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REVIEW

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Was Chagas disease responsible for Darwin's illness? The overlooked eco-epidemiological context in Chile

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Abstract

The source of Darwin's illness has been a contentious issue in the literature for almost 70 years. Different causal factors have been invoked to account for his symptoms, including Chagas disease. The Chagas hypothesis is based upon Darwin's diary, in which he narrates his experience with kissing bugs, the main vector of the protozoan *Trypanosoma cruzi*, the etiological agent of Chagas disease. In this contribution, we examine the consistency of the "Chagas disease hypothesis" in the light of current ecological and epidemiological knowledge of the disease in Chile. According to his diary and letters, during his overland trips, Darwin slept in rural houses and outdoors for 128 days in a "hyperendemic" area for Chagas disease, more than exposing him to kissing bugs. This observation conveys a likely additional source of infection than previously considered, which might reinforce the idea that Chagas disease contributed to Darwin's manifest physical deterioration.

Keywords: Chagas disease, *Triatoma*, *Mepraia*, Kissing bug, Vector-borne disease, Darwin's illness

Background

In December 1831, the young British naturalist Charles Darwin embarked on the H.M.S Beagle to South America and other destinations to make geological observations and collect samples of flora and fauna. During his five-year trip, Darwin explored diverse coastal and inland habitats, but it was in Chile that he made his most extensive overland trips. In these excursions, the naturalist was exposed to various infectious disease agents, many of them endemic to South America, and completely unknown at that time in terms of their symptoms, etiological agent and/or vectors involved in their transmission. Since 1838 until his death in 1882, Darwin suffered from palpitations, lassitude, headaches, shivering, tremulousness, sleeplessness, and flatulence, which allowed him to work only few hours a day. During this period, he also showed an obsessive concern for his physical health, which was recorded in detail in his Health Diary. According to some authors, Darwin suffered gastrointestinal and cutaneous disorders, intermittent fevers, and fatigue even before his voyage on the Beagle, especially after unpleasant episodes or stressful and post-traumatic emotional situations [1–3]. Psychiatrist Ralph Colp suggested that the diseases experienced by Darwin in adulthood may have been of psychosomatic origin, as product of the stress related to the public reception of his evolutionary theory [2, 4, 5], which together other social activities, such as meeting people, public gatherings, church attendance, and hurried correction of page proofs, may have contributed to his symptoms. It was parasitologist Saul Adler [6] who first suggested the possibility that Darwin's illness could be a consequence of a chagasic condition. Chagas disease, a chronic illness caused by the flagellated protozoan *Trypanosoma cruzi*, was described in 1909 by the Brazilian physician and pioneering infectologist Carlos Chagas, 27 years after Darwin's death.

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Therefore, it was impossible for physicians at Darwin's time to associate his symptoms with the disease caused by *T. cruzi*. Adler highlighted a paragraph from Darwin's diary, where the first encounter of the naturalist with the blood-sucking insects is narrated:

> *We slept in the village of Luxan, which is a small place surrounded by gardens, and forms the most southern cultivated district in the Province of Mendoza, it is five leagues south of the capital. At night I experienced an attack (for it deserves no less a name) of the Benchuca, a species of Reduvius, the great black bug of the Pampas. It is most disgusting to feel soft wingless insects, about an inch long, crawling over one's body. Before sucking they are quite thin, but afterwards they become round and boated with blood, and in this state are easily crushed. ([7], p. 330)*

This encounter occurred during the visit of Darwin to the village of Luján, Argentina, after crossing the Andes from Chile in March 1835. Currently, "the great black bug" that Darwin noted in his diary is known to be *Triatoma infestans*, the most important insect vector of *T. cruzi* in southern South America. This kissing bug is widely distributed in the seven countries to the south of the Amazon basin [8], being responsible for the infection of approximately 6-7 million people [9].

