TITLE PAGE

DRUG RESISTANT TB: UK MULTICENTRE STUDY (DRUMS): TREATMENT, MANAGEMENT AND OUTCOMES IN LONDON AND WEST MIDLANDS 2008-2014.

Running title: Drug resistant TB in the UK

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Highlights:

- Treatment practices and outcomes for MDR-TB treatment in the UK are described.
- Treatment success is high limited by adherence rather than microbiological failure.
- Variations in public health practice and housing lead to long hospital admissions.
- New models and infrastructure are required to reduce poor adherence.
- New methods using whole genome sequencing are required to shorten hospitalisation.

ABSTRACT

Objectives: Detailed information regarding treatment practices and outcomes of MDR-TB treatment in the UK is required as a baseline for care improvements.

Methods: 100 consecutive cases between 2008 and 2014 were reviewed retrospectively at 4 MDR-TB treatment centres in England to obtain information on drug treatment choices, hospital admission duration and outcomes for MDR-TB.

Results: Initial hospital admission was long, median 62.5 (IQR 20-106, n=92) days, and 13% (12/92) of patients lost their home during this period. Prolonged admission was associated with pulmonary cases, cavities on chest radiograph, a public health policy of waiting for sputum culture conversion (CC) and loss of the patient's home. Sputum CC occurred at a median of 33.5 (IQR 16-55, n=46) days. Treatment success was high (74%, 74/100) and mortality low (1%, 1/100). A significant proportion of the cohort had "neutral" results due to deportation and transfer overseas (12%, (12/100)). 14% (14/100) had negative outcomes for which poor adherence was the main reason (62%, 9/14).

Conclusions: Successful outcome is common in recognised centres and limited by adherence rather than microbiological failure. Duration of hospital admission is influenced by lack of suitable housing and some variation in public health practice. Wider access to long-term assisted living facilities could improve completion rates.

MAIN TEXT

INTRODUCTION:

Although Multidrug resistant tuberculosis (MDR-TB) represents only 1.4% of tuberculosis (TB) cases in England and Wales, therapy is arduous for patients, usually consisting of 18-24 months of treatment with drugs with multiple adverse events, and prolonged hospital admissions[1, 2]. For the National Health System (NHS) the costs are estimated at ten times that for fully sensitive TB[3].

Patients receive individualised treatment in the UK based on international guidance[4-6]. However, within guidance there is scope for differing practice between centres[4-7]. Final outcome data are collected by Public Health England (PHE) for all TB cases but most of the individual treatment and management decisions are not recorded[2]. Furthermore, early indicators of treatment response which have public health implications are not routinely collected (e.g. sputum culture conversion (CC)).

New diagnostics and treatments[8] are becoming available but without a detailed baseline and assessment of the impact on treatment outcomes and costs will not be possible[8-10]. Here we present a cohort drawn from four UK MDR-TB treatment centres to better understand current management, isolation decisions and outcomes.

METHODS:

Setting: Data were collected through clinical records and hospital database review at 4 TB treatment centres. These act as regional referral hubs for MDR-TB treatment and were in data collection order St Mary's Hospital, Imperial College NHS Trust, London (centre 1), The Heartlands Hospital, Birmingham (centre 2), the Royal Free Hospital, Hampstead, London (centre 3), St George's Hospital, Tooting, London (centre 4). Data were also collected at referring hospitals if patients were treated under a shared care model. All 4 centres provide negative pressure isolation rooms both in a ward and intensive care setting for the admission period. Centre 2 also acts as a centre for thoracic surgery and receives national referrals. Drug treatment is undertaken according to the WHO guidelines and local practices[4, 5]. Directly observed therapy (DOT) is recommended[11, 12]. Active drugs were defined as according to the original WHO classes 1-4 plus clofazemine and linezolid[4].

