Manuscript
Click here to view linked References

Scrub typhus: a new cause of acute undifferentiated febrile illness in Latin America?

Carlos Ramiro Silva-Ramos[a], Fernando de Castro Jacinavicius[b], Thomas Weitzel[c,d,*], David H. Walker[e], Álvaro A. Faccini-Martínez[e,f,**]

[a] Grupo de Enfermedades Infecciosas, Departamento de Microbiología, Facultad de Ciencias, Pontificia Universidad Javeriana, Bogotá, Colombia.

[b] Laboratório de Coleções Zoológicas, Instituto Butantan, São Paulo, Brazil.

[c] Laboratorio Clínico, Clínica Alemana de Santiago, Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

[d] Instituto de Ciencias e Innovación en Medicina (ICIM), Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile.

[e] Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA.

[f] Committee of Tropical Medicine, Zoonoses and Travel Medicine, Asociación Colombiana de Infectología, Bogotá, Colombia.

Corresponding authors:

** Department of Pathology, University of Texas Medical Branch, University Blvd., Galveston, TX 77555-0609, USA. Tel: +14093927432. E-mail address: afaccini@gmail.com, alfaccin@utmb.edu (Á.A. Faccini-Martínez)

or:

* Clínica Alemana, Av. Vitacura 5951, Santiago, Chile. Tel: +56222101111. E-mail address: tweitzel@alemana.cl (T. Weitzel)

Keywords: Scrub typhus, *Orientia*, Latin America, fever, travel

Classical scrub typhus or tsutsugamushi disease, caused by rickettsial bacteria of the species *Orientia tsutsugamushi*, is a re-emerging vector-borne infectious disease that affects more than one million people annually in the Asia-Pacific region, where it is an important cause of treatable undifferentiated febrile illness [1]. However, if confused with other etiologies and not adequately treated, case fatality rises significantly and reaches a mean value of 6%, but rates up to 70% have been reported [2].

Scrub typhus in countries of Asia, islands of the western Pacific and northern Australia is transmitted by the larval stage of trombiculid mites, known as chiggers, mainly different species of *Leptotrombidium*. Chiggers also serve as the reservoir of the pathogen, maintaining *O. tsutsugamushi* through transstadial and transovarial transmission [1]. Outdoor activities, which predispose humans to be attacked by chiggers (e.g., land clearing, logging, eco-tourism, military operations, rice farming, collecting firewood), are recognized as risk factors for infection. Historically, endemic regions of scrub typhus, the so-called "tsutsugamushi triangle," range from southeastern Siberia in the North, the Kamchatka Peninsula in the East, and Pakistan in the West, to the northern Australia in the South [1].

Clinically, scrub typhus is one of the eschar-associated rickettsioses. After the painless chigger bite, a necrotic eschar forms at the inoculation site, containing high bacterial loads that spread regionally through lymphatic vessels and systemically via blood vessels. Shortly after, generalized infection of endothelial cells causes systemic manifestations such as fever, rash, and a variety of non-specific symptoms (e.g., headache, myalgia, night sweats), which are accompanied by alterations of laboratory parameters such as elevation of C-reactive protein and liver enzymes [1]. Severe cases develop respiratory, neurological, and cardiovascular damage.

Until very recently, *O. tsutsugamushi* was considered the exclusive member of the *Orientia* genus. However, the global epidemiology of this and possible other *Orientia* species remained uncertain due to the lack of studies and insufficient scientific interest in the disease and its vectors [3,4]. The existence of scrub typhus outside the tsutsugamushi triangle was initially suggested 70 years ago by a study that reported antibody and skin reactivity to *O. tsutsugamushi* antigens in febrile patients and healthy controls from Rwanda [5]. Further serological evidence derived from three case reports of travelers suffering from scrub typhus after returning from trips to Africa (Republic of Congo, Cameroon, and Tanzania) and serosurveys in East Africa (Kenya, Djibouti) and West Africa (Sao Tome and Principe) [5,6]. Recent molecular studies detected DNA of *Orientia* spp. or closely related bacteria in rodent tissue samples (Senegal), blood from a healthy dog (South Africa), and chigger mites (Kenya) [5]. In 2006, the first molecularly confirmed scrub typhus case outside the tsutsugamushi triangle was diagnosed in a traveler who visited Dubai (United Arab Emirates). The infection was caused by a new species, *Candidatus* Orientia chuto [7]; nevertheless, no further cases have been detected in this region.