After his experience in Argentina and back on the Beagle anchored in Valparaíso, Chile, Darwin took a long trip on horseback to Coquimbo, Copiapó, and Caldera, where he then embarked on a trip to Iquique on the Pacific coast, ca. 2000 km northwest of Luján. There, again he observed the feeding behavior of kissing bugs. He remarked that their bites were painless and that after feeding, individuals endured for several months without eating:

> *One which I caught at Iquique (for they are found in Chile and Peru) was very empty. When placed on table, and though surrounded by people, if a finger was presented, the bold insect would immediately protrude its sucker, make a charge, and if allowed, draw blood. No pain was caused by the wound. It was curious to watch its body during the act of sucking, as in less than ten minutes it changed from being as flat as a wafer to a globular form. This one feast, for which the benchuca was indebted to one of the officers, kept it fat during four whole months; but, after the first fortnight, it was quite ready to have another suck. ([7], p. 330)*

What Darwin could not know at that time is that "benchucas" (vinchucas, the colloquial word in Spanish) are often infected themselves by the protozoan *T. cruzi*, which inhabits the last portion of the insect's digestive tract. From there, they may be transmitted to humans when kissing bugs defecate on the skin of their victims near the site of a bite. At that moment, *T. cruzi* percolates from the insect feces to the human blood vessels. Kissing bugs, in turn, become infected when they feed on the infected blood of a broad spectrum of mammals, that includes armadillos, marsupials, rodents, bats, wild primates, among others, as well as some domestic pets and livestock [8–11].

In humans, Chagas disease presents two main stages of development: The acute phase, which lasts for 1-2 months after infection. During this phase, a local skin nodule called chagoma may appear at the site of infection, creating in some cases a conspicuous edema and conjunctivitis, called the Romaña sign [8, 12]. At this stage, humans may suffer fever, lymphadenopathy, hepatosplenomegaly, myocarditis, and meningoencephalitis, the last two pathologies conveying the highest risk to life if untreated [12]. After the acute phase the chronic stage begins, which consists of an indeterminate amount of time with no specific symptoms or detectable lesions. About 70 % of infected people will remain asymptomatic for life, with 20-30 % developing severe symptoms up to 25 years after infection. These include: (a) deformations and dysfunctions of the heart muscle expressed as cardiomyopathy, arrhythmias, cardiac decompensation, and even sudden death, (b) deformations and dysfunctions of the digestive tract such as megacolon, megaesophagus, chronic constipation, and intestinal obstruction, and (c) neurological disorders often expressed by signs of dementia.

The controversy

It is unknown whether Darwin suffered heart or digestive tract deformities but judging by his letters and Health Diary (reviewed extensively in 2), the excessive fatigue and chronic digestive discomfort may have been related, in principle, to Chagas disease. However, as with other hypotheses raised to explain Darwin's illness, the Chagas hypothesis is hard, if not impossible, to confirm rigorously. This limitation has led to an increasing controversy about the idea that Darwin was truly infected with *T. cruzi* [2, 13]. On the one hand, supporters of the Chagas hypothesis rely mostly on clinical evidence coherent with the symptoms described by the naturalist in his Health Diary, as well as on the scanty notes recorded in Darwin's Beagle diary (e.g., [2, 6, 14–18]). On the other hand, a wide range of diagnoses for Darwin's illness have been hypothesized, including Crohn's disease [19], irritable bowel syndrome [20], lactose and food intolerance [21], inherited pathological mtDNA mutation [22, 23], among other diseases (see reviews in 21), which suggests that

more than one causal factor might be invoked. Perhaps the most important observation to the Chagas hypothesis was raised in the 60 s by the British parasitologist Alan W. Woodruff, who in a series of articles questioned the idea that Darwin's afflictions occurred due to infection with *T. cruzi* (e.g., [1, 24, 25]). Woodruff's objections developed along the following five lines of reasoning: (1) the kissing bugs that attacked Darwin in Argentina could have been free of *T. cruzi*; (2) usually people become infected as a result of a long exposure to kissing bugs, not only once as indicated in Darwin's diary; (3) stomach symptoms could have hardly occurred in the absence of heart damage; as Darwin's physical activity does not seem to have been affected, some of his digestive problems could have been present before the voyage of the Beagle; (4) Darwin's most critical events occurred during stressful situations, which is consistent with psychosomatic disorders; and (5) some of the symptoms initially ascribed to Chagas disease are also compatible with other illnesses, such as primary tuberculosis [1] and psychosomatic paroxysmal tachycardia [24]. With all these elements at hand, the final diagnosis of Woodruff was that Darwin presented a state of anxiety with obsessive characteristics and psychosomatic manifestations [25].

