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# Erythema exudativum multiforme–like exanthema in a patient with Q fever: a case report and literature review

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**Abstract**

Q fever is a rare worldwide zoonosis, caused by the rickettsial bacteria *Coxiella burnetii*. There are many clinical manifestations of infection, but the most common ones are fever, atypical pneumonia, and/or liver disease. Cutaneous involvement, however, is not a typical feature of Q fever, but it is nevertheless present in up to 20% of cases. We present a 42-year-old male patient with Q fever and erythema exudativum multiforme (EEM)–like parainfectious exanthema, which to the best of our knowledge has not been described before. We recommend considering *Coxiella burnetii* infection in the differential diagnosis of an EEM-like rash in a patient with an unexplained or "query" fever.

**Keywords:** Q fever, *Coxiella burnetii*, erythema exudativum multiforme, parainfectious exanthema, rickettsial infection

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## Introduction

Q fever, a rare worldwide zoonosis, is caused by an obligate intracellular Gram-negative bacteria *Coxiella burnetii* (1–3). It is a highly infectious organism, extremely resistant to heat, drying, and many common disinfectants. Humans are highly susceptible to the infection, and in some cases only a few organisms are required to cause the disease. A self-limiting febrile illness with pulmonary and/or hepatic involvement is the typical clinical presentation. It can progress to a chronic disease with endocarditis, chronic hepatitis, osteomyelitis, and endovascular infections (2–5). Cutaneous affliction is not a characteristic feature, but its incidence is probably underestimated. We present a patient with Q fever and erythema exudativum multiforme (EEM)–like parainfectious exanthema.

## Case report

A 42-year-old male patient with a medical history of depression presented to our dermatology department with a 5-day history of non-pruritic and painless generalized erythematous rash. One day before the appearance of the rash he reported feeling ill with a sore throat and fever of 38 °C. His travel history included several visits to Bosnia and Herzegovina, where he consumed various types of meat (e.g., lamb and pork), raw milk, and other dairy products. He was working as a hazardous waste transporter, but he denied being in direct contact with animals. His drug history included sertraline and olanzapine.

His general practitioner prescribed him azithromycin, which was switched to clindamycin after a single dose because of the occurrence of skin lesions. Due to persistent fever and rash, he was examined by an infectious disease specialist. With regard to normal chest X-ray and elevated levels of inflammatory markers (CRP 206 mg/l, reference range up to 5 mg/l; PCT 1.03 µg/l, reference range up to 0.24 µg/l), antibiotic treatment was switched to moxifloxacin with suspicion of an infection of unknown origin, and the patient was referred to the dermatology clinic for further evaluation.

Clinical examination revealed coalescing erythematous and purpuric macules on the dorsum of the feet and lower legs, and spreading to the thighs and gluteal area (Fig. 1). On the trunk and the upper extremities, the lesions were more pinkish and annular, and in some places they had an atypical target-like shape with palpable borders (Fig. 2). Individual lesions were also present on the face. On the hard palate, a discrete enanthem was noticed, but the rest of the mucosae were intact. The patient was admitted with suspicion of an EEM-like parainfectious exanthem, and the differential diagnoses included a generalized form of EEM minor, Sweet syndrome, urticarial and leukocytoclastic vasculitis, and lupus erythematosus. Skin biopsy was performed, and the histopathology results revealed a non-specific, discrete, mostly superficial, perivascular focal interface dermatitis (Fig. 3), which might represent reactive changes (drug-related, infectious, or parainfectious). Features suggestive of Sweet syndrome, EEM, or vasculitis were not seen. The result of direct immunofluorescence microscopy was minimal and not significant.

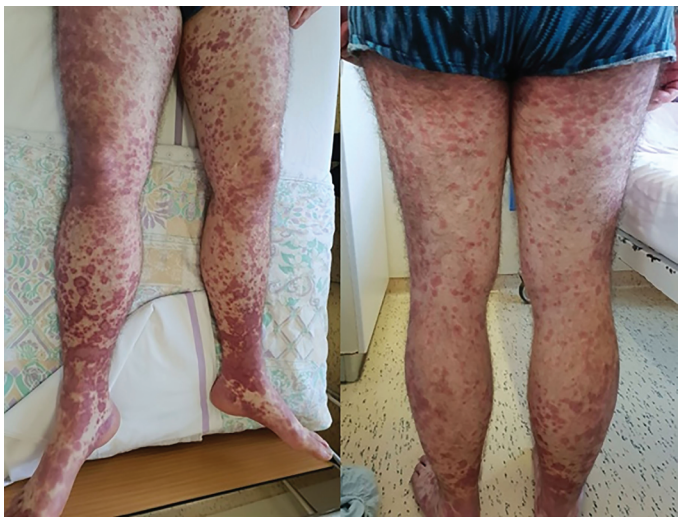

Figure 1 | Cutaneous lesions at the time of presentation: coalescing purpuric lesions on the lower extremities.

