The First Confirmed Pediatric Chronic Osteomyelitis due to *Coxiella Burnetii* in Oman

Nawal Al-Kindi[1*], Mubarak Al-Yaaqoubi[1], Yahya Al-Rashdi[2], Azza Al-Rashdi[3], Abdullah Al-Ajmi[4] and Amal Al-Maani[5,6]

[1]Medical microbiology department , Khowla Hospital, Oman.
[2]Clinical pharmacy department , Khowla Hospital, Oman.
[3]Central Public Health Laboratories (CPHL), Darsait, Muscat, Oman.
[4]Orthopaedic department , Khowla Hospital, Oman.
[5]Peadiatric Infection Disease department, The Royal Hospital, Oman.
[6]Directorate general for diseases surveillance and control, Oman.

Received: 10 February 2021

Accepted: 26 July 2021

***Corresponding author:** nawalakindi@gmail.com

DOI 10.5001/omj.2023.03

ABSTRACT

We describe here the first confirmed case in Oman of chronic osteomyelitis due to *Coxiella burnetii* in a previously healthy 4 year old Omani child. Although Q fever is reported to be endemic in the Middle East, the disease remains underdiagnosed because of the variable range of clinical presentations of Q fever particularly in children. Furthermore, worldwide data from Q fever cases in children are limited. After laboratory confirmation of *C. burnetii* infection using molecular and qualitative and quantitative serological assays, our case was successfully managed with a combination of oral ciprofloxacin and cotrimoxazole treatment. The duration of antimicrobial treatment and follow-up were prolonged and guided by clinical, radiological and serological responses.

Keywords *Coxiella burnetii* , osteomyelitis , ankle joint , zoonotic , molecular- testing .

INTRODUCTION

Q fever is a zoonotic infection which occurs worldwide and is caused by infection with the bacteria *Coxiella burnetii. C. burnetii* is a fastidious obligate intracellular microorganism. It forms a hardy spore-like state which allows it to resist desiccation and extreme temperatures. *C. burnetii* can survive for long periods of time in the environment and may be carried long distances by wind.[1-4] Cattle, sheep, and goats are commonly infected and transmission happens mainly by breathing in dust contaminated with infected animal body fluids or by ingestion of contaminated dairy products.[3,4] Q fever can occur during any month of the year, however most cases are reported in the spring and early summer months. This timeframe is also the peak of birthing season for cattle, sheep and goats. In 2003 a report from Oman showed that examination of sera from 54 healthy goats revealed that 28 (52%) had been infected[5]. More recently, a conference paper in 2015 on a very large study of 278 randomly selected herds of camels and 1193 camels revealed that the seroprevalence in camels in Oman was 19.4% with an individual seroprevalence range of 1.4% to 32.5% and a herd level seroprevalence of 5.4% to 52.4% in the different governorates of Oman.[6] The authors of this latter study concluded that Coxiellosis is endemic in camels in Oman.[6]

In humans, and especially among children, the majority of cases of Q fever are asymptomatic. Only 40% show clinical signs that range from acute flu-like illness to hepatitis, pneumonia and endocarditis[7]. The chronic form of the disease can develop in 1–2% of patients.[7,8] Studies have shown that people with a history of heart valve defects, endocarditis, or heart valve implants may have increased risk of chronic infection and severe disease. Unlike adults, children are less likely to have symptoms and have a milder form of the illness. Although Q fever is self-limiting in a vast majority of children, it can follow a course of relapsing febrile illness lasting for several months to years in some children.[7]

The first clinical case of Q fever in Oman was reported in 1997 with presentation of chronic pericarditis and a second case was reported in 1999 presenting with acute pneumonia.[9] Both of these cases occurred in adults. The first confirmed paediatric chronic Q fever endocarditis was reported recently 2019 in a child with congenital heart disease who was treated successfully with combination antibiotics.[10] A 2003 publication of a study performed in 2001 on the seroprevalence in 102 adults from the northern Oman provinces revealed that 9.8% were seropositive for previous *C. burnetii* infection.[5] We describe here the first confirmed case of chronic osteomyelitis due to *Coxiella burnetii* in a previously healthy Omani child who had contact with animals

