

# Zoonotic febrile illnesses misdiagnosed as COVID-19: a review of reported clinical cases

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## SUMMARY

COVID-19 is a zoonotic coronavirus disease caused by SARS-CoV-2. Its fast spreading by aerosol transmission has made it a highly contagious disease, causing the most recent 2020 pandemic. Although it mainly affects the respiratory system, atypical forms of the disease have been described, including developing an undifferentiated febrile illness without respiratory symptoms, that can represent a diagnostic challenge, mainly in tropical areas where several zoonotic febrile diseases are circulating. Thus, despite the broad clinical spectrum of COVID-19, in the tropics, other zoonotic etiologies should always be considered as differential diagnoses. According to our case reports review, eight different zoonotic febrile diseases misdiag-

nosed as COVID-19 have been reported in the available scientific literature of four databases. These were only suspected due to the epidemiological history. Thus, making a complete and detailed clinical history of a febrile patient in the tropics is essential to suspect the etiology and request the necessary confirmatory tests. Therefore, COVID-19 must be included as a differential diagnosis of undifferentiated febrile illness in the tropics, but other zoonotic infectious diseases must not be ruled out.

**Keywords:** *Anaplasma*, *Babesia*, *Borrelia*, COVID-19, Crimean-Congo virus, Febrile illness, Hantavirus, *Lep-tospira*, *Rickettsia*, Zoonoses.

## INTRODUCTION

In December 2019, several patients with pneumonia of unknown origin were reported in Wuhan province, Hubei, China, and sequencing analysis indicated a novel coronavirus which was designated as “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” [1-3].

SARS-CoV-2 (Coronaviridae family, *Betacoronavirus* genus) is a positive single-stranded RNA virus and the causative agent of coronavirus disease of 2019 (COVID-19), which has become the third highly pathogenic human disease due to zoonotic coronaviruses; its faster spreading has made COVID-19 a highly contagious disease and the cause of the recent 2020 pandemic which has become the most critical global health problem in the last century that is still affecting several countries worldwide [4-7].

SARS-CoV-2 is mainly spread by aerosol transmission. It reaches up to the upper airway infecting epithelial cells, where it multiplies and then

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disseminates to the lower airway affecting the lungs [8]. In approximately 80% of patients, a mild self-limited disease involving only the upper respiratory tract is developed [8]. However, in the remaining 20%, a severe form occurs in which viruses infect the alveolar cells, causing inflammation and apoptosis which damage the lung parenchyma, causing pneumonia which progress to acute respiratory distress syndrome that can be life-threatening due to respiratory failure [8].

During the early months of the COVID-19 pandemic, almost every country worldwide adapted the case definition provided by World Health Organization (WHO) to their specific circumstances, observing a significant heterogeneity in COVID-19 case definition [9]. The most current case definition provided by WHO was updated on July 22, 2022, in which suspected, probable, and confirmed cases were established (available in WHO/2019-nCoV/Surveillance\_Case\_Definition/2022.1).

Clinically, COVID-19 is not specific, it has not a pathognomonic clinical manifestation that differentiates it from other respiratory infectious diseases [9, 10]. Several COVID-19 clinical presentations have been described, being classified as atypical forms which require a high level of clinical suspicion [11]. One of these is the development as an undifferentiated febrile illness without respiratory symptoms; the development of COVID-19 as a febrile illness in tropical areas may mimic several etiologies of tropical febrile diseases, most zoonotic [12, 13].

The present review aims to evidence cases of zoonotic tropical febrile illnesses misdiagnosed as COVID-19 to understand that SARS-CoV-2 infection overlaps several underrated etiologies of zoonotic tropical febrile diseases.

## ■ MATERIALS AND METHODS

We conducted a comprehensive literature research using PubMed MEDLINE, EMBASE, Scopus and BVS in order to identify studies on zoonotic febrile illnesses misdiagnosed as COVID-19. We used the terms “misdiagnosis”, “COVID-19,” and “febrile”. Of all the scientific publications available from the research performed, we chose the studies in which there were case reports of a zoonotic febrile illness initially misdiagnosed as COVID-19.