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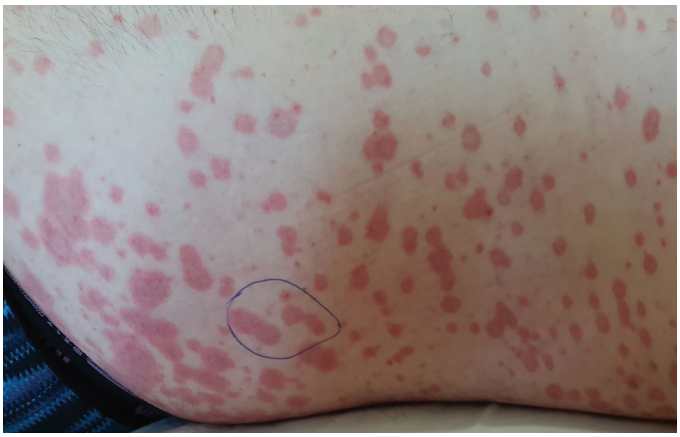

Figure 2 | Atypical target-like pinkish plaques with slightly palpable borders on the trunk and upper extremities.

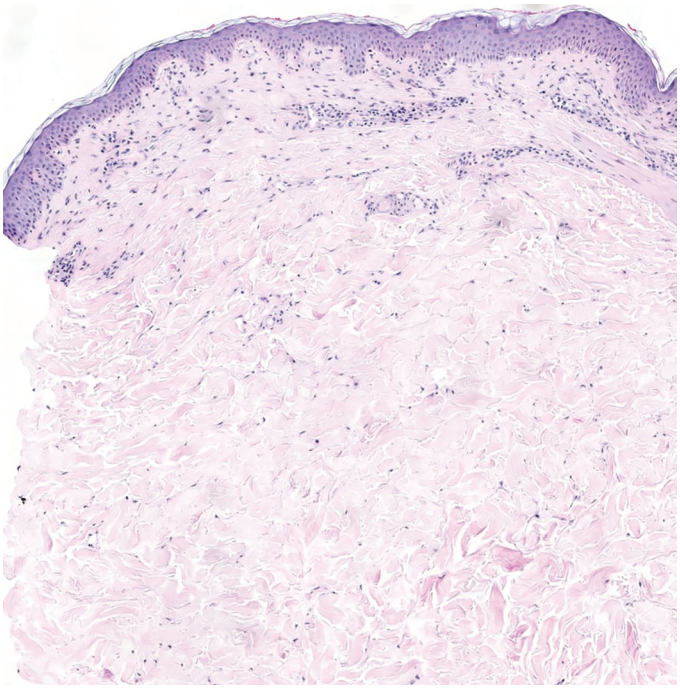

Figure 3 | Histopathology showing non-specific, discrete, mostly superficial, perivascular focal interface dermatitis.

Leukocytes, blood urea nitrogen, creatinine, electrolytes, alkaline phosphatase, albumins, tumor markers, and protein electrophoresis were within normal limits. Mild lymphopenia (0.88 × $10^9$/l, reference range 1.10–3.50 × $10^9$/l) with persistent elevation of inflammation markers (SR 61 mm/h, reference range 0–15 mm/h; CRP 165 mg/l, reference range up to 5 mg/l; PCT 1.16 µg/l, reference range up to 0.24 µg/l; segmented neutrophils 7.37 × $10^9$/l and 82.4%, reference range 1.50–7.40 × $10^9$/l and 40.0%–80.0%) and liver function tests (ALT 0.99 µkat/l, reference range up to 0.77 µkat/l; gGT 2.94 µkat/l, reference range up to 0.92 µkat/l) were noted in the laboratory results. Proteinuria (3 AU, reference range up to 0 AU) was present on urinalysis, as well as in the 24-hour urine sample (0.83 g, reference range up to 0.15 g), but was negative on repeat urinalysis (on the 6th and 11th day of hospitalization). Cryoglobulins, anti-neutrophil cytoplasmic antibodies, and extractable nuclear antigen antibodies were negative. HEP-2 test showed weak positive anti-smooth muscle antibodies (1 AU, reference range up to 0 AU). Levels of C3 complement were also slightly elevated (1.33 g/l, reference range 0.60–1.30 g/l) and of C4 decreased (0.005 g/l, reference range 0.10–0.30 g/l).

