Treatment outcome of multi-drug resistant tuberculosis in the United Kingdom: retrospective-prospective cohort study from 2004 to 2007

L F Anderson (Laura.Anderson@phe.gov.uk)[1], S Tamne[1], J P Watson[2], T Cohen[3], C Mitnick[4], T Brown[5], F Drobniewski[5], I Abubakar[1,6]
1. Public Health England, Respiratory Diseases Department, TB Section, London, United Kingdom
2. Department of Respiratory Medicine, Leeds General Infirmary, Leeds, United Kingdom
3. Department of Epidemiology, Harvard School of Public Health, Boston, United States
4. Department of Global Health & Social Medicine, Harvard Medical School, United States
5. Public Health England, National Mycobacterial Reference Laboratory, Centre for Immunology and Infectious Disease, Barts and The London School of Medicine and Dentistry, London, United Kingdom
6. Research Department of Infection and Population Health, University College London, London, United Kingdom

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United Kingdom (UK) guidelines recommend at least 18 months treatment for patients with multidrug-resistant tuberculosis (MDR-TB). Prior to 2008, data on treatment outcome were only available at 12 months and therefore the proportion completing treatment was unknown. This retrospective-prospective cohort study reports on treatment outcomes for MDR-TB patients notified between 2004 and 2007 and examines factors associated with successful outcomes. 70.6% (144/204) completed treatment in 24 months or more, 6.9% (14) stopped treatment, 6.9% (14) died, 7.8% (16) were lost to follow up, 0.5% (1) relapsed and 4.4% (9) were transferred overseas. Following adjustment for age, being non-UK born, non-compliance and having co-morbidities, treatment with a fluoroquinolone (OR 3.09; 95% CI 1.21-7.88; p<0.05) or bacteriostatic drug (OR 4.23; 95% CI 1.60-11.18; p<0.05) were independently associated with successful treatment outcome. Treatment completion for MDR-TB cases remains below the World Health Organization (WHO) target. Our findings support current WHO guidelines for MDR-TB treatment. The UK should consider adopting individualised regimens based on WHO recommended drugs, taking into account drug sensitivities. Improving treatment completion rates will be key to tackling further drug resistance and transmission from untreated infectious cases.

Introduction

Multidrug-resistant TB (MDR-TB) remains a threat to the global tuberculosis (TB) control effort [1]. In the United Kingdom (UK), the annual number of culture confirmed cases of MDR-TB increased from 28 to 58 between 2000 and 2009 [2] and there were a total of eight extensively drug-resistant (XDR) cases reported (data unpublished). The prolonged treatment associated with MDR-TB and the often severe adverse effects of second-line antibiotics increases the challenges to achieve treatment completion. The rise in the number of MDR-TB cases has important implications for clinical management, social support and financing of TB control programmes [3]. Internationally, in resource rich settings, initial empirical treatment of MDR-TB patients should be based on past drug resistance results for patients with a previous TB episode, drug resistance profiles of an identified source case, or the levels of background drug resistance in the patient's country of origin [4,5]. This should be followed by individually adapted drug regimens once drug susceptibility results become available [4].

In 2008, the World Health Organization (WHO) recommended that the MDR-TB treatment regimen should ideally consist of a combination of ethambutol and pyrazinamide, an injectable agent (e.g. aminoglycosides), a fluoroquinolone and if necessary, a bacteriostatic drug should be added to give a total of at least four drugs to which resistance has not been demonstrated. Antibiotics with unknown efficacy should only be used when better options are exhausted [4]. Recently published WHO guidelines recommend the inclusion of the bacteriostatics ethionomide or prothionamide and either cycloserine or p-aminosalicylic acid in the regimen [5]. The treatment should last at least 20 months in total [5] and be supervised by directly observed therapy (DOT) [4].

In the UK, there is no recent national guidance for MDR-TB treatment [6,7]. The National Institute for Health and Clinical Excellence (NICE) guidelines published in 2011, did not specifically address the treatment of MDR-TB but suggested to consult experienced clinicians who specialise in MDR-TB treatment and care [8]. Data on the effectiveness of different drug combinations for MDR-TB are limited [5] and in the UK, it is

currently unknown which treatment regimens are most commonly used.

For cases notified in the UK in 2010, the proportion of MDR-TB cases completing treatment was 72.1% [9] which was below the WHO and UK treatment completion targets of 75% [10] and 85%, respectively, [11] but higher than the European Union (EU) target of 70% [12]. Prior to 2008, data on treatment outcome was only available at 12 months after the start of treatment and therefore it has been unclear how many cases completed treatment at 24 months. The enhanced surveillance of treatment outcome monitoring of MDR-TB cases allows treatment regimens and management to be assessed and progress towards achieving targets set by WHO [10], the EU [12] and the UK [11] to be evaluated over time.

The aims of this study were to determine the number and proportion of MDR-TB patients completing treatment who were diagnosed in the UK between 2004 and 2007, to describe the clinical characteristics of patients and to examine factors associated with a successful treatment outcome, loss to follow up and death.

Methods

All patients diagnosed with MDR-TB in England, Wales and Northern Ireland between 2004 and 2007 were included in the study. Treatment outcomes for all years were collected in 2009. Patients still on treatment at 24 months were followed up prospectively for treatment outcome on an annual basis until June 2012. All patients were followed up for a minimum of four years for relapse.

The following definitions and terms were used:
MDR-TB was defined as TB resistant to at least isoniazid and rifampicin.

Treatment regimen

Drugs used for treatment were categorised in five groups based on WHO criteria [4] (Table 2). To calculate the number of effective drugs used for treatment, in accordance with current guidelines, Group 5 agents, rifabutin (not recommended due to cross-resistance with rifampicin [4]) and drugs assumed to be ineffective due to phenotypic resistance testing methods were subtracted from the number of drugs in the initial regimen. A drug change was defined as an unexpected and unplanned addition, subtraction or substitution of a drug in the treatment regimen.