## ■ REPORTED CASES OF MISDIAGNOSED ZOO NOTIC FEBRILE ILLNESSES

A search for case reports due to zoonotic febrile diseases which were initially misdiagnosed as COVID-19 was done from January 1<sup>st</sup>, 2020, until December 31<sup>st</sup>, 2022, and a total of eighteen case reports were found in four scientific literature databases (PubMed MEDLINE, Embase, Scopus, BVS) (Table 1).

**Case No. 1.** In Rheinfelden, Germany, a 35-year-old patient, a chronic smoker, who worked as a nurse, attended medical consultation due to fever, sore throat, and cough. He was clinically diagnosed with COVID-19, and supportive therapy was prescribed. Two days later, recurrent fever and generalized body aches developed. SARS-CoV-2 PCR was performed with negative results. The patient’s general condition deteriorated with tachycardia, jaundice, and severe myalgia. Laboratory parameters were consistent with acute liver and kidney failure, thrombocytopenia and leukocytosis were also evidenced. An abdominal ultrasound evidenced intrahepatic cholestasis, and choledocholithiasis was ruled out. Viral hepatitis serology was also performed, which gave negative results, and *Leptospira* serology resulted in positive outcomes. Fluid replacement and ceftriaxone were prescribed, and the patient significantly improved. The gardening practice was a presumptive risk factor [14].

**Case No. 2.** In Southern California, United States of America (USA), a 25-year-old febrile patient with headache, myalgia, chills, and other non-specific clinical manifestations was initially diagnosed with a viral syndrome and was tested multiple times for COVID-19. Ibuprofen, acetaminophen, ceftriaxone, and azithromycin were given, but the patient did not improve. After two weeks of symptomatology, murine typhus was suspected due to a history of working as a dog trainer. Serology evidenced titers above 1:256, for which doxycycline was given, and the patient finally recovered [15].

**Cases No. 3-8.** Six pediatric cases (ages 9 to 14) suspected of multisystem inflammatory syndrome due to SARS-CoV-2 were attended in Houston, Texas, USA. Serology and PCR for SARS-CoV-2

**Table 1 - Data on case reports of zoonotic febrile illnesses misdiagnosed as COVID-19.**

<i>Reference</i>	<i>Case</i>	<i>Age (gender)</i>	<i>Origin</i>	<i>Diagnosis</i>	<i>Clinical manifestations</i>	<i>Laboratory parameters</i>	<i>Treatment</i>	<i>Outcome</i>
Vogel N et al. 2020 [14]	1	35 (M)	Germany	Leptospirosis	Fever, cough, sore throat, body ache, tachycardia, jaundice, myalgia	Thrombocytopenia, leukocytosis, hypoalbuminemia, ↑Cr, ↑Urea, ↑uric acid, ↑AST, ↑ALT, ↑GGT; ↑TBil, ↑DBil,	Hydration, ceftriaxone	Recovered
Patel HM 2020 [15]	2	25 (M)	United States	Murine typhus	Fever, headache, myalgia, chills, vomiting, diarrhea, cough, congestion, fatigue, dizziness, back pain, tachycardia, body aches	Bandemia, lymphopenia, ↑ESR	Doxycycline	Recovered
Alamarat Z 2020 [16]	3 to 8	9, 11, 11, 13, 13, 14*	United States (6/6)	Murine typhus (6/6)	Fever (6/6), tachycardia (6/6), tachypnea (6/6), rash (6/6), myalgia (5/6), cough (5/6), abdominal pain (5/6), sore throat (4/6), vomiting (4/6), diarrhea (1/6), fatigue (1/6)	↑AST (6/6), ↑ALT (6/6), ↑LDH (6/6), ↑Ferritin (6/6), ↑D-dimer (6/6), ↑CRP (6/6), ↑Procalcitonin (6/6), leucopenia (3/6), neutrophilia (3/6), thrombocytopenia (3/6), lymphopenia (2/6)	Doxycycline (4/6) None (2/6)	Recovered (6/6)
Wormser GP et al. 2021 [17]	9	36 (M)	United States	Lyme borreliosis and Babesiosis	Fever, erythematous skin lesion, myalgia, stiff neck, fatigue, low back pain, paresthesias, right knee swelling, inability to concentrate, lightheadedness, palpitations, dyspnea, bradycardia, heart block	ND	Ceftriaxone, doxycycline	Recovered
Wormser GP et al. 2021 [17]	10	69 (F)	United States	Babesiosis	Fever, weakness, anorexia	ND	Azithromycin, atovaquone	Recovered
Wormser GP et al. 2021 [17]	11	56 (M)	United States	Human granulocytic anaplasmosis	Fever, rigors, headaches, joint pain	ND	None	Recovered