Nasopharyngeal swabs for pathogenic and atypical bacteria, and SARS-CoV-2 were negative. Blood cultures and serology tests for human immunodeficiency virus, hepatitis B and hepatitis C virus, *Treponema pallidum*, cytomegalovirus, parvovirus B19, and antistreptolysin O were negative except for Epstein–Barr virus (EBV; IgM anti-VCA: positive [68.6 U/ml, reference range 36.0–43.9 U/ml]; IgG anti-VCA: positive [71.6 U/ml, reference range 18.0–21.9 U/ml]; IgG anti-EBNA: positive [85.9 U/ml, reference range 18.0–21.9 U/ml]; IgG anti-EA: negative) and cytomegalovirus (IgG: positive [85,6 U/ml, reference range 0.6 - 0.69 U/mL]; IgM: positive/negative [20.2 U/ml, reference range 30–34.9 U/ml]). Positive serology results for EBV in conjunction with the negative real-time polymerase chain reaction (RT-PCR) blood test indicated a previous infection.

Local steroid therapy was introduced for the patient's exanthem, which showed rapid improvement with almost complete regression on the 5th day after admission (Fig. 4). However, he continued to have afternoon/evening spikes of fever (up to 38.8 °C) and high levels of inflammation parameters, and so moxifloxacin

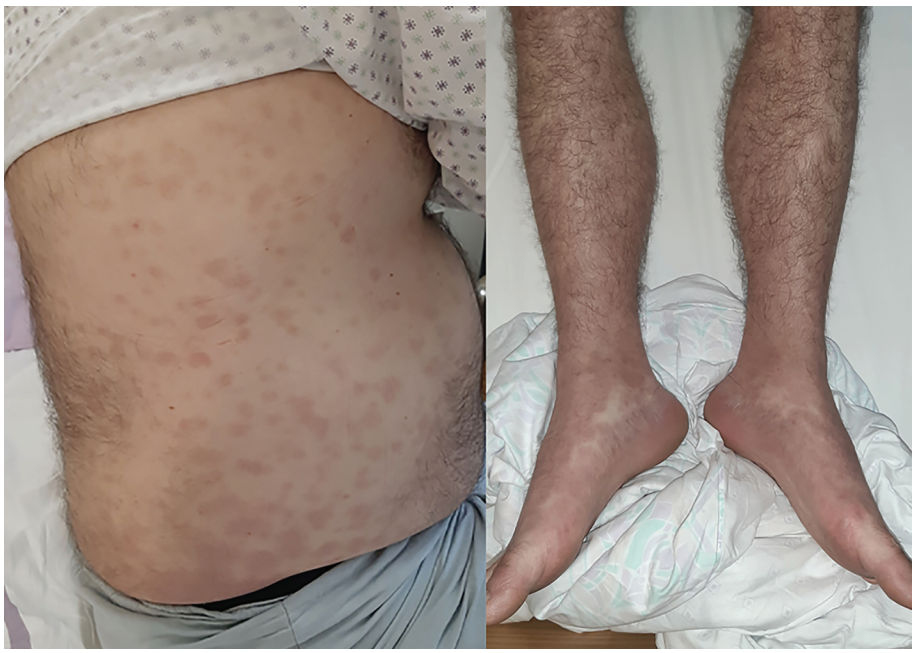

Figure 4 | Cutaneous lesions at discharge: residual macules in regression.

was stopped after 2 days of therapy and switched to piperacillin/tazobactam (4.5 g t.i.d. i.v.). Nevertheless, the fever did not resolve and additional microbiology tests were performed, including serology for *C. burnetii*, *Rickettsiaceae*, and *Brucella* sp. The serology tests were positive for *C. burnetii* (phase I, IgG: reactive 1:64, IgM: negative; phase II, IgG: reactive 1:1024, IgM: reactive 1:256; reference range 1:64), whereas the RT-PCR blood test was negative. Treatment with doxycycline 100 mg b.i.d. was started immediately, and the patient's condition quickly improved. The patient became afebrile, and piperacillin/tazobactam was discontinued on the next day. Abdominal ultrasound and transthoracic echocardiography were also performed and were normal. Blood results showed a decrease of inflammatory markers. Liver function tests were still slightly elevated at discharge but demonstrated a steady decrease. At the follow-up visit 2 weeks after completing the 14-day treatment with doxycycline, the patient reported feeling well with no relapse of the rash. Repeat serology tests showed an increase of phase I IgG antibodies and elevated levels of phase II antibodies in the same titers as in the first sample (phase I, IgG: reactive 1:28, IgM: negative; phase II, IgG: reactive 1:1024, IgM: reactive 1:256; reference range 1:64).

