INTRODUCTION

The global incidence of tuberculosis (TB) infection was estimated by the WHO to be 10 million cases in 2018, 85% of whom had pulmonary TB (pTB) infection (WHO 2019). In Europe, the extra-pulmonary TB (EPTB) incidence is increasing, accounting for 22.6% of new cases reported in 2017 (ECDC 2019). Furthermore, the incidence of articular TB infections has risen in Europe (Jutte 2004, Lesic 2010). This is reflected in UK surveillance data, where in 2017, 2.2% of new TB cases presented with non-spinal bone infections (Kruijshaar 2009, PHE 2018). Globally, this rise in EPTB infections has largely been ascribed to a growing population of immunosuppressed patients including those on long-term steroids and biologic therapies, as well as to an ageing population (Pigrau-Serrallach 2013, Byng-Maddick 2016). However, in low-incidence countries in Europe the rise in articular TB infections has also been attributed to increasing rates of migration (Jutte 2004, Krujishaar 2009).

EPTB infection is thought to occur through haematogenous, contiguous or lymphatic spread in the primary infection stage, when mycobacteria can spread to any organ or tissue and remain dormant for years. Articular infection most commonly affects weight-bearing large joints such as the spine, knees and hips. Infection is often slowly progressing with joint effusions and pain, progressing to the formation of sinus tracts and eventually to complete joint destruction (Hogan 2017). Initial symptoms are vague and may mimic other conditions such as bacterial osteoarticular infection. This can result in significant diagnostic delay, especially in settings where TB is non-endemic and clinical suspicion is low (Erdem 2005, Broderick 2018). Most studies describing osteoarticular TB have focused on paediatric populations or on spinal TB with only a few published case series of extra-spinal articular TB in adults (Ali 2012, Johansen 2015, Lesic 2010, Qian 2018, Talbot 2007).

In the UK, the National Institute for Clinical Excellence (NICE) advises management of all cases of EPTB without central nervous system (CNS) involvement with the same regimen as pTB; using standard quadruple therapy; defined as 6 months of Rifampicin and Isoniazid, with the addition of Ethambutol and Pyrazinamide for the first two months (NICE 2016). This is in line with WHO guidance, however, the joint ATS/IDSA guidance in the United States, suggests extending osteoarticular TB treatment to a total of 9 months (WHO 2017, ATS/IDSA 2016). There are no national or international guidelines for surgical intervention in extraspinal osteoarticular TB. However, there is limited evidence to support decisions regarding duration of anti-tuberculous

therapy (ATT) and need for surgical intervention. Therefore, current practice is based on expert opinion.

Our institution serves a population of 2.6 million people in East London who have among the highest incidence rates of TB reported nationally; with the average annual rate between 2016-2018 ranging from 23.4/100,000 population in Tower Hamlets to 49.3/100,000 population in Newham (PHE 2019, CQC 2017). We performed a retrospective observational study of adult cases of extra-spinal articular TB with the aim of characterising demographics, presenting features, diagnostic delay and treatment outcomes.

METHODS:

All cases of extra-spinal articular TB diagnosed at our institution between 1 January 2004 and 31 December 2014 were included and identified from the London TB Register (LTBR). Demographic data extracted from the LTBR of extra-spinal articular TB cases were compared to controls with TB at all other sites. Data analysis was performed in STATA. Data were presented as crude proportions of the overall population. Baseline demographics between cases and controls were compared using chi square for categorical variables and Mann-Whitney-U test for continuous variables.

A detailed case notes review of all extra-spinal articular TB cases was performed. Cases were excluded if they were <16 years old, if the infection did not involve an extra-spinal joint or if there was insufficient clinical data. Data were collected on demographics, prior TB infection and treatment, co-morbidity including HIV co-infection, clinical presentation, microbiological and histopathological findings. Information on time from presentation to diagnosis and time to starting anti-tuberculous therapy (ATT) as well as data on treatment type and outcome including complications and surgical interventions were collected. For the purposes of this study serum 25-hydroxyvitamin D (25[OH]D) levels >50 nmol/L were considered sufficient, 25-50 nmol/L insufficient, and <25 nmol/L deficient (NICE 2018).

