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Are we missing opportunities to confirm the diagnosis of tuberculosis by microbial culture?

Zaid Al-Nakeeb [a,1], Vandana Gupta [b,*], Christine Bell [b,2], Mark Woodhead [b,3]

[a] The University of Manchester, Oxford Road, Manchester M13 9PL, UK
[b] Department of Respiratory Medicine, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK

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Summary
Setting: Tuberculosis (TB) incidence is rising globally, with drug resistance becoming increasingly problematic. Microbiological confirmation ensures correct anti-tuberculous chemotherapy.
Objective/design: We retrospectively analysed all TB cases diagnosed in Central Manchester in 2009 investigating how often we are not achieving microbiological diagnosis, factors influencing this and whether opportunities to obtain microbiological samples are missed.
Results: 128/156 (82%) cases had samples sent for microbiology. Factors affecting this included disease site, with ocular disease least likely to be sampled ($p < 0.0001$), and patient age (with children less likely to be sampled $p = 0.002$). Ethnicity did not affect sampling (n.s.). Overall, 92/156 (59%) cases were culture positive. Negative culture was related to specimen type ($p < 0.0001$) and patient age ($p = 0.019$), with children significantly less likely to have a positive culture. Ethnicity and disease site did not affect culture results. There was a trend towards culture positivity being more common in pulmonary (75%) than non-pulmonary (46%) disease (n.s.). In only 7 (4%), could samples have been sent where they were originally absent (3) or further samples obtained where the cultures proved to be negative (4).
Conclusion: Despite an overall culture positive rate of 59%, opportunities to achieve microbiological confirmation are seldom missed. In our centre, which is typical of UK practice, this

* Corresponding author. Tel.: +44 161 276 4381; fax: +44 161 276 4989.
E-mail addresses: mmmp5za3@doctors.org.uk (Z. Al-Nakeeb), vandanagupta@doctors.org.uk (V. Gupta), christine.bell@cmft.nhs.uk (C. Bell), mark.woodhead@cmft.nhs.uk (M. Woodhead).
[1] Tel.: +44 161 306 6000.
[2] Tel.: +44 161 276 4387; fax: +44 161 276 4989.
[3] Tel.: +44 161 276 4381; fax: +44 161 276 4989.

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lack of capacity to increase microbiological confirmation, particularly in an era of increasing importance of extra-pulmonary TB, is concerning. Improvements in sample acquisition and laboratory methods are urgently required.

Introduction

Globally the impact of tuberculosis (TB) is vast; in 2011 there were 8.7 million new cases and 1.4 million deaths, with only 66% diagnosed and notified to national programmes [1]. The World Health Organisation (WHO) recommends that guidelines for diagnosis and culture are followed at a national level, according to national TB incidence and prevalence of drug resistance. TB cases in the UK rose from 6724 in 2000—8963 in 2011 [2]. There was an overall culture positive rate of 59%, which was higher in pulmonary (70%) versus non-pulmonary (48%) disease. Currently the National Institute of Clinical Excellence (NICE) guidance recommends that pulmonary disease is diagnosed by the collection of multiple sputum samples (spontaneous or induced) or broncho-alveolar lavage, with treatment commenced soon after samples are taken [3]. NICE also recommend extra-pulmonary TB diagnosis, if suspected, is achieved by sending samples for TB culture. In the UK in 2011 52% of cases had pulmonary disease, a fall from 59% in 2000—2003 [2]. The proportion of extrapulmonary disease is higher in non UK-born cases [2]. TB incidence has risen in Central Manchester between 2000 when there were 114 notifications and 2009 when there were 196 [4].

Drug resistance makes management more complicated and expensive and is an important cause of mortality and morbidity. A gradual rise in some drug resistances is being seen in the UK [2] in 2011 multi-drug resistance or MDR-TB (resistance to at least rifampicin and isoniazid) was seen in 1.6% cases overall and resistance to at least one first line antibiotic was seen in 8.4%. Internationally, the full extent of drug resistance is unknown but China, Russia and India appear to have the highest incidence. Countries in the former Soviet Union have a high incidence of drug resistance, coupled with low rates of sensitivity testing and appropriate treatment [5].

It is therefore vital to obtain samples for microbiological culture and sensitivity to provide absolute confirmation of the diagnosis of tuberculosis and to ensure adequate treatment and prevent spread of drug-resistant disease.

