***Brucella melitensis* prosthetic joint infection in a traveller returning to the UK from Thailand: case report and review of the literature**

Joseph M Lewis1,2, Jonathan Folb3, Sanjay Kalra4, S Bertel Squire1,5, Miriam Taegtmeyer1,5, Nick J Beeching1,3, 5,6

1 Tropical and Infectious Disease Unit, Royal Liverpool University Hospital, Liverpool, UK

2 Wellcome Trust Liverpool Glasgow Centre for Global Health Research, Liverpool, UK

3 Brucella Reference Unit, Liverpool Clinical Laboratories, Royal Liverpool University Hospital, Liverpool, UK

4 Department of Orthopaedics, Royal Liverpool University Hospital, Liverpool, UK

5 Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

6 NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool, L69 7BE, UK

**Abstract word count: 253**

**Word count: 1599**

**Tables: 1**

**References: 36**

**Running head: *Brucella* prosthetic joint infection**

**Key words: Brucellosis; prosthetic joint infection; travel medicine; returning traveller**

**Corresponding Author:**

Joseph M. Lewis

Wellcome Trust Liverpool Glasgow Centre for Global Health Research

Block E Royal Infirmary Complex

70 Pembroke Place

Liverpool

L69 3GF

Email: joseph.lewis@liverpool.ac.uk

T: +44 7969 419910

***Brucella melitensis* prosthetic joint infection in a traveller returning to the UK from Thailand: case report and review of the literature**

**Abstract**

**Background**

*Brucella* spp*.* prosthetic joint infections are infrequently reported in the literature, particularly in returning travellers, and optimal treatment is unknown.

**Method**

We describe a prosthetic joint infection (PJI) caused by *Brucella melitensis* in a traveller returning to the UK from Thailand, which we believe to be the first detailed report of brucellosis in a traveller returning from this area. The 24 cases of *Brucella*-related PJI reported in the literature are summarised.

**Results**

The diagnosis of *Brucella*-related PJI is difficult to make; only 30% of blood cultures and 75% of joint aspiration cultures were positive in the reported cases. Culture of intraoperative samples provides the best diagnostic yield. In the absence of radiological evidence of joint loosening, combination antimicrobial therapy alone may be appropriate treatment in the first instance; this was successful in 6/7 [86%] of patients, though small numbers of patients and the likelihood of reporting bias warrant caution in drawing any firm conclusions about optimal treatment. Aerosolisation of synovial fluid during joint aspiration procedures and nosocomial infection has been described.

**Conclusions**

*Brucella*-related PJI should be considered in the differential of travellers returning from endemic areas with PJI, including Thailand. Personal protective equipment including fit tested filtering face piece-3 (FFP3) mask or equivalent is recommended for personnel carrying out joint aspiration when brucellosis is suspected. Travellers can reduce the risk of brucellosis by avoiding unpasteurised dairy products and animal contact (particularly on farms and abattoirs) in endemic areas and should be counselled regarding these risks as part of their pre-travel assessment.

***Brucella melitensis* prosthetic joint infection in a traveller returning to the UK from Thailand: case report and review of the literature**

* 1. **Introduction**

Brucellosis is a zoonotic infection transmitted to humans from fluids of infected animals or through consumption of unpasteurised dairy products [1]. It is caused by *Brucella* spp., intracellular Gram-negative coccobacilli. Four species cause most cases of human disease, each with a different animal host reservoir: *B. melitensis* (goats, camels) is most common, followed by *B. abortus* (cattle), *B. suis* (pigs) and *B. canis* (dogs). Infections with new species such a *B. pinnepedialis* and *B. ceti* (marine animals) are occasionally recognized [2]. It can cause an acute febrile illness after a usual incubation period of 1-4 weeks, ranging up to 6 months, or chronic infection, which can be without focus or can affect any organ system. Osteoarticular involvement is the most common focal presentation. Diagnosis is usually based on serology, augmented when possible by culture of *Brucella* organisms from blood, synovial fluid, or bone. Promising molecular methods are in development. Treatment is usually with combination therapy of doxycycline, rifampicin +/- an aminoglycoside for 6-12 weeks [1]. Prosthetic joint infections (PJI) caused by *Brucella spp.* are uncommonly reported in the literature. We describe a PJI caused by *Brucella melitensis* in a traveller returning to the UK from Thailand, the first detailed report of brucellosis in a traveller returning from this area; we also present a review of the 24 reported cases of Brucella-related PJI in the literature.