Mycobacterial cultures were performed using BACTEC (BACTEC International Ltd, Kent, United Kingdom) incubation technology and Löwenstein-Jensen media slopes as per national laboratory standards for microbiology investigation (PHE SMI 2018). Molecular diagnostics were not routinely

available at our centre during the majority of the study period therefore results have not been presented.

Ethics approval was not required as data collection was anonymous, retrospective and completed with institutional permission as confirmed by advice from the Health Research Association.

RESULTS:

Over the 11-year study period, 6,146 individuals with active TB were identified at our institution of which 146 (2.4%) had articular TB excluding spinal TB. There was no difference in median age between groups; 31 years and 32 years for extra-spinal articular TB and controls respectively (p=0.57) (table 1). However, 70.6% of extra-spinal articular cases were male compared to 59.5% of controls (p=0.007). Articular TB cases were more likely to be of Bangladeshi ethnicity (28.7% vs 18.0%) or Pakistani ethnicity (24.0% vs 16.1%) and were less likely to be of Black-African ethnicity (9.5% vs 19.8%) (p<0.001). More non-UK born cases had articular TB than controls, but this did not reach statistical significance (90.3% vs 85%, p=0.097).

93 individuals with extra-spinal articular TB were included in the case series, making up 1.5% of the total TB cohort at our centre. The median age was 30.5 years (IQR 25-46), and cases were predominantly male (67, 72.0%) and of South Asian ethnicity (83, 89.2%). The majority of cases were migrants (85, 88.5%) (Table 2). The median time from entering the UK to diagnosis was four years (IQR 3-12 years). 53 (56.9%) cases were referred to TB clinic from primary care. Seven (7.6%) patients reported prior TB infection; one with culture confirmed fully sensitive *M. tuberculosis* hip joint infection had been treated for TB infection of the same joint 50 years previously and had undergone multiple operations as a child. Four (4.3%) cases were immunosuppressed (one had cytokine 1 deficiency, one on azathioprine and prednisolone for idiopathic pulmonary fibrosis, one on sulphadiazine and prednisolone for rheumatoid arthritis and one had multiple myeloma which was untreated) and none were HIV-infected. Thirteen (13.9%) had concurrent pTB and 31 (33.3%) had concurrent EPTB at another site.

The most commonly affected joints were the knee (22, 23.7%) and elbow (18, 19.4%) (Table 3). There were four (4.3%) cases of prosthetic joint infection; two affecting total hip replacements, and two affecting total knee replacements. The most frequent presenting symptoms were joint pain in 87 patients (93.5%), joint swelling in 68 (73.1%), and joint stiffness in 60 (64.5%). Weight loss was reported in 35 (37.6%), night sweats in 25 (26.8%) and fever in 23 (24.7%) cases. Twelve (12.9%) reported prior trauma to the affected joint, and 12 (12.9%) had sinus tracts communicating with the joint space at presentation. The median durations of pre-healthcare and healthcare associated delay were 16 and 6 weeks respectively. However, delay of diagnosis was longer for women, individuals >30 years old, migrants and those presenting with shoulder and foot infections (Figures 1 and 2). Many cases received an alternative diagnosis prior to consideration of a diagnosis of TB. These included osteoarthritis, seronegative arthropathy, musculoskeletal malignancy, adhesive capsulitis (frozen shoulder) and lateral epicondylitis (tennis elbow).

Clinical specimens were obtained by synovial or joint biopsy (42, 45.2%), joint aspiration (27, 29.0%), incision and drainage (25, 26.9%), joint washout (5, 5.4%), lymph node aspiration or biopsy (6, 6.5%). Respiratory samples were obtained from eight (8.6%) cases; including sputum (5, 5.4%), mediastinal lymph node biopsy (2, 2.2%) and bronchoalveolar lavage (1, 1.2%). Eighteen (19.4%) cases underwent more than one invasive diagnostic procedure prior to diagnosis. Ziehl-Neelsen staining of clinical specimens was performed in 76 (81.7%) cases, mycobacterial culture in 75 (80.6%) cases, and histological or cytological examination in 43 (46.2%) cases (Figure 3). Where mycobacterial culture was performed, 57/75 (76%) were positive for *M. tuberculosis*. Of these, 53/57 (92.9%) were fully drug sensitive, 3/57 (5.2%) were isoniazid-monoresistant and 1/57 (1.7%) was rifampicin-monoresistant.

