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Fluoroquinolones and isoniazid resistant TB: implications for the 2018 WHO guidance

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Take-home message: WHO has assessed regimen recommendations for isoniazid resistant TB to be of very low certainty. The addition of fluoroquinolones to a 12 month (isoniazid, rifamycin, ethambutol, short duration pyrazinamide) regimen may be unnecessary in certain settings.

ABSTRACT

Introduction 2018 World Health Organization (WHO) guidelines for the treatment of isoniazid (H) resistant (Hr) tuberculosis recommend a four-drug regimen- rifampicin (R), ethambutol (E), pyrazinamide (Z) and levofloxacin (Lfx)- with or without H ([H]RZE-Lfx). This is used once Hr is known, such that patients complete six months of Lfx (≥6[H]RZE-6Lfx). This cohort study assessed the impact of fluoroquinolones (Fq) on treatment effectiveness, accounting for Hr mutations and degree of phenotypic resistance.

Methods This was a retrospective cohort study of 626 Hr tuberculosis patients notified in London, 2009-2013. Regimens were described and logistic regression undertaken of the association between regimen and negative regimen-specific outcomes (broadly, death due to tuberculosis, treatment failure, disease recurrence).

Results Of 594 individuals with regimen information, 330 (55.6%) were treated with (H)RfZE (Rf= rifamycins) and 211 (35.5%) with (H)RfZE-Fq. The median overall treatment period was 11.9 months and median Z duration 2.1 months. In a univariable logistic regression model comparing (H)RfZE with and without Fqs, there was no difference in the odds of a negative regimen-specific outcome (baseline (H)RfZE, cluster-specific odds ratio 1.05 [95% confidence interval 0.60-1.82], p-value 0.87; cluster NHS Trust). Results varied minimally in a multivariable model. This odds ratio dropped (0.57 [0.14-2.28]) when Hr genotype was included, but this analysis lacked power (p=0.42).

Conclusions In a high-income setting, we found a 12 month (H)RfZE regimen with a short Z duration to be similarly effective for Hr TB with or without a Fq. This regimen may result in fewer adverse events than the WHO recommendations.

INTRODUCTION

Isoniazid (H) is a key drug used in the treatment of both tuberculosis disease (TB) and latent TB infections (LTBI). Research into H resistant (Hr) TB has been neglected in favour of studies of simultaneous Hr and rifampicin (R) resistance (Rr) i.e. multidrug resistance (MDR).[1] Globally, 7.1% of new incident TB patients between 2003 and 2017 had Hr disease without associated Rr (henceforth known as 'Hr TB') and 7.9% of previously treated patients.[2] The distribution of Hr TB varies substantially by country.[1, 3]

Hr has been associated with poor treatment outcomes, the need to tailor treatment regimens, and the development of additional drug resistance during treatment.[1] A meta-analysis of randomised controlled trial (RCT) data, controlling for regimen, demonstrated that incidence rates of treatment failure were 10.9 times higher in Hr TB versus drug sensitive disease (95% confidence interval {CI} [5.9-20]).[4] In the same study, relapse rates in Hr TB were 1.8 fold higher [1.2-2.6], and acquired drug resistance 5.1 times higher [2.3-11.0].

Given these concerns, policymakers have issued specific treatment guidance for Hr TB. In 2018 the World Health Organization (WHO) conditionally recommended a regimen of R, ethambutol (E), pyrazinamide (Z) and levofloxacin (Lfx) with or without H ([H]RZE-Lfx), to be initiated once Hr is confirmed.[5] If treatment starts before Hr is known, it is continued until Lfx is used for six months, even if the duration of the other drugs is therefore longer (≥6[H]RZE-6Lfx). In the absence of rapid molecular testing for Hr, overall treatment duration is thus seven and a half to nine months, depending upon whether liquid or solid culture is used.[6] WHO assessed the evidence underlying this regimen to be of very low certainty.[5] Within the UK, the National Institute for Health and Care Excellence (NICE) recommends a nine month regimen of two months of RZE, followed by seven months of RE.[7] This can be extended to 12 months' duration (10-month continuation phase), if disease is extensive. The American Thoracic Society is currently revising its guidance.[8] In 2003, they recommended a six-month regimen of RZE, plus a fluoroquinolone [Fq] for extensive disease.[9] All bodies acknowledge the need for future studies to optimise regimens e.g. to determine the implications of the resistance-causing Hr mutation(s).

In light of the 2018 WHO recommendations, we undertook a retrospective cohort study to identify the treatment regimens currently being used for Hr TB in a high-income setting with universal healthcare (London, UK). We assessed the importance of including Fqs during treatment, accounting for baseline Hr phenotype and genotype.

METHODS

Study population

We included all patients aged 18 and over notified in England (as a statutory requirement) to Public Health England (PHE)'s Enhanced TB Surveillance system (ETS) between 1st January 2009 and 31st December 2013 with disease caused by phenotypically Hr *Mycobacterium tuberculosis*. Baseline demographic and basic clinical and microbiological data were available from PHE. Individuals notified in London formed the retrospective cohort; additional data collection for these individuals is described below.

Treatment regimens

Detailed regimen, adherence and regimen-specific outcome information was gathered from clinical notes at the last hospital to treat the patient recorded by PHE (Supplementary File 1).