The controversy on Darwin's illness resurfaced in 1984, when the physician Ralph Bernstein [26] proposed that Darwin suffered a typical progression of Chagas disease symptoms. Beginning with an acute phase in 1834-1835, followed by an asymptomatic latent phase from 1835 to 1841, and an extensive period with manifest physical discomfort from 1841 to 1865. The final stage, from 1866 until his death in 1882, was one of a relatively good health, which is coherent with an asymptomatic or quiescent chronic disease process. Shortly after Bernstein publication, two other clinicians provided an additional defense of the Chagas hypothesis, objecting to Woodruff's arguments again [15, 16]. The authors indicated that during Darwin's trip to Chile and Argentina, in 1834-1835, he may have been bitten by additional triatomines, since his clinical symptoms began five years after, in 1839-1840, once in England. This delay would be consistent with the existence of a latency period (i.e., indeterminate phase) typical of Chagas disease. The authors hypothesized that *T. cruzi* produced an organic lesion in Darwin's stomach and intestine, which did not evolve into the severe physical malformations shown by chronic Chagas disease patients, such as megaesophagus and megacolon. Rather, according to these authors, *T. cruzi* may have produced a secondary chagasic condition that involved a parasympathetic denervation of the gastrointestinal tract, which renders the tract more sensitive to sympathetic stimulation, causing dysfunctional motility and secretory functions [15, 16]. Thus, the first clinical manifestation of the secondary chagasic condition in Darwin would have begun in 1840 with episodes of extreme spasmodic flatulence that tormented him for the rest of his life. The second clinical manifestation occurred in 1842, when the high sensitivity to sympathetic stimulation made Darwin susceptible to stomach disorders [2, 5]. The timing of the digestive symptoms was objected [1], suggesting that the naturalist presented symptoms before his trip to South America. However, this assertion was subsequently criticized as young Darwin defined himself as a healthy person, presenting physical discomfort only before the departure of the Beagle from Devonport, distressed by the prospect of a long separation from loved ones [15]. While correlative evidence seems to support the Chagas disease hypothesis at present, additional evidence pointing in the same direction is welcome. In this contribution, we provide ecological and epidemiological information to suggest that Darwin's trips in north-central Chile conveyed a higher likelihood of infection, due to a greater contact rate with wild and domestic infected blood-sucking reduviids than previously considered.

The putative eco-epidemiological context during Darwin's trips

Currently, all the four kissing bug species described in Chile are known to be naturally infected with *T. cruzi*. Interestingly, none of them had been described when Darwin visited Chile, suggesting that the naturalist was not familiar with these blood-sucking insects. (1) *Triatoma infestans* (Klug 1834), a nocturnal species that inhabits different countries in South America from Ecuador line to 46° S in Argentina. In Chile, this species inhabits the north-central area [27, 28], and it is mostly associated with cracked mud walls in houses, chicken coops, corrals and cellars, but in the past decade has been described in wild state [29, 30]. (2) *Mepraia spinolai* (Porter 1933) (synonymy *Triatoma spinolai*, [31]), an endemic diurnal species distributed only in north-central Chile around quarries, rock crevices, bird nests and the burrows of wild mammals [32–34]. (3) *Mepraia gajardoi* [35], another diurnal species distributed in the coastal areas of northern Chile [36], that inhabits rocky areas and the nests of seabirds [35, 37]. Like *M. spinolai*, nymphs of this species camouflage themselves in the presence of the appropriate sandy substrate [38]. (4) *Mepraia parapatrica* [36] is distributed in a very restricted coastal area of northern Chile, where it has been found in peridomestic environments associated with mammals (goat corrals), and in wild environments associated with reptiles (lizards) or seabirds (Dominican gull and Humboldt penguin) [39, 40].