Eighty-six (92.5%) cases received standard quadruple ATT (two months rifampicin (R) + isoniazid (H) + pyrazinamide (Z) + ethambutol (E) followed by four months RH). Four (4.3%) with drug-resistant infections received alternative regimens. Of the three cases with isoniazid monoresistance, one received 2RHZE followed by 10RE, one received 2RHZE followed by 12RE, and one received 9RE + moxifloxacin. The case with rifampicin mono-resistance received 2RHZE followed by 16ZE. In three (3.2%) cases there was insufficient information on the ATT regimen. The median duration of therapy (excluding those lost to follow up or with drug-resistant TB) was 6 months (IQR 6-9) (Table 3). Longer regimens were used for shoulder and foot TB; median duration 10.5 months (IQR 7.5-15) and 9 months (IQR 6-12) respectively. Six (6.5%) developed adverse drug reactions (ADR) to therapy; minor

skin rash in two (2.2%), transient arthropathy secondary to pyrazinamide in two (2.2%) and isoniazid-related peripheral neuropathy in one (1.1%) case. None with ADRs required interruption or change in treatment regimen. Another two (2.2%) patients stopped ATT early; one patient declined further treatment after 2 months and died 5 months later from pneumonia, and one stopped ATT after 5 months and had no re-infection or persistent symptoms after medical therapy.

Median duration of study follow-up was 7.4 years (IQR 5.9-9.7 years) with six cases (6.5%) lost to follow up during ATT due to emigration or death from unrelated causes. The majority were successfully treated; 85 (91.4%) completed treatment (table 3). Four (4.3%) patients had recurrence of TB infection; two in the knee joint (both had fully sensitive culture positive TB treated for 6 and 12 months with recurrence at three and four years after treatment), and two in the ankle joint (one developed CNS TB five months after completing nine months of therapy for fully sensitive TB, and one developed disseminated disease four years after completing 18 months of therapy and was subsequently found to have a cytokine 1 deficiency). Four patients died within one year of presentation to TB services due to unrelated causes. Of those who died the mean age was 78.5 years (range 71-89 years), and the affected joint was the knee in two cases, elbow in one case and ankle in one case.

Seven (7.5%) patients required articular surgery following ATT for residual joint pain, deformity and loss of function; three had total hip replacements, three had total knee replacement and one patient with ankle TB had plantar fusion with intra-medullary nail insertion. There were no significant differences between those who underwent surgery and those who did not in terms of gender, age, ethnicity, migration status or duration of ATT, however, numbers were small.

DISCUSSION

We describe the clinical characteristics and treatment outcomes of a large cohort of adult extra-spinal articular TB cases in East London. Cases were predominantly young, male and of South Asian ethnicity and site of disease was most commonly in the large joints. The majority of cases were migrants (85, 88.5%) with a median time since migration to the UK of four years and there was a low burden of immunosuppression, indicating that migration may be the primary factor responsible for the rising incidence in articular TB in the UK as previously suggested by Kruijshaar et al (Kruijshaar

2009). Significant delays between symptom onset and presentation were identified, with potentially avoidable healthcare-related contribution to this. Ninety-one out of 93 patients completed TB treatment, and only 7.5% required surgical intervention.

A recent analysis of TB surveillance data from 27 European countries examined risk factors for EPTB and found that osteoarticular TB was associated with age <15 years (aOR 4.48) or >65 years (aOR 3.33), female sex (aOR 1.63), and Indian subcontinent origin (aOR 6.83) or African origin (aOR3.83) when compared with pTB (Sotgiu 2017). When comparing articular cases with non-articular cases in our study of adult patients there was no difference in mean age (p=0.57). Other studies have found that among EPTB patients, migrants are diagnosed with TB at a significantly younger age than native patients (Qian 2018, Johansen 2015, Sandher 2007, Talbot 2007). A female preponderance has been noted in osteoarticular TB cohorts in both low- and middle-income countries (Lesic 2010, Ali 2012) but is contrary to our cohort where a significantly higher proportion of males among articular TB cases was seen (p=0.007).

Articular TB cases in our study were more likely than non-articular TB cases to be of South Asian origin. Indeed, ethnicity has previously been found to be a determinant of clinical TB phenotype; with demonstration of a positive association between South Asian ethnicity and EPTB independent of mycobacterial lineage (Pareek 2013). It is possible that genetic polymorphisms predispose to EPTB or articular TB. An increased risk of spinal TB with certain polymorphisms involved in vitamin D3 and immune function has been reported (Selvaraj 2004, Aravindan 2019). However, further research is required to characterise their role and this association is likely to be due to a complex interaction among multiple host genetic, mycobacterial and environmental factors.