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Reference	Case	Age (gender)	Origin	Diagnosis	Clinical manifestations	Laboratory parameters	Treatment	Outcome
Tendulkar P et al. 2021 [18]	12	23 (M)	India	Leptospirosis	Fever, shortness of breath, yellowish expectoration, loose stools, tachypnea, respiratory failure	Leukocytosis, neutrophilia, lymphopenia, ↑Urea, ↑Cr, ↑TBil, ↑DBil, ↑AST, ↑ALT, ↑ALP, ↑GGT	Doxycycline	Deceased
Cetin S and Sahin AM 2021 [19]	13	57 (M)	Turkey	Hantavirus infection	Fever, fatigue, hyporexia, myalgia, arthralgia, tachycardia, oliguria	Leukocytosis, thrombocytopenia, ↑Urea, ↑Cr, ↑CRP, ↑D-dimer, ↑Ferritin, ↑AST	Hydration, Supportive therapy	Recovered
de Lemos ERS et al. 2022 [20]	14	24 (M)	Brazil	Hantavirus Cardiopulmonary Syndrome	Fever, headache, dry cough, diarrhea, hyporexia, respiratory discomfort, dry cough, hemoptysis, tachycardia, prostration, nausea, vomiting, dyspnea	Normal WBC with left shift, bandemia, thrombocytopenia, ↑AST, ↑ALT	Oxygen therapy, amoxicillin/ clavulanic acid, oseltamivir	Deceased
Mardani M et al. 2022 [21]	15	41 (M)	Iran	Crimean-Congo hemorrhagic fever	Fever, myalgia, malaise, coffee ground vomitus, melena,	Thrombocytopenia, ↑PTT, ↑AST, ↑ALT, ↑Ferritin, ↑LDH, ↑D-dimer, ↑CRP	Ribavirin	Recovered
Turmel JM et al. 2022 [22]	16	83 (F)	Martinique	Leptospirosis	Fever, dyspnea, myalgia, arthralgia, diarrhea	Lymphopenia, thrombocytopenia, ↑Cr, ↑BUN, ↑CRP, ↑AST, ↑ALT	Amoxicilin, steroid therapy	Recovered
Elçi H and Orhan Ö 2022 [23]	17	3 (M)	Turkey	Leptospirosis	Fever, cough, weakness, abdominal pain, tachycardia, tachypnea	Thrombocytopenia, ↑CRP	Hydration, cefotaxime, doxycycline	Recovered
Barbina S et al. 2022 [24]	18	72 (F)	United States	Spotted fever group rickettsiosis	Fever, myalgia, fatigue, dry cough, nausea, hyporexia, headache, oral lesions, non-pruritic rash, arthralgia, mental fogginess, myodesopsia, blurry vision	Hyponatremia, ↑AST, ↑ALT, ↑CRP,	Doxycycline	Recovered

\* No data regarding genre was available.