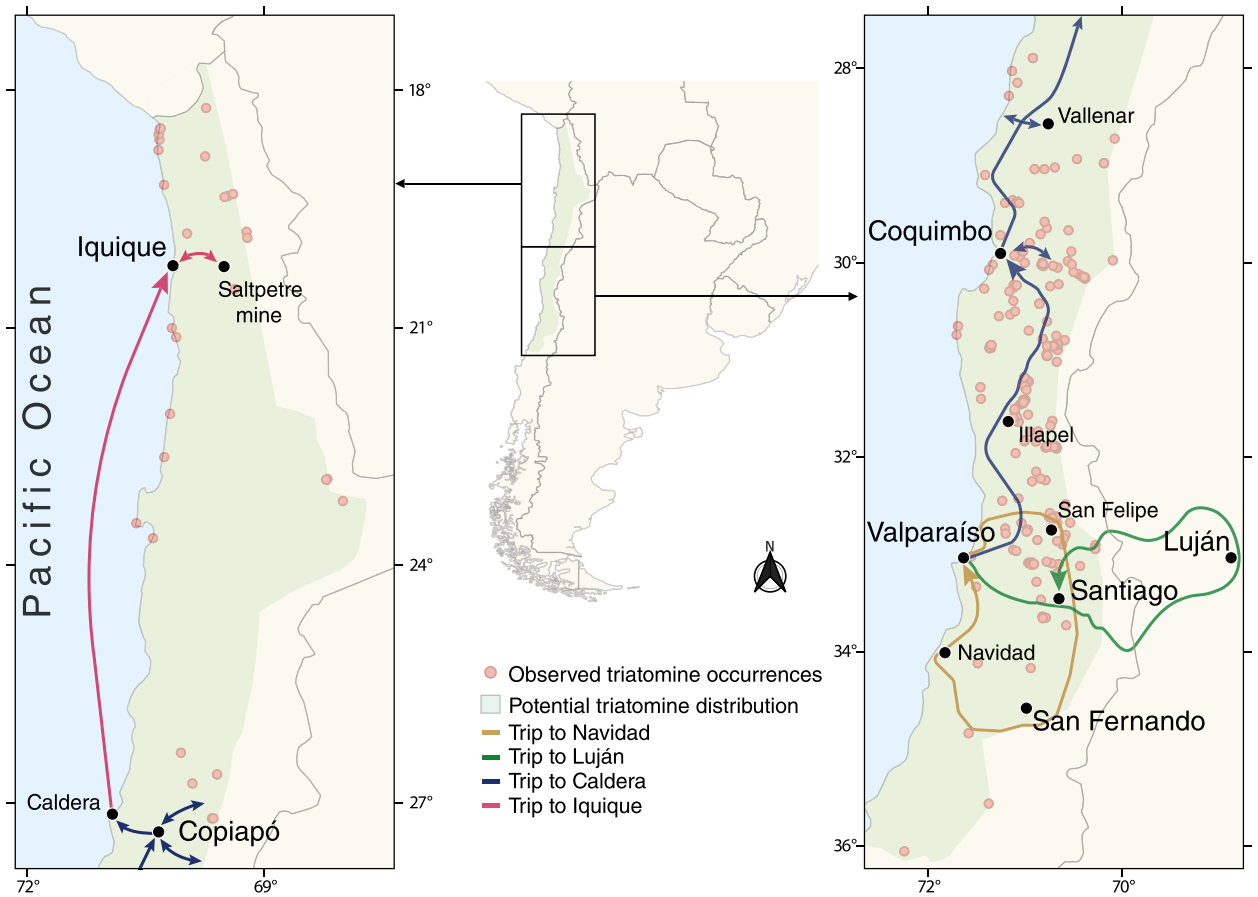

Fig. 1 Map depicting the routes followed in Darwin's four trips performed between 1834-1835 to north-central Chile, a hyperendemic area of Chagas disease. Trip to Navidad (1834): 14-27 August, 6-27 September (Valparaíso - Campana mountain - Santiago - Cauquenes Hot Spring - Navidad -Valparaíso). Trip to Luján (1835): 18 March - 10 April (Santiago - Piuquenes Pass - Luján - Mendoza - Uspallata Pass - Santiago). Trip to Caldera (1835): 27 April - 5 July (Valparaíso - Limache - Illapel -Coquimbo - Freirina - Vallenar - Copiapó - Caldera). Trip to Iquique (1835): 13-14 July (Iquique -Huantajaya Mine - Santa Rosa Mine - La Noria Saltpetre - Iquique). Route reconstructions are based on Darwin's diary (Darwin 1845). Black dots: cities or towns. Pink dots: observed *Triatoma infestans*, *Mepraia spinolai*, *Mepraia gajardoi* and *Mepraia parapatrica* occurrences in the past century and nowadays. Green area represents the potential species distribution in Chile (all species combined) based on Species Distribution Modeling (SDM) [28, 34]

Between 1834 and 1835, young Darwin made four extensive overland trips using pack animals to move around in what is currently the north-central area of continental Chile. He spent many nights in rural houses and outdoors across his routes [7]. Darwin's encounter with kissing bugs on his trip to Mendoza has been widely used as circumstantial evidence to support the Chagas disease hypothesis (see review in 2). However, as the detractors of this hypothesis state, a single contact event does not ensure protozoan transmission [1]. In what follows, we present ecological and biogeographical evidence, along with epidemiological data on the wild and domestic *T. cruzi* transmission cycles that suggest Darwin was sufficiently exposed to kissing bugs during the trips in Chile to raise the probability of infection. Figure 1 depicts, in red dots, cumulative recordings of kissing bug populations infected with *T. cruzi*. Likewise, the green area indicates the sites potentially suitable for kissing bug occurrence according to predictions based on species distribution modeling (SDM) [28, 41].