A small proportion of our patient cohort (7.6%) reported prior TB infection; a similar rate to that reported in other cohorts (Ali 2012, Talbot 2007). In one case, *M. tuberculosis* infection was confirmed in the same joint which had been affected by TB 50 years previously. Jeddo et al reported a similar case of smear positive hip TB presenting 40 years after the initial treatment (Jeddo 2014).

Only 4.3% of our cohort were immunosuppressed and none were found to be HIV-infected. This is in contrast to prior studies that have reported articular involvement predominantly in the context of immunosuppression (Pigrau-Serrallach 2013, Calle 2018, Hodkinson 2009). Vitamin D deficiency has been associated with the osteoarticular TB, predominantly among paediatric patients (Dabla 2016). A significant proportion of patients had deficient or insufficient vitamin D levels which may have contributed to the development of articular TB. Other host immunologic factors such as tumour necrosis factor-α gene mutations have been shown to predispose to the development of osteoarticular TB, however, only one patient in our cohort had an identified innate immune defect (Lv 2016).

The knee and elbow joints were the most commonly affected joints in our cohort. Infection has previously been described as preferentially affecting weight-bearing joints such as the hip and knee, with elbows rarely being affected (Mariconda 2007, Johansen 2015). Constitutional symptoms including weight loss, fevers and night sweats were not common in our patient cohort except in those with concurrent pulmonary or disseminated TB infection. This absence of constitutional symptoms is consistent with reports in other extra-pulmonary sites and emphasises the need for a high index of clinical suspicion in patients with articular symptoms from TB endemic areas. Fistulation or sinus formation, a feature indicative of chronic inflammation as it occurs in TB infection, was present in 12.9%. Rates of fistulation in previous series were as high as 19.6% (Ali 2012). Sinus formation and fistulation should prompt early mycobacterial culture as it is rarely caused by other infections.

A significant number of patients reported prior injury to the affected joint (12%), including two out of 11 (18%) of elbow cases. Prior trauma delayed the TB diagnosis as symptoms were initially ascribed to mechanical causes rather than joint infection. A diagnosis of joint TB following joint trauma has previously been described and may be as a result of the bacilli seeding to areas of damaged synovium or bone via haematogenous spread or reactivation or dormant bacilli in articular tissue due to the inflammatory response to trauma (DuBrow 1975, Vargaonkar 2015, Pigrau-Serrallach 2013).

A significant number of patients in our cohort presented to the hospital on multiple occasions and 20 percent of patients underwent multiple invasive procedures prior to correct diagnosis. Average

time from presentation to diagnosis was 16 weeks in our study compared to four weeks reported in a large register-based study in Denmark (Johansen 2015) although shorter than a study involving 113 cases of bone and joint TB in China that reported a median time to diagnosis of 13.2 months (Chen 2015). EPTB has previously been found to be associated with longer delays when compared to pTB (Tattevin 2012). Nationally, one third of patients with pTB experience delays of more than four weeks, with delays highest in those born in the UK and aged over 65 years (PHE 2018).

While our data also demonstrate increasing delays in diagnosis of older patients, we demonstrated longer delays among migrants and among women. Both migration and female gender have previously been associated with longer delays in TB diagnosis and treatment, and this may be due in part to barriers in access to healthcare, including financial and language barriers (Storla 2008). Furthermore, stigma towards TB patients can differentially affect women and impact negatively on help-seeking behaviour (Karim 2007). However, we found that on average symptomatic women took 10 weeks longer to present to services and 6 weeks longer to be diagnosed with TB after presentation. This suggests that the observed gender disparity stems from both patient and healthcare systems delays, and TB services should consider focused social support for women as well as community and healthcare provider education.

Interestingly, more than half of the patients were referred directly to the TB clinic by their general practitioner, and these patients had a two week longer delay in diagnosis when compared to patients referred from secondary care. Time from symptom onset to diagnosis in our cohort was also significantly longer for shoulder TB; a finding replicated in other reports where diagnostic delay was up to five years from symptom onset, which may be attributable to misdiagnosis as frozen shoulder (Darraj 2018, Li 2012).