Regimens were described and categorised. The rifamycins (Rf) R and rifabutin (Rb) were grouped together, as were the injectables, Fqs other than moxifloxacin (M), and the previously named group 4/5 drugs.[10, 11] A binary regimen variable was created of RfZE regimens in the presence or absence of H with or without an additional Fq: (H)RZE versus

(H)RZE-Fq/M. If additional drugs were also included, the regimen was not counted within the binary variable.

The presence of high-dose H within the regimen was documented, as was whether Rf, Z or E were dosed thrice weekly (as opposed to more frequently). The length of time a patient was treated before the regimen was adapted to account for Hr (which was dependent on the duration of drug sensitivity testing; DST) was grouped 0-<2, 2-<6 and ≥6 months.

Genotyping and phenotyping
Phenotypic DSTs for first line drugs were conducted on baseline samples. DSTs for second line drugs were conducted if resistance to R or two or more other first line drugs (but not H alone, although this could be requested) was detected. These results were recorded within ETS. Patients were grouped according to the baseline drug resistance pattern of their disease.

The degree of phenotypic resistance to H was extracted from the National Mycobacterial Reference Service (NMRS) South system (Supplementary File 1).

Whole genome sequencing (WGS) to detect resistance mutations was undertaken for a subset of patients among those notified 2012-13 using an Illumina HiSeq at the PHE central sequencing unit.[12]

Other exposure variables
Age, sex, being born in the UK, ethnic group, social risk factors (homelessness, problematic drug use, problematic alcohol use, and imprisonment), previous diagnosis of TB and inpatient information came from ETS. Decisions surrounding the grouping of these variables are documented in Supplementary File 1.

An outbreak of Hr TB has been present in (mainly north) London since 1995.[13, 14] Due to awareness of this outbreak among clinicians, patients with epidemiological risk factors consistent with the outbreak- in which non-adherence was common and treatment outcomes poor- may have been treated differently from other patients.

An additional variable documented if a patient had issues adhering to treatment, according to their clinical notes (Supplementary File 1).

Outcomes
A patient's treatment period for Hr TB is made up of up to three components- the regimen used prior to Hr being known, the regimen used once Hr is known, and (potentially) a further regimen or regimens if the Hr regimen is insufficiently effective. Overall treatment outcomes (available in ETS) capture this entire period. Regimen-specific outcomes, taken from clinical notes, document the effectiveness of the Hr regimen and thus capture only the first two components (Table 1). For the regression model, the neutral and positive groups were merged to create a binary outcome.

Table 1: Classification of regimen-specific outcomes
Regimen-specific outcomes (extracted from clinical notes) presented in detail. The first outcome arising per patient was documented, unless a negative outcome occurred after one that is neutral. MIRU-VNTR- Mycobacterial Interspersed Repetitive Unit-Variable Number of Tandem Repeats, PHE-Public Health England, TB- tuberculosis

Regimen-specific outcome	Components	Comments
Negative	Treatment completed, followed by recurrence. Outcome missing, but recurrence. Neutral outcome, followed by recurrence.	Recurrence of disease 12 months or more after notification. Recurrences documented until the end of 2015 (the most recent available data at the time of analysis). If disease recurred after the end of treatment at any time and the patient re-presented to the same hospital this also classified as a negative outcome.
	Died due to TB or death TB-associated two weeks or more after starting treatment	Death before two week threshold considered to be too early to be influenced by the treatment.[15]
	Treatment stopped early or regimen changed due to worsening/not improving, treatment failure, adverse events, or the development of additional drug resistance	Length extended, antibiotics added/removed, frequency altered, dose altered, treatment stopped.
	Additional drug resistance developed during treatment	To any drug.
Neutral	Died from TB or death TB-associated within two weeks of starting treatment	Death before two week threshold considered to be too early to be influenced by the treatment.[15]
	Died from non-TB related causes, or cause unknown	
	Treatment stopped early or regimen changed due to non-adherence, loss to follow up, patient choosing to cease their medication, pregnancy, or comorbidities	
	Patient transferred to another hospital during their treatment	No further documentation. Transfer before any negative outcomes occurred.
Positive	Treatment completed as initially prescribed (once Hr known). Treatment completed, no recurrence	

Analysis
Data were cleaned in Microsoft Excel and analysed in Stata 15.

The characteristics of the London cohort were assessed. Descriptive analyses of the regimens used were undertaken, followed by regression analyses. Initially, individuals with additional phenotypic drug resistance identified in baseline samples taken were excluded from the regression models, unless resistance was to streptomycin (S). This was because S is not routinely used in the treatment of drug sensitive or MDR TB in the UK.[7, 16] Random effects univariable logistic models were built to examine the impact of different factors on the likelihood of negative regimen-specific outcomes, with a random effect included on NHS Trust to adjust for clustering.

A multivariable logistic model was then built, using the binary regimen categorisation as the main exposure and including a random effect on NHS Trust. Details of confounder selection, etc. are presented in Supplementary File 1.

Sensitivity and extended analyses
Four additional logistic regression models were run. The first included Hr genotyping results. Next, adherence was substituted for thrice weekly dosing. The third included all patients, regardless of whether they were resistant to drugs in addition to H (and S). The fourth was a

post hoc model adjusting for factors associated with the use of Fqs.

