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Q fever in Tunisia, an underestimated infection

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Q fever is a common zoonosis with almost a worldwide distribution caused by *Coxiella burnetii*. Farm animals and pets are the main reservoirs of infection and transmission to humans is usually via inhalation of contaminated aerosols. Infection in humans is often asymptomatic, but it can manifest as an acute disease (usually a self-limited flu-like illness, pneumonia or hepatitis) or as a chronic form (mainly endocarditis). The aim of this review was to describe epidemiological and clinical features of Q fever in Tunisia. A systematic review of all published studies of Q fever in Tunisia was conducted. Although prevalence of immunoglobulins anti-*C. burnetii* was high among animals and blood donors, Q fever was rarely reported and frequently misdiagnosed by physicians.

Key words: Q fever, *Coxiella burnetii*, epidemiology, Tunisia.

INTRODUCTION

Q fever is a zoonotic infection caused by the pathogen *Coxiella burnetii*, which can cause acute or chronic disease with protean manifestations. The designation Q fever (from Query) was made in 1935 following an outbreak of febrile illness in an abattoir in Queensland, Australia. Q fever is a common zoonosis with almost a worldwide distribution. Farm animals and pets are the main reservoirs of infection and transmission to humans is usually via inhalation of contaminated aerosols. Infection in humans is often asymptomatic, but it can manifest as an acute disease (usually a self-limited flu-like illness, pneumonia or hepatitis) or as a chronic form (mainly endocarditis) (Raoult and Marrie, 1995). In Tunisia, researchers started to look for these diseases among patients since 1954 using old technic (Maurin, 1954). In 1984, Kennou and Edlinger confirm existence of antibodies again *C. burnetii* in Tunisian healthy population (Kennou and Edlinger, 1984). Although prevalence of immunoglobulins anti-*C. burnetii* was high among animals and blood donors, Q fever was rarely reported and frequently misdiagnosed by physicians.

The economic impact of this infectious disease is certainly high. First, Q fever is endemic in our livestock and it is a major cause of abortion, in the other hand, in human, Q fever, in its chronic form, can be responsible for long hospital stay and chronic treatment and follow up for some specific patients. Therefore, physicians as well as veterinarians should be aware regarding this zoonosis. This study aims to review epidemiological status and to describe clinical features of Q fever in Tunisia through literature review.

METHODOLOGY

A systematic review was conducted to determine epidemiological

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status and clinical features of Q fever in Tunisia. Systematic and comprehensive searches were developed with a clinical librarian and designed for optimal retrieval. The electronic databases MEDLINE/PubMed, Embase, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for literature until July 31, 2021. Key words used were Q fever, *C. burnetii* and Tunisia. All types of studies of any design which describe Q fever among human and animals in Tunisia were searched for. 21 published studies were revised and analyzed and 20 were included in this review (14 in human and 6 in animals), one study was excluded because of duplication. All studies were published in English and/or French languages.

RESULTS AND DISCUSSION

Microbiology

C. burnetii is a short, pleomorphic rod that is a strict intracellular bacterium. While previously designated as a *Rickettsia*, *C. burnetii* has been re-classified as a Proteobacteria, which is closer to *Legionella* and *Francisella* (Stein et al., 1993). In mammals, the usual host cell of *C. burnetii* is the macrophage, which is unable to kill the bacterium. *C. burnetii* lives and multiplies in a single, large, acidic vacuole, which results from the fusion of cell lysosomes (Maurin et al., 1992). In addition, a sporulation-like process protects the organism from the external environment, where it can survive for long periods of time. An important characteristic of *C. burnetii* is its antigenic variation, called "phase variation". When *C. burnetii* express phase I antigen it is highly infectious and a single bacterium is sufficient to infect a human. This is the form that is isolated from animals or humans. After sub culturing *C. burnetii* in cells or embryonated eggs, modification of its lipopolysaccharide (LPS) capsule results in an antigenic shift to the phase II form, which is not infectious. This antigenic shift can be measured and forms the basis for differentiating acute from chronic Q fever (Raoult and Marrie, 1995).