The yield of mycobacterial culture in articular TB is low due to the pauci-bacillary nature of the synovial fluid (Pigrau-Serrallach 2013). Mycobacterial culture was performed in 80% of patients in our cohort, of whom 76% were culture positive. This is a higher positivity rate when compared with most reported cohorts from high to middle TB incidence settings where reports range from 28-33% (Ali 2012, Sotgiu 2017). However, studies from other low-incidence areas report culture-positivity rates of 69-87% (Talbot 2007, Johansen 2015). Drug resistance was uncommon in our cohort; similar to the overall figure of 7.7% reported in the London TB cohort in 2016 and lower than reports of

10.2% in Europe (PHE London report 2017, Johansen 2015). While not in routine use during our study period, mycobacterial PCR has been reported to have sensitivity of 72-82% in bone and joint TB and its use in selected patients may help to reduce time to diagnosis (Gu 2015, Broderick 2018).

We observed treatment completion rates of 91.4% and few adverse drug reactions. No deaths were attributed to TB infection and there were four recurrences of articular TB. There are no prospective clinical trial data to guide choice of regimen and duration of ATT in osteoarticular TB. There is limited evidence of adequate penetration of first line drugs into synovium and synovial fluid apart from ethambutol and rifampicin where levels appear to be excellent (Tuli 1977, Thabit 2019).

Only 7.5% of patients within our cohort required surgery following ATT, predominantly total-knee and total-hip replacements. This is in contrast to reports from other centres in low TB incidence countries where more than one third of patients required surgery and mortality was recorded as high as 25% (Lesic 2010, Qian 2018, Johansen 2015). Due to the retrospective nature of our study, we were unable to assess functional outcomes following surgery, however, excellent surgical outcomes during and after ATT have previously been reported (Kim 2013, Kumar 2015, Tiwari 2017).

The strength of this study is that it is the largest observational cohort in a low TB incidence country of exclusively articular TB infection reported in the literature. We excluded spinal TB from this study because it is a distinct clinical entity to peripheral articular TB (just as bacterial discitis is a distinct entity to bacterial septic arthritis) and raises distinct research questions with regards to clinical management (in particular regarding diagnostic interventions, therapeutic surgical interventions, and potentially regarding the optimal choice and duration of anti-tuberculous regimen). However, as this study is retrospective, it relied on information documented in clinical records or the LTBR database. As data on quality of life and pain scores were not systematically recorded in routine TB clinic records, the study did not assess these health outcomes.

Future studies of the management and long-term health outcomes of articular TB are urgently needed, including evaluation of molecular diagnostics in articular tissue and fluid samples, appropriate duration of medical treatment, and the role of surgical intervention.

CONCLUSION

This study demonstrates significant diagnostic and treatment delays for patients with extra-spinal articular TB who are often subjected to multiple invasive diagnostic procedures before a diagnosis of TB is made. Standardised pathways for the investigation of chronic inflammatory arthropathy including early liaison with TB specialists are essential to avoid such delays. Targeted TB education sessions for orthopaedic and physiotherapy teams may raise awareness about the signs and symptoms of osteoarticular TB and prompt earlier investigation and referral. The role of surgery remains unclear but the results from our small cohort suggest good outcomes from 6-9 months of ATT. Future work is required to focus on the host factors that predispose certain individuals to articular TB infection.

TABLES AND FIGURES

Table 1 – Demographics of extra-spinal articular tuberculosis cases (n= 146*) and controls with tuberculosis affecting any other site (n= 6000)

	Extra-spinal articular cases	All other TB cases	P value
Male, n (%)	103 (70.6)	3572 (59.5)	0.007
Age, median, IQR	31 (25-44)	32 (24-45)	0.57
Ethnic Group, n (%)			<0.001
Bangladeshi	42 (28.8)	1083 (18.0)	
Indian	39 (26.7)	1467 (24.5)	
Pakistani	35 (24.0)	968 (16.1)	
Black African	14 (9.6)	1188 (19.8)	
Black Caribbean	2 (1.4)	124 (2.1)	
White	4 (2.7)	484 (8.1)	
Other	10 (6.9)	686 (11.4)	
Region of birth, n (%)			0.007
South Asia	102 (71.3)	3159 (55.0)	
Asia - other	2 (1.4)	212 (3.7)	
Europe	16 (11.2)	1084 (18.9)	
Americas	2 (1.4)	131 (2.3)	
Africa	21 (14.7)	1159 (20.2)	
Oceania	0 (0)	3 (0.1)	
Migration status, n (%)			0.097
UK born	14 (9.7)	851 (14.6)	
Non-UK born	131 (90.3)	4993 (85.4)	

