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GENERAL ORTHOPAEDICS

Musculoskeletal tuberculosis in Bradford

12 YEARS OF OUTCOMES AND OBSERVATIONS IN A HIGH-INCIDENCE REGION OF THE UK

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Aims

Tuberculosis (TB) is one of the biggest communicable causes of mortality worldwide. While incidence in the UK has continued to fall since 2011, Bradford retains one of the highest TB rates in the UK. This study aims to examine the local disease burden of musculoskeletal (MSK) TB, by analyzing common presenting factors within the famously diverse population of Bradford.

Methods

An observational study was conducted, using data from the Bradford Teaching Hospitals TB database of patients with a formal diagnosis of MSK TB between January 2005 and July 2017. Patient data included demographic data (including nationality/date of entry to the UK), disease focus, microbiology, and management strategies. Disease incidence was calculated using population data from the Office for National Statistics. Poisson confidence intervals were calculated to demonstrate the extent of statistical error. Disease incidence and nationality were also analyzed, and correlation sought, using the chi-squared test.

Results

Between January 2005 and July 2017, 109 cases of MSK TB were diagnosed in Bradford. Mean incidence was 1.65 per 100,000 population, per calendar year (SD 0.75). A total of 38 cases required surgical intervention. Low rates of antimicrobial resistance were encountered. A low rate of loss to follow-up was observed (four patients; 3.7%). Overall, 94.5% of patients (n = 103) were successfully treated. 67% of patients (n = 73) reported their country of origin as either India, Pakistan, or Bangladesh. These ethnicities account for around 25% of the local population.

Conclusion

Bradford maintains a high prevalence of MSK TB infection relative to national data; the prevalence within the local immigrant population remains grossly disproportionate. Typical associated factors (HIV/hepatitis coinfection, drug resistance), have only modest prevalence in our dataset. However, local socioeconomic factors such as deprivation and poverty appear germane as suggested by global literature. We advocate a high degree of suspicion in treatment of atypical infection in any area with similar population factors to ensure timely diagnosis.

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Introduction

Tuberculosis (TB) is the biggest isolated communicable causes of mortality in the modern world (more than HIV/AIDS).[1] Between 2000 and 2017, a global decrease in both incidence and mortality, with deaths falling from 23% to 16%, followed a call for global focus on the disease led by the World Health Organization (WHO) and United Nations (UN).[1,2] Although TB is traditionally thought of as a pulmonary disease, it can manifest throughout the body, and reports

Table I. Disease incidence in Bradford for years 2005 to 2016. 2017 data (partial) are not included. Calculated incidence is given as cases per 100,000 population per calendar year.

Year	Total TB diagnoses	MSK TB diagnoses, %	MSK TB diagnoses, %	Local population, n*	Incidence MSK TB (per 100,000)
2005	146	7	4.79	491,361	1.31
2006	152	6	3.95	495,658	1.12
2007	148	8	5.41	501,357	1.50
2008	149	8	5.37	507,323	1.50
2009	196	18	9.18	512,392	3.37
2010	154	7	4.55	518,002	1.31
2011	153	16	10.46	523,115	2.99
2012	158	9	5.70	524,386	1.68
2013	139	8	5.76	525,936	1.50
2014	91	5	5.49	527,567	0.94
2015	97	6	6.19	529,879	1.12
2016	82	8	9.76	532,539	1.50
Total	1,665	106			
Mean (SD)	138.75 (20.76)	8.83 (4.00)	6.38 (2.16)	515,792.92 (13,969.87)	1.65 (0.75)

*Office of National Statistics mid-year population estimates 2001 to 2017.[10]
MSK, musculoskeletal; SD, standard deviation; TB, tuberculosis.

of musculoskeletal (MSK) involvement stretch back to the late 18th century, following Sir Percivall Pott's description of tuberculous spondylitis in 1779.[3] TB is a 'notifiable' diagnosis in the UK, a status requiring clinicians to notify statutory authorities, including Public Health England (PHE), of new cases. This enables accurate and timely monitoring of outbreaks or epidemics across the country.

