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Rickettsia felis Pulmonary Infection Detected via Metagenomic Next-Generation Sequencing in a Clonorchiasis Patient: A Case Report

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Abstract: *Rickettsia felis* (*R. felis*) is a Gram-negative obligate intracellular bacterium with a global presence across various hosts, including mammals, humans, and ectoparasites. Herein, we present a case of *R. felis* infection in a previously healthy 43-year-old male with a history of *Clonorchis sinensis* and recent corticosteroid use. The identification of *R. felis* was accomplished through metagenomic next-generation sequencing (mNGS) of the patient's bronchoalveolar lavage fluid (BALF). This case represents the first documented pulmonary infection caused by *R. felis* in China, confirmed by mNGS analysis of bronchoalveolar lavage fluid (BALF) and reported from Shenzhen, China.

Keywords: mNGS technology, *Rickettsia felis*, bronchoalveolar lavage fluid, pulmonary infection

Introduction

Rickettsia felis (*R. felis*) is an intracellular pathogen classified within the spotted fever group of Rickettsia, exhibiting a global distribution in mammals, humans, and ectoparasites.[1] Diagnosing *R. felis* encephalitis presents considerable challenges and is frequently subject to delays.[2] In China, the incidence of *R. felis* among patients with fever of unknown origin (FUO) has been reported to be approximately 2.14% (4/187).[3] The enhanced detection of *R. felis* infections in recent years can be attributed to the increasingly widespread adoption of metagenomic next-generation sequencing (mNGS), a potent diagnostic tool for pathogen identification.[4,5] Unlike traditional methods, which require targeted hypotheses about potential pathogens, mNGS allows for the unbiased detection of a wide range of pathogens, including bacteria, fungi, viruses, and parasites, directly from clinical samples. This makes it particularly valuable in cases of rare or emerging infections, such as *R. felis*. As an emerging pathogen, *R. felis* has been reported in multiple countries across various continents, including the United States, Europe, and Africa. Its identification in China adds to the growing body of evidence that *R. felis* infections are becoming more widely recognized, especially with the advent of advanced molecular diagnostic tools. To date, only two clinical infection cases caused by *R. felis* have been documented in Guangdong, China.[3] While *R. felis* infections typically present with nonspecific symptoms such as fever, rash, or gastrointestinal complaints, respiratory involvement is rare, with only a handful of cases described in the literature. In this report case, we detail a pulmonary infection attributed to *Rickettsia felis* in a male patient. The patient's recent history of Clonorchis sinensis infection and corticosteroid use further complicates the clinical picture, so advanced diagnostic method such as mNGS is necessary to identify co-infections.

Case Presentation

In May 2023, a 43-year-old male patient was referred to our hospital and subsequently admitted to our department due to a persistent cough and fever (Timeline in Figure 1). Twelve days before prior to admission, the patient developed a high-grade

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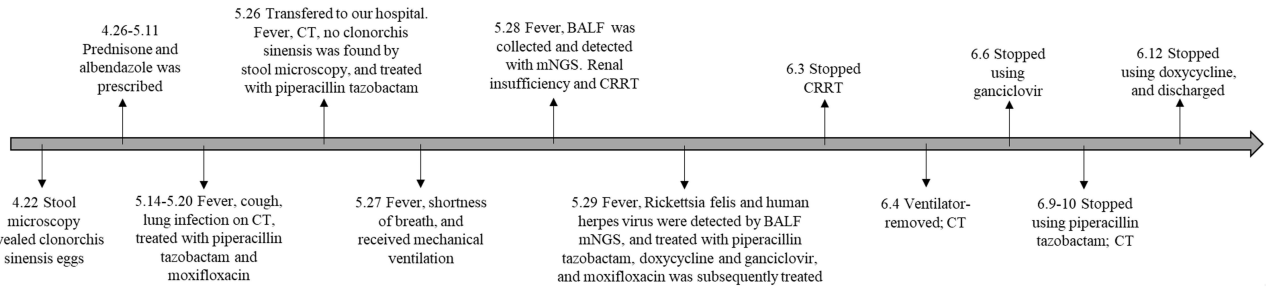