*Any case with tuberculosis infection affecting an extra-spinal joint space

TB = tuberculosis; IQR = interquartile range

Table 2 – Characteristics of extra-spinal articular tuberculosis cases (n= 93*)

Male, n (%)	67 (72.0)
Age, median (IQR)	30.5 (25-46)
Ethnicity, n (%)	
South Asian	83 (89.2)
African-Caribbean	6 (6.5)
Caucasian	2 (2.2)
Arab	2 (2.2)
Route of referral to TB clinic, n (%)	
Referred from primary care	53 (57.0)
Referred from secondary care	40 (43.0)
Previous TB infection, n (%)	7 (7.6)
Pulmonary TB	2 (2.2)
Extra-pulmonary TB	5 (5.4)
TB contact reported, n (%)	5 (5.4)
HIV co-infection, n (%)	0 (0.0)
Immunosuppressed, n (%)	4 (4.3)
Diabetes mellitus, n (%)	8 (8.3)
Vitamin D*, n (%)	
Sufficient	2 (2.2)
Deficient	26 (27.9)
Insufficient	8 (8.6)
Not measured	57 (61.3)
Concurrent pulmonary TB, n (%)	13 (13.9)
Concurrent extra-pulmonary TB, n (%)	31 (33.3)
Lymph node	21 (21.9)
Other musculoskeletal	9 (9.4)
Spine	7 (7.3)

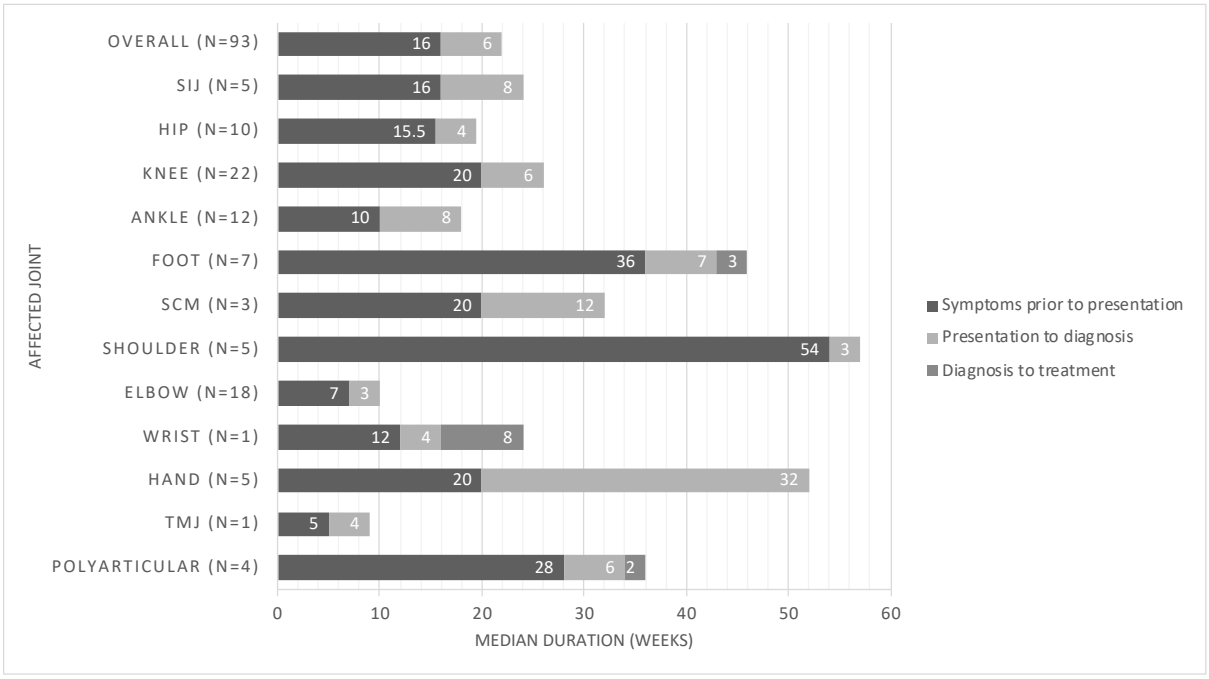
*Cases with incomplete data were excluded.
**Serum 25-hydroxyvitamin D (25[OH]D) levels >50 nmol/L were considered sufficient, 25-50 nmol/L insufficient, and <25 nmol/L deficient.
IQR = interquartile range; TB = tuberculosis; HIV= human immunodeficiency virus