The City and District of Bradford, in West Yorkshire, has a long industrial heritage stemming from iron, coal, and its textile mills in the 18th and 19th centuries.[4] It also has a long modern history of immigration to the District, with settlers from Ireland and Germany in the mid-19th century, and Poland, Ukraine, India, Pakistan, and Bangladesh in the post-war years of the 20th century.[5,6] Today, Bradford is home to a large and vibrant immigrant South Asian population, one of the largest in the UK.[7]

Bradford Teaching Hospitals NHS Foundation Trust operates from six sites in the Bradford district, including two hospitals with inpatient capacity. It is responsible for hospital services to the city district of Bradford and surrounding communities, to a local population of over 500,000. Bradford Royal Infirmary (BRI) is a major teaching hospital with inpatient capacity of around 780 beds, and provides all the urgent/emergency services to the Trust. Local Clinical Commissioning Groups (CCGs) are responsible for the commissioning of district NHS services across the primary and secondary care groups, and general practitioners in the Bradford area make acute secondary care referrals directly to the BRI.

Previous studies from this department in 1974[8] and 2007[9] highlighted the high proportion of MSK TB in the immigrant population of this diverse, growing city.[8,9] The clinical landscape has changed significantly since each of these studies, with the emergence of HIV in the 1980s (a now frequently cited risk factor for coexistent TB infection), the increase in multidrug-resistant strains, as well as modernized screening, diagnostic tools, and pharmacological protocols over the last 15 years.

This study examines the local disease burden of MSK TB in the civic region of Bradford and reports clinical practice, patient outcomes, and common presenting factors to assist timely diagnosis and successful management of this scarcely seen disease. This will be achieved by reporting the demographic trends and local incidence of MSK TB over the preceding decade. These data, in addition to local treatment regimes, treatment outcomes, and association of risk factors within the study population, will be considered against the concurrent national context of declining incidence.

Methods

All cases were identified retrospectively from our TB service database, collating all new diagnoses of TB in Bradford Teaching Hospitals between January 2005 and July 2017. Following the definition detailed below, a new MSK TB database was created. Patient care records, pathology results, and imaging studies were reviewed for all cases. Patient demographic data were collated, including age, country of birth, and date of entry to the UK (where applicable). Further data were collated for site(s) of disease, positive culture/histology results, antibiotic chemotherapy regime employed, evidence of antibiotic resistance, the need for surgical management, and total duration of treatment. Contemporaneous local population data were acquired from the Office of National Statistics (ONS) national mid-year reports.[10]

MSK TB was defined as radiological evidence (on plain film radiograph, CT, or MRI)[11] of an extrapulmonary