Figure 1 The treatment timeline. BALF, Bronchoalveolar lavage fluid.
Abbreviations: CRRT, Continuous Renal Replacement Therapy; CT, computed tomography.

fever peaking at 39.1 °C, accompanied by a worsening cough. Cytomegalovirus and other pathogens were not detected in the local hospital, with empirical antiviral and antibacterial therapy (oseltamivir, moxifloxacin and piperacillin-tazobactam), the patient still had hypoxemia, cough and fever. Upon seeking urgent medical care for wheezing and dyspnea, a chest computed tomography (CT) scan revealed bilateral pulmonary infiltrates. During the physical examination at our facility, the patient exhibited a respiratory rate of 35 breaths per minute and maintained an oxygen saturation level of 96% while receiving high-flow nasal cannula (HFNC) therapy with a fraction of inspired oxygen (FiO_2) at 0.60 and a flow rate of 50 liters per minute. Auscultation disclosed bilateral wet rales in the lungs, and lower extremity edema was observed, and no rashes and any tick-bite wounds were present on the skin or oropharynx.

The patient resided in Shenzhen, China, and reported daily consumption of one pack of Chinese liquor, with no history of cigarette smoking. Prior to his illness, he had ingested raw freshwater fish. Despite not owning any pets, he had potential exposure to stray cats in the neighborhood. No recollection of tick or mite bites was reported prior to the onset of his illness. The patient's health was generally good until one month before his current admission when he began experiencing fatigue and developed jaundice. He sought medical attention at a local hospital, where stool microscopy identified eggs of *Clonorchis sinensis*. Based on these findings, a clinical diagnosis of clonorchiasis was made, and a treatment regimen of prednisone and albendazole was initiated. Subsequent stool microscopy re-evaluation confirmed the resolution of the *Clonorchis sinensis* infection.

Upon admission, blood tests revealed elevated levels of highly sensitive C-reactive protein (hs-CRP), procalcitonin, and conjugated bilirubin, as detailed in Table 1. Given the results of the routine blood work and CT scan, the patient was promptly started on empirical treatment with intravenous piperacillin-tazobactam and moxifloxacin, broad-spectrum antibiotics. By the second day of hospitalization, due to worsening shortness of breath, the patient required endotracheal intubation, and sedation, and was placed on mechanical ventilation. The patient's APACHE II score was 18, indicating a state of critical illness. On the third day, samples of peripheral blood and bronchoalveolar lavage fluid (BALF) were collected for metagenomic next-generation sequencing (mNGS) analysis using the MGISEQ-200 platform (China). Concurrently, the patient developed acute kidney injury (AKI) and was underwent continuous renal replacement therapy (CRRT) via a central venous catheter. The mNGS results on the fourth day revealed the presence of *Rickettsia felis* with 4,764 high-confidence sequence reads, 346796 bp the genome covered total length, 1.21X the average depth. The *Rickettsia felis* DNA sequences accounted for 23.35% of the genome coverage in the BALF. Human betaherpesvirus 5 (CMV) with 8,567 reads, and Escherichia coli with 2,296 reads in the BALF sample. In the blood sample, CMV was detected with 5,047 reads (Table 2). Notably, microscopy of the BALF did not indicate the presence of parasites, and stool microscopy was negative for *Clonorchis sinensis* eggs. Subsequent to these findings, the patient was treated with oral doxycycline (100 mg twice daily), intravenous ganciclovir and piperacillin-tazobactam leading to a rapid clinical improvement. By the 10th day of hospitalization, the patient successfully weaned off mechanical ventilation and continued to recover. On the 12th hospital day, ganciclovir was discontinued because low-level cytomegalovirus viremia (<500 copies per milliliter) was detected. Subsequent chest CT imaging revealed progressive amelioration of the patient's pulmonary lesions (Figure 2). The patient was discharged without the need for supplemental oxygen on the 17th day.