However, the most significant epidemiological novelty related to scrub typhus came from South America, where in 2011, the disease was first suspected in a biologist, who returned from fieldwork on Chiloé Island, southern Chile [8]. In the following years, scrub typhus was diagnosed in various island inhabitants, confirming the first autochthonous focus of the infection outside Asia-Pacific [9]. Since then, further scrub typhus cases were detected in various other regions of continental Chile (Los Lagos, Aysén, and Bio Bio) [10], recently extending southwards into subantarctic latitudes [11]. The clinical presentation of scrub typhus in Chile is similar to the disease in Asia-Pacific. Almost all patients present with fever accompanied by cutaneous manifestations (maculopapular rash and eschar) as well as chills, headache, myalgia, and night sweats [12]. In contrast to the experiences from Asia-Pacific, scrub typhus in Chile frequently affects travelers [13]. Phylogenetic analyses demonstrated that the infection in Chile is caused by a novel *Orientia* species, *Candidatus* Orientia chiloensis [14]. In addition, a newly identified chigger mite species, *Herpetacarus* (*Abonnencia*) *eloisae*, collected from rodents on Chiloé Island, was found infected with *Orientia* spp., suggesting its possible role as vector [15,16].

Although studies on scrub typhus in the Americas mainly derive from Chile, this rickettsiosis might also occur in other Latin American countries. A retrospective study among febrile patients in the Peruvian Amazon (Loreto Department) provided the first serological evidence of exposure to *Orientia* species in tropical South America. Although the seroprevalence was low (5.3%) and molecular evidence was not found, one febrile patient, stationed in a rural military camp near Iquitos, showed IgG seroconversion to *Orientia* spp. [17]. An even broader distribution of *Orientia* pathogens was suggested by a recent study in Central America, demonstrating a seroreactivity rate of 5.6% (including 4.3% seroconversion) to *O. tsutsugamushi* antigens among military personnel returning from long-term deployment to Honduras [18].

Our knowledge of trombiculid mites in Latin America, including the presumed vectors of scrub typhus, is scarce and fragmentary. The countries that are best sampled are those in which there were expeditions to discover the local fauna, such as Venezuela [19] and Panama [20], as well as those that have or had experts in the taxonomy of chiggers, such as Mexico [21] and Brazil [23]. Furthermore, species diversity and exact taxonomy are uncertain since many species are only known from the type series. Therefore, many questions on the Neotropical chigger fauna, host associations, and vector competence are unanswered. Clinical cases of human chigger bite reactions (trombiculiasis) have been reported from different Latin American countries, but mostly without correct identification of the involved species [23-28]. Only *Apolonia tigipioensis* and *Eutrombicula* spp. have been identified parasitizing humans in South America [29-32], while *Herpetacarus* spp., the proposed vector of scrub typhus in Chile, was exclusively collected from small mammals [16,33]. However, recent findings from Chile suggest that members of this genus are anthropophilic, strengthening their probable role as vector (M.C. Silva-de la Fuente and T. Weitzel, unpublished observations).

In many low- and middle-income countries, causes of febrile disease are incompletely understood [34]. The recent discovery of a new *Orientia* species causing scrub typhus in Chile and serological evidence in Peru and Honduras suggest that *Orientia* spp. should be considered a possible etiology of febrile illness in Latin America especially in rural populations and travelers with nature contact. This paradigm shift regarding scrub typhus - formerly a geographically limited disease in Asia-Pacific, now more widespread including Latin America - will probably expand to regions in Africa and the Middle East [35]. Further studies are necessary to understand the global epidemiology of *Orientia* and other neglected *Rickettsia* species and their vectors. In the meantime, physicians should maintain a high level of clinical awareness and include scrub typhus in the differential diagnosis of febrile patients, including travelers, even if they were exposed in countries that are not known to be endemic.

Funding

This work was supported by FAPESP under code 2019/19853-0 to FCJ, the Agencia Nacional de Investigacion y Desarrollo (FONDECYT Regular N° 1170810) to TW, a National Institutes of Health Fogarty International Center training grant to DHW, and a Fogarty fellowship grant (N° 2D43TW010331) to ÁAFM.