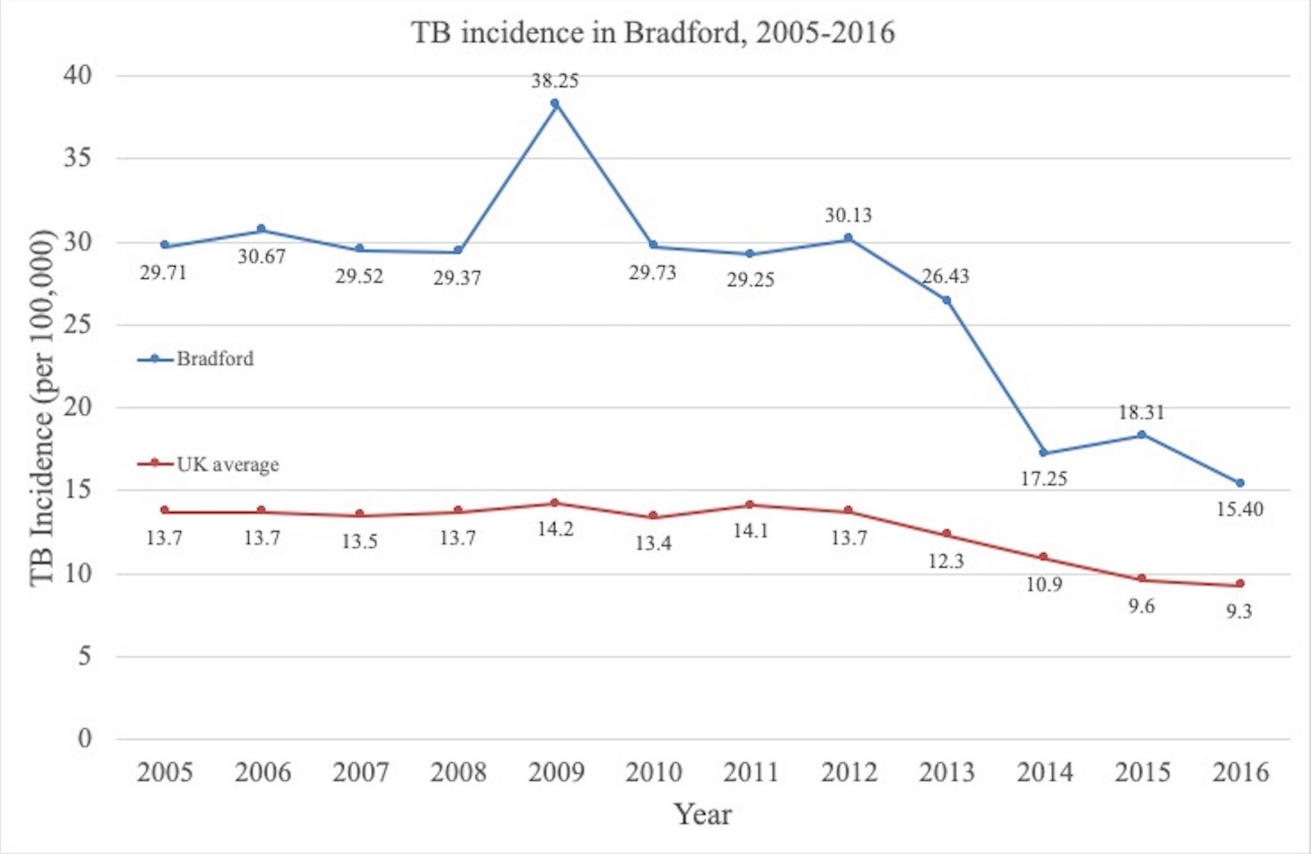

Fig. 1

Graph showing tuberculosis (TB) incidence 2005 to 2016 for the Bradford locality and the UK. Upper and lower Poisson confidence intervals for local calculated incidences were all < 4×10^{-4}.

bone or soft-tissue focus, with or without specific radiological features of concern for TB, in addition to one or more of the following: biopsy demonstrating positive culture for *Mycobacterium tuberculosis*, positive histological evidence, or clinical features of concern for TB. Features of clinical concern included recent travel to high burden countries (within last two years), identification through contact tracing and clinical symptoms/signs of TB (persistent cough, night sweats, or weight loss). Cases not involving musculotendinous units or bone, such as nodal disease (cervical chain, axillary, etc.), intracranial/intrapharyngeal, and intrathoracic foci, and visceral and genitourinary pathology, were excluded. MSK TB cases also involving pulmonary/visceral foci were included; however, mention of the non-MSK foci was omitted. It is worth noting that further modern diagnostic tests, such as genetic assays (e.g. polymerase chain reaction) or other molecular techniques, were subsequently introduced to our department, post-dating the study period.

Annual population estimates were collected from the ONS annual mid-year population estimate reports.[10] Estimated annual incidence figures (presented in cases per 100,000 population, per calendar year) were calculated using the ONS mid-year population data and annual number of new diagnoses identified through interrogation of our local TB database. The regional population, as described by the ONS report, was understood to equate to the acute catchment area of BRI and its TB service.

Statistical analysis. Statistical analysis of Poisson confidence intervals (CIs) to estimate error for calculated annual incidence data was performed using RStudio v. 1.3.1056 (R Foundation for Statistical Computing, Austria), under General Public Licence. Calculation of chi-squared was performed using Excel for Mac 2016 (Microsoft, USA), using $p < 0.05$.

Results

Demographic details and incidence. A complete summary of the data can be found in Supplementary Table i. Over 12.6 consecutive years, between January 2005 and July 2017, 109 cases of MSK TB were diagnosed and treated in Bradford Teaching Hospitals (Table I; Figures 1 and 2).