Microbiology and definitions: All cultures positive for acid alcohol fast bacilli (AAFB) were sent to the National Mycobacterium Reference Laboratory hospital (NMRL) and PHE Regional Centre for Mycobacteriology

(Birmingham) for identification, phenotypic drug susceptibility testing (DST) and molecular identification. A negative culture for *Mycobacteria tuberculosis* (*Mtb*) was determined after 42 days of incubation. Sputum culture conversion (CC) from positive was defined as the date of the first of two samples cultured to negativity taken at least 30 days apart, or culture negativity on one sample with no further samples and no positive samples in the 7 days prior. Time to CC was defined as the time between MDR-TB drug initiation and CC. Culture reversion (CR) to positive was defined as one sample that was culture positive taken over 30 days from the date of initial sputum CC or one positive sputum after the end of the injectable if CC not documented. Standard definitions were used for MDR-TB and XDR-TB and for pulmonary (PTB) and extra pulmonary tuberculosis (EPTB)[13]. Treatment outcomes were adapted from Anderson et 2013[14]. (**Table 1**) An initial hospital admission was defined as any inpatient stay in hospital during which MDR-TB treatment was initiated. Duration of admission was defined as the time between admission and final discharge date. Discharge sputum status was defined by the last sputum taken before discharge and can be seen in **Table 2**.

Study population and eligibility criteria: The first hundred consecutive patients, over 14 years of age, treated for MDR-TB from 2008 onwards, with a diagnosis of MDR-TB made in the UK, who had initiated treatment at least 3 months prior to the time of data collection in 2014 and who were treated for any period at one of the four hospitals were included. No patient who met these criteria was excluded. The cohort represents 20-25% of MDR-TB cases in England and Wales during this period[2]. The cohort was split into two according to date of treatment start (the 51st patient started treatment in spring 2011) due to newer molecular diagnostics[15] available in the latter part of the cohort and new treatment guidance[5, 16].

Statistical analysis: Time to culture conversion and the duration of the initial hospital admission were investigated using regression analysis techniques on a derived 4-category variable for the former and the logarithmic transform for the latter to achieve valid models fit. Multivariable models were selected using explanatory variable accounting for both statistical parsimony and clinical relevance. Details on statistical methodologies are given in appendix 1. STATA software was employed for data analyses (StataCorp.2015 S*tata Statistical Software: Release 14. College Station,* TX:StataCorp LP).

Ethics: The study was deemed to be a service evaluation at the NHS ethics board (NRES committee London-City and East). Consent was given by the Confidentiality Advisory Group (GAG) for access to clinical records review.

RESULTS:

Treatment initiation and demographics.

Baseline demographic information is presented in **Table 3.** Fifty nine (n=100, 59%) cases were referred for tertiary care from district general hospitals for MDR-TB treatment initiation and on going care and/or surgical assessment. Ninety three (n=100, 93%) cases were treated as MDR-TB for their first episode of TB in the UK. Seven (n=100, 7%) had previously been treated for fully sensitive TB in the UK and evolved MDR-TB due to documented (4 cases) or presumed (2 cases) poor adherence; or high organism load as evidenced by large cavities (1 case). One case of MDR-TB evolved into XDR-TB during treatment. This case was treated with DOT for 6 months followed by weekly reviews with dossette box pill counts until the diagnosis of XDR-TB was made. Sputum culture conversion occurred at 72 days (Table 8 case 2). Culture reversion and onward resistance was postulated to be due to poor adherence in the dossette box phase, poor absorption due to chronic diarrhoea from para-aminosalicylic acid (PAS), poor penetration of drugs to cavities or a combination of these factors (case number 2 table 8).

Initial regimen choices at the point that a diagnosis of TB was made and reasons for choices are summarised in **Table 4**. Seventy four (n=100, 74%) patients started treatment with a regimen suitable for fully sensitive TB [11] and were then switched to a MDR-TB regimen at a median of 28 days (interquartile range (IQR) 10.5-54.5 days). Twenty three (n=100, 23%) were started directly on an MDR-TB regimen at the point that a TB diagnosis was made. The data was missing for 3 patients. Excluding those with data missing the median time between starting these two regimens reduced significantly from 35 (IQR 14-61) days during the first half cohort (2008-

2011) to 19 (IQR 7-38) days for the second half of the cohort (2011-2014)(p=0.048). The reason for initiation of an MDR-TB regimen changed over time with 34 (n=49, 69%) starting due to DST results in the earlier cohort compared to 19 (n=50, 38%) in the later cohort (p=0.003). In comparison an increase in MDR-TB treatment initiation based on molecular analysis was observed over time: 58% started due to molecular assessment in the latter cohort compared to 29% (p=0.005) in the earlier cohort. In total 7 (n=99, 7%) patients were started on MDR-TB regimen based on epidemiological data. Initial MDR-TB drug choices are presented in table 4.