Treatment outcomes

Standard treatment outcomes routinely collected for surveillance in the UK are:

Completed treatment: Completed a full course of therapy within 12/24 months of starting treatment/notification.

Lost to follow up: Defined as failure to obtain contact with the patient before the end of treatment so that treatment outcome is not known.
Treatment stopped: Patient found to have stopped treatment (by choice) or for any other reason not mentioned below.
Still on treatment: Patient is still on treatment at 12/24 months due to

(a) initially planned e.g. in patients with TB affecting the central nervous system (CNS) or drug resistance;
(b) interruption as a result of side effects/intolerance, non-compliance, other interruption in taking treatment for two months or more;
(c) change in the treatment regimen due to intolerance/side effects, drug resistance (initial or acquired), failure to culture convert or poor clinical response.

Transferred out: Responsibility for patient's care transferred to another clinical team within the UK.
Transferred out overseas: Responsibility for patient's care transferred to another clinical team outside the UK. This treatment outcome was collected in addition to those above as part of this study.

Data collection

Demographic and clinical characteristics of patients were obtained from the Enhanced TB Surveillance system (ETS) which is the web-based TB notification system in the UK. Questionnaires were sent by mail to treating clinics to collect further information on: treatment outcome reported at 12 and 24 months, social risk factors (current or a history of alcohol or drug misuse, homelessness, imprisonment, smoking), co-morbidities (diabetes, chronic liver or renal disease, chronic hepatitis B or C positive and receiving immunosuppressive therapy), the initial drug regimen for MDR-TB, treatment start date, details of changes in treatment, duration of treatment (planned and given for those who completed treatment), DOT (defined as direct observation of ingestion of anti-TB treatment by a health professional in the community, the home or the clinic) and non-compliance (interruption of treatment for two consecutive months or more without medical approval or non-compliance reported by medical staff).

All questionnaires were returned. Previous history of TB diagnosis was self-reported and recorded in ETS; in addition, information from previous episodes diagnosed in the UK was ascertained through a search of ETS to complete missing data. Mortality data from the Office of National Statistics was searched manually for cases that were lost to follow up or had an unknown cause of death.

TB was considered to have caused or contributed to death if this was reported in ETS and/or recorded on the death certificate; ICD10 codes A15-A19 [13]. Human immunodeficiency virus (HIV) infection status was attained by record linkage as previously described [2]. Matching was not carried out on cases aged younger

Box

Treatment outcome categories, multidrug-resistant tuberculosis, United Kingdom

Treatment outcome category		
Successful	Adverse	Neutral
Treatment completed at 24 months or longer.	Treatment completed at 12 months.	The patient was transferred out overseas.
	Treatment completed at 24 months or longer but patient relapsed.	The patient died but TB was incidental to death.
	The patient died and TB caused or contributed to death or the relationship between the two was unknown. This includes patients diagnosed but not initiated on treatment prior to death.	
	Treatment stopped.	
	Lost to follow-up.	

Outcome categories were based on criteria by Ditah et al. (2007) [15].

than 15 years (10/204; 4.9%) as HIV infection in children is reported separately.

Laboratory methods

Drug susceptibility and strain typing data for cultured isolates of *Mycobacterium tuberculosis* complex were available from the UK Mycobacterial Surveillance Network (MycobNet). Drug susceptibility testing (DST) was carried out using the proportion or the resistance ratio method [14]. MDR-TB cases, notified in the UK (excluding Scotland) between 2004 and 2007, were identified by matching laboratory isolates to case reports in ETS [2], including those who subsequently developed MDR -TB during treatment. Cases of laboratory cross-contamination were excluded. Drugs with borderline resistance were considered to be resistant. The number of additional drugs to which MDR isolates were resistant was based on the resistance profile prior to the initiation of MDR-TB treatment.

Statistical analysis

The demographic and clinical characteristics of cases, drug resistance and the treatment regimen, management and outcome were described. Logistic regression modelling was used to calculate odds ratios for factors associated with a successful treatment outcome. All variables independently associated with treatment outcome in the univariate analysis ($p<0.2$) were considered in the multivariable model to evaluate the effect of drug treatment on outcome. A likelihood ratio test was used to investigate whether interactions between the different drug classes should be included in the final model. Individual co-morbidities were not considered in the multivariate analysis due to co-linearity with co-morbidity.

Ciprofloxacin is no longer recommended for use and therefore we did not include it as a variable in the model as it is no longer relevant for consideration in future treatment of MDR-TB.

Outcome categories were based on criteria by Ditah et al. (2007) [15] but were modified for the study population of drug-resistant, rather than fully sensitive TB cases (Box 1). Neutral outcomes (n=10) and patients who did not initiate treatment because they were diagnosed post mortem (n=3) were excluded from this part of the analysis.

Additional analyses using a chi-square test were undertaken to determine factors associated with the following adverse outcomes: (i) loss to follow up (included all MDR-TB cases) and (ii) death (included all patients with a known vital status at 24 months and excluded those transferred overseas or lost to follow up). Statistical analyses were carried out using Stata version 10.0.

Results

Demographic, clinical and social characteristics

There were 204 culture-confirmed cases of MDR-TB diagnosed in the UK between 2004 and 2007. Just over half of these cases resided London and the majority were 15 to 44 years old, non-UK born and of Indian subcontinent or Black African ethnicities (Table 1). Pulmonary disease was most common (70.1%, 143/204); 61.5% (88/143) of these cases, were sputum smear positive. Only 30.4% (56/184) of patients had a previous history of TB diagnosis. Of those with information recorded on social risk factors and co-morbidities, 18.6% (32/172) had at least one social risk factor and 26.7% (49/183) had a co-morbidity, of which HIV infection was most common (Table 1).