Mean patient age in the dataset was 41.2 years (14 to 86). The observed male:female sex ratio was 62:47. Subsequent loss to follow-up prior to completion of treatment was 4/109 cases (3.7%). Median follow-up/

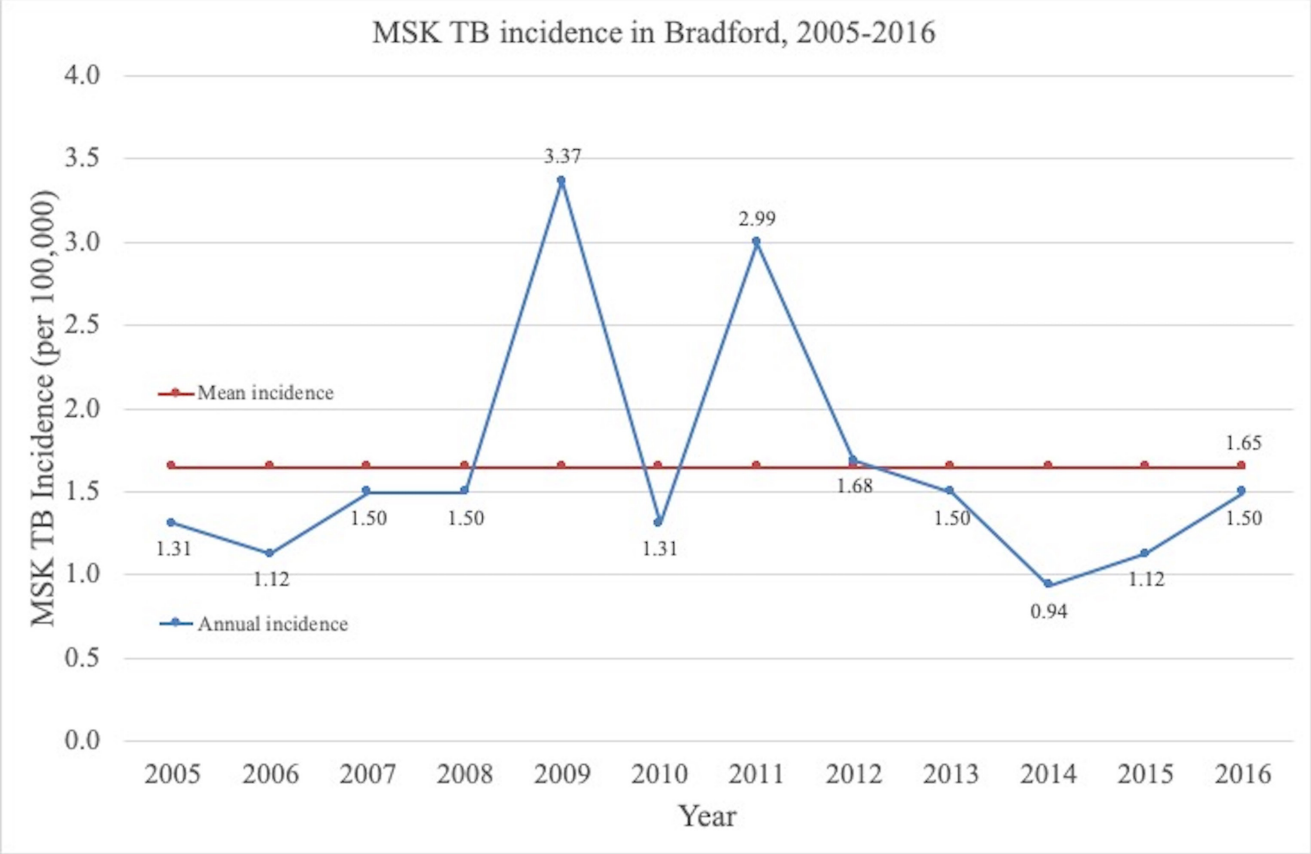

Fig. 2

Graph showing local musculoskeletal tuberculosis (MSK TB) incidence by year from 2005 to 2016. Upper and lower Poisson confidence intervals for local calculated incidences were all < 5.5×10^{-5}.

treatment duration was 12 months (interquartile range (IQR) 6 to 12); mode was 12 months. Treatment duration ranged from six to 24 months.