Fourteen (n=100, 14%) patients were treated with sub-optimal regimens (defined as less than 4 drugs that were later shown to be active) at the start due to underestimating the degree of resistance. The information was missing for one patient. All patients had their regimens reviewed and if needed augmented when DST information was available.

Admission to hospital

Sixty six (n= 68, 97%) cases diagnosed with PTB and 26 (n=32, 81%) diagnosed with EPTB were admitted to hospital at the start of treatment **(Table 5).** Two cases with PTB were not admitted at the start of treatment due to violence in one case and reclassification as latent TB in the other (both smear negative). In the latter case symptoms, radiology and sputum had all normalised on first line therapy by the time of MDR-TB diagnosis. The median length of stay was 62.5 (IQR 20-106, range 3-513) days**.** Loss of home during admission occurred in 13% of cases.

In a multivariate model, in comparison with the admission duration for EPTB cases without cavities (27 days, see CONSTANT in **Table 6**), patients with PTB were admitted to hospital almost 3 times longer (2.7 times, 95% CI 1.84- 4.02) and those patients with cavities almost 2 times longer (1.8 times, (95% CI (1.21-2.59)). Patients who suffered loss of home during their admission were admitted almost twice as long (1.81, 95%CI 1.22-2.7). Discharge prior to confirmation of culture conversion was associated with shorter admission.

Fifty-four (n=66, 82%) cases with PTB were sputum smear negative on discharge, four were smear positive (n=66, 6%), three had no sputum sent within 70 days of discharge (2 smear positive, 1 smear negative, all culture positive) three were recurrent defaulters with variable results on each self-discharge (none were smear positive on discharge), one died and one did not have any sputum sent (sputum induction was attempted, the case was diagnosed radiographically as having PTB and a neck lymph node aspirate revealed *Mtb* on culture).

Of the 16 patients who were smear negative and did not have a negative culture result available at discharge, 8 were subsequently culture positive and 8 culture negative. All four of those with a smear positive result at discharge were subsequently found to be culture positive. Two were documented to have stopped coughing at discharge and two were asked to self-isolate at home.

Thirty-eight (n=66, 58%) PTB cases were discharged smear negative with one or more sputa that were culture negative. The proportion at each site discharged with at least one culture negative differed as follows: 3 (n=9, 33%) at centre 1, 13 (n=18, 72%) at centre 2, 6 (n=17, 35%) at centre 3, and 16 (n=20, 80%) at centre 4 (p=0.01) (n=64, 2 not admitted, 1 died, 1 recurrent defaulter data not available).

Twenty-eight patients (n=100, 28%) required readmission during their treatment period to hospital with a range of 0-6 readmissions per person and 49 readmissions in total **(Table 7).** For 46 readmissions for which the duration and reason for readmission were documented the median duration of readmission was 5.5 days (IQR 1-38, range 1-400) and the total readmission days was 1971 days. Three patients required legal orders[17] to ensure readmission which were effective in one case at assisting completion of therapy.

Clinical treatment outcomes

Culture conversion (CC) and time to CC were documented in 53 (84%) and 46 (73%) of culture positive cases respectively (**Table 8 and 9)**. 3 patients culture converted on fully sensitive TB medications before the start of the MDR-TB regimen. A proportional odds model revealed that the odds of culture converting in over 60 days compared to less than 60 days was 5.8 (5.78, 95% CI 1.4-23.7, p=0.015) times greater for those with cavities compared to those without (keeping smear status constant) and 2.8 (2.79, 95% CI 0.9-8.9, p= 0.08) times

greater for those with smear positive sputum compared to those without (keeping cavity status constant) (**Further information in online supplement, Appendix Table 1**).

