infected neonatal puppies with *L. infantum* parasites in their organs [7]. Vida et al. (2016) followed three remaining puppies from the Boggiatto et al. (2011) litter after whelping from an infected bitch, who was oligosymptomatic [9]. These dogs were tested for parasite load and immunologic response every 6 months for 6 years to assess progression of disease [9]. One dog was oligosymptomatic and had a positive antibody titer and intermittent qPCR positivity [9]. The second dog was asymptomatic, had positive antibody titers, and had a strong $CD4^+$ T cell response [9]. The third dog was considered healthy [9]. All three dogs had either positive qPCR or IFAT and had $CD4^+$ T cell proliferation and IFN-γ production to *L. infantum* antigen over the 6-year follow-up period [9]. This study showed that dogs from an infected bitch had variable responses in disease progression and immunologic response, but each dog had evidence of infection [9].

Toepp et al. (2019) evaluated the risk of offspring being positive for *L. infantum* during their lifetime if the dams had confirmed *L. infantum* infection [8••]. The authors found that these dogs had 13.84 times higher risk of being positive for *L. infantum* during their lifetime compared to dogs born to a diagnostically negative dam from the same kennels [8••]. Based on the data from this study, vertical transmission of *L. infantum* had a basic reproductive number of 4.16 [8••]. Additionally, 19 of 20 dogs followed until death had confirmed CanL as the cause of death [8••]. This study revealed the significance of *L. infantum* propagating through generations of dogs. It is essential to prevent breeding of infected dams to prevent further transmission of *L. infantum* [8••].

Canine Imported and Autochthonous Cases

Dogs are considered the main reservoir species of *L. infantum* among endemic areas with competent sand flies, such as the Mediterranean Basin, southern Europe, South America, and northern Africa [49]. Sand flies can infect naïve dogs during blood meals, and conversely, infected dogs can transmit parasites to naïve sand flies. Dogs without clinical signs of disease are also infectious to sand flies and thus transmit *Leishmania* parasites [49]. However, dogs with clinical signs have been shown to be more infectious to sand flies than subclinical dogs, although precise disease scores were not used [49, 50]. There are more infected, subclinical dogs than diseased dogs [51].

In the U.S., infected dogs were imported from Europe hundreds of years ago, and the parasites have persisted largely through vertical transmission [7, 8••, 9, 52]. There are also imported cases from competent sand fly-endemic areas, which have potential to propagate infections via vertical transmission in the U.S. For example, a U.S. Boxer with no travel history but whelped from a dam native to an endemic part of Spain, developed CanL, including granulomatous cutaneous lesions, anemia, hyperglobulinemia, hypoalbuminemia, and lymphadenomegaly [53]. This Boxer was euthanized approximately three years after its CanL diagnosis [53]. Additionally, Gin et al. (2021) found 125 *L. infantum*-positive dogs in the U.S. and Canada between 2006 and 2019 with at least 60 of these dogs having documented foreign travel to endemic areas [54]. Military working dogs are also at-risk for *L. infantum* infection; for example, 54/378 dogs evaluated by Seal et al. (2022) were *Leishmania*-positive, with 44/54 of these dogs having reported travel to or inhabitance in endemic areas [55].

Autochthonous CanL cases have occurred in the U.S. [56] largely due to vertical transmission. Foxhound kennels have reported CanL cases in the U.S. since 1980 [56, 57]. Some autochthonous CanL cases were infected via direct contact from dog bites or fights with an infected dog; the infected dog had evidence of previous importation from endemic areas [56]. Some studies report *L. infantum*-positive dogs with no recorded foreign travel history and unconfirmed mode of transmission [54, 55].

Besides vertical transmission of *L. infantum*, there is possibility of future autochthonous canine cases due to bites from infected sand flies within non-endemic regions. Within the U.S., autochthonous CanL cases from a known sand fly transmission of *Leishmania* parasites have not been reported. However, in controlled laboratory settings, sand flies became infected with *L. infantum* after biting naturally infected hounds, and they also transmitted *L. infantum* to hamsters [23]. This controlled laboratory experiment shows potential for *L. infantum* to be transmitted by a competent sand fly vector if the particular vector was present in natural settings within the U.S. [23].

In contrast to the visceral form (CanL), autochthonous canine cutaneous cases have been reported within the U.S. sand flies in Texas and Mexico have transmitted *L. mexicana* to dogs and cats (Fig. 1) [58–61]. Additionally, an equine cutaneous case of *L. siamensis* infection was diagnosed in a Morgan mare in Florida with no international travel history (Fig. 1) [62].

Human Imported and Autochthonous Cases

In humans, imported cases of both cutaneous and visceral forms of leishmaniasis have been reported in the U.S. A traveler was likely infected in southern France and developed VL upon return to the U.S. [63]. This traveler had signs such as fever, splenomegaly, and pancytopenia [63]. Some signs that are reported in human VL cases but rarely in dogs include fever, abdominal pain, and ascites [51]. Travelers returning from Costa Rica and Panama developed CL, caused by *L. panamensis* or *L. braziliensis* [64, 65]. One of these patients with *L. panamensis* infection also traveled to the Florida Keys before visiting Central America [65].