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Cr: Creatinine; CRP: C-reactive protein; DBil: Direct bilirubin; F: Female; GGT: Gamma-glutamyl transferase; M: Male; PTT: Partial thromboplastin time; TBil: Total bilirubin.

were negative in all six cases. Clinical manifestations included fever (6/6), tachycardia (6/6), tachypnea (6/6), rash (6/6) (maculopapular [1/6], macular [3/6], papular [2/6]), myalgia (5/6), cough (5/6), abdominal pain (5/6), sore throat (4/6), vomiting (4/6), diarrhea (1/6) and fatigue (1/6). Regarding laboratory parameters, liver enzymes, lactate dehydrogenase, ferritin, D-dimer, C-reactive protein, and procalcitonin were elevated in all cases; leucopenia, neutrophilia, and thrombocytopenia were evidenced in three cases, and lymphopenia was evidenced in two cases. All patients had previous exposure to dogs; in two of them, canine flea infestation was reported; thus, murine typhus was suspected. Doxycycline was prescribed only in four cases, but all had a complete clinical resolution. A first serology was performed, and anti-*Rickettsia typhi* IgM was evidenced in all cases, and anti-*R. typhi* IgG was evidenced in five of them. Convalescent serum was obtained in four patients, showing in all cases an increase in the titers of anti-*R. typhi* IgM/IgG, reinforcing the diagnosis of murine typhus in all cases [16].

**Case No. 9.** A 36-year-old patient from Westchester County, New York state, USA, with an erythematous skin lesion, was initially diagnosed with cellulitis, and cephalexin was administered. Although skin lesions resolved, the patient developed fever with multiple non-specific symptoms, for which SARS-CoV-2 PCR was requested with negative results. In the following days, bradycardia and partial heart block also developed, and the patient was hospitalized with a presumptive diagnosis of Lyme carditis. IgG and IgM immunoblots were performed, both evidencing antibodies against *Borrelia burgdorferi*. Ceftriaxone and doxycycline were administered, and the patient completely improved. Also, a *Babesia microti* PCR was done in a blood sample which came out positive, and although babesiosis was not treated, it resolved without antiparasitic drugs [17].

**Case No. 10.** In Westchester County, New York state, USA, a 69-year-old febrile patient with weakness, anorexia, and a history of tick bites was initially evaluated for COVID-19 by a SARS-CoV-2 PCR which came out as negative fourteen days later. After, a blood smear and a blood PCR showed positive results for *B. microti*. Lyme bor-

reliosis and *Anaplasma phagocytophilum* were also evaluated, but both resulted negative. Azithromycin and atovaquone were administered, after which symptoms were resolved [17].

**Case No. 11.** In Westchester County, New York state, USA, a 56-year-old patient with a tick bite history presented with fever, rigors, headaches, and joint pains and was evaluated twice for SARS-CoV-2 PCR, both of them negative. An *A. phagocytophilum* PCR was performed on a blood sample, which came out as positive, as well as positive IgG (titers of 1:320) and IgM (titers >1:256) antibodies against *A. phagocytophilum*. No antibiotic treatment was administered, but the patient improved and resolved the disease [17].

**Case No. 12.** In Rishikesh, India, a 23-year-old patient, a chronic smoker with a history of farming activity, presented with fever, shortness of breath, yellow expectoration, loose stools, and an oxygen saturation of 62% was initially diagnosed with COVID-19 pneumonia. Dexamethasone and other supportive measures were given, however, SARS-CoV-2 PCR and serology tests were negative multiple times. Tachypnea and respiratory failure were established in the following days of hospitalization. Laboratory parameters showed a direct hyperbilirubinemia, and *Leptospira* enzyme-linked immunoassay (ELISA) IgM and hepatitis A, B, C, and E serology were requested, being all hepatitis tests negative. Doxycycline was administered, but the clinical condition worsened, and the patient died during the hospital stay. After, the *Leptospira* IgM test came out, showing positive results, which were more than twice the normal value [18].

**Case No. 13.** In Giresun, Turkey, a 57-year-old man with a history of contact with a COVID-19 case presented with fever, fatigue, hyporexia, myalgia, arthralgia, tachycardia, and COVID-19 was presumed. Laboratory parameters showed thrombocytopenia and an elevation of urea, creatinine, C-reactive protein, D-dimer, ferritin, and aspartate aminotransferase. Hydration, moxifloxacin, and favipiravir were prescribed. SARS-CoV-2 PCR was performed twice, giving negative results. Urea and creatinine values increased more, and there also was a decrease in urine output. Due to this, thrombocytopenia, and considering the geographic region, Hantavirus IgM/IgG was request-



ed, which gave positive results using indirect immunofluorescence assay. Hydration and supportive treatment were administered, and the patient recovered [19].