Nationality, immigration status, and ethnic background are routinely recorded at first clinical review for purposes of risk stratification, contact tracing, and disease surveillance. In total, 20/109 patients were confirmed as having been born in the UK. The remaining 89 cases were all members of the local immigrant population (Table II). A chi-squared test for independence was performed using data from the ONS 2011 census (most recent) to determine the relation of MSK TB diagnosis within the immigrant population versus UK-born local populations,[7] which demonstrated that members of the immigrant population were more likely to be diagnosed with MSK TB than UK-born locals ($p < 0.001$).

Of the 89 patients born elsewhere, 83 provided a date of entry to the UK. Mean time from entry to the UK to diagnosis was 13.76 years (0.75 to 54) and median was five years. The data showed a large variance with an IQR of 23 years. There was significant skewing of the dataset (Figure 3).

Variance in anatomical focus. Overall, 33 of the 109 patient cases were shown to have multifocal (most commonly thoracic) disease, giving a total case number of 149 (Table III). In total, there were 65 cases involving 80 spinal foci; the majority of these were within the thoracolumbar spine. Of the 38 cases of truncal pathology (chest and/or abdominal wall, psoas involvement), 21 also involved a spinal focus. Of the four pelvic cases, one also had a spinal focus, and of the three skull cases, one had a separate spinal focus. There were seven cases of intra-articular pathology: two sacroiliac joint, one hip, one knee, one ankle, one talonavicular joint, and one elbow. The lower and upper limbs accounted for only 14 and ten foci, respectively.

Treatment regimens and risk factors. Overall, 91/109 patients had positive cultures for *M. tuberculosis* documented (83.5%). The remaining 18 were treated empirically following imaging and positive histological diagnosis (n = 1) or clinical diagnosis as described previously.

Three patients had sensitivity studies demonstrating multidrug-resistant (MDR) strains of *M. tuberculosis*. Another three patients displayed features of isolated

Table II. New diagnoses of musculoskeletal tuberculosis by patient country of origin in Bradford (2005 to 2017).

Origin	n
Indian subcontinent*	73
India	16
Pakistan	50
Bangladesh	5
UK	20
Sub-Saharan Africa†	11
Eritrea	3
Gambia	2
Somalia	1
Zimbabwe	1
Uganda	1
South Africa	1
Malawi	1
Other	
Trinidad	1
Slovakia	1
Afghanistan	1
Yemen	1
Indonesia	1
Total, n	109

*Two unknown.
†One unknown.

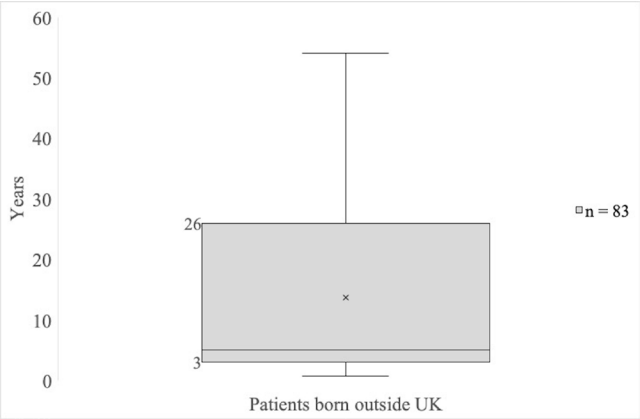

Fig. 3
Time from patient entry to UK to tuberculosis diagnosis.

Table III. Individual muscoloskeletal tuberculosis disease foci by anatomical site.

Site	Total
Spine, n	80
Cervical	6
Thoracic	31
Lumbar	33
Sacral	6
Whole spine	1
Unclassified	3
Trunk, n	38
Lower limb, n	14
Upper limb, n	10
Pelvis, n	4
Skull, n	3
Total, n	149

Isoniazid resistance on sensitivity testing. All completed treatment and were successfully discharged using a modified treatment regime, informed by laboratory sensitivity studies.

The standard antimicrobial treatment regime involved six months of combination therapy, commencing with Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. After two months (unless resistance/non-response to treatment was evident), the regime was typically reduced to a combination of Rifampicin and Isoniazid alone. This regime extended to a minimum duration of 12 months for cases with spinal involvement. Pharmacological regimes were reviewed according to laboratory sensitivities when available. In cases of Isoniazid resistance, Isoniazid was substituted with Levofloxacin for the initiation phase, with Rifampicin and Ethambutolthen used for the continuation phase. In patients with MDR TB, regimens were formulated based on sensitivity data and input following discussion in regional MDTs. Other second-line substitutions for MDR TB may include Streptomycin, Linezolid, and Amikacin.