Ethical permissions

PHE is legislated by the National Information Governance Board to hold and analyse surveillance data for public health purposes under Section 251 of the NHS Act 2006. This retrospective cohort study was approved by the London Camberwell St Giles Research Ethics Committee (16/LO/1269) and given permission to undertake data extraction without consent also under Section 251 (Confidentiality Advisory Group reference 16/CAG/0092).

RESULTS

Patient population

1,228 individuals with Hr TB were notified in England between 2009 and 2013 (Figure 1). Of these, 626 (51.0%) were notified by 31 hospitals (Supplementary File 2) in London (19 NHS Trusts). One hospital had only a single patient and was not approached for local approvals. The baseline characteristics of the London cohort are described in Table 2.

Table 2: Baseline characteristics of study participants

Demographic and clinical baseline characteristics of the 626 individuals in the London cohort. Col.- column, CNS- central nervous system, No.- number, TB- tuberculosis, ±- with or without, -ve- negative, +ve- positive

Exposure variables		London	
		No.	Col. %
Overall		626	100
Year			
	2009	137	21.9
	2010	118	18.8
	2011	141	22.5
	2012	125	20.0
	2013	105	16.8
	Missing	0	0.0
Sex			
	Male	380	60.7
	Female	246	39.3
	Missing	0	0.0
Age (years)			
	18-37	358	57.2
	38-57	199	31.8
	58-77	62	9.9
	≥78	7	1.1
	Missing	0	0.0
UK born			
	No	497	79.4
	Yes	121	19.3
	Missing	8	1.3
Ethnic group			
	White	97	15.5
	Black African	125	20.0
	Black Other	45	7.2
	Indian subcontinent	270	43.1
	Other	85	13.6
	Missing	4	0.6
Social risk factors			
	No or unknown	510	81.5
	One or more ever	37	5.9
	One or more current	79	12.6
Previous TB diagnosis			
	No	575	91.9
	Yes	20	3.2
	Missing	31	5.0
Inpatient			
	No	422	67.4
	Yes	190	30.4
	Missing	14	2.2
Site of disease			
	Pulmonary ± extrapulmonary, smear +ve	194	31.0
	Pulmonary ± extrapulmonary, smear –ve	159	25.4
	Meningeal TB or other CNS involvement	24	3.8
	Other extrapulmonary	249	39.8
	Missing	0	0.0
Part of outbreak			
	No	501	80.0
	Yes	65	10.4
	Missing	60	9.6
Any additional drug resistance			
	No	453	72.4
	Yes	173	27.6

Phenotypic testing for non-H drug resistance revealed that 173/626 (27.6%) patients within the London cohort had additional drug resistance at baseline (Supplementary File 3). The most common resistance was towards S (139/626 [22.2%]).

The majority of samples were documented in the NMRS system as highly Hr at baseline (495/626; 79.1%). Three (0.5%) displayed borderline results, one was listed as drug sensitive (0.2%) and 35 (5.6%) were present in the system but did not have their Hr levels logged. 47 individuals could not be found within NMRS, but were recorded as Hr within ETS.

Regimen-specific outcomes

Regimen-specific outcomes were available for 592/626 patients (94.6%; Table 3). 97 (16.4%) had a negative outcome.

Table 3: Regimen-specific outcomes and availability of regimen data

Regimen-specific outcomes and treatment regimen availability for the 592/626 (94.6%) of individuals with an outcome recorded in the London cohort. E- ethambutol, R- rifampicin, TB- tuberculosis

Outcome	Negative	Neutral	Positive
Frequency of outcome (% out of 592)	97 (16.4)	87 (14.7)	408 (68.9)
Details of outcome	➢ 3 recurrences after treatment was completed ➢ 2 recurrences after an otherwise neutral or missing outcome ➢ 3 patients developed additional drug resistance (two to R and one to clarithromycin; additionally one patient developed resistance to E and one R, but this was pre-dated by other negative outcomes) ➢ 1 patient stopped treatment for negative reasons ➢ 7 patients had the length of their treatment extended for negative reasons ➢ 78 treatment regimen changes by other means for negative reasons ➢ 3 deaths from TB more than two weeks after treatment started		
Number with regimen data (column %)	95 (97.9)	79 (90.8)	408 (100.0)
Details of regimen data			➢ 374 with regimen data for the full duration of treatment ➢ 7 partial uncertainties surrounding the drugs present in the regimen ➢ 27 some date information missing

Relationship between treatment regimens and regimen-specific outcomes

Of the 626 patients, 582 (93.0%) had both a regimen-specific outcome recorded and treatment information. Of these, 538 (92.4%) were not resistant to drugs in addition to H, apart from S, and 84 had a negative regimen-specific outcome (three of which were recurrences). 498/538 (92.6%) were treated with (H)RfZE or (H)RfZE-Fq/M (Table 4). For a more detailed description of the treatment regimens, see Supplementary File 4.