**Case No. 14.** In Bento Gonçalves, Rio Grande do Sul state, Brazil, a 24-year-old patient presented with fever, headache, dry cough, diarrhea, and hyporexia two weeks after travel to Paraná and Santa Catarina, which was initially diagnosed as influenza-like syndrome receiving anti-inflammatory and analgesic drugs. The following day respiratory discomfort, dry cough with blood, tachycardia, prostration, nausea, vomiting, and dyspnea were developed, with an oxygen saturation of 90%. Laboratory parameters showed a left shift with normal white blood cell count, thrombocytopenia, and elevated liver enzymes. Binasal cannula oxygen therapy, amoxicillin/clavulanic acid, and oseltamivir were prescribed. However, the patient progressed to respiratory failure requiring mechanical ventilation in an intensive care unit suspected of COVID-19, and a day later, the patient died. SARS-CoV-2 PCR gave negative results, and dengue and influenza were also ruled out. A relative said that the patient visited an abandoned warehouse during the trip, raising suspicion of hantavirus cardiopulmonary syndrome for which a PCR to orthohantavirus was performed, showing positive results [20].

**Case No. 15.** In Tehran, Iran, a 41-year-old man with a history of fever, myalgia, malaise, coffee ground vomitus, and melena was previously managed as a COVID-19 case with conservative measures, but he did not improve. The only relevant epidemiological history was a recent travel to Karbala, Iraq. Laboratory parameters showed thrombocytopenia, prolonged partial thromboplastin time, elevated liver enzymes, ferritin level, and lactate dehydrogenase. Hepatitis A, B, C, and cytomegalovirus were investigated, but all tests were negative. Due to the recent travel and the clinical and laboratory results, Crimean-Congo hemorrhagic fever (CCHF) was evaluated, and ribavirin therapy was started. Both ELISA IgG/IgM antibodies and PCR against the CCHF virus were positive. PCRs for SARS-CoV-2, influenza A, and B viruses were also performed, all negative. The patient improved and was discharged without symptoms [21].

**Case No. 16.** In Martinique island, a French overseas department, an 83-year-old patient with fever, dyspnea, myalgia, arthralgia, diarrhea, and an oxygen saturation of 88% was diagnosed as severe COVID-19 pneumonia with a “false negative” SARS-CoV-2 PCR. Laboratory parameters showed lymphopenia, thrombocytopenia, elevated creatinine levels, blood urea nitrogen, C-reactive protein, and liver enzymes. Other respiratory pathogens, including influenza, respiratory syncytial, metapneumovirus, rhinovirus, and *Legionella pneumophila*, were investigated, all being negative and dengue virus tests. The following day, his respiratory condition worsened, requiring an intensive care unit with oxygen and corticoid therapy. Novel SARS-CoV-2 PCRs were performed twice, and an IgG/IgM serology anti-SARS-CoV-2 was all negative. Two days later, the patient improved and left the intensive care unit, and a novel anti-SARS-CoV-2 IgG/IgM serology was also performed, being negative. Due to the endemicity on the island, leptospirosis was suspected; ELISA IgM anti-*Leptospira* was performed, showing positive results with a titer of 1/6400; microagglutination and PCR tests were also performed, but both were negative. Due to the seropositive result, a new PCR was performed retrospectively on a sample taken days before, which turned out to be positive, and a diagnosis of pulmonary leptospirosis was made. The patient has also reported contact with rats present in the garden. Although the patient showed clinical improvement, amoxicillin was prescribed, and steroid therapy continued showing continuous improvement [22].

**Case No. 17.** In Mardin, Turkey, a 3-year-old male patient was attended with fever, cough, weakness, and abdominal pain. Laboratory parameters showed mild thrombocytopenia and elevated C-reactive protein. Due to a history of domestic contact, he was suspected of COVID-19, and hydration and cefotaxime were prescribed. After it was reported that the patient’s family lived in a village and worked as farmers, leptospirosis was considered, and doxycycline was administered. *Leptospira* PCR was ordered, which showed positive results. SARS-CoV-2 PCR was also performed twice, both negative. The patient improved and was discharged [23].