CASE REPORT

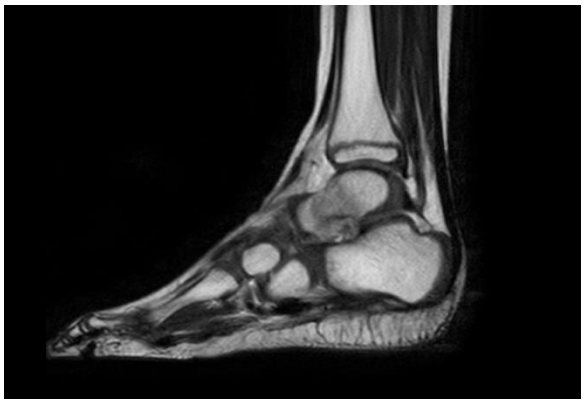
A previously well 4 year old Omani girl from Masirah Island in the eastern part of the country, presented with a 6 week history of mild pain after sustaining trauma to her left ankle after a fall while playing in the garden. Her parents noticed swelling of the left ankle and had taken her to local health centres and private clinics where she was commenced on courses of antibiotics but the swelling did not resolve. The child was admitted to Khowla Hospital , the major trauma & orthopaedics hospital in Oman, on 7th July 2019 with presentation of osteomyelitis of left talus bone as seen on magnetic resonance imaging (MRI). Review of the MRI by an orthopaedic surgeon and radiologist confirmed the presence of a cavitary lesion on left talus with surrounding oedema and periosteal collection suggesting osteomyelitis (Figures 1A-B). On admission, the child underwent debridement and drainage of her lesion. Intra operational finding showed clinical evidence of osteomyelitis of left talus bone with cavitary lesion with pus and granulation tissue. The intraoperation samples were collected while the child off antibiotic and sent for microbiological and histopathological testing. Postoperatively, the child was started on iv cloxacillin assuming that the most likely cause of

osteomyelitis for her age is methicillin sensitive S*taphylococcus aureus*. She remained haemodynamically stable and afebrile. A baseline blood work up revealed normal white blood cell count of 7.3 x 10^3/uL; - Absolute Neutrophil Count: 3.3 x 10^3/uL; – Platelets: 353 x 10^3 /uL; C Reactive Protein: <1 mg/L; Renal Function Tests ; Liver Function Tests and coagulation tests were normal. Blood cultures (3bottles) were negative after prolonged incubation. Bone biopsy and pus samples were also negative for bacterial growth after prolonged incubation of 2 weeks and gram stain showed few polymorphonuclear cells but no organisms were seen. The bone and pus samples were investigated for tuberculosis (TB) , *Brucella* and *Coxiella* using polymerase chain reaction (PCR) as the parents gave a history of animal contact and consumption of raw milk. Furthermore, it was revealed that the child's grandmother kept goats and sheep at a farm beside the house. Some of the animals had died immediately after giving birth. Laboratory investigations for mycobacterial infection on bone and pus specimens included Zeil-Nelsen stain for Acid-Fast Bacilli, Mycobacterial culture and PCR(Cepheid GenXpert,Xpert MTB/RF). All tests were negative. *Brucella* was suspected and samples were sent to the Central Public Health Laboratories (CPHL) for multiplex zoonotic PCR (Fast Track Diagnostics, Tropical Fever Africa PCR kit) which tests for 3 microorganisms ;*Brucella, Coxiella* burnetii and *Streptococcus Pneumoniae*. Due to animal exposure and raw milk consumption , brucella was highly suspected but unexpectedly its PCR turn to be negative. Also, pneumococcus PCR was negative ,but the *Coxiella burnetiid* PCR was positive form both samples with a very low CT (Cycle of Threshold)values of 22 and 28 respectively(bone and pus).A blood sample sent for *Coxiella burnetii* PCR was negative.*C. burnetii* serology (Virion Serion ELISA classic *Coxiella burnetii* phase 1 and phase 2 serology) was indicative of chronic infection and were IgG phase 1 positive and IgA phase 1 positive. The IgG phase 2 was positive , while the IgM phase 2 was negative. Samples were sent to a specialist research laboratory (Laboratoire