* 1. **Materials and Methods.**
		1. **Case Report**

A 51-year old UK resident attended our clinic on 5 May 2015 with a 21-day history of daily rigors, profuse sweating attacks and high fever. He had returned from Thailand three months earlier. He also had pain and swelling in his left knee, in which he had an uncomplicated total knee replacement 5 years previously for early onset osteoarthritis following trauma. The only abnormalities on examination were fever of 38.3°C and a small effusion in the symptomatic knee. Blood cultures yielded Gram-negative coccobacilli after 3 days (BioMerieux Bact/ALERT blood culture system), identified as *Brucella melitensis* by matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Bruker microflex LT), but not before two laboratory scientists had been exposed to open bacterial culture plates. The organism was confirmed as *B. melitensis* biotype 3 in the Veterinary Investigation Centre in Weybridge. Standard agglutination tests for brucellosis were suggestive of chronic infection, with IgG titres of >1:2560 and IgM 1:80.

Aspiration of the knee was carried out by the orthopaedic team, equipped with personal protective equipment [PPE] consisting of gown, gloves, apron, visor and filtering face piece-3 [FFP3] respirator. Cloudy fluid was aspirated; this contained over 6000 lymphocytes/mm3 and cultured *Brucella melitensis* after 7 days. The patient commenced doxycycline and rifampicin 600mg daily for 6 months, together with parenteral gentamicin 5mg/kg/day for the first 14 days, with resolution of his symptoms and preservation of his implant without revision surgery. Twelve months later he has fully recovered with no signs of loosening of the joint prosthesis on plain x-rays. The exposed laboratory personnel were given doxycycline 100mg twice daily for 21 days as postexposure prophylaxis according to UK guidelines [3].

The patient made frequent visits to Thailand where he had most recently stayed with a friend on his farm in Nakom Pathom province from 11 December 2014 to 8 January 2015. During that time, he helped deliver several parturient goats and handled newly born kids and other products of conception with his bare hands. He had not consumed unpasteurised dairy products and had no contact with cattle or buffaloes. Two farm workers had contemporaneous fevers, only recognised to be due to brucellosis and treated appropriately after our patient was diagnosed.

* + 1. **Literature review**

PubMed and Scopus databases were searched using the search string *(((((((prosth\*) OR replacement)) OR arthroplasty)) AND (((knee) OR hip) OR joint))) AND brucell\*.* Studies were reviewed and data extracted by one author (JL), with no restriction on date or language.Prosthetic joint brucellosis was defined as either a) *Brucella* spp. recovered from prosthetic joint synovial fluid culture OR b) signs and symptoms consistent with PJI AND *Brucella* spp. recovered from blood OR positive serology (standard agglutination test [SAT] titre > 1:160 OR fourfold rise in titre between acute and convalescent samples).

**3.1 Results and discussion**

The search returned 48 results in Scopus and 26 in PubMed. After removal of duplicates, 47 remained. 18 reports contained data on 23 patients with of *Brucella*-related prosthetic joint infection including 5 knees in 4 patients; only 3 were in returning travellers [4–21]. Table 1 summarises all 24 cases including: gender, country of exposure, type of implant and time to symptom onset. In all cases *Brucella spp*. were recovered from blood, synovial fluid or operative tissue sample. No diagnoses were made using serology alone.

It is possible to draw several conclusions from these cases; *Brucella-*related PJI is a late complication of joint arthroplasty, with a median onset of 36 months after the procedure. The diagnosis can be difficult to make: only 30% (3/10) of reported blood cultures and 75% (9/12) of reported joint aspiration samples cultured *Brucella* organisms. Culture of intra-operative tissue samples probably provides the best yield and confirmed the diagnosis in 15/24 cases; in these 15 cases joint aspiration was either not carried out (12/15) or was culture-negative (3/15). In the absence of radiological evidence of implant loosening, medical management with antibiotics alone appears to be effective in the first instance; of 24 patients with 27 infected prosthetic joints, 7 patients (with 9 infected prosthetic joints) had radiologically well-seated implants with no abscess or draining sinus. These patients underwent antibiotic treatment alone for between 6-52 weeks, with cure in 6/7 patients (8/9 joints) and failure of medical therapy necessitating surgery in only one patient (one joint). One patient with an infected joint that was radiologically well seated had a draining sinus, but was successfully treated with debridement and adjuvant antibiotics without explant of the prosthesis. However, caution must be exercised in drawing firm conclusions on optimal treatment from these data, given the small numbers and the likelihood of selection bias inherent in case reports.