Epidemiology of Q fever in Tunisia

Q fever in animals

Mammals, birds, and arthropods may be reservoirs for *C. burnetii*, but the main reservoir is ticks (Raoult and Marrie, 1995). The most commonly identified sources of human infection are farm animals, such as cattle, goats, and sheep. However, pets, including cats, rabbits, pigeons, hedgehogs, and dogs may serve as sources of urban outbreaks of human disease (Stein and Raoult, 1999; Balti et al., 2021). Q fever can cause abortions in sheep and goats and low birthweight in offspring of cattle. High concentrations of *C. burnetii* may occur in the placenta of infected animals. In Tunisia, a study conducted in 1997, showed that 40% of sheep from different regions were seropositive for *C. burnetii*, in addition, this bacteria was the abortive agent in 17% of sheep and goats (Rekiki et al., 2005). In recent study conducted during 2016-2017, among healthy camels, 44% of them were found to have positive *C burnetii* serology done by ELISA, a meaningful high sero-positivity was observed in female camels with a previous history of abortion (70%) (Selmi et al., 2018). In a study conducted by Selmi et al. (2018) among 327 partially engorged ticks collected from camels, *C. burnetii*, was detected in 3.6%, genotyping and phylogenetic analysis of obtained *C. burnetii* revealed 99 to 100% similarity to the pathogenic *C. burnetii* strains isolated from humans, this finding raises the possibility of the involvement of *Hyalomma* tick species in the active diffusion of these bacteria among camels, other domestic animals and humans (Selmi et al., 2019). Another recent study confirmed the high prevalence of Q fever in animals in Tunisian farms, authors concluded that Q fever increased when the intensive farm was exposed to carnivores and when the cleaning practices were not respected, while it decreased when a suitable quarantine was introduced for any introduction of a new animal. Good hygiene and sanitation practices on-farm should be handled as strategies to deal with this zoonotic pathogen in herds (Barkallah et al., 2018).

Q fever in human

Humans are incidental hosts for infection with *C. burnetii*. Occupational exposure to *C. burnetii* among veterinarians may occur through inhalation of contaminated aerosols arising from the placenta or parturient fluids of infected livestock. *C. burnetii* human infection has also resulted via the following routes: a) trans placental transmission to the fetus, b) intradermal inoculation, and c) blood transfusions. Consumption of raw milk is an additional cause of infection (Salifu et al., 2019; Shishido et al., 2016; Ghanem-Zoubi and Paul, 2020). Q fever can occur in any age group, but infection is most common between the ages of 30 and 70 years. Men are more frequently diagnosed with Q fever than women (Tissot et al., 1992). This can be explained by the fact that men are more exposed to the reservoir, and they have activities that generate aerosols infected by *C. burnetii.* Otherwise, women and children are more likely to have asymptomatic infection (Tissot et al., 1992). Since the clinical presentation is nonspecific, recognition of cases depends upon astute clinicians and the availability of a reference laboratory. Thus, incidence figures for the disease vary widely. Q fever is rampant in endemic mode with the possibility of epidemic outbreak.

Blood samples (1888) from febrile and non-febrile patients from six African countries were investigated retrospectively for Q fever infection by molecular assays showed a prevalence ranging from 0.3 to 0.5% (Angelakis et al., 2014). In Tunisia, Q fever is an endemic

disease, but rarely diagnosed and confirmed by physicians. In fact, in 1983, Kennou and Edlinger (1984) found that prevalence of *C. burnetii* antibodies among healthy population was 8.7% (3). Another study conducted in 1993, noted that 26% of blood donors in the Tunisia eastern central region (Sousse, Monastir) had antibodies to *C. burnetii*, majority of them were male (Letaief et al., 1995). During the same period, among 300 inpatients presented with acute fever, *C. burnetii* serology was done for all patients, showed a typical profile of acute Q fever among 2% of patients and old contact with *C. burnetii* in 29% of cases (Omezzine-Letaief et al., 1997). In addition, a serological survey carried out during 2004, among 47 inpatients with unexplained fever, acute Q fever had been confirmed in 8 cases (17%) (Kaabia et al., 2006).