In Central Manchester we have seen an increase in the proportion of cases where samples were sent for microbiological confirmation. 69% had samples sent to microbiology in 2000 and 79% in 2009 [6], but despite this we have been concerned there may have been missed opportunities to obtain proof of the causative organism. We therefore undertook this study to investigate how often we sent samples and how often we achieved microbiological confirmation of TB. We examined what factors affected both sampling and culture results. In addition, we further investigated cases where there were no samples or negative cultures to assess whether there were missed opportunities for microbiological confirmation.

Methods

A retrospective analysis was carried out on all cases (adult and paediatric) diagnosed with TB at Central Manchester NHS Foundation Trust (CMFT) in 2009 identified from our TB database. CMFT is a 1400 bed hospital serving an inner-city population with considerable ethnic diversity, typical of UK cities. The TB unit co-ordinates the treatment of all active TB in this population, regardless of disease site or underlying disease, with treatment adhering to NICE guidance. Around 200 cases per year are seen (accounting for 1/4 cases in Northwest England), of which 50% are pulmonary and 10% have co-existing HIV infection. TB cases in Manchester are similar to those in the rest of the UK, in terms of ethnicity of patient and site of disease [2]. Central Manchester is however under resourced compared to other cities regarding TB nurse to notification ratio and there has recently been a significant increase in clinic numbers compared to other UK cities [4].

TB cases were defined as any subjects who were notified to the HPA as being treated for active TB or any subject restarting TB treatment who had relapsed within 12 months of previous treatment. No cases were retreated in the study period and therefore no cases were counted twice. Demographic details, site of disease, types of specimens and results of TB culture were recorded from computer records, case notes and TB nurse records. Cases were analysed in detail for reasons why specimens were not taken or culture positivity was not confirmed. A judgement was made on whether this was acceptable or non-acceptable management based on the clinical circumstances surrounding the case. Outcome data and relapse rates were also recorded.

Routine investigation of pulmonary TB at CMFT includes obtaining 3 adequate sputum samples or bronchoscopic samples, unless the procedure is contra-indicated. For non-pulmonary disease, Fine needle aspiration (FNA) or biopsy of disease site is routinely performed, except in ocular TB. Clinically acceptable cases were deemed as those in which in the view of the authors and doctors managing the patient an acceptable balance was achieved between the need for invasive procedures, potential harm to the patient and delays in starting treatment, weighed against need to commence treatment in a relatively short time frame.

Culture positivity and whether samples were sent for culture were compared with site of disease, age of patient, ethnic origin and sample type. Statistical analysis was carried out using the software package SPSS. The Chi squared test was used to compare numbers of samples sent for culture and culture positivity with site of disease, age of patient, ethnic origin and sample type.

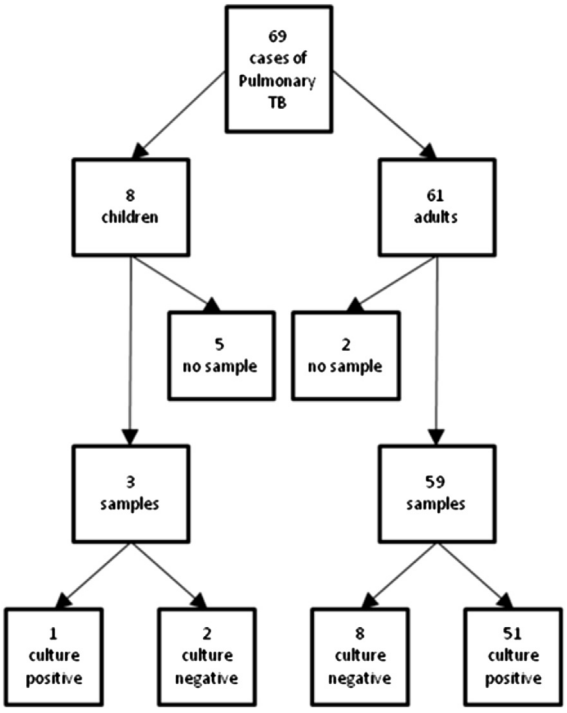

Figure 1 Pulmonary TB in Central Manchester.

Results

There were 167 cases treated at CMFT in 2009. 11 cases were withdrawn due to diagnosis occurring in other Trusts leaving 156 cases. 69 cases (44%) were pulmonary (represented in Fig. 1), and 87 cases (56%) were extrapulmonary, with the most common extrapulmonary sites being lymph node, eye and pleura.