Seventy four (n=100, 74%) cases had a successful outcome. Poor adherence was the main reason for negative outcomes (Table 1) accounting for at 64% (9/14) of these cases. The other negative treatment outcomes were as follows. One patient chose fully informed and adherent to stop treatment early due to his perceived reduced ability to concentrate at work (346 days of therapy). Modifications of the drug regimen had been made including cessation of cycloserine 8 months earlier. There were no other cases where adverse effects lead to overall early cessation. One patient had treatment stopped due to previous psychiatric illness re-emerging (528 days of therapy), two informed the service of moving overseas but failed to give contact details, and one died in association with severe immunosuppression secondary to HIV (CD4 count 5 cells/μL)[18] despite effective treatment for MDR-TB (sputum CC achieved).

The three patients who recurrently defaulted from treatment all had treatment initiated on 4 occasions or more and have been admitted back to an isolated hospital bed when they became infectious. In two cases a part 2A order was used to assist isolation. They all had housing at the time of discharge from hospital, a financial support package and DOT was attempted. Adherence became impossible once discharged due to chaotic lifestyles. None of these patients were admitted to an assisted living facility for patients with TB.

DISCUSSION

We provide a uniquely detailed data-set on a complete and unselected cohort of MDR-TB patients treated in the UK. We hope to have captured some of the granularity of clinical practice and provide a baseline for future UK research. We show rapid culture conversion is achieved and the successful outcome of 74% is above the average for both Europe (49%)[19, 20] and globally (54%)[19, 21]; and similar to other studies reporting high success[22]. We also found a low number of deaths - one of the lowest frequencies reported[21-24]. Treatment success for XDR-TB was also good, and an improvement on previous UK reports. Although small numbers of XDR-TB patients these results go against international data showing worse outcomes compared to MDR-TB [25, 26].

We also show that there was a reduction in the delay between initiation of standard quadruple drug therapy and MDR-TB treatment over the period of this study. Even so, between 2011 and 2014, the median delay was still 18 days in sputum smear positive patients, leaving considerable room for further improvement with the routine rapid use of molecular diagnostics not currently available at all referral hospitals at the time.

Successful outcomes are limited in this cohort by the large number of cases with a “neutral” outcome (transferred overseas or deported) 12% **(Table 1)** which is higher than that reported elsewhere [22, 23]. If those with neutral outcomes are removed the success rate rises to 84%, close to the 85% success target of the Chief Medical Officer[27]. For those with negative outcomes adherence to treatment rather than mycobacterial resistance is the main limitation. Our cohort often ceased treatment early due to default and poor adherence compared to the other high success cohorts[22-24]. Traditional risk factors for poor adherence (alcohol, drug use, chaotic lifestyles) and management methods (positive incentives and pastoral support verses negative incentives and the law) for poorly adherent patients are not always explicitly described, but in one US study 9-15% of cases had enforcement orders for isolation and/or DOT compared to 3% who had use of legal orders in our study[28].

Shorter treatment duration through the use of new drugs, delaminid and bedaquiline[8, 29] with higher efficacy, is likely to improve completion rates, speed up culture conversion and reduce duration of long hospitalisation in the future[10, 30-32]. A 12 month regimen has recently become a WHO recommended option for selected patients who are supported to achieve full adherence and have no additional resistance (eg: pyrazinamide)[33, 34]. Currently, randomised controlled trial results are awaited for these shorter regimens [33]. However, until shorter more efficacious regimens become reality for all patients, there needs to be effective means to support patients through long courses of therapy. In the UK positive incentives for adherence in the form of assistance with housing, financial support and pastoral support in the manner of the TB nurses and outreach workers are feasible. However, there is not routine access to long term assisted living

facilities for patients with TB where social and job support, drug and alcohol assistance, 24 hour DOT and even sports facilities could be made available, as in the centralised Netherlands model of care (verbal correspondence). Of note, Case 1 in Table 7 completed therapy after default only after an admission to a long term residential facility providing many of the features available in the Dutch model. Similar facilities could assist in completion rates for those able to adhere in hospital initially and to culture convert. However, the management of defaulters who are potentially infectious and not able to adhere long enough to culture convert is an issue. In this situation, the UK has limited legal powers to enforce isolation (while the patient is infectious only) through Part 2 A orders[17], no powers to enforce DOT and no access to locked robust and appropriate facilities for infectious patients. Strengthening of these provisions centrally or locally would be helpful in the management of the relatively small number of patients who require substantial resource.