Cerba, Saint-Ouen-l'Aumône, France) for immunofluorescence analysis (IFA)as the test is not available locally. IFA results confirmed the diagnosis of chronic *C. burnetii* infection with high level for IgG antibodies of both phase 1 and 2. The *C. burnetii* IgG phase 1 titre was 1:2048 and IgM phase 1 of < 1:32. The *C. burnetii* IgG phase 2 titre was 1:512 and the IgM phase 2 of 1:<1:32(table1) . Histopathological examination of explanted tissue of pus and bone revealed evidence of granulomas suggestive of chronic infection (Figures 2A-B). Throughout her stay, the child remains stable. She was started on a combination of three drugs (iv ciprofloxacin, iv cotrimoxazole and oral rifampicin) targeting *C. burnetii*. She received 2 weeks of this combination therapy but she could not tolerate oral rifampicin which was stopped at the end of week 2. She completed 3 weeks of iv antibiotics when a decision was made to switch her to oral antibiotics (ciprofloxacin and cotrimoxazole). At this time she started to bear weight on her left foot and the swelling reduced. The surgical site was cleaned and she was followed up regularly by wound care nurse. Doxycycline and Hydroxychloroquine were not used because of safety issues in children. Management involved a multodisplinary team with members including paediatric infectious disease consultants, microbiologists and orthopaedic surgeon consultants . The child was discharged on 31st July 2019 and her parents were counselled about her infection and her management plan. Regular visits to the orthopaedic surgeon and paediatric infectious disease clinics were scheduled. The child was doing well and complying with her medications. A repeat IFA was done 3 months after treatment initiation and showed a 50% reduction in titers (table1). During follow up visits the child was doing well and lt foot x-ray showed improved infection. The child was referred to an immunologist to exclude possible primary and secondary immunodeficiency disorder and fortunately, no immunological defect was confirmed. At 14 months after antibiotic treatment initiation , the child showed very good clinical , laboratory and radiological response , so antibiotics treatment was stopped and a follow up left ankle X

ray was done and showed completely resolved lessen (Figure 3). A follow up sample for IFA was sent to same reference laboratory and results are awaited. The child is doing well with schadualed visits to pediatric infection disease and orthopedic clinics before final discharge.

A.



B.

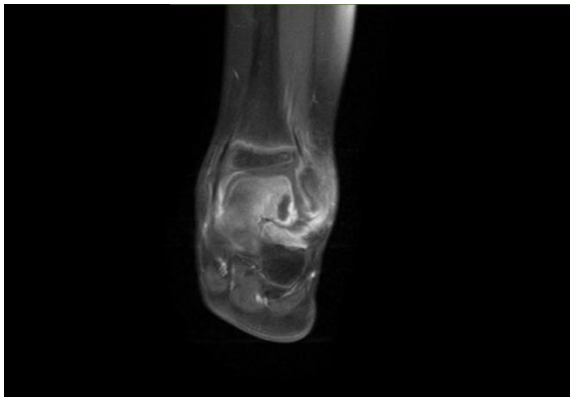
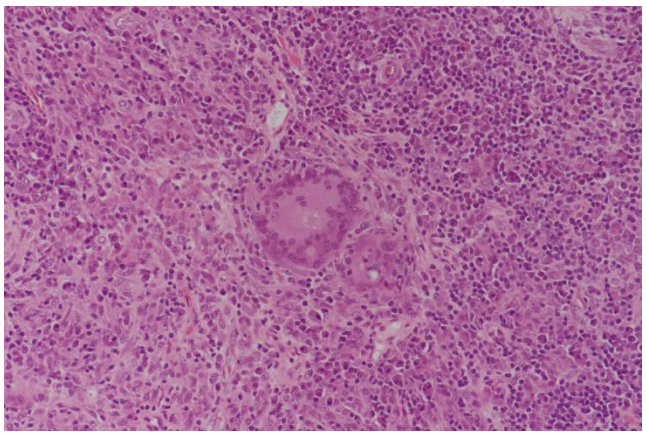


Figure 1: Left foot MRI at presentation showing talus cavitary lesson with periosteal collection.

A. (20X MNG)



B. (20X Inflamed synovium)

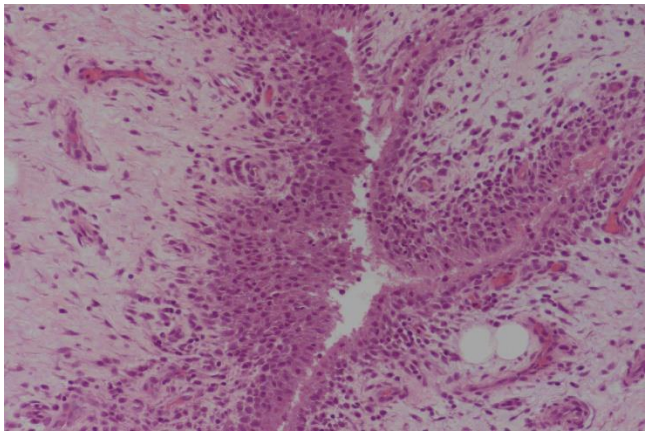


Figure 2: Histopathology sections of the bone tissue biopsy taken intraoperatively.