Table 1 Laboratory Test Results of the Patient

Variable	Result			Reference Range
	Admission	1 week	2 weeks	
White blood cell ($\times 10^9$/L)	8.5	7.59	4.89	3.5–9.5
Hemoglobin (g/L)	67	84	91	130–175
Leukocyte count ($\times 10^9$/L)	1.05	1.85	1.51	1.1–3.2
Platelet count ($\times 10^9$/L)	65	76	175	125–350
Highly sensitive C-reactive protein (mg/L)	73.96	45.96	11.28	0–5
PCT (ng/mL)	3.1	0.21	0.17	<0.05
ALT (UI/L)	59	26	34	9–60
AST (UI/L)	94	36	41	17–59
Total bilirubin (μmol/L)	260.3	74	59.2	3.0–2.2
Conjugated bilirubin (μmol/L)	164.4	14	11.8	0–5
Creatinine (μmol/L)	194.3	177.2	91.9	58–110
Prothrombin time (PT) (s)	21.2	15.5	15.3	9.8–12.1

Abbreviations: PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 2 The Pathogen by mNGS in BALF and Blood Samples

Sample	Pathogen	Sequence Reads
BALF	*Escherichia coli*	2296
BALF	CMV	8567
BALF	*Rickettsia felis*	4764
Blood	CMV	5047

Discussion

Rickettsia felis belongs to the transitional group of rickettsiae and was initially characterized in 1990,[6] which is recognized as an emerging pathogen, its primary vector is the cat flea (*Ctenocephalides felis*). However, it is essential to consider the potential role of various other arthropods as vectors, including different species of fleas, ticks, mites, and lice, which should not be overlooked.[7] The first documented case of human disease attributed to *Rickettsia felis* dates back to 1994 in the United States.[8] Subsequently, human cases of *Rickettsia felis* infection have been reported worldwide.[9–18] A retrospective study in China showed that the incidence of *Rickettsia felis* infection in patients with fever of unknown origin was 2.14%.[3] According to the available search results, no specific data regarding the fatality rate of *R. felis*. Clinically, *R. felis* infections typically present with fever, rash, eschar, and gastrointestinal symptom, neurological signs.[3,19] Respiratory signs is not traditionally thought to be associated with *Rickettsia felis* infection although several case reports have been described previously. The first case of *Rickettsia felis* presenting with cough and radiologic infiltrates was reported in Mexico in 2006, diagnosed by serologic testing and polymerase chain reaction (PCR).[13] In addition to the present case, we encountered seventeen other cases of *Rickettsia felis* presenting with respiratory signs in the literature (Table 3).

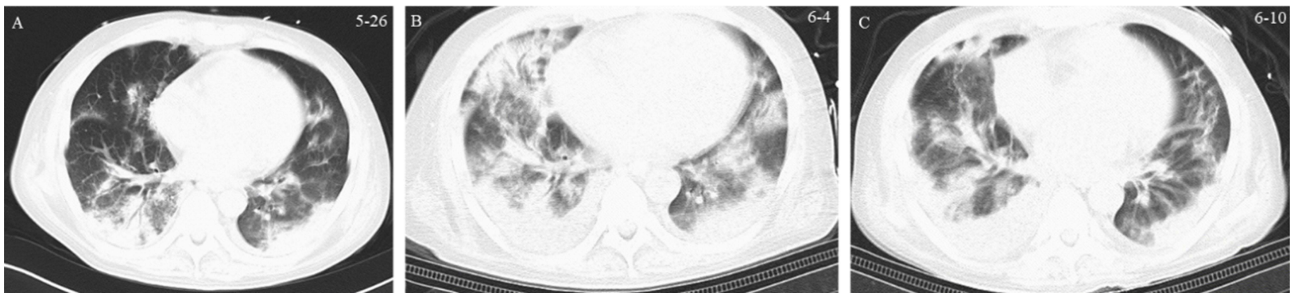

Figure 2 Presentation of pulmonary CT scan. Chest CT performed on admission (**A**), on day 10 (**B**), and on day 16 (**C**).