Clinical manifestations

Patients with Q fever present with a wide spectrum of disease manifestations. While for some patients the clinical manifestations of acute or chronic infection are severe, the clinical signs and symptoms of Q fever are mild or absent in others.

Acute Q fever (AQF)

The incubation period for acute infection is approximately 20 days (range 14 to 39) (Raoult et al., 2005). Patients with acute Q fever can present with any of the following manifestations.

Flu-like illness: A self-limited flu-like syndrome is the most common manifestation of acute infection. The onset is typically abrupt, with high-grade fevers (40°C), fatigue, headache, and myalgia being the most frequent associated symptoms. In such patients, the headaches are usually severe and can be associated with photophobia. Febrile episodes usually last from one to three weeks.

Pneumonia: Most cases of Q fever pneumonia are mild, and patients present with a non-productive cough and fever. However, acute respiratory distress may occur in some patients. Findings on the chest radiograph are not specific and resemble a viral pneumonia. Pleural effusion may also occur, but it is uncommon. In addition to respiratory symptoms, patients often have extra pulmonary manifestations including severe headaches, myalgia, and arthralgia. Symptoms can last from 10 to 90 days. Mortality rates are low (ranging 0.5 to 1.5%) (Raoult and Marrie, 1995). Among 240 Tunisian patients admitted for acute exacerbations of chronic obstructive pulmonary disease, acute Q fever was diagnosed in 6.6% (Messous et al., 2018).

Hepatitis: Patients with hepatic involvement present with high liver enzymes and can also have: hepatomegaly, which usually occurs without jaundice, an acute febrile episode. Prolonged fever of unknown origin with characteristic granulomas on liver biopsy. The granulomas appear to be "doughnut-like" because they contain a lipidic vacuole surrounded by a fibrinoid ring (Dauby et al., 2020).

Other manifestations of acute Q fever: They include maculopapular or purpuric rash (10%), pericarditis and/or myocarditis (1%), myocarditis can be a particularly severe (Fournier et al., 2001), aseptic meningitis and/or encephalitis (1%) (Bernit et al. 2002). Other rare features were described like neuritis, hemolytic anemia, thyroiditis, gastroenteritis, pancreatitis, lymphadenopathy mimicking lymphoma, erythema nodosum, orchitis, and acute acalculous cholecystitis (Rolain et al., 2003).

In Tunisian studies, the main clinical presentations of acute Q fever were interstitial pneumonia, isolated fever or associated with cytolysis (Bellazreg et al., 2009; Kaabia and Letaief, 2009), and one case of chronic fever of unknown origin with granulomatous in liver biopsy (Omezzine-Letaief et al., 1997). Recently two cases of acute Q fever were published, the first case, was a 19 year-old healthy patient with myocarditis (Hammami et al., 2021), the second, an acute fever in patient treated by Etanercept for Ankylosing Spondyloarthritis (Guiga et al., 2021), both patient treated by doxycycline and their outcome was favorable.

Q fever in pregnancy

Pregnant women presenting with acute Q fever are significantly more likely to be asymptomatic than other patients, however, Q fever may result in obstetrical complications such as spontaneous abortion, intrauterine growth retardation, intrauterine fetal death, oligoamnios, and premature delivery (Ghanem-Zoubi and Paul, 2020), in Tunisian pregnant woman, Q fever studies are rare, its prevalence is unknown, only one study investigated the relationship between miscarriage in humans and infections caused by zoonotic bacteria and genital pathogens, did not find any link between *C. burnetii* and abortion (Smaoui et al., 2019).

Chronic Q fever (CQF)

It is rare; reported in less than 5% after acute illness, occurred within few months, years or decades after AQF. Pregnancy, cardiac and valve diseases and immunosuppression are high risks for later CQF.

Infective endocarditis with negative blood cultures on prosthetic valve or preexisting lesions is the most common form of CQF (Kampschreur et al., 2015), followed by

infection on aneurysm or vascular prosthesis (Botelho-Nevers et al., 2007). The prognosis of CQF is pejorative with high mortality.