U.S. military members are at risk of leishmaniasis largely due to deployments to competent sand fly-endemic areas, such as Middle Eastern countries [66]. CL is the most common form in the U.S. military with *L. major* being the most common etiologic agent [66]. Asymptomatic VL is also reported in U.S. military members deployed to Iraq, as Mody et al. (2019) found 39/200 (19.5%) deployers with *L. infantum* infection [67]. Additionally, military members are at-risk for zoonotic VL especially among canine military units [66].

Human autochthonous CL has been reported in Texas (Fig. 1). A man living in central Texas became infected with *L. mexicana* and developed dermatologic lesions on his legs persisting for over 1 year [20•]. Kipp et al. (2020) caught sand flies near the patient's home and found infected sand flies, largely *Lutzomyia* spp. [20•]. Two men in Oklahoma had CL, although the *Leishmania* spp. was unconfirmed [13]. McIlwee et al. (2018) reported 41 autochthonous human CL cases from 2006 to 2017 in the U.S. [68••]. Most of these cases were infected with *L. mexicana* [68••]. A woman in Arizona also had autochthonous CL, but the etiologic species was undetermined after sequencing (Fig. 1) [69]. Interestingly, a 1-year-old boy from North Dakota was infected with *L. donovani* complex, which caused a focal periocular lesion, and determined to have CL (Fig. 1) [70].

Insights for Vaccination and Prevention

While three vaccines are currently approved and available for dogs in Europe and Brazil [71], there are no licensed vaccines for canine leishmaniosis in the U.S. vaccine effectiveness varies by product [71]. Current vaccines may provide immunoprotection, and the LeishTec®. Vaccine has reduced progression of CanL and mortality [72•]. Toepp et al. (2018) conducted a blinded, controlled field trial with 557 asymptomatic dogs randomized to receive the LeishTec® vaccine or placebo of sterile water [72•]. Asymptomatic dogs that received LeishTec had statistically decreased clinical score (these dogs were 33% less likely to have clinical progression of disease compared to dogs receiving placebo) [72•]. Additionally, asymptomatic dogs less than 6 years old receiving placebo had 3.129 ($p = 0.0245$) times the risk of mortality during the study period compared to dogs receiving LeishTec® [72•]. Among dogs that became symptomatic for CanL during the study period, there were more dogs from the placebo group that became symptomatic, had progression of disease, and died [72•]. Therefore, this study concluded that dogs considered healthy but infected could benefit from vaccination [72•].

In a follow-up study by Toepp et al. (2018), a safety analysis of the LeishTec® vaccine trial revealed a 3.09% occurrence of mild adverse effects among vaccinated dogs [73]. The authors found that six of the approximate 300 included dogs had severe adverse effects from either the vaccine or placebo, and there was no difference in the number of dogs having severe adverse effects between the two groups [73].

There are no vaccines available for human leishmaniasis. Several vaccine candidates are in preclinical trials, and a few candidates are in clinical trials. Vaccine candidates include killed parasite vaccines, recombinant protein vaccines, DNA vaccines, and chimeric vaccines [74]. Preclinical vaccine candidates assessed in murine models include CRISPR-edited *centrin* gene knockout strain of *L. major* (LmCen$^{-/-}$) and ChimeraT recombinant vaccines [75, 76]. Previously, killed vaccines Leishvaccine and autoclaved *L. major* (ALM) vaccine reached phase II, although Leishvaccine underperformed in phase III, and the ALM vaccine had limited immunoprotection in phase II [74, 77]. The DNA vaccine ChAD63-KH also reached phase II and has potential for therapeutic uses in addition to prevention [77]. A recombinant vaccine in phase II is Leish-F1, designed for VL protection [74, 77]. Challenges for leishmaniasis vaccines include market profit potential, demand for vaccines, protection against different *Leishmania* spp., and effectiveness outside of clinical trials [74, 78].

For prevention of CanL in endemic areas or for dogs traveling to endemic areas, there are insecticides and repellents commercially available to deter sand fly bites (such as collar and spot-on formulations) [41]. Regardless of geographic location, *Leishmania*-positive dogs should not be bred or used as blood donors [41]. Dogs at-risk should be tested for *Leishmania* infection before being bred [41].

For human leishmaniasis prevention, methods include residual insecticide spraying in households, removal of sand fly breeding habitats, insecticide-treated bed nets or clothing, and controlling animal reservoirs [79].

Conclusions

Within the U.S., there is potential for sand flies to expand their distribution due to climate change [17]. Consequently, CL cases could become more prevalent in the southern states. As *Leishmania*-infected dogs have experimentally contributed to sand fly transmission of *L. infantum* [46••], which causes visceralizing disease, there is a risk of potential autochthonous zoonosis in the U.S. Continued vigilance for responsible animal breeding and practice of vector prevention measures is warranted.

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Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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