Due to the nonspecific nature of these symptoms, *R. felis* infections can be easily mistaken for other febrile conditions, leading to frequent underdiagnosis. While quantitative PCR (qPCR) remains the preferred diagnostic method for patients presenting with classical symptoms of rickettsial disease,[24] diagnosis can be challenging due to the nonspecific clinical presentation in some patients. In such scenarios, metagenomic next-generation sequencing (mNGS) offers a more comprehensive approach to pathogen detection and screening.

mNGS stands out as an unbiased and expedient method for pathogen detection, capable of directly sequencing DNA or RNA from clinical samples. It has garnered extensive application across various medical domains.[24] Unlike conventional diagnostic methods, mNGS may concurrently detect a wide array of pathogens in a single clinical sample, including bacteria, fungi, viruses, and parasites, without depending on a clinician's conjecture regarding the potential pathogen. This capability is particularly beneficial for pinpointing rare or novel infectious agents, where mNGS provides unparalleled advantages. Additionally, mNGS can deliver test results within 24 hours, substantially shortening the time required for pathogen identification. The accumulation of numerous successful case reports and research studies underscores the significant promise of mNGS in advancing diagnostic capabilities for infectious diseases.

The initial differential diagnosis in this case was challenging, since the patient had cough, fever, hypoxemia, and pulmonary infiltrates. A relatively comprehensive infection test was conducted at the local hospital and the result was negative. In addition, the patient's symptoms did not abate after 12 days of anti-infective treatment at the local hospital. Consequently, we hypothesized that his pneumonia might have been induced by an organism that was difficult to detect. The patient's history of exposure to stray cats, along with prior laboratory results and treatment response at the local hospital, verified the presence of *Rickettsia felis* in the patient's bronchoalveolar lavage fluid (BALF) through mNGS testing. This signified a pulmonary infection caused by *Rickettsia felis*. However, this patient's skin was normal on physical examination, the patient's route of infection with *Rickettsia felis* needs to be determined. The cat flea, *Ctenocephalides felis*, may serve as the vector for *Rickettsia felis* infection as this patient had contact with stray cats. Detecting *R. felis* in blood appears more rational, as the transmission of *Rickettsia felis* from the skin to humans through cat fleas primarily results in bloodstream infection. In our case, *Rickettsia felis* was identified using mNGS in respiratory samples, but not in blood samples, which is actually not uncommon. Research indicates that *Rickettsia felis* can be transmitted through aerosols. Reports indicate that booklice, ubiquitous in the environment (including dust), may serve as hosts for *Rickettsia felis*, with humans potentially becoming infected by the inhalation of contaminated booklice particles.[25] Doxycycline is the antibiotic of choice for treating rickettsial infections,[26] and there have been reports from Germany, Spain, and Taiwan of higher doses of doxycycline being successfully used to manage feline rickettsial disease, with patients experiencing prompt relief of symptoms.[10,11,14] This aligns with the clinical course observed in this case, where the patient demonstrated significant improvement following the mNGS-based detection of *Rickettsia felis* and subsequent treatment with doxycycline. The detection of cytomegalovirus in blood and bronchoalveolar lavage fluid by mNGS suggests that the patient may be co-infected with cytomegalovirus. Considering the patient's recent steroid treatment and the negative results of cytomegalovirus testing at the local hospital, we concluded that the patient had a secondary co-infection with cytomegalovirus on the basis of *Rickettsia felis*

Table 3 Characteristics of Cases Reported Presenting with Respiratory Signs Attributed to R. felis

Year	Area	Number of Cases	Signs and Symptoms	Diagnostic Method	Sample Type	Patient Outcome	Reference
2006	Mexico	1	Fever, cough, maculopapule	PCR and serologic testing	Blood	Recovered	[13]
2010	Senegal	2	Fever, cough, rhinitis	PCR	Blood	Recovered	[20]
2014	Thailand	2	Fever, cough, and chest pain, myalgia, arthralgia, headache, abdominal pain	PCR and serologic testing	Serum	–	[19]
2017	Ghana	6	Fever, cough	PCR	Blood	–	[21]
2021	Taiwan	1	Fever, ARDS, myalgias.	Serologic testing	Serum	Dead	[22]
2022	China	4	Fever, lung lesions	PCR and serologic testing	Serum	–	[3]
2024	Senegal	1	Fever, shortness of breath	tNGS and mNGS	Serum	–	[23]

infection. *Escherichia coli* (*E. coli*), identified using metagenomic next-generation sequencing, was not considered the primary causative pathogen of the pulmonary infection due to lack of response to piperacillin-tazobactam treatment at the local hospital. The patient did not receive the correct anti-infective treatment at the local hospital and became seriously ill due to uncontrolled infection.