Sixteen patients (with 17 infected joints) had features of loosening on imaging; these all underwent either 1- or 2-stage revision of their prosthesis alongside antibiotic therapy, all with favourable outcome. One patient was lost to follow up. Follow up was for a median of 24 months.

These cases also provide some guidance on appropriate infection control measures when considering a diagnosis of *Brucella-*related PJI. Infection of laboratory staff by exposure to *Brucella* spp. is well recognised. Procedures that generate aerosolized bacteria provide the highest risk of exposure [22]. Synovial fluid from *Brucella*-infected joints is likely to have a lower bacillary load than culture bottles or plates and therefore exposure to synovial fluid during joint aspiration or joint revision surgery probably represents a lower risk exposure. Nevertheless, a case of transmission during joint aspiration has been described, to a radiology technician who assisted with injecting synovial fluid from a *Brucella*-infected joint from a syringe into a sample container[20]. Neither UK [3] nor US guidelines [23] provide recommendations for risk assessment of potential *Brucella* exposure outside the laboratory, or recommendations for PPE while performing joint aspiration or surgery. We recommend that healthcare workers undertaking aspiration of or surgery on joints in which *Brucella* infection is suspected or confirmed are outfitted with PPE including gown, visor and fit-tested FFP3 respirator or equivalent.

Brucellosis is not a diagnosis that would usually be considered in a traveller returning from Thailand [24]. Two cases acquired in Thailand have been mentioned in passing in reviews of children[25] and adult[26] travellers returning to North America and Europe respectively. Foci in China, Mongolia and Central Eurasia are well recognised but the range of other countries newly affected by brucellosis continues to expand [2,27–30]. Human infections are under-reported compared to the patchy knowledge of its increasing incidence in livestock in South Asia [31]. A boy acquired brucellosis from raw goat’s milk in Penang, Malaysia in 2010 and a German visitor acquired brucellosis in Myanmar from drinking lassi [32]. An outbreak of caprine and human brucellosis in Ratchaburi Province in Thailand was investigated in 2003 [33] and there have been sporadic case reports and more recent reviews of emerging brucellosis endemicity in Thailand over the past decade [34–36]. As demonstrated by our patient, the highest risk to humans in Thailand is exposure to parturient goats (*B. melitensis*) but there is a separate risk of *B. abortus* transmission from buffaloes. Diagnosis of illness in travellers can highlight the presence of locally unrecognised infections, as shown by this patient and his contacts.

**4.1 Conclusion**

In conclusion, we report the first detailed case report of brucellosis in a traveller returning from Thailand. Clinicians should consider brucellosis as well as the more commonly encountered causes of fever in returnees from this area. Brucellosis should be included in the list of possible causes of an infected prosthetic joint in patients who have an appropriate epidemiological risk and PPE, including fit-tested masks, should be used by operators undertaking joint aspiration or surgery in such cases. Though the small number of cases identified in this review warrants caution about drawing any firm conclusions regarding optimal treatment, in the absence of implant loosening, treatment with antibiotics may be appropriate in the first instance. There are no specific strategies for avoidance of *Brucella* spp. PJI beyond those needed by all travellers to prevent brucellosis. These include the avoidance of unpasteurised dairy products (including lassi and buffalo milk or cheese) and animal contact (particularly in farms or abattoirs) in endemic areas. Travellers (with or without prosthetic joints) should be made aware of these risks as part of their standard pre-travel assessment.

**Acknowledgments.**

Preliminary data about this patient were published on-line in May 2015 *(11)*, and reported through the GeoSentinel network (of which LSTM is a contributing centre). We thank the patient for consenting to his details being published.