**Case No. 18.** In Charleston city, South Carolina, USA, a 72-year-old febrile patient accompanied by myalgia, fatigue, and dry cough was initially clinically diagnosed with influenza after a negative COVID-19 test. Supportive measures and oseltamivir were recommended, but several days later, the patient remained febrile, and nausea, hyporexia, headache, two painful oral lesions, and a non-pruritic diffuse rash developed. The patient lived in an urban coastal region of South Carolina, USA, and owned a dog that often roams the backyard. Laboratory parameters showed hyponatremia and elevated liver enzymes. Another COVID-19 test was performed, as well as influenza and herpes simplex tests, all negative. The patient was diagnosed with unspecific viral illness plus dehydration, for which intravenous fluids and hydrochlorothiazide were administered, and the patient was discharged. The next day, arthralgia was developed, tick-borne illnesses tests were ordered, empiric doxycycline was administered, and the patient began to improve in the following weeks. IgG (1:1024) and IgM (>1:64) antibodies to spotted fever group (SFG) rickettsiae antigens were both positive, giving the diagnosis of SFG rickettsiosis. Two weeks after the onset of symptoms, the patient experienced mental foginess, myodesopsia, and blurry vision, which were compatible with retinal vasculitis due to SFG *Rickettsia* infection. Laboratory parameters normalized, and ocular symptoms improved after antibiotic treatment [24].

## ■ DISCUSSION

Eighteen zoonotic febrile illnesses misdiagnosed as COVID-19 have been found in available scientific databases, between Jan 1, 2020, to Dec 31, 2022. Seven cases of murine typhus, four cases of leptospirosis, two cases of hantavirus infection, and one case of Lyme borreliosis/babesiosis coinfection, babesiosis, anaplasmosis, SFG rickettsiosis, and CCHF.

Murine typhus is a vector-borne infectious disease caused by *R. typhi* that usually develops as a mild non-specific febrile illness [25-27]. Although rodents are the main reservoirs in its classic cycle, opossums have been suggested to be involved in an alternate cycle, and other animal species like cats and dogs might also be playing important eco-epidemiological roles [28-30]. We found seven cases of murine typhus misdiagnosed as COV-

ID-19 [15, 16]. Six of them were pediatric patients, in which has been described that sore throat and gastrointestinal manifestations are more common than the classic triad (fever, rash and headache) [16, 26, 31]. Clinically, all seven patients presented with a non-specific febrile illness. In all of them, the only relevant epidemiological history to suspect murine typhus was contact with dogs, and in two patients, dogs' flea infestation was observed [16]. Although the role of dogs in the eco-epidemiology of murine typhus is still not clear, they could be acting as incidental hosts [30]. Without this antecedent, the non-specific clinical presentation was insufficient to suspect in murine typhus.

Leptospirosis is a rodent-borne infectious disease caused by several pathogenic *Leptospira* spp. Clinically, it is highly variable, ranging from a mild non-specific febrile illness to severe forms like Weil's syndrome [32, 33]. Although kidneys and liver are the primary injured tissues, other organs, like lungs can be affected in 20 to 70% of cases, and most resolve mildly without sequelae [33, 34]. Four cases of leptospirosis misdiagnosed as COVID-19 were found in available scientific literature. All of them developed febrile respiratory illness, which may have led to misdiagnosis; however, in one case [14], jaundice was also developed, which helped to diagnose leptospirosis. In three cases, laboratory parameters included at least two of the following: kidney failure features, liver damage features, and thrombocytopenia, which can also indicate leptospirosis [14, 18, 22, 35]. Contact with rodents or their excreta is the leading risk factor for acquiring the disease; however, other environmental, occupational, and recreational activities may also generate a risk for human infection [36]. In only one of the cases, contact with rodents was reported [22]. Gardening, although it may not have a high association with leptospirosis, in some cases can be the only background, as was reported in one case [14, 37]. The remaining two cases, working as a farmer and living in a farmers' village were the only antecedents that helped to reach the diagnosis of leptospirosis; performing different farming activities have already been reported to be significant risk factors for leptospirosis [18, 22, 38, 39].