Conclusion

In summary, swift pathogen identification and immediate initiation of appropriate antibiotic therapy are crucial for favorable patient outcomes in infections. As an advanced molecular diagnostic tool, mNGS can facilitate the rapid and accurate identification of infectious agents in the clinical setting.

Abbreviations

R.*felis, Rickettsia felis*; mNGS, metagenomic next-generation sequencing; FUO, fever of unknown origin; CT, computed tomography; HFNC, high-flow nasal cannula; FiO_2, fraction of inspired oxygen; APACHE Acute Physiology and Chronic Health Evaluation; BALF, blood and bronchoalveolar lavage fluid; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; qPCR, quantitative polymerase chain reaction; tNGS, targeted next-generation sequencing.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was approved by the committee on the ethics of medicine, Shenzhen Second People's Hospital (2022007).

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report. And the consent form is available for reviewing by the editor when needed. Details of the case can be published without institutional approval.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no potential conflicts of interest for the research, authorship, and/or publication of this article.

References

1. Angelakis E, Mediannikov O, Parola P, Raoult D. *Rickettsia felis*: the complex journey of an emergent human pathogen. *Trends Parasitol*. 2016;32(7):554–564. doi:10.1016/j.pt.2016.04.009
2. Sekeyova Z, Danchenko M, Filipcik P, Fournier PE. Rickettsial infections of the central nervous system. *PLoS Negl Trop Dis*. 2019;13(8):e0007469. doi:10.1371/journal.pntd.0007469

