Table 1: Clinical treatment outcome definitions for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Successful outcomes	Neutral outcomes	Negative outcomes
Treatment completed: completed the duration as per treating physician's choice	Transferred overseas: care transferred to a medical team overseas	Death: any death for any cause during the course of treatment
	Deportation/repatriation: removal by UKBA out of the UK	Lost to follow up: Any patient lost within the UK
		Lost overseas: Any patient known to have gone overseas without transfer of care to a medical team.
		Treatment stopped: any patient who does not complete the prescribed duration of treatment for any reason and does not fit the 'recurrent defaulter' definition.
		Recurrent defaulter: any patient who has started MDR-TB treatment more than twice and has not completed any of the treatment courses due to poor adherence.

UKBA=UK Border Authority. Definitions adapted from Anderson et 2013 (14)

Table 2: Discharge sputum status of last sputum obtained before discharge for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Smear positive	A positive sputum smear for AAFB taken within 21 days from discharge and no negative cultures available at the time of discharge.
Smear negative	A smear negative result taken under 42 days from discharge (and thus no cultures negative at 6 weeks available).
Smear negative plus one culture negative	The last sputum taken was smear negative and a smear and culture negative result from a sputum taken over 42 days from discharge is also available.
Smear negative plus over one culture negative	The last sputum taken was smear negative and more than one smear and culture negative results from sputa taken over 42 days from discharge and at least 7 days apart are available.
No sputum sent within 70 days from discharge	No samples for over 70 days from discharge and the last sputum result was culture positive.
No sputum sent	No sputum sent during diagnosis or admission.

MDR-TB= Multidrug resistant tuberculosis, AAFB=acid alcohol fast bacilli

Table 3: Demographics and background information for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Characteristic		Number (% unless otherwise indicated)
Median age in years (IQR) (n=100)		28.5 (24-38)
Male gender (n=100)		68/100 (68)
HIV infected (n=100)		5/100 (5)
Recent immigrant (< 2 years) (n=98)		39/98 (40)
Country of birth (n=100)	UK	12/100 (12)
	Western and Northern Europe other	1/100 (1)
	Chinese subcontinent	10/100 (10)
	Indian subcontinent	37/100 (37)
	Africa	18/100 (18)
	Eastern Europe + Russia	22/100 (22)
Recourse to public funds (n=93)		57/93 (61)
Admitted from prison (n=100)		5/100 (5)
Previous DST fully sensitive TB in the UK (n=100)		7/100 (7)
Type of TB (n=100)	MDR-TB	79/100 (79)
	MDR-TB +FLQ resistance	13/100 (13)
	XDR-TB*	8/100 (8)
Prothionamide resistance**(n=99)		36/99 (36)
Ethambutol resistance** (n=100)		53/100 (53)
Pyrazinamide resistance** (n=100)		44/100 (44)
Resistance to all injectable agents ***		6/100 (6)
Location of TB (n=100)	Pulmonary	45/100 (45)
	Extra-pulmonary only	32/100 (32)
	Both pulmonary and extra-pulmonary	23/100 (23)
Site/s of extra-pulmonary cases (not exclusive) (n=55)	Spinal	14/55 (25)
	Lymph node	17/55 (31)
	Pleural/empyema	7/55 (13)
	Musculoskeletal (excludes spinal)	7/55 (13)
	Pericardial	2/55 (4)
	Abdominal	4/55 (7)

	Millary (chest radiology)	1/55 (2)
	CNS (tuberculoma)	1/55 (25)
	urine	2/55 (4)
Culture confirmed (n=100) (any site)		98/100 (98)
Smear positive sputum (n=68)		47/68 (69)
Culture positive sputum (n=68)		63/68 (93)
Unilateral parenchymal changes where baseline CXR available (n=65)****		27/65 (42)
Bilateral parenchymal changes where baseline CXR available (n=65)****		31/65 (48)
Unilateral cavities where baseline CXR available (n=65)****		20/65 (31)
Bilateral cavities where baseline CXR available (n=65)****		5/65 (8)

IQR=interquartile range, TB=tuberculosis, CXR= chest radiograph, MDR-TB= multidrug resistant tuberculosis, XDR-TB = extensively resistant tuberculosis, MDR-TB +FLQ= MDR-TB plus fluroquinolone resistance, n= number of cases for whom information is available. *Includes a patient that started with MDR-TB and converted to XDR-TB during treatment. **Resistance based on phenotypic drug sensitivity testing (DST) and includes two patients treated on epidemiological grounds where resistance pattern of source patient was known. ***All injectable agents=amikacin, capreomycin, kanamycin, streptomycin. ****Those negative on chest radiograph were diagnosed either on sputum culture or on computed tomography as pulmonary TB.