## Discussion

The main reservoirs of *C. burnetii* are cattle, sheep, and goats; however, a wide range of domestic and feral animals, and even ticks, can be the source of infection. Infection occurs by inhalation of dust contaminated by infected animals' feces, urine, milk, and birth products (i.e., the placenta or amniotic fluid). Ingestion of unpasteurized dairy products is a possible, although minor, route of transmission (1-4). Activities such as birthing, slaughtering, or butchering infected animals, which often have no symptoms, carry a very high risk of infection, but any handling of animals or animal tissues, fluids, secretions, or products may be the cause of infection (5). Furthermore, *C. burnetii* can survive for long periods of time in soil and dust, which wind can spread over several kilometers, and thus even people that are not in direct contact with animals can be infected. Person-to-person transmission is possible via transplacental exposure, sexual contact, blood transfusion, and transplantation (6–8). The exact route of infection was difficult to establish in our patient; however, ingestion of various dairy products and inhalation of infected dust particles during waste transport both seem plausible.

The incubation period of Q fever is typically 2 to 3 weeks (7, 8). There are no characteristic features of acute infection, and a very variable presentation is common. Most cases are asymptomatic (60%) or manifest as a self-limiting disease with fever, headache, and respiratory symptoms (dry cough or chest pain) or jaundice in the case of hepatic involvement as the leading symptom. In chronic infections, endocarditis, chronic hepatitis, osteomyelitis, and endovascular infections are well-documented complications (3–5, 9–11). Q fever does not display a characteristic cutaneous rash, which can sometimes be observed in other infections, such as erythema infectiosum in parvovirus B19 infection or the distinctive pinkish-red rash in scarlet fever. Contrary to other rickettsial infections, cutaneous impairment is rarely seen, suggesting that, although rickettsemia occurs, invasion and destruction of endothelium is not a prominent feature in infection with *C. burnetti*. Nevertheless, cutaneous lesions are present in up to 20% of cases (2, 3, 9) and may also be underestimated (10, 12). Most commonly, non-specific maculopapular and purpuric eruptions (9, 13, 14) were observed, but other patterns have also been reported: erythema nodosum (9, 14, 15), leukocytoclastic vasculitis (16) and other types of vasculitis (5, 17), lobular panniculitis (10), erythema annular centrifugum (11), generalized petechiae (13), and skin ulcer (18). To the best of our knowledge, no erythema exudativum multiforme–like rash in a patient with Q-fever has been reported so far.

A generalized form of EEM minor was also included in our differential diagnosis; however, histopathological findings did not support this diagnosis. Non-specific histopathological findings with the clinical appearance of atypical target lesions led us to a diagnosis of EEM-like exanthema. This type of exanthema has been described in association with SARS-CoV-2 infection, which was excluded in our case (19, 20).

In our patient, fever, rash, and respiratory symptoms were also accompanied by slight elevation of liver enzymes, which resolved with convalescence. Liver enzyme levels can be elevated in up to 85% of patients with Q fever. Hepatitis has been reported in 7.4% to 61.9% of cases (1–3). Heart involvement is also common, especially in chronic infections, presenting as endocarditis in 73% of cases (2).

Diagnosis of Q fever relies on serological testing, and acute Q fever has a typical serological pattern. There are two distinct antigenic phases (phase I and phase II); in acute infection, antibody levels to phase II antigen are higher than to phase I antigen, whereas the reverse might be true in chronic infection. Titers of anti-phase II IgG of ≥ 1:200 and titers of anti-phase II IgM of ≥ 1:50 are recommended for the diagnosis of acute Q fever, and titers of anti-phase I IgG ≥ 1:800 for the diagnosis of chronic Q fever (21). When these values are not attained, paired samples 3 to 6 weeks apart are required, with first sample taken within a few days after the onset of the symptoms. In the 1st week of symptoms, IgG titer is typically low or negative. After 3 to 6 weeks, a fourfold or greater increase in IgG antibody levels is seen, which is diagnostic for Q fever. IgM antibodies are less specific, can be falsely positive, and remain elevated for months or longer after the disease has completely resolved (6, 21–23). In our patient, diagnosis was confirmed with high titers of anti-phase II IgG antibodies in the first sample. During the acute phase, RT-PCR can also be used for diagnostics, but it is most sensitive in the first 2 weeks of the disease and rapidly declines once the antibodies appear (22–26). This might be the explanation for the negative RT-PCR result in our patient because it was performed more than a week after the onset of the symptoms.