Darwin's first trip in central Chile occurred on August 14th, 1834 (see Fig. 1; trip to Navidad) when he left Valparaíso to visit Campana mountain. He camped on the mountain and then, on the way down, passed through several towns and hills before arriving in Santiago on August 27th. He stayed a few days in Santiago and on September 6th he continued his trip south following suggestions of French naturalist Claude Gay. After visiting several sites of geological interest, on September 19th Darwin began to feel ill, apparently due to a *Salmonella*

Fig. 2 Camouflaged nymph of *Mepraia spinolai* (left). This natural behavior is performed by small, medium, and large-sized nymphs (0.4-1.5 cm length) of all *Mepraia* species when the appropriate substrate is provided. Adult female of *Mepraia gajardoi* with a feces droplet (right). Defecation usually occurs during or right after a blood meal, potentially resulting in *Trypanosoma cruzi* transmission through self-inoculation. Photographs by Rodrigo Medel and Vicente Valdés, respectively

typhoid type of infection, arriving in Valparaíso in poor physical condition on September 27th [7]. Along this trip, he visited known areas of high kissing bug occurrence, staying in rural houses, visiting rocky outcrops, and quarry zones (shown as red dots in Figs. 1, and [29, 32–34, 42, 43]). Therefore, during this 36-day trip, Darwin was exposed to potential daytime and/or nighttime attacks from *M. spinolai* and *T. infestans*, respectively. In his diary, Darwin indicates that following this trip he was ill in bed until the end of October, apparently due to a severe gastrointestinal infection [19].

Darwin's second trip began on March 7th, 1835, when he departed from Valparaiso to Santiago and then to Luján, Argentina. He crossed the Andes Mountains through a pass located southeast of Santiago (see Fig. 1; trip to Luján), arriving Villa de Luján on March 25th. In this trip he first saw *T. infestans* and took the famous note in his diary indicated above. On his return to Chile, he visited Mendoza and crossed the Andes again, descending through the Aconcagua Valley and arriving in Santiago on April 10th. As in his first trip, Darwin would have been exposed to Chagas disease vectors, especially in the Province of Mendoza and other areas of Chile where infestation of homes was quite common. On this second trip, the naturalist was exposed for 20 days to Chagas disease vectors, discounting the days in the high mountains, where no record of kissing bugs exists.

Darwin's longest trip began on April 27th, 1835, when he departed on horseback from Valparaíso towards Coquimbo, and then, after spending some days in the port, he continued the trip to Caldera, where the Beagle was waiting for him. During this journey, Darwin traveled across the semi-arid and arid areas of north-central Chile, the region with the highest levels kissing bug occurrence (see Fig. 1; trip to Caldera). He visited several mines, active or abandoned, conditions the wild kissing bug, *Mepraia spinolai*, often inhabits [33, 34, 44, 45]. Interestingly, *Mepraia* nymphs (0.4-1.5 cm length) show a remarkable camouflaging behavior in their rocky microhabitats, which consists of the adhesion of particles of sandy substrate to their exoskeleton using their hind legs (Fig. 2), making them difficult to detect to the inexperienced eye [38, 46]. At night, Darwin often slept outdoors, but also spent several nights in rural mud and straw ranches, which often had colonies of *T. infestans* hidden in crevices, becoming active at night searching for blood [32]. Therefore, throughout this 70-day trip, Darwin may have been exposed to daytime and night contacts with both the wild and domestic kissing bug species present in this area. Especially compelling is the letter written to his sister Catherine on May 31st, after arriving in Coquimbo, where Darwin indicates he decided to sleep outside rural houses to avoid being bitten at night:

> *It is impossible to sleep in the houses, on account of the fleas. Before I was fully aware of this, I have risen in the morning with my whole shirt punctured with little spots of blood, the skin of my body is quite freckled with their bites. I never formerly had an idea, what a torment, in this hot, dry climates, this ravenous little wretches could be. ([47], p. 449)*