In a recent systematic review of *C. burnetii* epidemiology in Africa, *C. burnetii* accounted for 1 to 3% of infective endocarditis in Tunisia (Ben et al., 2014). Rekik et al. (2009) in their series of 48 patients with prosthesis valve endocarditis, collected during 10 years (1997-2006) from tertiary care hospital in central Tunisia, one patient had chronic Q fever. Others cases reports were published; all were endocarditis with negative blood culture in immunocompetent patient. The first case, a 35-year-old man, who had recurrent endocarditis (4 episodes) on mitral prosthetic valve. Q fever serology requested only in the fourth episode, showed profile of chronic Q fever. Despite appropriate antibiotics, the patient died after prosthetic valve disinsertion (Ameur et al., 1997). The second case, a 42-year-old patient, with history of mitral and aortic rheumatic disease, presented shortness of breath and fever, since more 3 months, he had splenomegaly. Cardiac echocardiography showed abscess of the mitro-aortic trigone. Blood culture was sterile*, C. burnetii* serology confirms the diagnosis of chronic Q fever with high titer of antibodies phase I. Patient underwent mitral and aortic valves replacement. He received doxycycline, hydroxychloroquine and ofloxacine for 18 months, with favorable outcome (Fradi et al., 2006). The third case, 48-year-old male patient, presented native aortic valve endocarditis with negative blood culture. Biological prosthesis insertion was done because of hemodynamic instability due to acute heart failure. Unfortunately, patient experienced postoperative bleeding with disseminated intravascular coagulation and died few days after cardiac surgery. Serology for *C. burnetii* was positive, with high titer for IgG phase I (1/6400). Culture of the valve remained sterile. Quantitative real-time PCR (qPCR) analysis of the valvular sample was strongly positive (355, 395, and 350 copies/mL) for *C. burnetii*. Whole genome sequencing of the strain was performed directly on the valvular sample to test whether direct sequencing would be feasible for such highly positive sample and to provide genomic data on a Tunisian strain (Delaloye et al., 2017)

Diagnosis

Nonspecific laboratory findings

In AQF, leucocytes count is often normal whereas thrombocytopenia is found in 25 to 30% of cases. Increased liver enzymes could be found up to 71% of cases, cholestasis is less common. In Tunisian series cases, normal WBC or leucopenia, and high liver enzymes (ALT/AST) were the most frequent laboratory findings (71.5%), followed by thrombocytopenia noted in57% (Bellazreg et al., 2009).

In CQF, an increase inflammatory markers is frequently seen sometimes along with circulating immune complexes, rheumatoid factors, microscopic hematuria and cryoglobulinemia.

Confirmatory diagnostic tests

Serologic Testing (Immunofluorescence Assay): The diagnosis of Q fever is confirmed serologically in majority of cases. In AQF, a fourfold rise in titer of phase II IgG between acute and convalescence samples is diagnostic of Q fever. A single serum specimen could be used for the diagnosis of AQF, a titer of phase II IgG > 1/128 in patient with prolonged febrile illness and clinical manifestations of Q fever is suggestive of AQF. IgM antibodies have limited diagnosis value. In CQF, continued increasing phase I IgG antibodies with a titer ≥ 1/1024 along with identifiable site of chronic infection such as endocarditis or endovascular infection is diagnostic of CQF (Kampschreur et al., 2015).

Nucleic acid detection by PCR: PCR has been successfully employed to detect DNA in both cell cultures and clinical samples (Stein et al., 1993). PCR testing can be performed on excised heart valve tissue from the site of active infection (even if frozen or embedded in paraffin), serum, cerebrospinal fluid, pleural fluid, bone marrow, bone and liver biopsies, breast milk, placenta, and fetal tissue**.** PCR testing was used to diagnose patients whom were suspected of having acute infection but initial serologic testing reveals no or low levels of antibodies. The PCR generally remains positive for 7 to 10 days in acute infection. PCR testing is also helpful in confirming the serologic diagnosis of endocarditis or vascular infection in patients who have persistent elevations of IgG anti-phase I titers.