CRediT authorship contribution statement

C. R. Silva-Ramos and Á. A. Faccini-Martínez wrote the draft manuscript; F. C. Jacinavicius, Á. A. Faccini-Martínez and T. Weitzel wrote the original manuscript; all authors critically reviewed the manuscript for relevant intellectual content; all authors have read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that the manuscript was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Kim IS, Walker DH. Scrub typhus. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical infectious diseases: principles, pathogens and practice. 3rd ed. New York: Elsevier; 2011, p. 334-8.

2. Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (*Orientia tsutsugamushi*). PLoS Negl Trop Dis 2015;9:e0003971.

3. Weitzel T, Makepeace BL, Elliott I, Chaisiri K, Richards AL, Newton PN. Marginalized mites: Neglected vectors of neglected diseases. PLoS Negl Trop Dis 2020;14:e0008297.

4. Salje J, Weitzel T, Newton PN, Varghese GM, Day N. Rickettsial infections: A blind spot in our view of neglected tropical diseases. PLoS Negl Trop Dis 2021;15:e0009353.

5. Richards AL, Jiang J. Scrub typhus: Historic perspective and current status of the worldwide presence of *Orientia* species. Trop Med Infect Dis 2020;5:49.

6. Yen TY, Zhang Z, Chao CC, Ching WM, Shu PY, Tseng LF, et al. Serologic evidence for *Orientia* exposure in the Democratic Republic of Sao Tome and Principe. Vector Borne Zoonotic Dis 2019;19:821-7.

7. Izzard L, Fuller A, Blacksell SD, Paris DH, Richards AL, Aukkanit N, et al. Isolation of a novel *Orientia* species (*O. chuto* sp. nov.) from a patient infected in Dubai. J Clin Microbiol 2010;48:4404-9.

8. Balcells ME, Rabagliati R, García P, Poggi H, Oddó D, Concha M, et al. Endemic scrub typhus-like illness, Chile. Emerg Infect Dis 2011;17:1659-63.

9. Weitzel T, Dittrich S, López J, Phuklia W, Martinez-Valdebenito C, Velásquez K, et al. Endemic scrub typhus in South America. N Engl J Med 2016;375:954-61.

10. Weitzel T, Martínez-Valdebenito C, Acosta-Jamett G, Jiang J, Richards AL, Abarca K. Scrub typhus in continental Chile, 2016-2018. Emerg Infect Dis 2019;25:1214-7.

11. Weitzel T, Aylwin M, Martínez-Valdebenito C, Acosta-Jamett G, Abarca K. Scrub typhus in Tierra del Fuego: a tropical rickettsiosis in a subantarctic region. Clin Microbiol Infect 2020;27:793-4.

12. Abarca K, Weitzel T, Martínez-Valdebenito C, Acosta-Jamett G. Tifus de los matorrales, una enfermedad emergente en Chile. Rev Chilena Infectol 2018;35:696-9.

13. Weitzel T, Acosta-Jamett G, Martínez-Valdebenito C, Richards AL, Grobusch MP, Abarca K. Scrub typhus risk in travelers to southern Chile. Travel Med Infect Dis 2019;29:78-9.

14. Abarca K, Martínez-Valdebenito C, Angulo J, Jiang J, Farris CM, Richards AL, et al. Molecular description of a novel *Orientia* species causing scrub typhus in Chile. Emerg Infect Dis 2020;26:2148-56.

15. Acosta-Jamett G, Martínez-Valdebenito C, Beltrami E, Silva-de La Fuente MC, Jiang J, Richards AL, et al. Identification of trombiculid mites (Acari: Trombiculidae) on rodents from Chiloé Island and molecular evidence of infection with *Orientia* species. PLoS Negl Trop Dis 2020;14:e0007619.

16. Silva-de la Fuente MC, Stekolnikov AA, Weitzel T, Beltrami E, Martínez-Valdebenito C, Abarca K, et al. Chigger mites (Acariformes: Trombiculidae) of Chiloé Island, Chile, with descriptions of two new species and new data on the genus *Herpetacarus*. J Med Entomol 2021;58:646-57.

17. Kocher C, Jiang J, Morrison AC, Castillo R, Leguia M, Loyola S, et al. Serologic evidence of scrub typhus in the Peruvian Amazon. Emerg Infect Dis 2017;23:1389-91.

18. Chao CC, Zhang Z, Belinskaya T, Chen HW, Ching WM. Leptospirosis and rickettsial diseases sero-conversion surveillance among U.S. military personnel in Honduras. Mil Med 2021;usab120.