Table 4: Univariable logistic regression of treatment regimen and associated factors as predictors of negative outcomes

Univariable logistic regression of treatment regimen and associated factors as predictors of negative regimen-specific outcomes. Included patients were notified in London, had regimen-specific outcome and regimen information, and their disease was without additional drug resistance, unless to streptomycin. Each model contains the patients without missing data. CI- confidence interval, Col.- column, E- ethambutol, Fq- fluoroquinolones, H- isoniazid, Hr- isoniazid resistance, No.- number, m- months, M- moxifloxacin, OR- odds ratio, p- p-value, Rf- rifamycin, Z- pyrazinamide

Exposure variables	London		Negative outcome		
	No.	Col. %	No.	Row %	OR [95% CI], p-value
Overall	538	100	84	15.6	-
Regimen					
(H)RfZE	306	56.9	46	15.0	p=0.93
(H)RfZE-Fq/M	192	35.7	30	15.6	1.02 [0.59-1.77]
Missing	40	7.4	8	20.0	
Thrice weekly dosing					
More frequent	464	86.2	66	14.2	p=0.15
Thrice weekly	53	9.9	12	22.6	1.81 [0.83-3.94]
Missing	21	3.9	6	28.6	
Time before HR known					
0-<2m	325	60.4	56	17.2	p=0.27
2-<6m	159	29.6	18	11.3	0.62 [0.34-1.13]
≥6m	10	1.9	2	20.0	1.11 [0.22-5.66]
Missing	44	8.2	8	18.2	
Phenotype					
Highly resistant	442	82.2	69	15.6	p=0.73
Resistant	36	6.7	5	13.9	0.88 [0.32-2.39]
Borderline, sensitive or results not logged	29	5.4	6	20.7	1.46 [0.55-3.88]
Missing	31	5.8	4	12.9	
Adherence issues or treatment gaps					
No or unknown	425	79.0	64	15.1	p=0.29
Not severe or of unknown severity	56	10.4	13	23.2	1.62 [0.80-3.28]
Severe	57	10.6	7	12.3	0.72 [0.30-1.73]

Differences in the odds of a negative regimen-specific outcome were not detected between patients treated with (H)RfZE (baseline) and (H)RfZE-Fq/M (cluster-specific odds ratio [OR] 1.02 95% CI [0.59-1.77], p-value 0.93; Table 4). None of the other treatment regimens or associated factors were found to be associated with the odds of negative outcomes (Table 4, Supplementary File 5). We observed more negative outcomes with the use of thrice weekly dosing versus more frequent dosing (OR 1.81 [0.83-3.94]), but this may have been a chance finding (p=0.15).

Seven exposure variables/confounders were included in the multivariable model regimen: thrice weekly dosing, Hr phenotype, sex, age (linear variable), ethnic group and previous TB diagnosis. Evidence for effect modification was not found. In the final multivariable model of 435 patients (Table 5), there was no discernible difference in the odds of a negative outcome between the two regimens (0.99 [0.53-1.85], 0.97). The association between thrice weekly dosing and negative outcomes was slightly strengthened in terms of the effect estimate (2.34 [0.90-6.09]), although the association observed could still have been due to chance (p=0.09).

Table 5: Multivariable logistic regression of treatment regimen as a predictor of negative outcomes

Multivariable logistic regression of treatment regimen as a predictor of negative regimen-specific outcomes in patients without additional drug resistance, unless to streptomycin, adjusted for all variables in the table. Model contains 435 patients. CI- confidence interval, E- ethambutol, Fq- fluoroquinolones, H- isoniazid, m- months, M- moxifloxacin, OR- odds ratio, p- p-value, Rf- rifamycin, TB- tuberculosis, Z- pyrazinamide

Exposure variables		OR [95% CI), p-value
Regimen		
	[H)RfZE	p=0.97
	[H)RfZE-Fq/M	0.99 [0.53-1.85]
Thrice weekly dosing		
	More frequent	p=0.09
	Thrice weekly	2.34 [0.90-6.09]
Phenotype		
	Highly resistant	p=0.66
	Resistant	0.64 [0.17-2.43]
	Borderline, sensitive or results not logged	1.40 [0.45-4.31]
	Missing	
Sex		
	Male	p=0.02
	Female	2.05 [1.13-3.71]
Age (years)		
	18-37	p=0.46
	Per 20 year increase	1.18 [0.75-1.86]
Ethnic group		
	White	p=0.15
	Black African	0.42 [0.15-1.18]
	Black Other	0.33 [0.08-1.39]
	Indian subcontinent	0.58 [0.23-1.45]
	Other	1.10 [0.42-2.92]
Previous TB diagnosis		
	No	p=0.13
	Yes	3.12 [0.75-12.91]

Impact of genotype and other sensitivity analyses

The most common Hr genotypes observed were *fabG1* C-15T (87/171, 50.9%) and *katG* S315T (75/171, 43.9%; Supplementary File 6). For 10/171 (5.8%) strains, sequencing either failed, no resistance mutations were detected, or it was not known whether the single nucleotide polymorphisms (SNPs) found generate drug resistance.

In a univariable model, no difference was seen in the likelihood of a negative treatment outcome between the *katG* S315T/N genotypes and a *fabG1* C-15T baseline (1.17 [0.42-3.31], 0.76). In a multivariable model, evidence for effect modification by genotype was not detected. Genotype was not independently associated with the outcome (Supplementary File 7). In this model, there was a suggestion that the odds of a negative regimen-specific outcome were reduced for (H)RfZE-Fq/M versus (H)RfZE (0.57 [0.14-2.28]), but we were under-powered for this analysis (p=0.42).