**Conflict of interest.**

**Nil**

**Funding.**

NJB is partially supported by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Emerging and Zoonotic Infections, a partnership between the University of Liverpool and Public Health England, in collaboration with the Liverpool School of Tropical Medicine. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England. JML is supported by the Wellcome Trust as a clinical PhD fellow (grant number 109105/Z/15/Z).

**References**

[1] Beeching N, Corbel M. Brucellosis. Chapter 194e. In: Fauci A, Braunwald E, Kasper D, Hauser S, Longo D, Jameson J, et al., editors. Harrison’s Priniciples Intern. Med. 19th ed., McGraw-Hill; 2015, p. 1–5.

[2] Pappas G. The changing Brucella ecology: novel reservoirs, new threats. Int J Antimicrob Agents 2010;36 Suppl 1:S8–11.

[3] Brucella Reference Laboratory Public Health England. Procedural Checklist to follow after a laboratory exposure to Brucella spp. Updated 28 March 2013 n.d. https://www.gov.uk/government/publications/brucella-reference-unit-bru-managing-laboratory-exposure (accessed September 27, 2015).

[4] Jones RE, Berryhill WH, Smith J, Hofmann A, Rogers D. Secondary infection of a total hip replacement with Brucella abortus. Orthopedics 1983;6:184–6.

[5] Agarwal S, Kadhi SK, Rooney RJ. Brucellosis complicating bilateral total knee arthroplasty. Clin Orthop Relat Res 1991:179–81.

[6] Ortí A, Roig P, Alcalá R, Navarro V, Salavert M, Martín C, et al. Brucellar prosthetic arthritis in a total knee replacement. Eur J Clin Microbiol Infect Dis 1997;16:843–5.

[7] Navarro V, Solera J, Martínez-Alfaro E, Sáez L, Escribano E, Pérez-Flores JC. Brucellar osteomyelitis involving prosthetic extra-articular hardware. J Infect 1997;35:192–4.

[8] Malizos KN, Makris CA, Soucacos PN. Total knee arthroplasties infected by Brucella melitensis: a case report. Am J Orthop (Belle Mead NJ) 1997;26:283–5.

[9] Ortega-Andreu M, Rodriguez-Merchan EC, Aguera-Gavalda M. Brucellosis as a cause of septic loosening of total hip arthroplasty. J Arthroplasty 2002;17:384–7.

[10] Weil Y, Mattan Y, Liebergall M, Rahav G. Brucella prosthetic joint infection: a report of 3 cases and a review of the literature. Clin Infect Dis 2003;36:e81–6.

[11] Kasim RA, Araj GF, Afeiche NE, Tabbarah ZA. Brucella infection in total hip replacement: case report and review of the literature. Scand J Infect Dis 2004;36:65–7.

[12] Cairó M, Calbo E, Gómez L, Matamala A, Asunción J, Cuchi E, et al. Foreign-body osteoarticular infection by Brucella melitensis: A report of three cases. J Bone Joint Surg Am 2006;88:202–4.

[13] Ruiz-Iban MA, Crespo P, Diaz-Peletier R, Rozado AM, Lopez-Pardo A. Total hip arthroplasty infected by Brucella: a report of two cases. J Orthop Surg (Hong Kong) 2006;14:99–103.

[14] Marbach F, Saiah L, Fischer J-F, Huismans J, Cometta A. Prosthetic joint infection of the knee due to Brucella spp . Rev Med Suisse 2007;3:1007–9.

[15] Tena D, Romanillos O, Rodríguez-Zapata M, de la Torre B, Pérez-Pomata MT, Viana R, et al. Prosthetic hip infection due to Brucella melitensis: case report and literature review. Diagn Microbiol Infect Dis 2007;58:481–5.

[16] Tassinari E, Di Motta D, Giardina F, Traina F, De Fine M, Toni A. Brucella infection in total knee arthroplasty. Case report and revision of the literature. Chir Organi Mov 2008;92:55–9.

[17] Dauty M, Dubois C, Coisy M. Bilateral knee arthroplasty infection due to Brucella melitensis: a rare pathology? Joint Bone Spine 2009;76:215–6.