Isolates were resistant to a median of four drugs (range 2-9) and were most commonly resistant to streptomycin (53.9%, 110/204) and ethambutol (35.3%, 72/204). There were no cases of XDR-TB. High proportions were resistant to a bacteriostatic agent (22.5%, 46/204), and to at least one (42.2%, 86/204) and two or more (24.0%, 49/204) second-line drugs. Fluoroquinolone resistance was uncommon (4.4%, 9/204) and 10.3% (21/204) were resistant to all first-line drugs.

Treatment regimen and management

Among the 94.6% (193/204) patients who began treatment the planned duration was recorded for 83.9% (162/193). The duration of the intensive treatment phase was not recorded. A treatment course shorter

Table 1

Characteristics of multidrug-resistant tuberculosis cases, United Kingdom, 2004–2007 (n=204)

Characteristic	n (%)
Living in London	
Yes	104 (51.0)
Sex	
Male	103 (50.5)
Age (years)	
0-14	10 (4.9)
15-44	170 (83.3)
45-64	17 (8.3)
≥ 65	7 (3.4)
Born in UK (n=201)	
Yes	31 (15.4)
No	170 (84.6)
Ethnicity (n=201)	
White	22 (10.9)
Black African	59 (29.3)
Indian subcontinent	78 (38.8)
Other	42 (20.9)
Previous diagnosis of TB (n=184)	
Yes	56 (30.4)
No	128 (69.6)
Site of disease	
Pulmonary, sputum smear positive	88 (43.1)
Pulmonary, other	55 (27.0)
Extrapulmonary disease only	61 (29.9)
Social risk factor (n=172)[a]	
Yes	32 (18.6)
No	140 (81.4)
Homelessness	9 (5.2)
Drug abuse	9 (5.2)
Alcohol misuse	12 (7.0)
Imprisonment	5 (2.9)
Smoking	21 (12.2)
Any co-morbidity (n=183)[b]	
Yes	49 (26.7)
No	134 (73.2)
Diabetes (n=192)	10 (5.2)
Chronic renal disease (n=192)	7 (3.6)
Chronic liver disease (n=192)	3 (1.6)
Immunosuppressive therapy (n=192)	4 (2.1)
Hepatitis B/C positive (n=192)	9 (4.7)
HIV positive (n=193)	30 (15.5)
Total	**204 (100)**

[a] Patients were coded as yes if they had "yes" for any social risk factor and no if they had "no" for every social risk factor included.

[b] Patients were coded as yes if they had "yes" for any co-morbidity and no if they had "no" for every co-morbidity included. If data were missing for one or more co-morbidities, they were coded as missing.

HIV: human immunodeficiency virus; TB: tuberculosis; UK United Kingdom.

than 18 months was planned for 11.1% (18/162) of patients but 23.2% (33/142) of those completing treatment, where a treatment start and completion date was available, actually received less than 18 months. The median treatment duration for cases completing treatment was 19 months (range 3–47) and increased from 18 to 23 months between 2004 and 2007.

The most common drugs used for treatment were pyrazinamide, moxifloxacin and ethambutol (Table 2). A median number of four effective drugs (range 0-8) were used in the initial drug regimen and 19.7% (38/193) of cases were treated with fewer than four effective drugs.

Over half of patients (54.4%, 105/193) had at least one change to their treatment regimen at some point during treatment. In the majority of these cases, the reason for this was not stated. When documented, most regimen alterations were in response to side effects or drug intolerance and only rarely in response to a change in drug susceptibility (data not shown).

Only 39.9% (77/193) of all patients and 53.1% (17/32) of those with identified social risk factors were placed on DOT. Main reasons for not administering DOT, where recorded, were a lack of indicators for non-compliance 40.0% (42/105), being an inpatient 25.7% (27/105) or using a dossette box as an alternative 11.4% (12/105).

Treatment outcome

A total of 70.6% (144/204) of patients successfully completed treatment at 24 months or more. For those with unsuccessful outcomes 6.9% (14/204) had their treatment stopped, 6.4% (13/204) died where TB was recorded as a causative or contributory factor or the relationship between the two was unknown, 7.8% (16/204) were lost to follow up, 2.9% (6/204) completed treatment within 12 months and 0.5% (1/204) completed treatment but relapsed. Ten of the 204 (4,9%) patients had neutral outcomes: nine were transferred overseas and mainly referred to clinics in resource-poor countries in Asia and Africa and one died where TB was incidental to death.

Factors associated with treatment success

Results of the univariate analysis are shown in tables 3 and 4. In the multivariable analysis patients receiving a fluoroquinolone or a bacteriostatic drug were more likely to have a successful treatment outcome compared to those who did not (Table 5). Treatment with an injectable agent did not have a significant effect on treatment outcome after adjusting for treatment with a fluoroquinolone and a bacteriostatic drug. No significant interactions were detected and all other factors remained significantly associated with treatment outcome, apart from having resistance to five or more drugs. Exploratory analyses were carried out to try to explain the relationship between resistance to five or more drugs and a successful outcome. Firstly, resistance to five or more drugs was added to the model,

Table 2

Drugs used for treatment of multidrug-resistant tuberculosis cases, United Kingdom, 2004–2007 (n=193)