Inclusion of other potential confounder sets in the multivariable model did not impact on our findings (Supplementary File 8).

DISCUSSION

In this analysis of Hr TB patients notified by London hospitals between 2009 and 2013, 16.4% of individuals had a negative outcome. (H)RfZE and (H)RfZE-Fq/M regimens were taken by 92.6% of individuals without additional drug resistance (apart from to S) and with both regimen and regimen-specific outcome data. Among these patients, we found no discernible difference in the odds of a negative regimen-specific outcome between (H)RfZE and (H)RfZE-Fq/M regimens. Examining individuals with a positive treatment outcome, the

overall duration of treatment was generally 12 months, with Z durations of two months in the initiation phase. After adjustment for Hr genotype, the likelihood of a negative outcome was found to be lower among individuals treated with (H)RfZE-Fq/M, but this analysis was under-powered.

Our findings sit in the context of preceding work on the relative efficacy and effectiveness of different regimens for Hr TB, including four meta-analyses.[17-20] Fregonese *et al.*'s individual-level patient meta-analysis, the foundation of the 2018 WHO guidelines, showed a value for including a Fq in continuous (H)RZE regimens, and suggested equivalence between six versus eight to nine months of (H)RZE.[17] The WHO acknowledge that overall treatment length findings may be subject to confounding by indication, due to patients with more complex sites of disease receiving longer regimens.[5]

Notably, global RCT evidence for the effectiveness of Fqs in non-MDR TB derive solely from the Rifaquin trial, as ReMox did not demonstrate non-inferiority when H was replaced with M for non-MDR TB.[21, 22] When considering the choice of Fq, although WHO recommends the use of Lfx, M was generally used in our study. Within Fregonese *et al.*, roughly equal numbers of studies used these two drugs, which were not directly compared. Comparative data are, however, available from a MDR TB trial (no difference in treatment outcomes when comparing the two drugs; fewer adverse events for M),[23] and rabbit and mouse models (M broadly superior over Lfx).[24, 25] Lfx doses in such studies may, however, have been too low.[26, 27] Further RCTs are required.

The above meta-analyses were unable to thoroughly consider the role of Hr genotype and phenotype in treatment decisions; the evidence from previous observational studies is unclear.[1, 28] Where adjustment for genotype in observational studies has been undertaken, it was largely for *inhA* and *katG.* In our cohort, with a very high prevalence of *fabG1* in addition to *katG* mutations, we find an indication that the Hr genotype is influential. *fabG1* is part of the *inhA* operon and is involved in fatty acid synthesis; SNPs within the gene are known to confer Hr.[29, 30]

The evidence currently underpinning global treatment guidelines for Hr TB is limited. Our study adds to this discussion, including consideration of the effect of resistance phenotype and genotype on the regimen-outcomes relationship. Importantly, in our core analysis, 192 patients received a Fq in addition to (H)RfZE, which provides substantial new evidence to that presented by Fregonese *et al*., whose analysis of treatment success included 251 patients receiving a Fq.[17] Our findings did not differ when site of disease was adjusted for as a confounder (including meningeal TB or other CNS involvement; data not shown) and when patients with additional drug resistance were included.

Within this study actual, rather than intended, treatment durations were captured, which prevented us from undertaking analyses of the impact of overall or drug-specific durations. Importantly, however, when considering nine versus 12 months of treatment the majority of negative outcomes occurred before nine months and the number of relapses was small, with two of the three occurring after more than 15 months of treatment. Thus our data may indicate the potential to shorten treatment to nine months in our setting. Some patient notes could not be accessed as patients had died. This was unlikely to have been of a magnitude sufficient to bias our findings. We did not differentiate between recurrence due to relapse versus reinfection, and thus may have over-estimated the number of negative outcomes (non-differential misclassification). Gaps in phenotypic data arose due to a) missing records within NMRS from a specific period and reference laboratory, and b) incomplete data entry into NMRS from the reference laboratory (cross-tabulations against patient characteristics did not indicate that this particularly affected any specific patient groups). The phenotypic and genotypic Hr patterns documented summarise that of the overall bacterial population; the presence of minor strains will not have been captured. Our findings about thrice weekly

dosing may represent the use of such a dosing pattern specifically among patients where directed observation of treatment was deemed necessary. HIV status, a potential confounder, was not obtainable during data collection.

Despite these limitations, there are important ramifications for our findings both nationally and internationally. We document a drug combination that differs from that recommended (with very low certainty) by the WHO,[5] which may be as effective. We note that, if the overall duration of treatment is long enough (12 months), a Fq may not be necessary in certain settings, even with relatively short durations (median two months in the initiation phase) of Z. Notably, in settings where DST occurs via phenotyping from cultures, the WHO regimen ≥6[H]RZE-6Lfx is likely to have total duration of seven and a half to nine months, when time to result is considered. This also affects the longer regimen in their six versus eight to nine month duration comparison; the latter translates to nine and a half to 12 months. By comparison, in settings undertaking rapid genotyping directly from patient samples, the WHO regimen duration would be six months and the average duration documented here approximately 10 months.