19. Brennan JM, Reed JT. A list of Venezuela chiggers, particularly of small mammalian hosts (Acarina: Trombiculidae). Brigham Young University Science Bulletin. 1975;20:45-75.

20. Brennan, JM, Yunker CE. The chiggers of Panama (Acarina: Trombiculidae). In: Wenzel RL, Tipton VJ editors. Ectoparasites of Panama. Chicago: Field Museum of Natural History. 1966; pp. 221–266.

21. Hoffmann A. Los trombicúlidos de Mexico (Acarida: Trombiculidae) Vol. 2. Universidad Nacional Autonoma de Mexico; 1990.

22. Jacinavicius FC, Bassini-Silva R, Mendoza-Roldan JA, Pepato AR, Ochoa R, Welbourn C, et al. A checklist of chiggers from Brazil, including new records (Acari: Trombidiformes: Trombiculidae and Leeuwenhoekiidae). Zookeys. 2018;743:1-41.

23. Chaccour CJ. Trombiculiasis: reporte de dos casos y revisión de la literatura. Dermatología Venezolana. 2005;43:18-21.

24. Tweeten KA, Muñoz-Bravo J. Qhapa, a pest causing skin irritations in Nor Yungas region of Bolivia, identified as a chigger mite, Eutrombicula batatas. Trop Doct 2008;38:63-4.

25. Beltrán M, Valdivia C, Ponce-Ramírez R, Chambergo M. *Trombicula autumnalis* (Isangos) en un jardín de niños de la selva peruana. Rev Peru Med Exp Salud Publica. 2009;26:58-60.

26. Martens H, de Mendonça Melo M, van den Bosch W, van Genderen PJ. A 'chigsaw' puzzle after a vacation in Brazil. Neth J Med 2012;70:321-5.

27. Eitrem R, Jaenson TG. Ihållande klåda orsakades av tropiskt löpkvalster. I Sverige okänt fenomen drabbade Brasilienresenär [Persistent pruritus caused by tropical chiggers. Trip to Brazil caused a phenomenon unknown in Sweden]. Lakartidningen. 2012;109:2358-9.

28. Bronshteyn AM, Kochergin NG, Malyshev NA, Konstantinov OK, Davydova IV, Burova SV. Trombikuliaz vs trombikuliaznyi dermatit u rossiiskikh turistov, posetivshikh tropicheskie strany [Trombiculiasis in Russian tourists travelled to tropical countries]. Epidemiologiya i infektsionnye bolezni. 2016;21:43-50.

29. Wharton GW, Fuller HS. A manual of the chiggers: The biology, classification, distribution and importance to man of the larvae of the family Trombiculidae (Acarina) Vol. 4. Memoirs of the Entomology Society of Washington; 1952.

30. Faccini JL, Santos AC, Santos SB, Jacinavicius FC, Bassini-Silva R, Barros-Battesti DM. Trombiculiasis in domestic goats and humans in the state of Maranhão, Brazil. Rev Bras Parasitol Vet 2017;26:104-9.

31. Bassini-Silva R, Jacinavicius FC, Muñoz-Leal S, Maturano R, Welbourn C, Ochoa R, et al. A new species of the genus *Eutrombicula* Ewing, 1938 (Trombidiformes: Trombiculidae) and new records for the species *Eutrombicula batatas* (Linnaeus, 1758) in Brazil. Acarologia. 2018;58:976-86.

32. Bassini-Silva R, Jacinavicius FC, Welbourn C, Ochoa R, Barros Battesti DM. Redescription of *Apolonia tigipioensis* Torres and Braga, 1938 (Trombidiformes: Leeuwenhoekiidae), Acarina. 2018;26:197-204.

33. Jacinavicius FC, Huang-Bastos M, Welbourn C, Ochoa R, Barros-Battesti DM, Bassini-Silva R. Contribution to the taxonomy and host-relations of the genus *Serratacarus* (Trombidiformes: Trombiculidae). J Med Entomol 2021;tjab041.

34. Prasad N, Murdoch DR, Reyburn H, Crump JA. Etiology of severe febrile illness in low- and middle-income countries: A systematic review. PLoS One. 2015;10:e0127962.

35. Walker DH. Scrub typhus - Scientific neglect, ever-widening impact. N Engl J Med 2016;375:913-5.