3. Teng Z, Zhao N, Ren R, et al. Human *Rickettsia felis* infections in Mainland China. *Front Cell Infect Microbiol*. 2022;12:997315. doi:10.3389/fcimb.2022.997315
4. Ye G, Yang L, Xu L, Pan Z, Dong Z. Neurological presentations caused by *Rickettsia felis* infection. *Br J Hosp Med*. 2021;82(6):1–2. doi:10.12968/hmed.2021.0212
5. Zhang L, Zhang J, Hu M, Feng X. 感染猫立克次体导致重症脑炎1例报告 (Severe encephalitis caused by infection of *Rickettsia felis*: a case report). *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2021;33(4):491–493. Dutch. doi:10.3760/cma.j.cn121430-20201110-00709
6. Perez-Osorio CE, Zavala-Velazquez JE, Arias LJJ, Zavala-Castro JE. *Rickettsia felis* as emergent global threat for humans. *Emerg Infect Dis*. 2008;14(7):1019–1023. doi:10.3201/eid1407.071656
7. Roucher C, Mediannikov O, Diatta G, Trape JF, Raoult D. A new Rickettsia species found in fleas collected from human dwellings and from domestic cats and dogs in Senegal. *Vector Borne Zoonotic Dis*. 2012;12(5):360–365. doi:10.1089/vbz.2011.0734
8. Schriefer ME, Sacci Jr JB, Dumler JS, Bullen MG, Azad AF. Identification of a novel rickettsial infection in a patient diagnosed with murine typhus. *J Clin Microbiol*. 1994;32(4):949–954. doi:10.1128/jcm.32.4.949-954.1994
9. Zavala-Velazquez JE, Ruiz-Sosa JA, Sanchez-Elias RA, Becerra-Carmona G, Walker DH. *Rickettsia felis* rickettsiosis in Yucatan. *Lancet*. 2000;356(9235):1079–1080. doi:10.1016/S0140-6736(00)02735-5
10. Richter J, Fournier PE, Petridou J, Haussinger D, Raoult D. *Rickettsia felis* infection acquired in Europe and documented by polymerase chain reaction. *Emerg Infect Dis*. 2002;8(2):207–208. doi:10.3201/eid0802.010293
11. Oteo JA, Portillo A, Santibanez S, Blanco JR, Perez-Martinez L, Ibarra V. Cluster of cases of human *Rickettsia felis* infection from Southern Europe (Spain) diagnosed by PCR. *J Clin Microbiol*. 2006;44(7):2669–2671. doi:10.1128/JCM.00366-06
12. Perez-Arellano JL, Fenollar F, Angel-Moreno A, et al. Human *Rickettsia felis* infection, Canary Islands, Spain. *Emerg Infect Dis*. 2005;11(12):1961–1964. doi:10.3201/eid1112.050711
13. Zavala-Velazquez J, Laviada-Molina H, Zavala-Castro J, et al. *Rickettsia felis*, the agent of an emerging infectious disease: report of a new case in Mexico. *Arch Med Res*. 2006;37(3):419–422. doi:10.1016/j.arcmed.2005.08.003
14. Tsai KH, Lu HY, Tsai JJ, Yu SK, Huang JH, Shu PY. Human case of *Rickettsia felis* infection, Taiwan. *Emerg Infect Dis*. 2008;14(12):1970–1972. doi:10.3201/eid1412.080515
15. Zavala-Castro J, Zavala-Velazquez J, Walker D, Perez-Osorio J, Peniche-Lara G. Severe human infection with *Rickettsia felis* associated with hepatitis in Yucatan, Mexico. *Int J Med Microbiol*. 2009;299(7):529–533. doi:10.1016/j.ijmm.2009.03.002
16. Renvoise A, Joliot AY, Raoult D. *Rickettsia felis* infection in man, France. *Emerg Infect Dis*. 2009;15(7):1126–1127. doi:10.3201/eid1507.090029
17. Ben-Zvi I, Meltzer E, Nogueras MM, Segura F, Bank I. First detection of human infection with *Rickettsia felis* in Israel. *Am J Med Sci*. 2010;340(4):343. doi:10.1097/MAJ.0b013e3181ebd715
18. Lindblom A, Severinson K, Nilsson K. Rickettsia felis infection in Sweden: report of two cases with subacute meningitis and review of the literature. *Scand J Infect Dis*. 2010;42(11–12):906–909. doi:10.3109/00365548.2010.508466
19. Socolovschi C, Mediannikov O, Sokhna C, et al. *Rickettsia felis*-associated uneruptive fever, Senegal. *Emerg Infect Dis*. 2010;16(7):1140–1142. doi:10.3201/eid1607.100070
20. Edouard S, Bhengsri S, Dowell SF, Watt G, Parola P, Raoult D. Two human cases of *Rickettsia felis* infection, Thailand. *Emerg Infect Dis*. 2014;20(10):1780–1781. doi:10.3201/eid2010.140905
21. Sothmann P, Keller C, Krumkamp R, et al. *Rickettsia felis* infection in febrile children, Ghana. *Am J Trop Med Hyg*. 2017;96(4):783–785. doi:10.4269/ajtmh.16-0754
22. Yang WH, Hsu MS, Shu PY, Tsai KH, Fang CT. Neglected human *Rickettsia felis* infection in Taiwan: a retrospective seroepidemiological survey of patients with suspected rickettsioses. *PLoS Negl Trop Dis*. 2021;15(4):e0009355. doi:10.1371/journal.pntd.0009355
23. Orf GS, Ahouidi AD, Mata M, et al. Next-generation sequencing survey of acute febrile illness in Senegal (2020–2022). *Front Microbiol*. 2024;15:1362714. doi:10.3389/fmicb.2024.1362714
24. Han D, Li Z, Li R, Tan P, Zhang R, Li J. mNGS in clinical microbiology laboratories: on the road to maturity. *Crit Rev Microbiol*. 2019;45(5–6):668–685. doi:10.1080/1040841X.2019.1681933
25. Mediannikov O, Bechah Y, Amanzougaghene N, et al. Booklice Liposcelis bostrychophila naturally infected by *Rickettsia felis* cause fever and experimental pneumonia in mammals. *J Infect Dis*. 2022;226(6):1075–1083. doi:10.1093/infdis/jiac282
26. Blanton LS, Walker DH. Flea-Borne Rickettsioses and Rickettsiae. *Am J Trop Med Hyg*. 2017;96(1):53–56. doi:10.4269/ajtmh.16-0537