Similar to other rickettsial infections, first choice of treatment is doxycycline (100 mg b.i.d. for 14 days) (6, 25, 27). Although resistance to doxycycline is not common, some doxycycline-resistant isolates do exist (28). Possible drug alternatives are fluoroquinolones (ciprofloxacin, ofloxacin, and moxifloxacin), macrolides (azithromycin), co-trimoxazole, and rifampin (6, 25, 27, 28).

Q fever is a worldwide infection, and reports show that most infections occur in spring and early summer months, which are also the peak of birthing season for cattle, sheep, and goats. In Slovenia an outbreak of the disease was reported in 2007 in a group of 93 students and professors from the Veterinary Faculty and Biotechnical Faculty after visiting a farm. However, its incidence in Slovenia is low, with only a few cases reported in recent years (one case in 2020, six cases in 2019, one case in 2018, and three cases in 2017). Most cases were imported from Bosnia and Herzegovina (29, 30). Despite focused efforts to develop Q fever vaccines, only one vaccine (Q-Vax®), is commercially available. The vaccine is

restricted to Australia, demands strict prevaccination screening, and is recommended for adults at risk of infection. The formalin-inactivated whole-cell vaccine provides reliable protection but can induce mild to severe adverse reactions if administered to individuals with prior exposure to the agent (31, 32).

## Conclusions

Q fever is a rare infection, not typically associated with cutaneous involvement; however, this association is probably underestimated. When encountering a patient with an EEM-like rash and an unexplained or "query" fever, infection with *C. burnetii* should be considered.