Culture

Although *C. burnetii* does not grow in routine blood cultures, culture of this organism can be performed on blood, bone biopsies, cardiac valves, and vascular samples.

Isolation of the bacteria by culture is not recommended for routine diagnosis. It is difficult, time consuming and dangerous requiring a biosafety level 3 laboratory.

In Tunisia, few referent laboratories, from academic hospitals, perform Q fever serology, they look for total Immunoglobulins against *C burnetii,* without differentiating between Phase I and II.

Treatment

AQF

Majority of AQF resolve spontaneously within 2 to 3

weeks. However, symptomatic or suspected AQF should be treated whereas the treatment is not routinely recommended for asymptomatic form or resolved symptoms if there is no risk factors to develop CQF. The first line antibiotic is doxycycline with a duration of 2 weeks. If this antibiotic is contraindicated, fluoroquinolones, macrolides, rifampicin and trimethoprim/sulfamethoxazol (cotrimoxazol) could be used. Thorough clinical assessment for all patients with AQF is recommended to look for any immunosuppression, pregnancy and cardiac valve defect or valve disease.

Clinical and serologic follow up monitoring is mandatory for all patients after AQF. This monitoring would be closer and longer in patients with cardiovascular risk factors (Melenotte et al., 2020).

CQF

The presence of a nidus of infection with increase of phase I IgG titer (≥ 1/1024) is an indicator to start treatment. The regimen of choice is the combination of Doxycycline with Hydroxychloroquine. The duration of the treatment is 18 to 24 months in case of infective endocarditis or vascular infection. For other CQF sites the duration depends on the clinical and serologic response. Surgical treatment might be necessary if no response to antibiotics. The hydroxychloroquine is contra-indicated in case of G6PD deficiency and in case of retinal or visual field deficits. In such situations, fluoroquinolones, rifampicin, macrolides and cotrimoxazol could be an alternative for the treatment.

Cured case is defined by decrease of phase I IgG (≤1/200) with recovery of clinical symptoms. After the treatment serologic monitoring every 6 months should be done for at least 5 years, lifelong if sever valvular disease (Melenotte et al., 2020).

Pregnant woman

Treatment of AQF in pregnant woman reduces risks of adverse consequences for the fetus, and conversion to CQF. Cotrimoxazol is the antibiotic of choice; it should be given throughout pregnancy except the last two weeks. Macrolides would be alternative for treatment of CQF in pregnant women (Ghanem-Zoubi and Paul, 2020).

Perspective

Actually, based on the recent knowledge on Q fever there is tendency to change the old classification of acute and chronic Q fever to: a) acute infection including flu like illness, pneumonia, hepatitis, acute endocarditis, and other rare manifestation, and b) persistent localized infection, including chronic endocarditis, vascular infection, bone and joint infection and other forms of persistent infection. Many retrospective studies highlighted the role of anticardiolipin antibodies as a useful biological predictive marker for acute Q fever complications, and relationship between persistent *C. burnetii* infection and non-Hodgkin lymphoma (Melenotte et al., 2020).

Conclusion

In Tunisia, although acute Q fever is endemic among animals and human, only few chronic Q fever cases were published, this disease is not considered as communicable diseases for notification that is why there is no available data from the official health authorities. The real frequency of *C. burnetii*, was not known, especially among patients with negative blood culture endocarditis. We think that chronic Q fever is underestimated in our country for many reasons, mainly lack of awerness among physicians regarding this infection, and unavailability of Q fever serology in majority of our laboratories. More epidemiologic studies are needed to determine the accurate incidence and prevalence of this zoonosis in Tunisia, especially among patient with negative blood culture endocarditis and women with recurrent miscarriage.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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REFERENCES

Ameur Y, Haouala H, Fehri W, Rahal N, Mhenni H, Guediche M (1997). *Coxiella burnetii* infectious endocarditis. Apropos of a case. Annales de Cardiologie et d'angeiologie (Paris) 46(10):671-673.