In addition to antimicrobial therapy, 37/109 patients underwent surgical management for 38 foci of infection. Indications for surgical intervention included open biopsy, or the presence of significant tuberculous mass/collection on imaging, requiring debridement and/or irrigation. In the case of spinal infection, decision to progress to surgical intervention was made by our local spinal surgery service in the nearby city of Leeds. Clinical evidence of significant neurological compression or a fluid collection of increasing size on serial imaging despite medical therapy were given indications.

All patients underwent testing for Hepatitis B (HBV) and HIV. No patients in the dataset were diagnosed with HIV at presentation or at follow-up. However, two patients subsequently tested positive for serum HBV antigen. Both cases were fully sensitive to the normal antimicrobial TB regime and had been resident in the UK for over 30 years.

Outcomes. In total, 86/109 patients (78.9%) successfully completed their treatment regime and were discharged, two of whom had previously shown recurrence from previous infection. Five of these patients received more than 12 months of treatment.

Of the group, 21 patients were non-attenders to outpatient review; however, all but three had available information on completion of treatment, while one patient died of unrelated causes. Therefore, only four patients were lost to follow-up (3.7%). A further two patients had evidence of ongoing disease at six- and 12-month follow-up. The remaining 17 were known to have completed six to 12 months of standard treatment

and did not return. Therefore, a total of 6/109 patients (5.5%) had not fully successfully completed treatment, including those with active recurrent disease and those lost to follow-up.

Of the five patients who underwent treatment for over 12 months (ranging from 14 to 24 months), all demonstrated a thoracolumbar spinal focus for their pathology. Only two of these patients required surgery in the form of debridement with spinal instrumentation. All completed treatment and were successfully discharged. Of a total of 12 cases involving surgery on a spinal focus, ten of these involved formal decompression with or without instrumentation. Postoperative follow-up data were available for nine cases. Of these, three had no significant neurological deficit preoperatively (altered sensation/hyperalgesia only). The remaining six cases had documented preoperative significant motor weakness or signs of myelopathy. Only one case of these six failed to display significant postoperative improvement following cervical decompression.

Discussion

In the UK during 2011, 8,963 new cases of TB were diagnosed and notified to PHE (an incidence of 14.4/100,000). Of these new cases, 83.6% occurred among a population born outside the UK.[12] Incidence rates have continued to fall in England year on year since 2011 (Figure 1). In 2017, PHE were notified of a total 5,102 new diagnoses.[13] For the first time, incidence during this period fell below ten cases per 100,000, classifying England as a low-incidence country according to WHO definitions.[13]

Mean annual incidence of TB remained high in Bradford between 2005 and 2017, at 27 cases per 100,000. This figure is similar to a reported 26 per 100,000 between 1999 and 2004.[9] In 2017, by CCG, Bradford district was reported as the highest incidence (outside of London) at ≥ 40.0/100,000 in 2017,[13] and has consistently reported a high disease burden for TB year on year. Despite ongoing improvement in national incidence over the last decade, local incidence remains high, although it has more recently displayed a downward trend. Mean annual incidence of MSK TB was found to be 1.65 cases per 100,000, although a large variance in the data precludes confident assertion of change over the time period (Figure 2).

Data indicated a local surge of TB diagnosis in 2009. The majority of these cases were found to be due to reactivation of latent infection. Screening for latent disease has become much more common, particularly in those entering the UK from high-burden countries around the world.

The 2011 national census results for the Bradford district reflected its famously diverse ethnicity, with 24.89% of the population declaring itself as Indian, Pakistani, or Bangladeshi,[7] three of the WHO's "high-burden countries" which account for over 80% of the world's TB cases.[1] Proportion of new TB incidence in patients originating from outside the UK has been falling in recent years; although still a clear majority, incidence in the immigrant population has halved since 2012 and is at its lowest rate since 2000.[13] Notably, while an increased incidence in the local immigrant population is certainly not unique to Bradford, the extent of its continued prevalence cannot be said to reflect national trends.