Table 1: IFA of serum samples sent to France twice:

	Phase1 IgG	Phase1 IgM	Phase2 IgG	Phase2 IgM
July 2019	1:2048	< 1:32	1:512	<1: 32
Nov 2019	1:1024	< 1:32	1:256	< 1:32

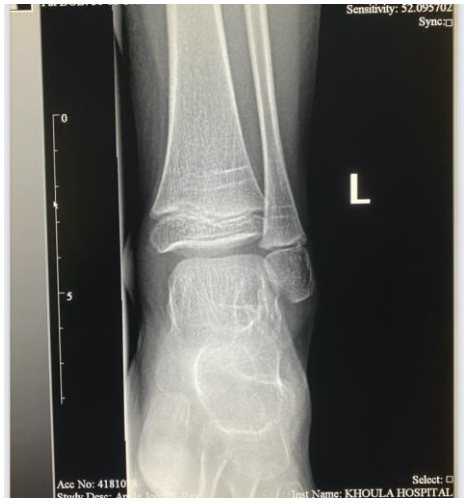


Figure 3: Left ankle Xray done at end of treatment course (after 14 months of antibiotics course).

DISCUSSION

Q fever is a zoonotic disease of public health importance and occurs worldwide. We report the first confirmed case of osteomyelitis due to *Coxiella burnetii* in a previously healthy Omani child. Q fever is a nationally notifiable disease in Oman. In a recent publication, health authorities in the country consider Q fever an emerging zoonotic infection which remains challenging.[11] However, larger seroprevalence studies need to be performed on cohorts of Omani children and adults. With regards to neighbouring countries, a recent study using real-time PCR detection of the *IS1111* gene confirmed that 4.2% of 216 suspected cases were positive for *C. burnetii*.[12] Similar prevalence was observed in East Azerbaijan and Mazandaran provinces of 3.6% and 5.3% respectively. However in North-eastern Iran, a slightly higher prevalence of 7.4% was observed.[13] Seroprevalence of IgG phase I and II antibodies in humans were reported to be 19.80% and 32.86%.[14] Variable seroprevalence have been reported in Egypt; 20% among adult blood donors in the Suez Canal area, 16% in the Nile Valley, and 10% in the Nile Delta.[15] Furthermore, antibodies to *C. burnetii* were reported in 18.3% of blood donors in Morocco and 26% in Tunisia.[16] Moreover a recent report described a cluster of 19 Q fever cases in a single tertiary centre in Saudi Arabia.[17] In Europe, the largest known epidemic of acute Q fever occurred over three years from 2007 to 2010 in the Netherlands with more than 4000 cases notified and resulting in 6 patients with chronic Q Fever deaths of related causes [18,19]

Despite having a substantial burden, only one vaccine was licensed in 1989 and in 2002 to combat Q fever disease, a nationally funded Q fever vaccination programme was introduced in Australia. Uptake rates were close to 100% in the high risk group of abattoir workers and 43% in farmers.[20] Between 2002 and 2006, Q fever notification rates declined by 50% particularly in young adult males.[20] As Jaff and Wilson in their recent commentary have stated that Q fever is endemic in the Middle East, we would highlight the positive implications for the introduction of the vaccine in this region.[21]

As symptoms can vary widely, clinical diagnosis of human Q fever cases based on clinical symptoms alone remains challenging. As a result, human Q fever cases remain undiagnosed because most clinicians fail to spot this disease in their differential diagnosis. Laboratory confirmation is therefore an essential requirement in the confirmation of a clinical diagnosis and is mainly based on serological tests, qualitative ELISA and quantitative IFA as the gold standard test. *C. burnetii* has two different antigenic phases which aid in the diagnosis: phase I and phase II. In acute cases of Q fever, the titre of antibody against phase II is usually higher than phase I antibody. Acute disease is mostly diagnosed via an increase in the antibody titre within three to four weeks of the onset of the disease. In comparison, in chronic cases, the titre of antibody is higher in phase I compared to phase II. This increase in the titre of antibodies in phases I and II may persist for months to years after the first infection of this disease.[8] The recent development of molecular PCR based tests allow diagnosis of early acute Q fever. The PCR tests in tissue samples from our patient showed very high *C. burnetti* loads and histological examination of tissues showed granuloma formation (Figure 2) providing definitive confirmation of infection. Nourse et al have suggested that children who develop chronic Q fever infection are likely to have a specific immunological defect which contributes to unfavourable host/pathogen interaction and delayed clearance of the infection.[22]