Table 4: Initial drug choices for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Characteristic		Total (% unless otherwise stated)	First half cohort 2008-2011 (% unless otherwise stated)	Second half cohort 2011-2014 (% unless otherwise stated)	P
Number started first on RHZE before switching to an MDR-TB regimen (n=97)		74 (76)	38 (78)	36 (75)	0.77
Number of days between RHZE and start of MDR-TB regimen (n=68) (IQR)		28(11-55)	35 (14-61)	19 (7-38)	0.05
Number of days between RHZE and start of MDR-TB regimen for smear positive patients only (n=31) (IQR)		18 (3-40)	25 (3-50)	18 (4-33)	0.55
Reason for starting a MDR-TB regimen (n=100)	Phenotypic Rifampicin resistance on culture (18=smear positive)	53 (53)	34 (69)	19 (38)	<0.01
	Molecular rifampicin resistance-on sputum (22=smear positive)	23 (23)	10 (20)	13 (26)	0.48
	Molecular rifampicin resistance-on a culture (4=smear positive)	17 (17)	4 (8)	13 (26)	0.02
	Epidemiological contact or previous history of MDR-TB (2=smear positive)	7 (7)	2 (4)	5 (10)	0.24
Starting regimen (n=98)	Injectable, FLQ, +/-EZ, Pto, Cs (1 plus Li)	42 (43)	17 (34)	25 (52)	
	Injectable, FLQ, +/-EZ, Pto, Cs + PAS (2 plus Li, 1 plus C)	13 (13)	4 (8)	9(19)	
	Injectable, FLQ, +/-EZ, Pto (1 plus Li)	10 (10)	7 (14)	3 (6)	
	Injectable, FLQ, +/-EZ, Pto, PAS (1 plus Li)	10 (10)	7 (14)	3 (6)	
	Injectable, FLQ, +/-EZ, PAS CS (2 plus Li, 1 plus C)	3	1	2	
	Injectable, FLQ, +/-EZ, PAS	5	5	0	
	Injectable, FLQ, EZ, Cs (2 plus Li + C)	4	1	3	
	Injectable, FLQ, +/-EZ,	3	1	2	

	No FLQ	6	5	1	
Sub-optimal regimen at start* due to underestimating resistance (n=99)		14 (14)	8 (16)	6 (12)	
Drug use at any time (n=100)	no injectable	2	2	0	
	pyrazinamide	91	42	49	
	ethambutol	72	33	39	
	amikacin	65	32	33	
	capreomycin	52	22	30	
	streptomycin	3	3	0	
	moxifloxacin (400mg)	87	43	44	
	levofloxacin (all dosed at 1g)	9	4	5	
	High dose moxifloxacin (>/=600mg)	8	4	4	
	prothionamide	86	41	45	
	cycloserine	88	39	49	
	PAS	63	33	30	
	Linezolid (600mg od or bd)	35	14	21	
	clofazimine	14	6	8	
	clarithromycin or azithromycin	14	12	2	
	meropenem plus A/C	4	2	2	
	A/C	8	4	4	
	Bedaquiline***	5	1	4	
Median duration of injectable agent, days (N=95)** (IQR) (Range)		182 (109-208) (20-1070)	166 (106-192) (30-1070)	184 (119-229) (20-740)	0.03
Number initially discharged on DOT or VOT (n=81)		37 (46)	17 (37)	20 (57)	0.02
Pulmonary surgery performed (n=100)		3			

n = number of cases for whom information is available, A/C=amoxicillin clavulanate, C=clofazimine, CS=cycloserine, E=ethambutol, FLQ=fluroquinolone, H=isoniazid, Li=linezolid, PAS= para-aminosalycylic acid, Pto=prothionamide, R= rifampicin, Z=pyrazinamide, IQR=interquartile range, DOT=directly observed therapy, VOT=video observed therapy. *A sub-optimal regimen was defined as under 4 active drugs (original WHO groups 1-4 [4]plus clofazimine and linezolid). **Excludes 2 who were not treated with an injectable agent and the 3 recurrent defaulters in whom total duration of injectable was not available.***Bedaquiline was used in 4 cases of XDR-TB and in one case of MDR-TB where multiple drug intolerances led to 6 drugs being stopped.