Samples not taken

The most common ethnic group in the cohort was Black/African (31.4%), followed by Pakistani (23.7%), Caucasian (16%) and Indian (10.9%). In total, 67.3% cases were born outside the UK. 120 cases were in the age group 17—64 (77%). 20 cases (13%) were in children.

128 (82%) patients had one or more specimens sent to microbiology for AAFB smear and culture. 28 (18%) patients had no specimens sent to microbiology. Factors which were associated with whether samples were sent to microbiology included disease site ($p < 0.0001$) (Table 1), with ocular disease being the least likely to be sampled, and patient age ($p = 0.002$) (Table 2). Children were less likely to have samples sent for culture, with 45% patients <16 years old having no samples sent compared with 12.5% patients aged 16—64. Ethnicity did not influence the frequency of sampling (n.s.).

Lack of specimens for culture was considered to be clinically acceptable in 25/28 cases (Table 3). Reasons for no sample included ocular disease (12 cases) and paediatric cases (9 cases) where potentially unacceptable invasive sampling would be required. The 3 potential missed cases (2% overall cases, 11% samples not sent) were all in non UK-born adults with abdominal disease who underwent invasive procedures, but where biopsies taken were sent for histology only.

Table 1 Frequency of samples sent for culture by disease site.

Disease site	*n*/Total	% sent for culture
Pulmonary	62/69	89.8%
Pleura	10/10	100%
Lymph Nodes	28/34	82.4%
Abdominal	7/8	87.5%
Disseminated	6/6	100%
Eye	0/12	0%
Other	15/17	88.2%
Total	128/156	82%

Samples culture negative

Of the subjects who had samples sent, 72% were culture positive and 28% were negative. There was a trend for culture positivity to be more common in pulmonary disease (75%) compared to non-pulmonary disease (46%) (n.s.). Non-pulmonary culture positive rates also tended to be less even in those where samples for culture had been taken: 40/66 (61%) non-pulmonary compared with 52/62 (84%) of all samples taken for cases with pulmonary disease ($p = 0.003$). Culture negative results were associated with patient age ($p = 0.019$) and specimen type ($p < 0.0001$). Again, children were less likely to have positive culture results, with 64% cases <16 years old had negative culture results compared with 26% 16—64 year olds ($p = 0.019$) (Table 2). Site of disease and ethnic origin did not significantly affect culture results. However, only 12% sputum samples were culture negative, compared to 43% lymph node aspirates and 100% of cases in which multiple sites were sampled (see Supplementary Table 1).

36/128 samples sent to microbiology were culture negative (28% samples sent, 41% overall). Lack of a positive culture was considered to be clinically acceptable in 32/36 cases which were culture negative (Table 4). The 4 cases (3% overall cases, 11% culture negative cases) which could have potentially been missed were due to pleural TB in adult patients born outside the UK, all of which did not have pleural biopsies. Many of the acceptable cases were in children or in cases where reasonable attempts to make a microbiological diagnosis had been made. 10 cases of pulmonary TB were culture negative, of which 2 were children. 2/3 children had gastric lavages and of the adults five had ≥ three sputum samples examined, one had a bronchoscopic sample examined and one had 2 sputum samples, one BAL, CSF and urine sample examined.

None of the culture negative cases or cases with no samples sent relapsed after treatment and all completed 6 months of treatment and were then discharged from the TB service.

Discussion

The most important finding of this study is that despite the overall low culture positive rate (59%), especially in those

Table 2 Frequency of samples sent for culture and culture positivity by age group.

Age group	Number sent for culture/Total	% sent for culture	Number culture positive/Total	% culture positive
	$p = 0.002$		$p = 0.019$	
<16	11/20	55%	4/11	36.3%
16-64	105/120	87.5%	78/105	74.2%
>64	12/16	75%	10/12	83.3%
Total	128/156	82.1%	92/128	71.8%

with extrapulmonary TB (46%), acceptable opportunities to obtain samples for culture were missed in relatively few cases. Similar proportions of culture confirmation were also seen nationally (overall 59%, pulmonary 70%, and extrapulmonary 45%) [2]. Extrapulmonary TB may be difficult to sample, as more invasive procedures are necessary. At CMFT, TB treatment is commenced after samples for microbiological confirmation have been obtained. TB treatment is unlikely to have influenced our findings therefore.