Table 3 – Treatment duration, completion, relapse and requirement of surgery of extra-spinal articular tuberculosis (TB) by joint affected (n=93)

Joint affected	Number (%)	Completed treatment, n (%)	Treatment duration*, median (IQR)	Relapse, n (%)	Required surgery, n (%)
Overall	93 (100)	85 (91.4)	6 (6-9)	4 (4.3)	7 (7.5)
Knee	22 (23.7)	20 (90.9)	6 (6-9)	2 (9)	3 (13.6)
Elbow	18 (19.4)	16 (88.9)	6 (6-6.5)	0 (0)	0 (0)
Ankle	12 (12.9)	11 (91.7)	6 (6-6)	2 (16)	1 (8.3)
Hip	10 (10.8)	10 (100)	6 (6-11)	0 (0)	3 (30.0)
Foot	7 (7.5)	5 (71.4)	9 (6-12)	0 (0)	0 (0)
Sacroiliac	5 (5.4)	5 (100)	9 (6-12)	0 (0)	0 (0)
Shoulder	5 (5.4)	5 (100)	10.5 (7.5-15)	0 (0)	0 (0)
Hand	5 (5.4)	4 (80)	6 (6-6)	0 (0)	0 (0)
Polyarticular	4 (4.3)	4 (100)	7.5 (6-11.5)	0 (0)	0 (0)
Sternoclavicular	3 (3.2)	3 (100)	6 (6-6)	0 (0)	0 (0)
Wrist	1 (1.1)	1 (100)	9 (n/a)	0 (0)	0 (0)
Temporomandibular	1 (1.1)	1 (100)	6 (n/a)	0 (0)	0 (0)

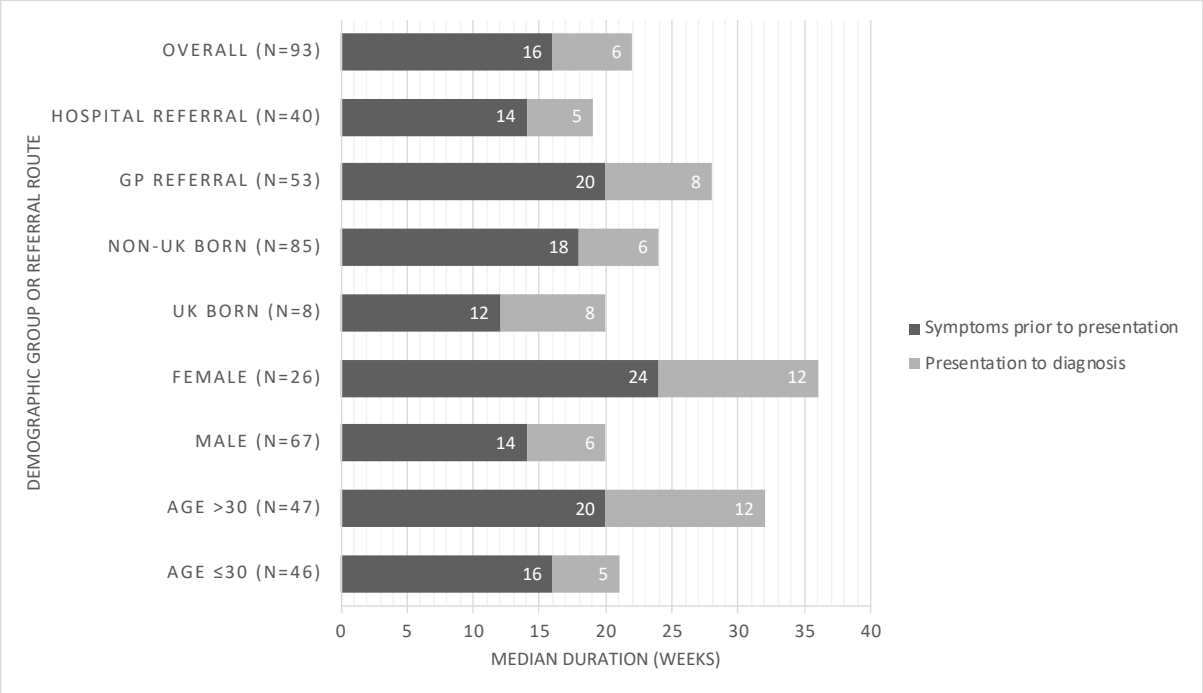
*Excluding those who died, emigrated, lost-to follow-up, stopped treatment early or had known drug resistant isolates
IQR = interquartile range