Global regimen choices will depend upon the trade-off between patient desire for regimens of minimal length, adherence concerns, adverse events, ease of administration, and cost. Costs are raised if fixed dose combination pills cannot be used and Fqs are added in. When it comes to comparing the likelihood of adverse events, the trade-off would be between a longer duration of E but shorter duration of Z in our predominantly used regimen, versus continued Z and the addition of LfX, as per the WHO recommendations. Each of these drugs has its own distinct adverse event profile.[23, 31]

Fq DST results are important when deciding on Fq use within a Hr regimen. Only 48 individuals in the London cohort had their baseline samples tested for resistance to M. In 2018 PHE rolled-out prospective WGS to provide routine resistance predictions and mutation identification, thus improving the rapidity of DST and coverage of second line testing. New molecular Hr tests can also aid rapidity, as the use of WGS still depends on culture.[32]

Within the limitations of an observational study, where the use of Fqs was not randomised, we find in a high-income setting with comprehensive patient management, a 12 month (H)RfZE regimen with a short Z duration to be similarly effective for Hr TB, with or without a Fq. Hr genotype may influence these findings. In the absence of Fqs and long durations of Z, this regimen may have fewer adverse events than the WHO recommended ≥6[H]RZE-6Lfx. RCTs analyses should be undertaken to provide stronger global recommendations.

CONFLICTS OF INTEREST

HRS reports grants from National Institute for Health Research, UK during the conduct of the study and grants from Medical Research Council, UK and Korea Health Industry Development Institute, outside of the submitted work. MF reports grants from Clinical Research Network, UK, during the conduct of the study. EA reports personal fees from Insmed, outside of the submitted work. IA reports grants from the National Institute for Health Research, UK and Medical Research Council, UK, outside the submitted work. All other authors have nothing to disclose.

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FIGURE LEGENDS

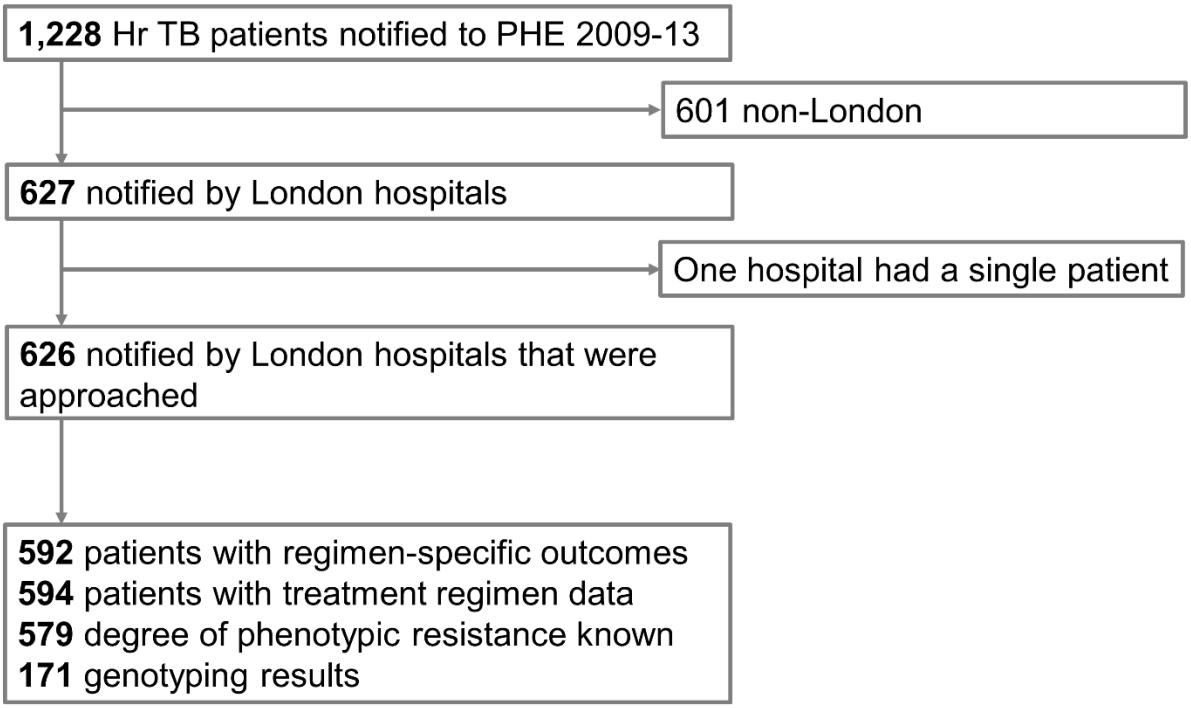

Figure 1: Flow chart of participants
Hr- isoniazid resistant, PHE- Public Health England, TB- tuberculosis

Supplementary File 1: Additional methods

REGIMEN AND ADHERENCE DATA EXTRACTION

A standardised form was used for data extraction from clinical notes. Data collection was completed on 15th December 2017. Drug names, start and end dates, dosing, and frequency of administration were collected, as well as any notation in a patient's notes by hospital staff of issues with adherence (including dates and the number of doses missed, where possible) and patient outcomes. Use of directly observed therapy (DOT) was also recorded. In the UK DOT is generally provided to patients deemed to be at especial risk of non-adherence, either at the start of treatment or during treatment, although some hospitals routinely DOT all patients for the first two months. It frequently is used with thrice weekly dosing. Duration calculations omitted gaps in treatment.