We have demonstrated an association between site of disease and the frequency of sampling. This is to be expected as some sites are easier and less hazardous to sample. 0/12 cases of presumed ocular TB had specimens sent for microbiological confirmation. Our centre has a high incidence of ocular TB as it is a tertiary referral centre for the North-West. A recent study of patients presenting with uveitis and evidence of active TB elsewhere or evidence of latent TB revealed that in 70% cases, inflammation resolved after a 6 month course of antituberculous therapy [7]. Thus, an approach of treatment based on characteristic clinical findings, with no other cause identified may be justified. Polymerase chain reaction (PCR) has been suggested as a diagnostic tool for detection of mycobacterial DNA in aqueous humor [8]. However, the sensitivity and specificity of this method has yet to be proven and the process is invasive.

Disease site was not related to whether TB cultures were positive. However, some sites only had few samples so it is difficult to draw conclusions. The type of sample taken was related to whether culture positivity was confirmed. 14 cases had lymph node aspirates sent for culture (including cases where samples may also have been taken from other sites), but only 50% returned positive. Lymph node aspirates have previously been demonstrated to yield between 46% and 62% positive results [9,10]. Lymph node biopsy increases culture positivity (71–97% [9,10], and in our study 89%), but is not available as quickly and more invasive. Use of endobronchial ultrasound guided sampling (EBUS) is a welcome advance, but culture positive rates even with this technique remain of the order of 50% [11]. Other specimens which yielded poor culture positivity were gastric aspirates (0%) and samples from multiple sites (0%). Our laboratory does not add bicarbonate to gastric samples prior to culture and so our culture data is lower than that reported in the literature (17.2%) [12]. However, there were only 4 gastric aspirates sent in our cohort, so it is difficult to draw robust conclusions from this. Most of the cases where samples were taken from multiple sites were either lymph node disease ($n = 5$) or disseminated disease ($n = 4$). All these were in non-UK born cases and history and radiology was highly suggestive of TB.

Whether samples were sent for culture also depended on patient age, with children less likely to be sampled. Sampling in children is more difficult than in adults. Hilar lymphadenopathy was the disease site in 7 of these cases and therefore would require invasive procedures to sample, which would involve risk, distress and general anaesthesia. The advent of EBUS may also be of use in the future in children [13].

Paediatric samples were also more likely to be culture negative. In children, gastric lavage has been the investigation of choice for pulmonary TB as it is relatively easy to perform and less invasive than bronchoscopy. Disease in children is typically paucibacillary so the yield of direct acid fast smear microscopy in sputum is low, and prolonged culture is needed [14]. However, the yield from gastric lavage is often also low (32%) [15] so new techniques for

Table 3 A summary of cases with no specimen sent.

Site of disease	Number	No sample	Reasons for no sample
Pulmonary	69	7	5 children age <8 1 85 yr old on LCP 1 age 31 refused bronchoscopy
Lymph node	34	6	3 children with hilar nodes 1 node had gone by time of biopsy 1 pelvic node in patient with cervical cancer 1 abdo node sampled at renal transplant
Gastrointestinal	8	1	84 yr old caecal biopsy only sent to histology
Eye	12	12	Inaccessible
Testicle	1	1	Biopsy to histology only
Cryptic	1	1	No site to sample

Table 4 A summary of cases with negative microbiology.

Site of disease	Number	Culture -ve	Reasons for negative sample
Pulmonary	69	10	2 children age <1 yr old 4 sputum only - 2 had ≥3 sputums taken - 1 had 1 sputum taken before placed on treatment (high risk renal patient) - 1 had 1 sputum taken before placed on treatment (high risk HIV patient) 1 had bronchoscopy, CSF and urine examined 1 bronchoscopy only 2 sputum and bronchoscopy
Lymph node	34	12	3 children with hilar nodes 1 node biopsy only 6 node aspirates + other site but with no node biopsy. 29–62 yr old. 1 node aspirate failed due to solidification of pus. Biopsy delayed until after treatment 1 node aspirate failed because node could not be palpated. (sputum x3, renal biopsy and urine taken)
Gastrointestinal	8	2	1 27 yr old had 6 sputum samples taken. 1 ascites aspirate taken only.
Pleura	10	3	3 pleural aspirates only, no biopsy.
Disseminated	6	3	1 pleura and abdo disease. Ascites and pleural aspirate taken. A&E admission so no time for biopsy. 1 pleura and LN disease. 12 yrs old therefore pleural aspirate and nasogastric secretions only. 1 pleura and LN disease. Pleural aspirate and bronchoscopy only. No biopsy
Bone/joint	4	1	Joint aspirate
Miliary	2	1	Sputum and gastric lavage (child)
CNS	3	1	Spinal aspirate
Skin	2	1	Skin biopsy
Nasal	2	1	Nasal swab
Pericardium	1	1	Pericardial and pleural aspirates

diagnosing TB in children are emerging: principally induced sputum [14] and nasopharyngeal aspiration [16].