Long hospital admissions are driven by many factors including the need to establish that treatment is effective (especially for the most resistant cases), severity of disease, socio-economic factors, adverse event management, adherence concerns and homelessness. Our retrospective study is limited by the lack of disease severity markers and other data which prospective collection would be more suited to in order to establish the exact reasons for individual hospital durations. However, the increase in admission time for pulmonary compared to extra-pulmonary patients, although not proven, suggests public health concerns related to infectiousness following discharge are an important factor. Despite consensual agreement by the majority of patients to admission, prolonged inpatient stays on the grounds of public safety raise ethical issues that require further study. The loss of home for 13% of patients (presumably due to loss of earnings and loss of private rental properties) has huge implications for the individual and society [35].

Ensuring non-infectiousness is important on discharge for MDR-TB patients due to the consequences of onward transmission. Decisions on when patients can be safely discharged are not supported by a strong evidence base and this is reflected in widely varying practice and guidance [11, 12, 36]. We show here that differing proportions of PTB patients are discharged with at least one sputum culture negative from each of the hospitals. This finding could represent differing demographics of patients but is also thought to be due to physicians at each of the sites using differing microbiological (smear negativity, culture conversion) and clinical criteria (cough cessation, ability to reliably self isolate) to assess whether a patient is non-infectious. For example site 4 currently routinely requires all patients are culture negative at discharge. Awaiting culture conversion is a delayed marker requiring 6 weeks from the last sputum and evidently results in longer admissions whereas relying on cough cessation or smear negativity may increase the risk of onward transmission. Development of improved criteria to determine safe discharge are needed using a combination of clinical features (cough resolution), time to culture positivity in frequently sent sputum samples[37], assays for viability of organisms, and genome sequencing to help reliable and rapid assessment of regimen effectiveness[38].

CONCLUSION

Outcomes for MDR-TB patients treated at specialist UK centres are good and limited by adherence rather than microbiological failure. Hospital admissions are long and the duration influenced by loss of housing and some variation in public health practice. Wider access to long-term assisted living facilities could improve completion rates.

Acknowledgements:

Maria Mercer and Vera Pavlova (Respiratory medicine, St George's Hospital, London), Marie O Donoghue (Division of medicine, Imperial College, London), Angelita Solamalai (Division of medicine, Royal Free Hospital, London), Veronica White (Respiratory Medicine, Royal London NHS Trust), Lucy Baker (Respiratory Medicine, University Hospital Lewisham).

Declaration of competing interests statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: AA has received a research studentship funding from The Jefferiss Charitable Trust (no grant number),

PB is funded by INNOVATE UK (UK Government Agency) in collaboration with QuantuMDx Ltd. No further information is declared.

Ethics

The study was deemed to be a service evaluation at the NHS ethics board (NRES committee London- City and East). Consent was given by the Confidentiality Advisory Group (GAG) for access to clinical records review. The data were anonymised onsite for off sites analyses. Data sharing with public health was according to Caldicott principles.

Contributorship statement

Contributors were as follows:

The conception and design of the work	Amber Arnold, Tom Harrison, Martin Dedicoat, Graham Cooke, Onn Min Kon, Angela Loyse, Philip Butcher
The acquisition of data	Amber Arnold, Martin Dedicoat, Graham Cooke, Onn Min Kon, Marc Lipman, Angela Loyse Acknowledged persons: Maria Mercer, Vera Pavlova, Marie O Donoghue, Angelita Solamalai
Analysis and interpretation of data.	All Authors
Drafting the work or revising it critically for important intellectual content	All Authors
Final approval of the version published	All Authors
Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	All Authors

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