While MSK TB is an uncommon presentation to the majority of orthopaedic departments in this country, Bradford has a reported history of high MSK TB prevalence dating back to the mid-1950s.[8] A more recent local study in 2007 referenced the resurgence of pulmonary TB (and concomitant MSK TB) within an industrialized conurbation.[9] TB prevalence remains higher in developing countries, and immigration from those countries has long been linked to an increase in disease incidence in destination countries.[14,15]

The diagnosis of MSK TB is notoriously challenging and has often been said to require a high index of suspicion, as appearances to admitting clinical staff may mimic more pedestrian infective processes.[16,17]

Our data clearly show the overwhelming majority of MSK TB cases to be diagnosed in the immigrant population: 81.7% of all MSK TB diagnoses in the study period (89 patients) were born outside the UK, and 67% of the cohort (73 patients) originated from one of the three countries of risk mentioned above (India, Pakistan, and Bangladesh). As such, 67% of new MSK TB diagnoses came from an ethnic background representing only 25% of the local population[7]. This fact reinforces the importance of proactive investigation and intervention in at-risk subsections of the community.

Of 83 cases in patients born outside the UK, time to diagnosis from entry to the UK was widely varied. Although from the data available it was not possible to establish the proportion of de novo active MSK TB compared to reactivated latent disease, the descriptive statistics (in particular data range of 0.75 to 54 years) suggest a large amount of latent disease being diagnosed many years later subsequent to reactivation. Half of these cases, however, were diagnosed within three years of entry to the UK, allowing for a considerable mix of de novo active disease and reactivated disease. It was not possible to ascertain likely relative ratio of these presentations from the data retrospectively; indeed, this would be challenging in a prospective study. Furthermore, data for these cases regarding recent travel and diagnosis subsequent to contact tracing were, unfortunately, not available.

The most common single focus of TB infection in this country remains pulmonary (54.4% in 2017).[13] The relative proportion of gross extrapulmonary TB diagnoses in the UK has, however, steadily increased from 40.9%

(2004) to 58% (2017). Of extrapulmonary TB cases in 2017, 6% were sited in bone, including the spine. The comparable rate of MSK TB within the local TB data shows an annual mean of 6.38% (SD 2.16; 2 to 10), which is proportionate to national incidence data.[13]

The most common site for MSK TB in our cohort was the thoracolumbar spine, as is frequently quoted elsewhere.[18,19] Although spinal infection in general remains a common diagnosis, a high index of suspicion is important to identify TB infection, despite the characteristic classical descriptions of Potts' disease on plain film radiographs.[3] Diagnosis of TB has historically been, and continues to be, avoidably delayed.[20–23] Advancing spinal infection can lead to significant instability, structural deformity, and significant neurological dysfunction or myelopathy if left untreated, requiring major surgical intervention.[24] Objective improvement in motor symptoms was common postoperatively in our cohort; however, some persistent features of altered sensation or hyperalgesia were frequently reported at follow-up. Typically, treatment of simple infective paraspinal collections or myelodiscitis remains non-surgical.[24] Nonetheless, radiologically guided aspiration/biopsy and culture for acid-fast bacilli in refractory uncomplicated spinal infections would seem germane.

A total of 38 cases (34.8%) required surgical intervention, principally in the form of debridement. The mainstay of treatment for MSK TB would appear to be pharmacological, with debridement and/or drainage employed only when specifically indicated.

Reports of drug-resistant, or multidrug-resistant strains of TB (MDR TB) have been rising globally for years. In 2017, 3.5% of new TB cases globally demonstrated multidrug resistance, a small increase from the previous year,[1] whereas reports from Europe in the last decade have revealed up to 35.5% of new cases identified as MDR TB.[25] Total case numbers of MDR TB on initial diagnosis in the UK from 2016 to 2017 have fallen from 60 to 55, respectively. However, the proportion of overall incidence for these consecutive years remained similar (1.7% and 1.8%).[13] Overall prevalence of resistant TB cases in our dataset was six from 109 (5.5%). Of note, three of these six cases displayed features of Isoniazid resistance, previously reported as significant in the Bradford region,[26] and the remaining three cases demonstrated MDR features. All but one case were subsequently successfully treated, suggesting that within our locality, MDR TB may not be as pertinent an issue as elsewhere.