Orthohantaviruses are negative-stranded RNA viruses classified into two major groups which cause hemorrhagic fever with renal syndrome (HFRS) or hantavirus cardiopulmonary syndrome [40]. Both

diseases present as non-specific febrile illnesses but develop hemorrhagic and renal or cardiopulmonary signs depending on the infecting virus [41,42]. Two cases of orthohantavirus disease misdiagnosed as COVID-19 were found in the scientific literature and were misdiagnosed as initial clinical presentations were non-specific. In one of the cases, no epidemiological history was reported, and the only finding to reach the diagnosis was the presence of fever, thrombocytopenia, and kidney failure, clinical findings which are considered characteristic features of HFRS in endemic areas [19, 43]. Orthohantaviruses are mainly transmitted to humans by inhaling aerosols contaminated with rodent excreta [44]. In one of the cases, although no contact with rodents was reported, the patient visited an abandoned warehouse, which in high proportion can be infested with rodents and represent a risk for rodent-borne infectious diseases, being this exposure antecedent the only information that helped to reach the diagnosis [20, 45, 46].

Lyme borreliosis is caused by *Borrelia burgdorferi* sensu lato complex. The most common clinical manifestation of early localized phase is erythema migrans, which can resolve even without antibiotic therapy; however, the spreading of the pathogen to other tissues can occur and generate local clinical manifestations [47]. Although in Case No. 9 erythema migrans was present, it was initially misdiagnosed as cellulitis. After, an unspecific febrile illness was developed for which COVID-19 was suspected. However, days after, the patient developed clinical features of Lyme carditis, adding to the fact that the patient came from an endemic area, helped to reach the suspicion of Lyme borreliosis [48, 49]. It is transmitted by *Ixodes* spp. ticks, which other human pathogens can also infect, like *Babesia microti* and *Anaplasma phagocytophilum*; thus, coinfections must be ruled out, which usually present with more evident symptomatology than Lyme borreliosis alone [47, 50]. In the reported case, babesiosis was also diagnosed, possibly contributing to the development of fever and non-specific symptoms [17].

Human babesiosis is caused by six *Babesia* species and two genetic variants [51, 52]. Clinically, it develops as a gradual and intermittent non-specific febrile illness [51]. The disease is usually mild, but severe forms can also occur [53]. In Case No. 10, mild babesiosis was developed, initially misdiagnosed as COVID-19 due to the non-specific symp-

tomatology. The case was notified in the same hospital as Case No. 9, and the only epidemiological background that helped to suspect the disease was the history of tick-bites. Also, other tick-borne etiologies were ruled out considering the endemic area, being *B. microti* the only pathogen detected [50].

Human granulocytic anaplasmosis caused by *A. phagocytophilum*, is often a mild and self-limited non-specific tick-borne febrile illness [54]. Nevertheless, due to its unusual presentation, its diagnosis requires a high suspicion of infection, even in endemic areas [55]. Case No. 11 was also notified in the same institution as Case No. 9 and 10. Initial misdiagnosis as COVID-19 was done due to the non-specific symptomatology. The history of tick bites was also the only crucial epidemiological background to suspect the disease, which was not treated, but clinically it resolved probably to its self-limited evolution.

SFG rickettsioses are a group of tick-borne infectious diseases caused by pathogenic SFG *Rickettsia* species. They develop as non-specific acute febrile illnesses with the presence of rash which has a particular presentation depending on the infecting *Rickettsia* species [25, 56]. Rocky Mountain spotted fever, caused by *R. rickettsii*, is the most important SFG rickettsiosis as it can develop as a severe disease, with a fatality rate as high as 95% [57, 58]. Case No. 18 initially presented as an influenza-like illness for which COVID-19 was first suspected. Rash developed several days later; however, COVID-19 was still considered as rash have also been reported to be associated with SARS-CoV-2 infection [59]. No history of tick exposure was reported; however, the patient lived in an endemic area of SFG rickettsioses, and was an owner of a dog that had a high risk for tick exposure, which represent a significant risk factor for having acquired the disease [60,61]. Although antibodies against *R. rickettsii* antigen were found, these can cross-react with other SFG *Rickettsia* spp., and due to the mild course of the disease, it is likely that other milder *Rickettsia* species present in the region (e.g., *Rickettsia parkeri*) may have been linked to Case No. 18, [62-64]. Further, clinical signs of retinal vasculitis were also developed, which, although not usual, can be linked to rickettsioses and developed as ocular manifestations [65].