Treatment groups	Number of cases	%
Group 1 - First line drugs	170	88.1
Isoniazid	6	3.1
Rifampicin	6	3.1
Ethambutol	126	65.3
Pyrazinamide	155	80.3
Rifabutin	4	2.1
Group 2- Injectable agents	139	72.0
Streptomycin	37	19.2
Amikacin	76	39.4
Capreomycin	30	15.5
Kanamycin	0	0
Group 3 - Fluoroquinolones	147	76.2
Levofloxacin	6	3.1
Moxifloxacin	129	66.8
Ofloxacin	14	7.3
Ciprofloxacin	44	22.8
Injectable and fluoroquinolone	111	57.5
Group 4 - Bacteriostatic drug	151	78.2
Ethionamide	11	5.7
Prothionamide	113	58.5
Cycloserine	69	35.8
Para-aminosalicylic acid (PAS)	19	9.8
Group 5 - Agents with unclear efficacy	83	43.0
Linezolid	8	4.1
Clofazimine	2	1.0
Amoxicillin	0	0
Imipenem	0	0
Clarithromycin	78	40.4
Other	13	6.7
Augmentin	2	1.0
Azithromycin	11	5.7
Total	**193**	**100**

[a] No longer recommended for use.

following adjustment for all factors associated with a poor treatment outcome (Table 5), and remained significant. Each treatment was then added separately and only adjustment for bacteriostatic drug treatment led to loss of statistical significance.

Factors associated with treatment stopped, mortality and loss to follow up

Reasons given for stopping treatment in 14 patients included 'non-compliance', resulting in the clinician's decision to discontinue treatment, 'patient's choice', 'pregnancy', 'side effects' and 'spontaneous recovery'.

Of the 14 patients who died, six died prior to starting treatment and three of these were diagnosed post mortem. Compared to cases who were known to be alive at the end of treatment, death was found to be strongly associated with having any co-morbidity ($p<0.0005$), and in particular with HIV ($p<0.0005$), diabetes ($p=0.002$) or chronic renal disease ($p=0.002$). Only being a new entrant to the UK (11/12 were in the UK ≤2 years prior to diagnosis, $p=0.030$, with six returning home) was associated with being lost to follow-up. Reasons given for completing treatment within 12 months were that 'the patient improved', 'it was the recommendation at the time' or 'it was initially planned and the patient was followed up instead'.

Discussion

The proportion of MDR-TB cases notified between 2004 and 2007 completing treatment in the UK was 70.6%. This was higher than the EU/European Economic Area (EEA) average of 30.9% [16] for 2007 MDR-TB cases and most other low incidence resource-rich countries[17-19]. This completion rate met the EU target of 70% [12] but was still below the WHO target of 75% [10] and the UK Chief Medical Officers action plan goal of 85%[11]. The treatment completion rate for MDR-TB cases in the UK has improved in recent years with 80% and 72% completing treatment for cases notified in 2009 [20] and 2010 [9], respectively.

Treatment with a fluoroquinolone or a bacteriostatic drug were statistically significantly associated with achieving treatment success, which provides further evidence to support the recent WHO recommendations to include drugs belonging to Groups 2, 3 and 4 in a treatment regimen for MDR-TB [5]. These findings have potential implications for the development of future national guidelines and the UK should consider adopting individualised regimens, based on the drug classes recommended by WHO for treatment of MDR-TB cases, taking into account DST results.

While the majority of patients appeared to have appropriate treatment according to WHO guidelines, approximately a quarter of patients had a substandard regimen with too few effective drugs or shorter treatment duration than required. DST results were not always used to ensure administration of effective individualised regimens. However, we note that DST results for most drugs other than isoniazid and rifampicin are less accurate [21] and therefore it is possible that these patients still received effective treatment.

The majority of patients, even those with social risk factors and those hospitalised, did not receive DOT although it is recommended for all MDR-TB patients [4]. Therefore greater use of DOT remains important until 85% treatment completion is achieved.

Table 3

Univariate analysis of drug resistance pattern, treatment regimen and treatment management associated with successful treatment outcome in patients diagnosed with multidrug-resistant tuberculosis, United Kingdom, 2004–2007 (n=191)

	Adverse treatment outcome (n = 47) n (%)	Successful treatment outcome (n = 144) n (%)	Unadjusted OR (95% CI)	P value
Drug resistance				
Number of drugs				0.017[a]
Resistance to 2-4 drugs at the start of treatment	42 (28.4)	106 (71.6)	1	
Resistance to 5 or more drugs at the start of treatment	5 (11.6)	38 (88.4)	3.01 (1.11-8.17)	
Group 1 - First-line drugs[b]				0.911
Susceptible	26 (24.3)	81 (75.7)	1	
Resistant	21 (25.0)	63 (75.0)	0.96 (0.50-1.87)	
Second-line drugs (Any)				0.429
Susceptible to all	19 (27.9)	49 (72.1)	1	
Resistant to at least one	28 (22.8)	95 (77.2)	1.32 (0.67-2.59)	
Group 2 - Injectable agent[c]				0.592
Susceptible	23 (26.4)	64 (73.6)	1	
Resistant	24 (23.1)	80 (76.9)	1.20 (0.62-2.32)	
Group 3 - Fluoroquinolone[d]				0.269
Susceptible	43 (23.8)	138 (76.2)	1	
Resistant	4 (40.0)	6 (60.0)	0.47 (0.13-1.73)	
Group 4 - Bacteriostatic drugs[e]				0.459
Susceptible	38 (25.9)	109 (74.1)	1	
Resistant	9 (20.5)	35 (79.5)	1.36 (0.60-3.08)	
Developed further drug resistance whilst on treatment				0.914
No	43 (24.7)	131 (75.3)	1	
Yes	4 (23.5)	13 (76.5)	1.06 (0.33-3.44)	
Initial treatment regimen				
Group 2 - Injectable agent[c]				0.010*
No	22 (36.7)	38 (63.3)	1	
Yes	25 (19.1)	106 (80.9)	2.45 (1.24-4.86)	
Group 3 – Fluoroquinolone[d]				0.000*
No	23 (44.2)	29 (55.8)	1	
Yes	24 (17.3)	115 (82.7)	3.80 (1.88-7.67)	
Ciprofloxacin				0.084
No	32 (21.6)	116 (78.4)	1	
Yes	15 (34.9)	28 (65.1)	0.51 (0.25-1.08)	
Group 4 - Bacteriostatic drugs[e]				0.000*
No	24 (50.0)	24 (50.0)	1	
Yes	23 (16.1)	120 (83.9)	5.22 (2.54-10.72)	
Treatment management				
DOT at any time during treatment				0.230
No/Unknown	32 (27.6)	84 (72.4)	1	
Yes	15 (20.0)	60 (80.0)	1.52 (0.76-3.06)	

DOT: directly observed therapy.