Due to the broad variety of clinical presentations of Q fever in children, Q fever remains underdiagnosed and data from Q fever cases in children are limited with isolated reports of chronic infection (Maltezou et al, 20012).[23] Q fever in children is reported to be asymptomatic in many cases with frequently described clinical symptoms such as onset of fever with respiratory and/or gastrointestinal symptoms.[24] Although rare, severe manifestations such as osteomyelitis have been described.[24] Although a combination of doxycycline plus hydroxychloroquine is recommended, we did not use this treatment option

for several reasons including the young age of our patient, risk of teeth discolouration and the questionable long term effectiveness of this treatment for osteomyelitis. Although our patient did not tolerate rifampicin, she was successfully managed with a combination of oral ciprofloxacin and cotrimoxazole treatment highlighting the need for further studies.

CONCLUSION

Q fever osteomyelitis is a rare and probably an underreported disease which may be prevalent in children in Oman. As doxycycline and hydroxychloroquine are not suitable for children, the most effective treatment for Q fever osteomyelitis needs to be recommended. In our patient, surgical debridement helped to establish the diagnosis and had therapeutic value as well. The effective treatment of our case with a combination of oral ciprofloxacin and cotrimoxazole should be considered in children. Guidelines on Q fever treatment in children are needed with recommendations on use and safety of doxycycline and hydroxychloroquine.

Disclosure The authors declared no conflict of interest.

Competing Interest. The authors declare that they have no competing interests.

Authors' contributions All authors have read and agreed to the final manuscript.

Ethics approval and consent to participate Not applicable.

Funding No funding was required.

Authors' contributions

Dr Nawal Al-Kindi : writing up the case report , responsible for diagnostic requesting and testing , following up case until case clinical , radiological and laboratory management is fully completed.

Dr Mubarak Al-Yaqoubi , diagnostic follow up and case report review.

Mr Yahya Al-Rashdi : monitoring antimicrobial dosing , frequency and monthly prescription.

Dr Azza Al-Rashdi : responsible for molecular testing in the central laboratory.

Dr Abdulla Al-Ajmi: orthopaedic surgery and general surgical management and care review .

Dr Amal Al-Maani : saw the case in infectious disease clinic for 18 months , responsible for overall case management and follow up, care report review.

Acknowledgments

All institutes were the case was investigated , managed and followed up . These include the Royal Hospital infection disease department , Khowla Hospital medical microbiology department , Khowla hospital orthopaedic department , khowla Hospital radiology department and the Central Public Health Laboratories (CPHL) where the RT-PCR testing was done.

REFERENCES

1. Maurin M, Raoult D. Q fever. Clin Microbiol Rev. 1999;12:518-553.
2. Norlander L. Q fever epidemiology and pathogenesis. Microbes Infect 2000;2:417-424.
3. Eldin C, Me ´lenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, et al. From Q fever to *Coxiella burnetii* infection: a paradigm change. Clinical microbiology reviews. 2017; 30(1):115–90. https://doi.org/ 10.1128/CMR.00045-16 PMID: 27856520
4. Angelakis E, Raoult D. Q Fever. Veterinary Microbiology. 2010; 140(3–4):297–309. https://doi.org/10. 1016/j.vetmic.2009.07.016 PMID: 19875249
5. Scrimgeour EM, Al-Ismaily SI, Rolain JM, Al-Dhahry SH, et al. Q Fever in human and livestock populations in Oman. Ann N Y Acad Sci 2003; 990:221–225.