PHENOTYPIC LEVELS OF DRUG RESISTANCE

607/626 (97.0%) of samples were phenotyped within a single reference laboratory, one sample at a second site external to London, and the rest within a second London reference laboratory. Drug sensitivity tests were performed to standard operating procedures across all sites.[1, 2] Resistance ratios were used to determine which strains were resistant to H and which highly resistant. The growth of test strains across three test slopes is compared to wild type strains and so, depending on the controls, the cut-off concentration threshold can vary. High levels of resistance are usually called when there is growth on all three slopes, including at the highest concentration (0.2mg/l H). Resistant, but not highly resistant, strains usually grown on two of the three slopes, up to 0.1mg/l H.

OTHER EXPOSURE VARIABLES

Site of disease was combined with smear status to generate a single variable with four strata: pulmonary with or without extrapulmonary site(s) smear positive, pulmonary with or without extrapulmonary site(s) smear negative or smear status missing, meningeal or other central nervous system (CNS) sites, other extrapulmonary sites only. The separate meningeal/CNS grouping was due to the difficulty of treating TB in these sites.

The presence of one or more social risk factors (homelessness, problematic drug use, problematic alcohol use, and imprisonment) and whether or not they were a current risk- was coded into a single variable.

'Severe' non-adherence to treatment was classed as treatment gaps of two months or more, or any period of taking less than 80% of prescribed doses.

MODEL BUILDING

Our knowledge of the literature and previous studies was used to decide on the *a priori* confounders age, sex, phenotype, thrice weekly dosing and adherence. Additional potential confounders were then identified through causal frameworks.[3] The model-building process to generate the final multivariable model has been described before.[4, 5] Briefly, we started with a model containing all *a priori* and potential confounders and undertook a step-by-step backwards deletion strategy that sequentially removed potential confounders that were not determined to fulfil the three rules of confounding, whilst retaining the *a priori* confounders *A priori* it was decided that model fit using linear and categorical variables for age, year and time before Hr was known would be compared in the model containing the final covariate set. Subsequently, thrice weekly dosing, adherence, Hr phenotype, and Hr genotype were assessed for effect modification within this model. All p-values quoted are from likelihood ratio tests. We undertook a complete case analysis.

Thrice weekly dosing and adherence were collinear, thus only thrice weekly dosing was included in the baseline model.

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Supplementary File 2: List of hospitals contributing data

The authors wish to endorse the following London, UK hospitals as data contributors for this study:

- Central Middlesex Hospital
- Charing Cross Hospital
- Chelsea and Westminster Hospital
- Croydon University Hospital
- Ealing Hospital
- Edgware Hospital
- Hammersmith Hospital
- Hillingdon Hospital
- Homerton Hospital
- King George's Hospital
- King's College Hospital
- Kingston Hospital
- London Chest Hospital (now closed)
- Mile End Hospital
- Newham General Hospital
- North Middlesex University Hospital
- Northwick Park Hospital
- Princess Royal University Hospital
- Queen Elizabeth Hospital
- Queen's Hospital (Romford)
- Royal Free Hospital
- St. George's Hospital (Tooting)
- St. Helier Hospital
- St. Mary's Hospital
- St. Thomas' Hospital
- University College Hospital
- University Hospital Lewisham
- West Middlesex University Hospital
- Whipps Cross University Hospital
- Whittington Hospital

Supplementary File 3: Additional drug resistance in the study population

DST results at baseline. Missingness documents that a sample was not tested against a particular drug. Col.- column, DST- drug sensitivity testing, No.- number

Exposure variables		England		London	
		No.	Col. %	No.	Col. %
Overall		1,228	100	626	100
Ethambutol					
	Sensitive	1,201	97.8	611	97.6
	Resistant	23	1.9	15	2.4
	Missing	4	0.3	0	0.0
Pyrazinamide					
	Sensitive	1,210	98.5	616	98.4
	Resistant	13	1.1	9	1.4
	Missing	5	0.4	1	0.2
Streptomycin					
	Sensitive	638	52.0	422	67.4
	Resistant	294	23.9	139	22.2
	Missing	296	24.1	65	10.4
Amikacin					
	Sensitive	111	9.0	55	8.8
	Resistant	0	0.0	0	0.0
	Missing	1,117	91.0	571	91.2
Kanamycin					
	Sensitive	89	7.2	37	5.9
	Resistant	0	0.0	0	0.0
	Missing	1,139	92.8	589	94.1
Capreomycin					
	Sensitive	108	8.8	54	8.6
	Resistant	2	0.2	1	0.2
	Missing	1,118	91.0	571	91.2
Ciprofloxacin					
	Sensitive	339	27.6	19	3.0
	Resistant	4	0.3	0	0.0
	Missing	885	72.1	607	97.0
Ofloxacin					
	Sensitive	101	8.2	47	7.5
	Resistant	0	0.0	0	0.0
	Missing	1,127	91.8	579	92.5
Moxifloxacin					
	Sensitive	102	8.3	48	7.7
	Resistant	0	0.0	0	0.0
	Missing	1,126	91.7	578	92.3
Azithromycin					
	Sensitive	151	12.3	0	0.0
	Resistant	1	0.1	0	0.0
	Missing	1,076	87.6	626	100.0
Clarithromycin					
	Sensitive	332	27.0	10	1.6
	Resistant	13	1.1	11	1.8
	Missing	883	71.9	605	96.6
Ethionamide					
	Sensitive	68	5.5	32	5.1
	Resistant	39	3.2	22	3.5
	Missing	1,121	91.3	572	91.4
Prothionamide					
	Sensitive	56	4.6	19	3.0
	Resistant	34	2.8	18	2.9
	Missing	1,138	92.7	589	94.1