Table 5: Length of stay during initial hospital admission for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Patient group		Any PTB (%)	Median duration of admission, days (IQR)	Only EPTB (%)	Median duration of admission, days (IQR)
Patients admitted to hospital (n=100, PTB, 68 + EPTB, 32)		66/68* (97)	83 IQR 44-116 Range 6-513	26/32 (81)	13 IQR 7-34 Range 3-250
MDR-TB Type of those admitted	MDR-TB (n=79)	50/52 (96)	84 58-116	23/27 (85)	12.5 6-30
	MDR-TB +FLQ (n=13)	10/10 (100)	50 (18-241)	1/3 (33)	55
	XDR-TB (n=8)	6/6 (100)	127 (34-216)	2/2 (100)	52.5 (9-96)
Microbiological status at discharge of those admitted to hospital~ (n=PTB,62+ EPTB, 26)	No sputum sent during admission	1/62 (2)	10 10-10	12/26 (46)	9 4-34
	Smear positive	4/62 (6)	15 12-33	0	-
	Smear negative	16/62 (26)	34.5 21.5-56	7/26 (27)	13 7-24
	Smear negative plus 1 negative culture	12/62 (19)	87.5 73.5-117.5	5/26 (19)	36 30-55
	Smear negative plus > 1 negative culture	26/62 (42)	115 79-154	2/26 (8)	129.5 9-250
	no sputum within 70 days from discharge'	3 (5)	107 94-112	0	-
Loss of home while an inpatient for those admitted** (n=PTB,65 + EPTB,26)		10/65 (15)	148.5 83-184	2/26 (8)	65 34-96
Discharge location (n=PTB, 64 + EPTB, 26)	Home prior to admission	47/64 (73)	63 31-92	22/26 (85)	10 6-24
	New home organised by patient	3/64 (5)	83 66-106	0	-
	New home organised by hospital, council, CCG or PHE	10/64 (15)	166.5 132-216	1/26 (4)	34
	Prison	4/64 (6)	130.5 95.5-197.5	1/26 (4)	34

	Transferred abroad	0	-	2/26 (8)	173 96-250

PTB=pulmonary TB, EPTB=extra-pulmonary only, MDR-TB= multidrug resistant tuberculosis, XDR-TB = extensively resistant tuberculosis, MDR-TB +FLQ= MDR-TB plus fluroquinolone resistance. ~See table 2 for definitions. CCG=Care Commissioning Group, PHE=Public Health England, * not all patients were admitted to hospital as shown in this table, the two pulmonary cases that were not admitted were both smear negative. **home loss defined as having a home prior to admission to hospital.

Table 6: Multivariable analysis of factors affecting length of hospital admission for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Variable	Multivariable analysis Multiple imputation estimation	
	ESTIMATE* (95% CI)	P-value
Pulmonary TB (PTB) versus extra pulmonary TB (EPTB)	2.78 (1.88-4.11)	<0.001
Presence of cavities verses no cavities on chest radiograph (data on all patients)	1.78 (1.22-2.60)	0.003
Lack of culture negative results verses smear and culture negative at discharge	0.37 (0.26-0.52)	<0.001
Loss of home during admission verses no loss of home	1.72 (1.07-2.76)	0.025
CONSTANT**	26.62 (17.9-39.6)	<0.001

* Estimates represent the multiple by which the geometric mean is multiplied.** The constant represents the geometric mean of length of stay for a patient who has extra-pulmonary TB (EPTB), with no cavities, who does not lose her home, and is culture negative on discharge. CI= confidence interval, MDR-TB= multidrug resistant tuberculosis.

Table 7: Readmission to hospital for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Reason for readmission (n=49)	number of admissions	Median duration in days (IQR)
IRIS, LN enlargement, on-going TB investigations	6	6 (1-38)
MDR-TB drug side effect related	18	4 (1-14)
Medical other	4	4 (1.5-8.5)
Culture reversion or potential for relapse as deemed by physician	10	143 (86-257)
Line related (inc infection, changes, clots etc)	5	1 (1-1)
Unknown/other	6	5 (1-9)

Data represents 49 readmissions (28 patients), IRIS=immune reconstitution syndrome, LN =lymph node, TB=tuberculosis, MDR-TB= multidrug resistant tuberculosis.

Table 8- MDR-TB treatment outcomes for 100 cases of MDR-TB diagnosed in London and West Midlands between 2008 and 2014.

Sputum culture conversion (cc)			Total (% or IQR)	MDR-TB (% or IQR)	MDR-TB + FLQ (% or IQR)	XDR-TB (% or IQR)
Culture positive sputum			63	50	8	5
Culture conversion documented* (n=63)			53/63 (84)	44/50 (88)	5/8 (62.5)	4/5 (80)
Median time to culture conversion**, days (n=46)			33.5 (16-55)	34 (18-50)	3 (0-85)	48.5 (20-72)
Culture conversion by 60 days (n=46)			35/46 (76)	30/37 (81)	3/5 (60)	2/4 (50)
Sputum culture reversion (n=63)***			6/63 (10)	3/50 (6)	0	3/5 (60)
End of treatment outcome**		Median duration on treatment, days (IQR)	Total N=100	MDR-TB (%) N=79	MDR-TB + FLQr (%) N=13	XDR-TB (%) N=8
Successful	Completed	720 (610-740)	74	58 (73)	10 (77)	6 (75)
Neutral	Transferred overseas	224 (197-425)	9	7 (9)	1 (8)	1 (13)
	Deported/repatriation	279 (199-485)	3	3(4)	0	0
Negative	Lost to follow up	-	0	0	0	0
	Treatment stopped	389 (221-514)	8	6(8)	1 (7)	1 (13)
	Recurrent defaulter	-	3	2 (3)	1 (7)	0
	Lost overseas	110 (20-200)	2	2 (3)	0	0
	Died	69	1	1 (1)	0	0