Angelakis E, Mediannikov O, Socolovschi C, Mouffok N, Bassene H, Tall A (2014). *Coxiella burnetii*-positive PCR in febrile patients in rural and urban Africa. International Journal of Infection Diseases 28:107-110.

Balti G, Galon C, Derghal M, Souguir H, Guerbouj S, Rhim A (2021). The North African Hedgehog: Suitable Wild Host for Infected Ticks and Fleas and Reservoir of Vector-Borne Pathogens in Tunisia. Pathogens 10(8):953.

Barkallah M, Gharbi Y, Hmani M, Mallek Z, Gautier M, Gdoura R, Fendri I (2018). Serological and molecular evidence of coxiellosis and risk factors in sheep flocks in central-eastern Tunisia. Comparative immunology, microbiology and infectious diseases 57:15-21.

Bellazreg F, Kaabia N, Hachfi W, Khalifa M, Ben Jazia E, Ghanouchi N (2009). Acute Q fever in hospitalized patients in Central Tunisia: report of 21 cases. Clinical Microbiology and Infection 5(2):138-139.

Ben VS, Rubach MP, Halliday JEB, Cleaveland S, Reddy EA, Crump JA (2014). Epidemiology of *Coxiella burnetii* infection in Africa: an OneHealth systematic review. PLOS Neglected Tropical Diseases 8:e2787.

Bernit E, Pouget J, Janbon F (2002). Neurological involvement in acute Q fever: a report of 29 cases and review of the literature. Archives of Internal Medicine 162:693.

Botelho-Nevers E, Fournier PE, Richet H (2007). *Coxiella burnetii* infection of aortic aneurysms or vascular grafts: report of 30 new cases and evaluation of outcome. European Journal Clinical Microbiology& Infectious Diseases 26:635.

Dauby N, Gomez Galdon M, Montesinos I, Van Esbroeck M, Sersté T (2020). Q fever associated granulomatous hepatitis. International Journal Infectious Diseases 95:113-114.

Delaloye J, Pillonel T, Smaoui M, Znazen A, Abid L, Greub G (2017). Culture-independent genome sequencing of *Coxiella burnetii* from a native heart valve of a Tunisian patient with severe infective endocarditis. New Microbes &New Infections 10(21):31-35.

Fournier PE, Etienne J, Harle JR (2001). Myocarditis, a rare but severe manifestation of Q fever: report of 8 cases and review of the literature. Clinical Infectious Diseases 32:1440.

Fradi I, Drissa MA, Cheour M, Drissa H (2006). Q fever endocarditis: a case report. Tunisie Medicale 84(10):660-662.

Ghanem-Zoubi N, Paul M (2020). Q fever during pregnancy: a narrative review. Clinical Microbiology and Infection 26(7):864-870.

Guiga A, Khalifa D, Ben YW, El Amri N, Atig A, Ghannouchi N (2021). Acute Q fever in an Ankylosing Spondyloarthritis Patient Treated with Etanercept. Case Reports in Rheumatology 1:9944387.

Hammami R, Bahloul A, Charfeddine S, Feki W, Ayed NB, Abid L (2021). Q fever presenting as myocarditis. Infectious Diseases Cases 23:23.

Kaabia N, Letaief A (2009). Q fever in Tunisia. Pathologie Biologie (Paris) 57(5):439-443.

Kaabia N, Rolain JM, Khalifa M, Ben Jazia E, Bahri F, Raoult D (2006). Serologic study of rickettsioses among acute febrile patients in central Tunisia. Annals of the New York Academy of Sciences 1078:176-179.

Kampschreur LM, Wegdam-Blans MC, Wever PC (2015). Chronic Q fever diagnosis-consensus guideline versus expert opinion. Emerging Infectious Diseases 21:1183.

Kennou MF, Edlinger E (1984). Current data on rickettsial diseases in Tunisia. Archives de L'institut Pasteur de Tunis 61(4):427-33.

Letaief AO, Yacoub S, Dupont HT, Le Cam C, Ghachem L, Jemni L (1995). Seroepidemiological survey of rickettsial infections among blood donors in central Tunisia. Transactions of the Royal Society of Tropical Medicine and Hygiene 89(3):266-268.