6. Hussain MH, Al-Makhladi S, Al-Rawahi A, Rajamony S, Al-Zadjali MS, Asubaihi S, Al-Sidairi T, Al-Maawali M. Seroprevalence of *Coxiella Burnetii* (Q Fever) antibodies in the camels (Camelus Dromedarius) of the Sultanate of Oman. Proceedings of the 4th Conference of ISOCARD, Kazakhstan. 2015. 251-252.
7. Anderson A, Bijlmer H, Fournier PE, Graves S, Hartzell J, Kersh GJ, Limonard G, Marrie TJ, Massung RF, McQuiston JH, Nicholson WL, Paddock CD, Sexton DJ. Diagnosis and Management of Q Fever — United States, 2013 Recommendations from CDC and the Q Fever Working Group. MMWR 2013;62 (3):1-32.
8. Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infect Dis. 2005 Apr;5(4):219-26.
9. Scrimgeour EM, Johnston WJ, Al Dhahry SHS, El-Khatim HS, John V, Musa M. First report of Q fever in Oman. Emerg. Infect. Dis. 2000;6:74−76.
10. AlAraimi H , Al-Alawi K, Al-Jardani A, Paul G, Al-Sukaiti N, Al-Farqani A and Al-Maani A. Chronic Q Fever Endocarditis in an Omani Child: The First Pediatric Case Report from Oman. Oman Medical Journal [2020], Vol. 35, No. 5: e180
11. Al Awaidy S and Al Hashimi H. Zoonotic Diseases in Oman: Successes, Challenges and Future Directions. Vector Borne Zoonotic Dis 2019; Sep 5:1-9.
12. Esmaeili S, Mohabati Mobarez A, Khalili M, MostafaviE, Moradnejad P. Genetic evidence of *Coxiella burnetii* infection in acute febrile illnesses in Iran. PLoS Negl Trop Dis 2019; 13(2): e0007181.https://doi.org/10.1371/journal. pntd.0007181
13. Khalili M, Reza Naderi H, Salehnia N, Abiri Z. Detection of *Coxiella burnetii* in acute undifferentiated febrile illnesses (AUFIs) in Iran. Tropical Doctor. 2016; 46(4):221–4. https://doi.org/10.1177/ 0049475515624855 PMID: 26767385

14. Mobarez AM, Amiri FB, Esmaeili S. Seroprevalence of Q fever among human and animal in Iran; A systematic review and meta-analysis. PLoS neglected tropical diseases. 2017; 11(4):e0005521. https:// doi.org/10.1371/journal.pntd.0005521 PMID: 28394889
15. Botros BA, Soliman AK, Salib AW, Olson J, Hibbs RG, Williams JC, Darwish M, el Tigani A, Watts DM J *Coxiella burnetii* antibody prevalence among human populations in north-east Africa determined by enzyme immunoassay. Trop Med Hyg. 1995;98(3):173-8.
16. Letaief AO, Yacoub S, Dupont HT, Le Cam C, Ghachem L, Jemni L, Raoult D. Seroepidemiological survey of rickettsial infections among blood donors in central Tunisia. Trans R Soc Trop Med Hyg. 1995; 89(3):266-8.
17. Elzein FE, Alsherbeeni N, Alnajashi K, Alsufyani E, Akhtar MY, Albalawi R, Albarrag AM, Kaabia N, Mehdi S, Alzahrani A, Raoult D. Ten-year experience of Q fever endocarditis in a tertiary cardiac center in Saudi Arabia. Int J Infect Dis. 2019;88:21-26. doi: 10.1016/j.ijid.2019.07.035. [Epub ahead of print]
18. van der Hoek W, et al. Smooth incidence maps give valuable insight into Q fever outbreaks in The Netherlands. Geospat Health. 2012;7(1):127–34.
19. Roest HI, et al. The Q fever epidemic in The Netherlands: history, onset, response and reflection. Epidemiol Infect. 2011;139(1):1–12.
20. Gidding HF, Wallace C, Lawrence GL, McIntyre PB. Australia's national Q fever vaccination program. Vaccine 2009; 27(14):2037-2041
21. Jaff D, Wilson P. Q Fever: A neglected disease in the Middle East. J Health Systems 2016;11(2):12-14.
22. Nourse C, Allworth A, Jones A, Horvath R, McCormack J, Bartlett J, Hayes D, Robson JM. Three cases of Q fever osteomyelitis in children and a review of the literature. Clin Infect Dis. 2004;39(7):e61-6.

23. Maltezou HC, Raoult D Q fever in children Lancet Infect Dis. 2002 Nov;2(11):686-91.
24. Slok ENE, Dijkstra F, de Vries E, Rietveld A, Wong A, Notermans DW, van Steenbergen JE. Estimation of acute and chronic Q fever incidence in children during a three-year outbreak in the Netherlands and a comparison with international literature. BMC Res Notes (2015) 8:456 DOI 10.1186/s13104-015-1389-0