While it is not possible to rule out that the "little spots of blood" indicated by Darwin were truly produced by fleas or bedbugs, kissing bugs also deposit reddish droplets near the place they bite after a blood meal (Fig. 2), as the ingestion of fresh blood stimulates defecation, especially in infected vectors [48]. As victims frequently rub the itching bite area, they push

the trypanosome-laden feces into the bite wound. In this way, *T. cruzi* enters the host's blood stream, initiating the acute stage of the disease. As the zone where Darwin experienced this uncomfortably situation (as written to his sister) corresponds to the area with the highest recorded occurrence of wild and domestic kissing bugs and highest proportion of infected people (43.6 % of people living in poor rural populations in the Coquimbo area were infected by *T. cruzi* at the end of the 20th century, 27), it is likely that Darwin was highly exposed to the disease in that region.

Darwin's fourth and last trip in northern Chile began on July 5th, when he embarked from Caldera to Iquique, a Peruvian territory at the time (see Fig. 1; trip to Iquique). Once in Iquique, on July 12th, Darwin made a short 2-day trek in July 13-14, to explore some saltpetre mines inland. He covered the 68 km route on mule back from Iquique to La Noria Saltpetre, arriving at sunset to spend the night at the house of the owner of one of the mines [49]. Interestingly, important foci of the domestic kissing bug, *T. infestans*, had been detected near the mine [27], which together with the finding of the wild kissing bug *Mepraia gajardoi* along the coast near Iquique [35], adds chances where Darwin may have been bitten and infected.

During his overland trips in north-central Chile, Darwin was possibly exposed to two diurnal vectors and one nocturnal vector. He spent a total of 128 days traveling through places where the percentage of *T. infestans* infected with *T. cruzi* ranges between 30 and 50% [27, 32], probably a conservative figure if extrapolated to 1834-1835 when the role of kissing bugs as disease vectors was unknown. The probability of a human becoming infected by an infected triatomine vector in one bite is 5.8×10^{-4} (95% CI = 2.6-11.0) [50]. Therefore, to become infected, a human would need to experience 900–4000 bites from infected kissing bugs. This figure is not excessively large considering the number of days Darwin was exposed to triatomine bugs. According to recent recordings, up to 20 approaches per hour of infected *M. spinolai* may occur in the hyperendemic area near Illapel [34], suggesting that Darwin had a high probability of becoming infected with *T. cruzi* due to bites either at night or during the day. The obvious question that follows is how do epidemiological parameters during Darwin's stay in Chile compare with those observed at present? It is likely that levels of infestation almost 200 years ago may have been higher than those observed at present. Vigorous control programs developed since 1950, overall improvement in the quality of housing, and higher socioeconomic standards, led to the declaration of Chile as a country free of vector-borne transmission of Chagas disease in 1999 [12]. In consequence, the figures reported in the last 70 years might underestimate the levels of infestation observed at the time of Darwin's trips in Chile.

Conclusions

By far the best way to solve the longstanding enigma of Darwin's illness would be to exhume the corpse from his grave at Westminster Abbey and to perform immunological analyses and/or look for DNA traces of the protozoan. Unfortunately, this procedure is not possible as English law does not permit exhumations, except under suspicion of murder. Notwithstanding, immunological studies performed on obituaries probably stamped by Darwin, as well as tests made on a blood stain present in his diary, failed to detect antibodies to *T. cruzi* [2]. However, the researchers involved in this study cautioned that these results do not rule out the Chagas hypothesis because the biological material used for immunological tests could have been degraded, hence rendering a false negative. In consequence, the source of Darwin's illness remains a mystery, and the evidence for the Chagas hypothesis is circumscribed to correlative medical diagnoses and a couple of notes in Darwin's diary. In the absence of forensic analyses, no evidence can conclusively support or reject the hypothesis that Charles Darwin suffered from Chagas disease. However, the novel ecological and epidemiological evidence presented here provides a contextual scenario that strongly suggests that during his overland trips, Darwin was sufficiently exposed to wild and domestic Chagas vectors to have contracted the disease. This new correlative evidence provides additional support for the Chagas disease hypothesis proposed almost 50 years ago.

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Authors' contributions
CB-M and RM conceived the study, collected the information, drafted the manuscript, and approved the final manuscript.

Declarations

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Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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