[a] Significance p<0.05.
[b] Group 1 oral agents Ethambutol or Pyrazinamide
[c] Group 2: Amikacin, Capreomycin, Kanamycin or Streptomycin.
[d] Group 3: Moxifloxacin, Ofloxacin, Ciprofloxacin.
[e] Group 4: Ethionamide, Prothionamide,Cycloserine, Para-aminosalicylic acid.

Table 4

Univariate analysis of demographic and clinical characteristics, social risk factors and comorbidities associated with successful treatment outcome in patients with multidrug-resistant tuberculosis, United Kingdom, 2004–2007 (n=191)

	Adverse treatment outcome (n = 47) n (%)	Successful treatment outcome (n = 144) n (%)	Unadjusted OR (95% CI)	P value
Living in London				0.288
Yes	28 (27.7)	73 (72.3)	1	
No	19 (21.1)	71 (78.9)	1.43 (0.73-2.79)	
Age				0.000[a]
0-14	1 (10.0)	9 (90.0)	2.36 (0.29-19.27)	
15-44	33 (20.8)	126 (79.2)	1	
45-64	6 (40.0)	9 (60.0)	0.39 (0.13-1.18)	
≥65	7 (100)	0 (0)	0 (0)[b]	
Sex				0.256
Male	27 (28.1)	69 (71.9)	1	
Female	20 (21.0)	75 (79.0)	1.46 (0.76-2.85)	
Born in the UK				0.026[a]
Yes	3 (10.0)	27 (90.0)	1	
No	44 (27.7)	115 (72.3)	0.29 (0.08-1.01)	
Ethnicity				0.877
White	5 (25.0)	15 (75.0)	0.84 (0.27-2.67)	
Black African	15 (28.3)	38 (71.7)	0.71 (0.31-1.60)	
Indian subcontinent	16 (21.9)	57 (78.1)	1	
Other	10 (23.8)	32 (76.2)	0.89 (0.36-2.21)	
Previous diagnosis of TB				0.532
No	28 (23.0)	94 (77.0)	1	
Yes	14 (27.4)	37 (72.6)	0.79 (0.37-1.66)	
Site of disease				0.279
Pulmonary sputum positive	23 (27.7)	60 (72.3)	1	
Pulmonary other	14 (28.0)	36 (72.0)	0.99 (0.45-2.16)	
Extrapulmonary disease only	10 (17.2)	48 (82.8)	1.84 (0.79-4.24)	
Social risk factor				0.443
No	29 (22.0)	103 (78.0)	1	
Yes	9 (29.0)	22 (71.0)	0.69 (0.29-1.66)	
Unknown	9 (32.1)	19 (67.9)	0.59 (0.24-1.45)	
Non-compliant[c]				0.019[a]
No	31 (21.1)	116 (78.9)	1	
Yes	10 (52.6)	9 (47.4)	0.24 (0.08-0.64)	
Unknown	6 (24.0)	19 (76.0)	0.85 (0.31-2.30)	
Comorbidity				0.001[a]
No/Unknown	28 (18.9)	120 (81.1)	1	
Yes	19 (44.2)	24 (55.8)	0.29 (0.14-0.61)	
Diabetes				0.014[a]
No/Unknown	41 (22.6)	140 (77.4)	1	
Yes	6 (60.0)	4 (40.0)	0.19 (0.05-0.73)	
Chronic renal disease				0.061
No/Unknown	43 (23.4)	141 (76.6)	1	
Yes	4 (57.1)	3 (42.9)	0.23 (0.05-1.06)	
Chronic liver disease				0.732
No/Unknown	46 (24.5)	142 (75.5)	1	
Yes	1 (33.3)	2 (66.7)	0.64 (0.06-7.31)	
Hepatitis B/C positive				0.408
No/Unknown	44 (24.0)	139 (76.0)	1	
Yes	3 (37.5)	5 (62.5)	0.53 (0.12-2.30)	
HIV-positive				0.048[a]
No/Unknown	37 (22.2)	130 (77.8)	1	
Yes	10 (41.7)	14 (58.3)	0.40 (0.16-0.97)	

[a] Significance p<0.05.

[b] Not estimable.

[c] Interruption of treatment for two consecutive months or more without medical approval or non-compliance reported by medical staff.

CI: confidence interval; HIV: human immunodeficiency virus; OR: odds ratio; TB: tuberculosis; UK: United Kingdom.

Table 5

Multivariate analysis of factors associated with successful treatment outcome (n=182)

Covariable	Adjusted OR (95% CI)	p-value
Age (years)		0.289
0-14	3.49 (0.32-38.1)	
45-64	0.46 (0.10-2.07)	
≥65	Not estimable	
Born in UK	0.45 (0.10-1.92)	0.2548
Non-compliant[a]	0.14 (0.04-0.49)	0.0079
Comorbidity	0.26 (0.09-0.71)	0.0090
Resistant to five or more drugs	2.17 (0.68-6.94)	0.1736
Group 2[b]- Use of injectable drug	1.49 (0.56-3.98)	0.4323
Group 3[c]- Use of fluoroquinolone	3.09 (1.21-7.88)	0.0191
Group 4[d]- Use of bacteriostatic drug	4.23 (1.60-11.18)	0.0036

[a] Interruption of treatment for two consecutive months or more without medical approval or non-compliance reported by medical staff.