Ethnicity of individuals was not related to whether samples were sent for culture or were culture positive. This is again to be expected but important given that cases in ethnic minorities are more likely to be extrapulmonary and have higher levels of drug resistance. Isoniazid resistance and MDR-TB are more common in ethnic minorities and individuals born outside the UK [17]. HPA figures have demonstrated 7.4% cases non UK-born have isoniazid resistance, compared to 6.3% UK born. In addition, 1.4% cases born outside the UK have MDR TB, in comparison with 0.6% UK born cases. In Central Manchester in 2009 4.7% of cases showed monoresistance and 0% MDR-TB.

In only 3/28 cases with absent samples was this considered to be non-acceptable. 2 cases involved lymph nodes in the abdomen and pelvis and 1 involved ileocaecal disease, in which samples were taken for histology only during surgical or endoscopic procedures. The patients were all born outside the UK in areas with high TB incidence. TB may not have been considered in the initial differential diagnosis highlighting the need for ongoing education and awareness for healthcare professionals. In addition, these procedures were likely to have been performed by surgeons who come across TB infrequently and therefore would only have formalin in which to place samples. Other specialties e.g. radiology may be more used to sending samples for mycobacterial culture. A previous retrospective analysis of abdominal TB at a centre in the UK revealed culture positive results in 39% cases overall [18]. When biopsies are taken, the culture positive rate can vary between 6% and 69% [19], again indicating the difficulties of confirming drug sensitivity in this disease. At CMFT TB culture was confirmed in 63% cases of abdominal TB.

When samples were sent for culture, 72% gave a culture positive result, giving an overall proportion of 59% cases being culture positive in our case series. Only 4 of these cases could have been managed differently on retrospective analysis. If samples are smear negative, culture results and sensitivity confirmation can take up to 6 weeks. The clinician often needs to start treatment before this and by the time negative results are returned, it may be too late for repeat sampling. Most centres will have had experience with histopathology results revealing caseating granulomas in high risk individuals but no positive microbiological cultures. The overall sensitivity of TB culture has been reported to be 80–85%, and the specificity 98% [20].

The 4 cases which could have been managed differently all involved adults born outside the UK with pleural effusions, where pleural fluid was sent for culture but no pleural biopsy was done. Pleural fluid is known to have low culture sensitivity (<40%) but pleural biopsy increases diagnostic yield to 91%, with culture confirmation in 56%

[21]. A recent case series also demonstrated that 55% individuals with tuberculous effusions will have positive cultures from induced sputum, another diagnostic tool which could be utilised [22].

Limitations of our study include diagnosis of TB in a single centre and therefore potential for lack of generalisability. Central Manchester NHS Foundation Trust also has a regional ophthalmology unit, accounting for the relatively high proportion of ocular TB. Our findings could be used to base a multi-centre study to allow a bigger sample size which may be more representative. There may be some subjectivity when defining what is acceptable to have been missed or not. The researchers have made a decision based on documentation in medical and nursing notes, on a retrospective basis. The results of all investigations and discussions may not have been available for review, and therefore may have lead to bias in interpretation.

Despite an overall culture positive rate of 59%, none of the patients in whom no samples were sent or were culture negative relapsed and all were discharged from the TB service. A previous study has also demonstrated that empirical treatment of pulmonary TB based on clinical and radiological features did not lead to any adverse outcomes in culture negative patients in whom the development of resistance might be expected to be less likely to occur [23,24]. The setting of the study is typical of practice throughout the UK and probably many other centres. The lack of an obvious and easy capability to increase culture positivity must be a concern, especially in this era of increasing extrapulmonary TB. Novel approaches (eg EBUS examination of mediastinal nodes) to invasive sampling and improvements in microbiological methods are going to be important for future successful case management.

Conclusions

In summary, culture positivity is slowly increasing, and is more common in pulmonary than extrapulmonary disease. The rise in the proportion of extrapulmonary cases and the lower culture positivity rate in this group is a particular concern. There were very few cases overall where opportunities to obtain samples and/or confirm culture and sensitivity were reasonably missed. In this era of drug resistance there is an increased need for invasive methods to provide samples for culture and improved microbiological methods to ensure correctly targeted antituberculous therapy in the individual patient and to accurately describe the pattern of drug resistance in the population.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.09.016.

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