MDR-TB= multidrug resistant tuberculosis, XDR-TB = extensively resistant tuberculosis, MDR-TB +FLQ= MDR-TB plus fluroquinolone resistance, IQR=interquartile range. * Sputum culture conversion (CC) from positive is 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. (see Table 8 for characteristics).****Defined in Table 1.

Table 9: Clinical details of sputum culture reversion cases and recurrent defaulter cases who were part of a cohort of 100 cases of MDR-TB

Case	MDR-TB Type	Extent of pulmonary disease	Time to CC (days)	Time to CR (days from start of MDR-TB Rx)	Initial MDR-TB regimen (final MDR-TB regimen for cases 5 and 6)	Cause of reversion	Repeat treatment	Regimen after culture reversion	outcome
1	XDR-TB	Bilateral Disease + Cavities	27	275	Cn, M (H), PAS, L, E, Z	Poor adherence despite DOT, alcohol excess, unsupported bed and breakfast accommodation	Readmitted under legal order, discharged to supported accommodation facility on DOT	Cn, L, PAS, Cs, Li, C, A/A, B, Cl	Completed at 1069 days: deported once completed
2*	XDR-TB (starts with MDR-TB)	Bilateral disease	72	234	Cn, M, PAS, E, CS, Az	Possible poor adherence once DOT stopped at 6 months, poor absorption due to chronic diarrhoea from PAS, poor drug penetration to cavity Treatment in DGH	Readmitted voluntarily Left upper lobectomy Discharged home on DOT	Ak, Cs, E, pto, C, Li, M/A,	Completed at 1092 days: no relapse at 1 year.
3**	XDR-TB	Bilateral Disease + Cavities	cultures negative at 282 + 291.***	463	AK, Z, Pas, CS, C, Li, Mero/A, V	non-resolving bronchopulmonary fistula. Adherence good.	Readmitted voluntarily Surgical repair of bronchopulmonary fistula Discharged to a new home found by family	Z, PAS, CS, C, Li, M/A, V	Completed at 1198 days. Well 3 months later
4	MDR-TB	Bilateral disease + Cavity	15	352	Ak, M, P, Cs, Z, E	large cavity adherence good	Declined lobectomy and no further culture positive samples a year later and cavity resolved without further intervention.	Ak, M, P, Cs, Z, E	completed
5	MDR-TB	Bilateral Disease + Cavities	****	****	Ak/Cap, Z, E, L, Pto, CS	Poor adherence.	Limited by ongoing poor adherence	Ak/Cap, Z, E, M, Pto, CS	Recurrent defaulter
6	MDR-TB	Bilateral Disease + Cavities	****	****	Cn, Pto, PAS, CS, Cl, Z,	Poor adherence.	Limited by ongoing poor adherence	Cn, Pto, PAS, C, Z, Li	Recurrent defaulter

MDR-TB= multidrug resistant tuberculosis, XDR-TB = extensively resistant tuberculosis, MDR-TB +FLQ= MDR-TB plus fluroquinolone resistance, CC=culture conversion, CR=culture reversion, DOT=directly observed therapy, PTB=pulmonary TB, DGH=district general hospital, Rx=treatment, N/A= not applicable * treated at a DGH and then once XDR-TB occurred transferred to teaching hospital which was not one of the 4 centres, referred for surgery at centre 4. **treated at a DGH throughout with referral to centre 4 for surgery. Cn=capreomycin, AK=amikacin, M= moxifloxicin, L =levofloxacin, C= clofazemine, Cl=clarithromycin, Li=linezolid, A/A=amoxicillin and co-amoxiclav, M/A=meropenem + co-amoxiclav, Z=pyrazinamide, E=ethambutol, H= high dose, B=bedaquiline (given for 6 months), Az=Azithromycin, Cs=cylcoserine, p=prothionamide, V=verapamil. ***sputum cultures not taken regularly before this point so it is unknown exact date culture conversion occurred. ****recurrently culture converting or only smear converting before default.
NB-no cases were HIV positive.