[b] Group 2: Amikacin, Capreomycin, Kanamycin or Streptomycin.

[c] Group 3: Moxifloxacin, Ofloxacin, Ciprofloxacin.

[d] Group 4- Ethionamide, Prothionamide,Cycloserine, Para-aminosalicylic acid.

CI: confidence interval; OR: odds ratio; UK: United Kingdom.

Mortality rates of 6.4% in our study, were similar to those observed for all TB cases in the UK in the same period (6.2%, 2004-2007) (data unpublished) and to other low incidence countries[16], although higher than expected for a population where most cases are 15 to 44 years old [22]. Similarly to other studies, death was significantly associated with presence of HIV infection [23-27], chronic renal disease [28,29] and diabetes [28,30]. Treatment of HIV co-infected patients is complicated due to a high tablet burden, increased drug side effects [31] and opportunistic infections. TB patients with chronic renal disease may also experience more treatment side effects and some TB drugs can directly damage kidney function [32]. Anti-TB treatment can worsen glycaemic control in patients with diabetes [30]. These problems are intensified in MDR-TB where treatment duration is prolonged and drug options are limited.

The association between successful treatment outcome and fluoroquinolone or bacteriostatic drug use, has been shown previously [21,27,33-37]. The relative infrequency of resistance to fluoroquinolones in our study further supports their use in MDR-TB treatment. Consistent with previous reports [38,39], ciprofloxacin was not shown to be an effective agent in the univariate analysis, supporting its recent exclusion from the list of recommended TB drugs [4].

Similarly to findings in resource-rich countries, where the majority of MDR-TB cases are imported, we detected high proportions of streptomycin and ethambutol resistance [17,18,21,40]. In contrast to other studies [41-47], the treatment success of UK MDR-TB patients is not affected by the number of additional drugs to which isolates are resistant, which may reflect the local availability of alternative second line antibiotics. The association between resistance to a greater number of drugs and a successful treatment outcome was not significant following adjustment for treatment with a bacteriostatic agent. A possible explanation for this is that those with fewer treatment options are more likely to receive a bacteriostatic which leads to treatment success.

Our study has several limitations. The small sample size limited our ability to detect the effect of individual antibiotics on treatment outcome or significant interactions. The initial drug resistance profile affects the choice of antibiotic used and therefore this may have confounded associations between antibiotics used and treatment outcome.

The treatment outcomes in the UK differ from the standard WHO definitions [48], which means that it is difficult to compare outcomes directly with other countries. For example, in the absence of bacteriological or radiological data at the end of treatment we were not able to determine whether patients who completed treatment had been successfully cured. The relapse rate in the UK however is low, despite lack of evidence of cure [49,50] and during the study period only one case relapsed and was appropriately categorised as unsuccessful.

The treatment outcome classification used in the statistical analysis was based on an approach by Ditah et al. [15] which also differs from other studies. Deaths where TB is incidental to death are usually classified as an unsuccessful outcome but we chose to exclude them from the analysis as the eventual outcome, for example had the patients not died for another reason, was unclear. The UK however, has a strong vital registration system and we are therefore confident that these deaths were not caused by TB.

The partly retrospective study design prevented time to event analysis as we did not have the dates for all outcome categories. Data sources used to complete the questionnaire may not have been as accurate or complete as they would have been in an entirely prospective cohort. This may be particularly true for variables that can vary in definition such as DOT or variables relying on comprehensive notes such as changes in treatment. Future prospective studies or randomised control trials will likely provide stronger evidence for the association between individual drugs and treatment outcome, as well as allow for the investigation of the role of treatment duration on treatment completion or cure.

Public health and clinical implications

Since 2011, WHO guidelines for MDR treatment regimens recommend the inclusion of an oral bacteriostatic drug in combination with a fluoroquinolone and an injectable agent. This study, in addition to a recent meta analysis of 9,153 patients [37], supports these guidelines and therefore, provided the future MDR-TB population remains similar to our study population, we recommend that a bacteriostatic drug should be considered an important part of all MDR-TB treatment regimens in the UK, taking into account drug susceptibility. However due to side effects associated with bacteriostatic drugs their use should be managed with care.

During our study period the WHO guidelines in use did not recommend one fluoroquinolone over another but moxifloxacin was more widely used, as many clinicians believe that it may be more potent. Current WHO guidelines [5] recommend the use of later generation fluoroquinolones such as moxifloxacin and levofloxacin and these have also recently been shown to be significantly associated with successful treatment outcomes [37].

The failure to take account of drug sensitivity results appropriately as shown in our study, could reflect a lack of experience in treating MDR-TB, possibly due to its rarity in the UK. If geographical considerations prevent all cases being managed in specialist centres, outcomes may be improved by advice from clinicians in the national web-based MDR-TB advisory service hosted by the British Thoracic Society [51].

Since the majority of cases who were lost to follow up returned to their countries of origin, efforts should be made to engage with national TB programs overseas at an early stage in treatment to ensure optimised continuation of management. Alternatively, patients should be supported to complete treatment in the UK, especially if they are returning to resource-poor countries where TB treatment and, in particular, the supply of effective second line antibiotics may not be guaranteed. Referring detainees prior to deportation to a TB service dedicated to improving health in mobile populations, such as TBNet (part of the Migrant Clinicians Network, USA), has been shown to result in high treatment completion rates [52] and this option should be explored for the UK.