Maurin J (1954). Investigations on the existence of Q fever in Tunisia by the reaction of deviation of the complement. Annales de l'Institut Pasteur 86(1):68-75.

Maurin M, Benoliel AM, Bongrand P, Raoult D (1992). Phagolysosomal alkalinization and the bactericidal effect of antibiotics: the *Coxiella burnetii* paradigm. Journal of Infectious Diseases 166(5):1097-1102.

Melenotte C, Million M, Raoult D (2020). New insights in *Coxiella burnetii* infection: diagnosis and therapeutic update. Expert Review of Anti-Infective Therapy 18(1):75-86.

Messous S, Grissa MH, Beltaief K, Boukef R, Nouira S, Mastouri M (2018) Bacteriology of acute exacerbations of chronic obstructive pulmonary disease in Tunisia. Revue Maladies Respiratoires 35(1):36-47.

Omezzine-Letaief A, Tissot-Dupont H, Bahri F, Ernez M, Raoult D, Jemni L (1997). Etude séroépidémiologique chez 300 malades fébriles hospitalizes dans un service de médicine et maladies infectieuses. Médecine Maladies Infectieuses 27:663-666.

Raoult D, Marrie T (1995). Q fever. Clinical Infectious Diseases 20(3):489-495.

Raoult D, Marrie T, Mege J (2005). Natural history and pathophysiology of Q fever. Lancet Infectious Diseases 5:219.

Rekik S, Trabelsi A, Znazen I, Maaloul M, Hentati I, Frikha M (2009). Prosthetic valve endocarditis: management strategies and prognosis: A ten-year analysis in a tertiary care center in Tunisia. Netherlands Heart Journal 17(2):56-60.

Rekiki A, Thabti F, Dlissi I, Russo P, Sanchis M, Pepin M (2005). Enquête sérologique sur les principales causes d'avortements infectieux chez les petits ruminants en Tunisie. Revue Médecine Vétérinaire 156(7):395-401.

Rolain JM, Lepidi H, Harlé JR (2003). Acute acalculous cholecystitis associated with Q fever: report of seven cases and review of the literature. European Journal of Clinical Microbiology and Infectious Diseases 22:222.

Salifu SP, Bukari AA, Frangoulidis D, Wheelhouse N (2019). Current perspectives on the transmission of Q fever: Highlighting the need for a systematic molecular approach for a neglected disease in Africa. Acta Tropica 193:99-105.

Selmi R, Ben SM, Mamlouk A, Ben YH, Messadi L (2019). Molecular detection and genetic characterization of the potentially pathogenic *Coxiella burnetii* and the endosymbiotic *Candidatus Midichloria mitochondrii* in ticks infesting camels (Camelus dromedarius) from Tunisia. Microbial Pathogenesis 136:103655.

Selmi R, Mamlouk A, Ben YH, Abdelaali H, Ben SM, Sellami K (2018). *Coxiella burnetii* in Tunisian dromedary camels (Camelus dromedarius): Seroprevalence, associated risk factors and seasonal dynamics. Acta Tropica 188:234-239.

Shishido AA, Letizia AG, Hartzell JD (2016). Q fever. US Army Medical Departmental Journal 68-70.

Smaoui M, Carole K, Sellami H, Kammoun S, Choura K, Maazoun L (2019). Human miscarriage and infection in Tunisia: Role of Mycoplasma hominis and high Waddlia seroprevalence. Journal of Infection in Developing Countries 13(5):410-418.

Stein A, Raoult D (1999). Pigeon pneumonia in provence: a bird-borne Q fever outbreak. Clinical Infectious Diseases 29:617.

Stein A, Saunders NA, Taylor AG, Raoult D (1993). Phylogenic homogeneity of Coxiella burnetii strains as determinated by 16S ribosomal RNA sequencing. FEMS Microbiology Letters 113(3):339-344.

Tissot DH, Raoult D, Brouqui P (1992). Epidemiologic features and clinical presentation of acute Q fever in hospitalized patients: 323 French cases. American Journal of Medicine 93:427.