## References


1. Tissot Dupont H, Raoult D, Brouqui P, Janbon F, Peyramond D, Weiller PJ, et al. Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. Am J Med. 1992;93:427–34.
2. Raoult D, Tissot-Dupont H, Foucault C, Gouvernet J, Fournier PE, Bernit E, et al. Q fever 1985–1998. Clinical and epidemiologic features of 1,383 infections. Medicine (Baltimore). 2000;79:109–23.
3. Tellez A, Sainz C, Echevarria C, de Carlos S, Fernandez MV, Leon P, et al. Q fever in Spain: acute and chronic cases, 1981–1985. Rev Infect Dis. 1988;10:198–202.
4. Knap N, Žele D, Glinšek Biškup U, Avšič-Županc T, Vengušt G. The prevalence of Coxiella burnetii in ticks and animals in Slovenia. BMC Vet Res. 2019;15:368.
5. Van Seventer JM. Principles of infectious diseases: transmission, diagnosis, prevention, and control. In: Quah, SR, editor. International encyclopedia of public health. Oxford: Elsevier; 2017. p. 22–39.
6. Centers for Disease Control and Prevention. Q fever [Internet]; 2019 [cited 2022 Nov 20]. Available from: https://www.cdc.gov/qfever/index.html.
7. Nacionalni inštitut za javno zdravje. Nalezljive bolezni: Vročica Q [Internet]. Ljubljana: Nacionalni inštitut za javno zdravje; c2015 [cited 2022 Nov 20]. Available from: https://www.nijz.si/sl/vrocica-q. Slovenian.
8. Maurin M, Raoult D. Q fever. Clin Microbiol Rev. 1999; 12:518–53.
9. Meriglier E, Asquier L, Roblot F, Roblot P, Landron C. A case of Q fever with erythema nodosum. Infection. 2018;46:127–9.
10. Galache C, Santos-Juanes J, Blanco S, Rodríguez E, Martínez A, Soto J. Q fever: a new cause of "doughnut" granulomatous lobular panniculitis. Br J Dermatol. 2004;151:685–7.
11. Betlloch I, Amador C, Chiner E, Varona C, Carbonell C, Vilar A. Erythema annular centrifugum in Q fever. Int J Dermatol. 1991;30:502.
12. Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infect Dis. 2005;5:219–26.
13. Boele van Hensbroek M, de Vries E, Dolan G, Schneeberger P. Rash and petechiae as presenting signs of Q fever. Pediatr Infect Dis J. 2000;19:358.
14. Argov O, Weintraub M, Charach G. "Doughnut" granulomas from erythema nodosum in acute Q fever. Isr Med Assoc J. 2008;10:241–2.
15. Vázquez-López F, Rippe ML, Soler T, Rodríguez A, Arribas JM, Pérez-Oliva N. Erythema nodosum and acute Q fever: report of a case with granulomatous hepatitis and immunological abnormalities. Acta Derm Venereol. 1997;77:73–4.
16. Koh SS, Li A, Cassarino DS. Leukocytoclastic vasculitis presenting in association with Coxiella burnetii (Q fever): a case report. J Cutan Pathol. 2018;45:71–3.
17. Duval X, Debord T, Fournier B, Darie H, Lemoing V, Roue R. Q fever with cutaneous and encephalitic involvement. Lancet. 1993;341:1094–5.
18. Vanden Bussche S, Smets K, Steelandt T, Van Eyken P, Caenepeel P, Robaeys G. A case of Q fever with hepatitis and an atypical skin lesion. Acta Gastroenterol Belg. 2018;81:441–2.
19. Torrelo A, Andina D, Santonia C, Noguera-Morel L, Bascuas-Arribas M, Gaitero-Tristán, et al. Erythema multiforme-like lesions in children and COVID-19. Pediatr Dermatol. 2020;37:442–6.
20. Daneshgaran G, Dubin DP, Gould DJ. Cutaneous manifestations of COVID-19: an evidence-based review. Am J Clin Dermatol. 2020;21:627–39.
21. Fournier PE, Marrie TJ, Raoult D. Diagnosis of Q fever. J Clin Microbiol. 1998;36: 1823–34.
22. NSW Health: Infectious diseases. Control guidelines. Appendix 5. Q fever laboratory result interpretation [Internet]. St Leonards NSW: State of New South Wales NSW Ministry of Health; c2022 [cited 2022 Nov 20]. Available from: https://www.health.nsw.gov.au/Infectious/controlguideline/Pages/qfever-appendix5.aspx.
23. Schneeberger PM, Hermans MHA, van Hannen EJ, Schellekens JJA, Leenders ACAP, Wever PC. Real-time PCR with serum samples is indispensable for early diagnosis of acute Q fever. Clin Vaccine Immunol. 2010;17:286–90.
24. Dupont HT, Thiron X, Raoult D. Q fever serology: cutoff determination for microimmunofluorescence. Clin Diagn Lab Immunol. 1994;1:189–96.
25. Marrie, TJ. antimicrobe.org: Coxiella burnetii (Q fever) [Internet]. Pittsburgh: Antimicrobe: infectious disease and antimicrobial agents; c2010–2017 [cited 2022 Nov 22]. Available from: http://www.antimicrobe.org/r08.asp.
26. Bae M, Jin CE, Park JH, Kim MJ, Chong YP, Lee SO, et al. Diagnostic usefulness of molecular detection of Coxiella burnetii from blood of patients with suspected acute Q fever. Medicine (Baltimore). 2019;98:e15724.
27. Rathore, Mobeen H. Rickettsial infection treatment & management [Internet]. New York; Medscape; c2021 [cited 2022 Nov 20]. Available from: https://reference.medscape.com/article/968385-treatment.
28. Kersh GJ. Antimicrobial therapies for Q fever. Expert Rev Anti Infect Ther. 2013;11: 1207–14.
29. Kokalj M, Grilc E, Poglajen S, Bajt M, Šplajt A, Arič T, et al. Vročica Q / mrzlica Q. In: Letno poročilo o zoonozah in povzročiteljih zoonoz, 2020. Ljubljana: Uprava za varno hrano, veterinarstvo in varstvo rastlin; 2022. p. 42–44. Slovenian.
30. Fafangel M, Sočan M, Frelih T, Klavs I, Grilc E, Grgič Vitek M, et al. Vročica Q. In: Epidemiološko spremljanje nalezljivih bolezni v Sloveniji v letu 2019 in 2020. Ljubljana: Nacionalni inštitut za javno zdravje; 2022. p. 119. Slovenian.
31. Australian Technical Advisory Group on Immunisation (ATAGI). Australian immunisation handbook: Q fever [Internet]. Canberra: Australian Government Department of Health and Aged Care; c2022 [cited 2022 Nov 20]. Available from: https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/q-fever.
32. Long CM. Q Fever vaccine development: current strategies and future considerations. Pathogens. 2021;10:1223.