[18] Erdogan H, Cakmak G, Erdogan A, Arslan H. Brucella melitensis infection in total knee arthroplasty: a case report. Knee Surg Sports Traumatol Arthrosc 2010;18:908–10.

[19] Nichols M, Thompson D, Carothers JT, Klauber J, Stoddard RA, Guerra MA, et al. Brucella abortus exposure during an orthopedic surgical procedure in New Mexico, 2010. Infect Control Hosp Epidemiol 2014;35:1072–3.

[20] Lowe CF, Showler AJ, Perera S, McIntyre S, Qureshi R, Patel SN, et al. Hospital-associated transmission of Brucella melitensis outside the laboratory. Emerg Infect Dis 2015;21:150–2.

[21] Carothers JT, Nichols MC, Thompson DL. Failure of total hip arthroplasty secondary to infection caused by Brucella abortus and the risk of transmission to operative staff. Am J Orthop 2015;44:E42–5.

[22] Traxler RM, Lehman MW, Bosserman EA, Guerra MA, Smith TL. A literature review of laboratory-acquired brucellosis. J Clin Microbiol 2013;51:3055–62.

[23] Laboratory-acquired brucellosis--Indiana and Minnesota, 2006. MMWR Morb Mortal Wkly Rep 2008;57:39–42.

[24] Leder K, Torresi J, Libman MD, Cramer JP, Castelli F, Schlagenhauf P, et al. GeoSentinel Surveillance of Illness in Returned Travelers, 2007–2011. Ann Intern Med 2013;158:456.

[25] Shen MW. Diagnostic and therapeutic challenges of childhood brucellosis in a nonendemic country. Pediatrics 2008;121:e1178–83. doi:10.1542/peds.2007-1874.

[26] Field V, Gautret P, Schlagenhauf P, Burchard G-D, Caumes E, Jensenius M, et al. Travel and migration associated infectious diseases morbidity in Europe, 2008. BMC Infect Dis 2010;10:330.

[27] Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos E V. The new global map of human brucellosis. Lancet Infect Dis 2006;6:91–9.

[28] Dean AS, Crump L, Greter H, Schelling E, Zinsstag J. Global burden of human brucellosis: a systematic review of disease frequency. PLoS Negl Trop Dis 2012;6:e1865.

[29] Gerada A, Beeching NJ. Brucellosis and travel. Travel Med Infect Dis n.d.;14:180–1.

[30] Norman FF, Monge-Maillo B, Chamorro-Tojeiro S, Pérez-Molina J-A, López-Vélez R. Imported brucellosis: A case series and literature review. Travel Med Infect Dis n.d.;14:182–99.

[31] Garin-Bastuji B, Jaÿ M, Mick V. Review and update in Brucellosis in Asia and Pacific Region: The 4th FAO‐APHCA/OIE/DLD Regional Workshop on Brucellosis Diagnosis and Control in Asia and Pacific Region 2014. Chang Mai,Thailand: n.d.

[32] Lewis J, Taegtmeyer M, Murray S, Folb J, Squire S, Beeching N. Brucellosis, human, melitensis – UK ex Thailand (Nakom Pathom). ProMED-Mail n.d.:20150521.3377052. www.promedmail.org (accessed September 19, 2015).

[33] Laosiritaworn Y, Hinjoy S, Chuxnum T, Vagus A, Choomkasien P. Re-emerging human brucellosis, Thailand 2003. Bull Dep Med Serv 2007;32:415–23.

[34] Wongphruksasoong V, Santayakorn S, Sitthi W, Chuxnum T, Pipatjaturong N, Kunthu A, et al. An outbreak of Brucella melitensis among goat farmers in Thailand, December 2009. Outbreak Surveill Investig Rep 2012;5:14–21.

[35] Ekpanyaskul C, Santiwattanakul S, Tantisiriwat W, Buppanharun W. Factors associated with seropositive antibodies to Brucella melitensis in the Nakhon Nayok, Thailand. J Med Assoc Thai 2012;95 Suppl 1:S40–6.

[36] Manosuthi W, Thummakul T, Vibhagool A, Vorachit M, Malathum K. Case report: Brucellosis: a re-emerging disease in Thailand. Southeast Asian J Trop Med Public Health 2004;35:109–12.