Conclusion

Our findings are in line with the international guidance for the use of a bacteriostatic drug in addition to an injectable agent and a fluoroquinolone for the treatment of MDR-TB. It is important to continue to monitor treatment outcomes of MDR-TB patients to improve treatment management policy. Further research should evaluate the role of DOT among MDR-TB patients in the UK. Patients should be given psychosocial support to improve treatment compliance.

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Conflict of interest

None declared.

References

1. World Health Organization (WHO). Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva: WHO; 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf
2. Anderson L, Moore J, Kruijshaar M, Pedrazzoli D, Bradshaw L, Crofts J, et al. Tuberculosis in the UK: report on tuberculosis surveillance in the UK 2010. London: Health Protection Agency; 2010. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1287143594275
3. White VL, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. Thorax. 2000;55(11):962-3. http://dx.doi.org/10.1136/thorax.55.11.962. PMid:11050268. PMCid:PMC1745633.
4. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. Geneva: WHO; 2008. Available from: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf
5. World Health Organization (WHO). Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. Geneva: WHO; 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf
6. Partners In Health (PIH). The PIH guide to the medical management of multidrug-resistant tuberculosis. Boston, MA: PIH; 2003. Available from: http://www.pih.org/library/pih-guide-to-the-medical-management-of-multidrug-resistant-tuberculosis
7. Department of Health (DOH). The Interdepartmental Working Group on Tuberculosis: The prevention and control of tuberculosis in the United Kingdom. London: DOD; 1998. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006196?IdcService=GET_FILE&dID=28094&Rendition=Web
8. National Institute for Health and Clinical Excellence (NICE). Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. 2011 update. http://www.nice.org.uk/nicemedia/live/13422/53642/53642.pdf
9. Pedrazzoli D, Anderson L, Lalor M, Davidson J, Abubakar I, Thomas L. Tuberculosis in the UK: annual report on tuberculosis surveillance in the UK, 2013. London. London: Public Health England; 2013. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139689583?utm_source%3D1be16992-d8f0-4483-8eb5-3137299827e1%26utm_medium%3Drss%26utm_campaign%3Dlong
10. World Health Organization (WHO). Global tuberculosis report 2012. Geneva: WHO; 2012. Available from: http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf
11. Department of Health (DOH). Stopping tuberculosis in England: an action plan from the Chief Medical Officer. London: DOH; 2004. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4100860.pdf
12. European Centre for Disease Prevention and Control (ECDC). Progressing towards TB elimination. A follow-up to the Framework Action Plan to Fight Tuberculosis in the European Union. Stockholm: ECDC; 2010. Available from: http://ecdc.europa.eu/en/publications/Publications/101111_SPR_Progressing_towards_TB_elimination.pdf
13. World Health Organization (WHO). International statistical classification of diseases and related health problems. 10th revision, edition 2010. Geneva: WHO; 2005. Available from: http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf

14. Drobniewski FA, Caws M, Gibson A, Young D. Modern laboratory diagnosis of tuberculosis. Lancet Infect Dis. 2003;3(3):141-7. http://dx.doi.org/10.1016/S1473-3099(03)00544-9
15. Ditah IC, Reacher M, Palmer C, Watson JM, Innes J, Kruijshaar ME, et al. Monitoring tuberculosis treatment outcome: analysis of national surveillance data from a clinical perspective. Thorax. 2008;63(5):440-6. http://dx.doi.org/10.1136/thx.2006.073916. PMid:17615085.
16. European Centre for Disease Prevention and Control (ECDC)/World Health Organization Regional Office for Europe. Tuberculosis surveillance in Europe 2008. Stockholm: ECDC; 2010. Available from: http://www.euro.who.int/__data/assets/pdf_file/0007/78856/E93600.pdf
17. Ferrara G, Richeldi L, Bugiani M, Cirillo D, Besozzi G, Nutini S, et al. Management of multidrug-resistant tuberculosis in Italy. Int J Tuberc Lung Dis. 2005;9(5):507-13. PMid:15875921.
18. Uffredi ML, Truffot-Pernot C, Dautzenberg B, Renard M, Jarlier V, Robert J. An intervention programme for the management of multidrug-resistant tuberculosis in France. Int J Antimicrob Agents. 2007;29(4):434-9. http://dx.doi.org/10.1016/j.ijantimicag.2006.11.023. PMid:17300920.
19. Eker B, Ortmann J, Migliori GB, Sotgiu G, Muetterlein R, Centis R, et al. Multidrug- and extensively drug-resistant tuberculosis, Germany. Emerg Infect Dis. 2008;14(11):1700-6. http://dx.doi.org/10.3201/eid1411.080729. PMid:18976552. PMCid:PMC2630755.
20. Pedrazzoli D, Fulton N, Anderson L, Lalor M, Abubakar I, Zenner D. Tuberculosis in the UK: 2012 report. London: Health Protection Agency; 2012. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317134913404
21. World Health Organization (WHO). Anti-tuberculosis drug resistance in the world: fourth global report. Geneva: WHO; 2008. Available from: http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf
22. Crofts JP, Pebody R, Grant A, Watson JM, Abubakar I. Estimating tuberculosis case mortality in England and Wales, 2001-2002. Int J Tuberc Lung Dis. 2008;12(3):308-13. PMid:18284837.
23. Haar CH, Cobelens FG, Kalisvaart NA, van Gerven PJ, van der Have JJ. HIV-related mortality among tuberculosis patients in the Netherlands, 1993-2001. Int J Tuberc Lung Dis. 2007;11(9):1038-41. PMid:17918662.
24. Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000-2003. Int J Tuberc Lung Dis. 2010;14(4):413-9. PMid:20202298. PMCid:PMC3005763.
25. Horne DJ, Hubbard R, Narita M, Exarchos A, Park DR, Goss CH. Factors associated with mortality in patients with tuberculosis. BMC Infect Dis. 2010;10:258. http://dx.doi.org/10.1186/1471-2334-10-258. PMid:20799975. PMCid:PMC2936899.
26. Duarte EC, Bierrenbach AL, Barbosa da SJ Jr, Tauil PL, de Fátima Duarte E. Factors associated with deaths among pulmonary tuberculosis patients: a case-control study with secondary data. J Epidemiol Community Health. 2009;63(3):233-8. http://dx.doi.org/10.1136/jech.2008.078972. PMid:19066188.
27. Balabanova Y, Radiulyte B, Davidaviciene E, Hooper R, Ignatyeva O, Nikolayevskyy V, et al. Survival of drug resistant tuberculosis patients in Lithuania: retrospective national cohort study. BMJ Open. 2011;1(2):e000351. http://dx.doi.org/10.1136/bmjopen-2011-000351. PMid:22123922. PMCid:PMC3225583.
28. Oursler KK, Moore RD, Bishai WR, Harrington SM, Pope DS, Chaisson RE. Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. Clin Infect Dis. 2002;34(6):752-9. http://dx.doi.org/10.1086/338784. PMid:11850859.
29. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest. 1998;114(5):1244-52. http://dx.doi.org/10.1378/chest.114.5.1244. PMid:9823996.
30. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg. 2009;80(4):634-9. PMid:19346391. PMCid:PMC2750857.
31. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MWR Recomm Rep. 2003;52(RR-11):1-77.
32. Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. Tuber Lung Dis. 1996;77(1):37-42. http://dx.doi.org/10.1016/S0962-8479(96)90073-8.
33. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One. 2009;4(9):e6914. http://dx.doi.org/10.1371/journal.pone.0006914. PMid:19742330. PMCid:PMC2735675.
34. Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ, et al. Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study. Eur Respir J. 2006;28(5):980-5. http://dx.doi.org/10.1183/09031936.06.00125705. PMid:16837502.
35. David HL, Laszlo A, Rastogi N. Mode of action of antimycobacterial drugs. Acta Leprol. 1989;7 Suppl 1:189-94. PMid:2503988.
36. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis. 2010;51(1):6-14. http://dx.doi.org/10.1086/653115. PMid:20504231.
37. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis, of 9,153 patients. PLoS Medicine. 2012;9(8):e1001300. http://dx.doi.org/10.1371/journal.pmed.1001300. PMid:22952439. PMCid:PMC3429397.
38. Moadebi S, Harder CK, Fitzgerald MJ, Elwood KR, Marra F. Fluoroquinolones for the treatment of pulmonary tuberculosis. Drugs. 2007;67(14):2077-99. http://dx.doi.org/10.2165/00003495-200767140-00007. PMid:17883288.
39. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Cochrane Database Syst Rev. 2008;(1):CD004795. PMid:18254061.
40. Lambregts-van Weezenbeek CS, Jansen HM, Nagelkerke NJ, van Klingeren B, Veen J. Nationwide surveillance of drug-resistant tuberculosis in the Netherlands: rates, risk factors and treatment outcome. Int J Tuberc Lung Dis. 1998;2(4):288-95. PMid:9559399.
41. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, Kliiman K, et al. Fluoroquinolones: are they essential to treat multidrug-resistant tuberculosis? Eur Respir J. 2008;31(4):904-5. http://dx.doi.org/10.1183/09031936.00159807. PMid:18378786.
42. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. Eur Respir J. 2009;33(5):1085-94. http://dx.doi.org/10.1183/09031936.00155708. PMid:19164345.
43. Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med. 2001;345(3):170-4. http://dx.doi.org/10.1056/NEJM200107193450303. PMid:11463011.
44. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet. 2005;365(9456):318-26. PMid:15664227.
45. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest. 2000;117(3):744-51. http://dx.doi.org/10.1378/chest.117.3.744. PMid:10713001.
46. Migliori GB, Lange C, Centis R, Sotgiu G, Mutterlein R, Hoffmann H, et al. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J. 2008;31(6):1155-9. http://dx.doi.org/10.1183/09031936.00028708. PMid:18515555.
47. Migliori GB, Sotgiu G, D'Arcy Richardson M, Centis R, Facchini A, Guenther G, et al. MDR-TB and XDR-TB: drug resistance and treatment outcomes. Eur Respir J. 2009;34(3):778-9. http://dx.doi.org/10.1183/09031936.00059409. PMid:19720816.
48. World Health Organization (WHO). Definitions and reporting framework for tuberculosis – 2013 revision. Geneva: WHO; 2013. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf
49. Leahy AU, Lipman M, Hetzel M, Kon OM, Hopkins S, Abubakar I. Do we need bacteriological confirmation of cure in uncomplicated TB? Eur Respir J. 2013;42(3):860-3. http://dx.doi.org/10.1183/09031936.00190912. PMid:24000254.
50. Crofts JP, Andrews NJ, Barker RD, Delpech V, Abubakar I. Risk factors for recurrent tuberculosis in England and Wales, 1998-2005. Thorax. 2010; 65(4):310-4. http://dx.doi.org/10.1136/thx.2009.124677. PMid:20388755.
51. British Thoracic Society (BTS). British Thoracic Society Tuberculosis Specialist Advisory Group. London: BTS; 2011. [Accessed 13 Sep 2013]; Available from: http://www.brit-thoracic.org.uk/delivery-of-respiratory-care/tuberculosis/bts-tb-specialist-advisory-group.aspx
52. Combellick J, Zuroweste E, Gany FM. TBNet: the impact of an innovative public-private intervention on tuberculosis control among an internationally mobile population. J Immigr Refug Stud. 2011;9(3): 229-241. http://dx.doi.org/10.1080/15562948.2011.592805