Tick-borne CCHF, caused by CCHF orthonairovirus, is one of the most serious infectious diseases which fatality rate is up to 73% [66, 67]. CCHF develops in four phases; during the pre-hemorrhagic



(second) phase, it develops as a non-specific febrile illness; and when hemorrhagic signs appear, they can range from petechial rash to large cutaneous ecchymosis, gastrointestinal and renal bleeding [68, 69]. Case No. 15 was initially misdiagnosed with COVID-19 due to the unspecific presentation of CCHF in its second phase. However, the development of hemorrhagic clinical manifestations and laboratory parameters helped to suspect the disease. The patient has also reported a recent travel to a region from Iraq, an endemic region considered a level 1 risk country in which CCHF cases are reported annually [70].

COVID-19 rapid spread made it an endemic infectious disease in all regions worldwide; thus, its correct diagnosis must be made properly [71]. Lessons from the COVID-19 pandemic showed that the clinical spectrum of the disease is very broad and highly variable, ranging from asymptomatic infections to severe respiratory damage that requires mechanical ventilation and could compromise the patient's life; and other atypical presentations without fever and respiratory symptomatology [10, 72]. Although COVID-19 represents one of the most important diseases nowadays, it must not mask other diseases that may have another type of therapeutic management [73]. Misdiagnosis during the COVID-19 pandemic has become highly frequent; several infectious diseases and chronic non-communicable diseases have been reported to be misdiagnosed with COVID-19, mainly when the clinical presentation had an atypical course [74]. Misdiagnosis occurs mainly with other etiologies that cause respiratory compromise, like several mycoses and bacterial infections, among others; however, it is possible that other non-specific infectious diseases might be misdiagnosed as COVID-19 [75, 76].

In the present manuscript, we analyzed eighteen cases of different zoonotic febrile infectious diseases misdiagnosed as COVID-19 at some stage in the natural course of the disease. Tropical febrile illnesses have a non-specific clinical presentation which includes fever and several influenza-like symptoms; regarding the etiology, they are difficult to distinguish one from another based only on the clinical history and physical examination [77]. COVID-19 has necessarily had to be included in the differential diagnosis of febrile patients in tropical areas as cases of undifferentiated acute febrile illness without clear respiratory symptoms

had already been reported [12]. However, despite the worldwide endemicity of COVID-19, in tropical areas, other zoonotic febrile infectious diseases must always be considered as differential diagnosis and should not be ruled out [13, 78]. Furthermore, forms of COVID-19, like multisystem inflammatory syndrome in children, can be caused by other etiologies, including some tropical febrile illnesses [79].

COVID-19 has become the most popular and important disease in the last few years, however, since its appearance, several diseases have been masked by it. Thus, in many regions, health personnel still consider COVID-19 as the main etiology to rule out during clinical care, however, physicians should always express a judgment of probability, seek confirmation or denial of the suspected disease, and not forget that there are also other pathologies besides those that are the most popular.

## ■ CONCLUSIONS

Although COVID-19 has become one of the etiologies of tropical febrile illnesses, it should not represent the first cause of fever in tropical regions. Other etiologies must be ruled out to avoid misdiagnosis. The development of a complete clinical history, in which all epidemiological backgrounds are detailed, may help the physician to suspect specific causes of febrile illnesses and request all the necessary tests to confirm the suspicion, and thus, be able to carry out the timely treatment to avoid possible fatal outcomes due to other etiologies that have specific antibiotic therapy.

## Declaration of competing interest

The authors have no conflicts of interest to disclose in relation to this work.

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