Figure 1 – Median duration of symptoms to presentation to healthcare, time from presentation to diagnosis, and time from diagnosis to initiation of treatment of extra-spinal articular tuberculosis cases in weeks (n= 93)



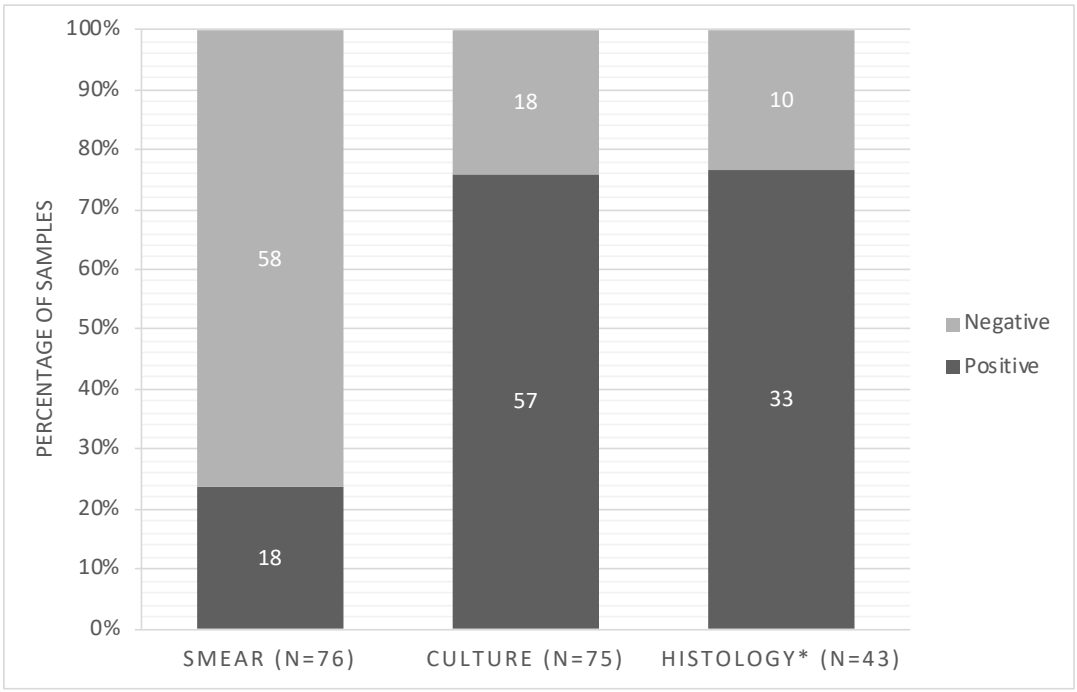
SIJ= sacroiliac joint; SCM= sternocleidomastoid joint; TMJ= temporomandibular joint; polyarticular= >2 joints extra-spinal joints affected

Figure 2 – Median duration of symptoms to presentation to healthcare and time from presentation to diagnosis of extra-spinal articular tuberculosis by demographic group and referral route in weeks (n= 93)



GP = general practitioner

Figure 3 – Microbiology and histopathology investigations in extra-spinal articular tuberculosis cases



*Positive histology was classified as observation of necrotising granulomas or non-necrotising granulomas. Only 5/43 (11.6%) of histological samples showed necrotising granulomas which were positive for acid-fast bacilli by auramine and/or Ziehl-Neelsen staining.

Disclosures: the authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements: We thank our colleagues from the TB specialist nursing teams, as well as physicians and biomedical scientists in the Respiratory, Infectious Diseases and Microbiology departments at Barts Health NHS Trust.

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