In developing countries, TB remains one of the leading opportunistic causes of morbidity/mortality in the HIV-positive population.[27] Of the estimated ten million individuals diagnosed worldwide with active TB in 2017, approximately 9% are thought to have been HIV-positive, and approximately 300,000 people around the world died from TB coexistent with HIV.[1] There were no identified cases within our dataset of concomitant HIV, and only two patients from 109 with positive Hepatitis B serology. Viral hepatitis, syphilis, and HIV co-infection have long been posited as risk factors for TB; the prevalence of these co-infections has been described repeatedly as linked to cohorts observed in conditions of poverty, incarceration (particularly in developing countries), or areas of poor sanitation.[28,29] High rates of HIV co-infection are typically reported from sub-Saharan Africa where the HIV burden is very high and may not be directly comparable to our local demographic.[18] Although Bradford is in a developed country, it has recently been ranked fifth most income-deprived local authority in England.[30] Social deprivation remains an issue frequently reported in the local TB population, and is likely to influence Bradford's high disease burden; furthermore, endemic drug abuse and poor sanitation are also frequently reported in Bradford, and are known to contribute to the spread of this disease.[28,31]

At the beginning of the 2010s, following the highest reported incidence of TB in England since the 1970s, improvement of national data for completion of treatment was urgently mandated.[32] Peak incidence in England was reported during 2011 (8,963 cases).[12] The WHO established a minimum target of 85% completion of treatment within 12 months of therapy commencing, and reported national data still fail to achieve this. Treatment completion rate was reported as 84.4% for cases notified in 2016.[13] Despite a significant level of poor outpatient attendance, only four patients (3.7%) were formally lost to follow-up. Two further patients had evidence of ongoing disease, and so six patients in total (5.5%) had not successfully completed treatment, leaving 94.5% of the study group who successfully completed their treatment regime. As such, our local performance against WHO targets is strong.

The limitations of this study reflect its observational and retrospective nature. Although the local clinical TB database was exhaustive, certain helpful data on recent travel and the proportion of new diagnoses achieved through contract tracing would have added further strength to our conclusions. In addition to this, as stated, the local population was understood to equate to the acute catchment area of BRI. This may not be entirely accurate, due to possible overlap between some CCG boundaries and nearby geographical catchment boundaries between neighbouring Trusts, such as Leeds Teaching Hospitals NHS Trust and Airedale NHS Foundation Trust. Some smaller parts of the granular data were absent from the database, but despite its size and the length of time reflected this was only a small amount; for example, the time between arrival in UK and diagnosis was unavailable in only six patients. One patient had no visible imaging to review due to diagnostic imaging being performed

elsewhere, and one patient had no information on sensitivities available. Data on anatomical focus, the incidence of biopsy, and incidence of successful microbial culture were available for all but one patient, who had no clinical data available at all. As such, the strength of our database was felt to be sufficiently robust so as to exert only minimal impact on the validity of our conclusions.

Once again, the data from our unit show a preponderance of MSK TB within the immigrant population compared to the UK-born population, especially within the cohort of the immigrant population originating from the Indian subcontinent. The success rate of pharmacological treatment for MSK TB in Bradford was high.

Although annual TB incidence in the region continues to fall, Bradford remains one of the areas in the country worst affected by the disease. Consequently, the data reinforce the need for a high level of suspicion in the prompt and successful diagnosis of MSK TB in geographical areas with a large proportion of at-risk populations, recently highlighted by Broderick et al.[23] Notably, however, relative MSK TB prevalence in Bradford was comparable to national data. The level of local social deprivation may bear closer scrutiny as to its association with increased MSK TB prevalence in the immigrant population.

Take home message

- Musculoskeletal tuberculosis (MSK TB) may mimic more typical infective organisms.
- High rates of MSK TB in Bradford are associated with its immigrant population and high levels of local deprivation.
- A high 'index of suspicion' based on known local risk factors may aid prompt diagnosis in populations with similar demographic characteristics.

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Supplementary material

Table of all musculoskeletel tuberculosis cases identified in Bradford between January 2005 and July 2017.

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