Supplementary File 3: continued

Exposure variables		England		London	
		No.	Col. %	No.	Col. %
Cycloserine					
	Sensitive	18	1.5	17	2.7
	Resistant	1	0.1	1	0.2
	Missing	1,209	98.5	608	97.1
Para-aminosalicylic acid					
	Sensitive	9	0.7	4	0.6
	Resistant	2	0.2	1	0.2
	Missing	1,217	99.1	621	99.2
Linezolid					
	Sensitive	69	5.6	31	5.0
	Resistant	0	0.0	0	0.0
	Missing	1,159	94.4	595	95.0
Rifabutin					
	Sensitive	171	13.9	18	2.9
	Resistant	0	0.0	0	0.0
	Missing	1,057	86.1	608	97.1

Supplementary File 4: Detailed drug and regimen information

Among individuals with a positive regimen-specific outcome

Detailed regimen duration information could only be analysed for patients with a positive treatment outcome, as only these individuals had full documentation of the use of each drug (and associated dates) across the entire treatment course. Individuals with other outcomes had regimens truncated to the date treatment stopped. Among the 408 individuals with a positive outcome, 374 (91.7%) had regimen data for the full duration of treatment. Thus the subsequent text describes the regimens used for these 374 patients.

The median overall treatment duration was 11.9 months and interquartile range (IQR) 9.3-12.1 months. This figure was slightly lower in the presence of Fqs (10.5 months), with a similar IQR (9.1-12.0). The median length of time on treatment before Hr was known was 1.8 months (IQR 1.1-2.2; eight individuals zero day delay) and after resistance was known 9.9 months (IQR 8.0-10.7).

372/374 individuals (99.5%) received R only, one Rb only, and one both drugs. (Across the entire cohort four patients were treated with Rb.) The median duration of Rf usage was 11.9 months (IQR 9.2 to 12.1). The median duration of E (371 individuals) was 11.8 months (9.1 to 12.1). These figures were 2.2 months (2.0 to 3.0; usually entirely in the initiation phase) for the 368 individuals given Z and 5.5 months (3.9 to 8.7) for the 151 given M. 400mg administered daily was the standard M dosage, with a few patients receiving 600mg. Six individuals received Fqs other than M (three ofloxacin, two Lfx, one ciprofloxacin), seven received group 4/5 drugs (five prothionamide, one prothionamide and cycloserine, one clarithromycin), and 11 injectables (eight S, three amikacin). Three of those receiving group 4/5 drugs and two receiving injectables had meningeal or spinal TB, or other CNS involvement. Five of the individuals receiving group 4/5 drugs and five receiving injectables had non-S additional drug resistance. Thirty five of the 374 individuals (9.4%) had their Rfs, E or Z dosed intermittently; this information was not known for seven patients. There was no evidence that any patients were given high dose H.

Thirteen detailed drug regimen categories were generated on the basis of the drugs within the regimen and Rf duration (Supplementary File 4 Table 1). The most common regimen categories were HRfZE (210/374, 56.1%) and HRfZE-M (119/374, 31.8%) (Supplementary File 4 Table 1). For these categories, the most common Rf duration was 9-12 months in both cases (116/210, 55.2% and 63/119, 52.9%, respectively).

369 of the 374 patients (98.7%) who completed treatment and had full regimen information had a documented date on which Hr was known. The most regimen initiated at this point (step-down regimen) was RfE (124/369, 33.6%), followed by RfZE (98, 26.6%) and RfZEM (77, 20.9%).

Table 1: Overall treatment regimens

Regimens used to treat Hr TB across the entire treatment course for the 374 patients who successfully completed treatment and had full regimen information available. Cat.- category, Col.- column, E- ethambutol, Fq- fluoroquinolone other than M, H- isoniazid, M-moxifloxacin, m- months, No.- number, Rf- rifamycin, +- plus additional drugs, (+)- with or without additional drugs

Regimen	No.	Col. %	Rifamycin duration	No.	Cat. %	Additional drugs	No.	Cat. %
HRfZE	210	56.1	≤6m	6	2.9			
			>6-≤9m	18	8.6			
			>9-≤12m	116	55.2			
			>12m	70	33.3			
HRfZE-M	119	31.8	≤6m	3	2.5			
			>6-≤9m	22	18.5			
			>9-≤12m	63	52.9			
			>12m	31	26.1			
HRfZE-M+	12	3.2				Injectables	6	50.0
						Injectables, group 4/5	2	16.7
						Fqs, group 4/5	2	16.7
						Group 4/5	2	16.7
HRfZE-Fq(+)	3	0.8				None	2	66.7
						Group 4/5	1	33.3
HRfZE+	2	0.5				Injectables	2	100.0
HRfZ-M	3	0.8						
HRfE-M	2	0.5						
HRfE	1	0.3						
RfZE-M	14	3.7						
RfZE(+)	5	1.3				None	4	80.0
						Injectables	1	20.0
RfE-M	1	0.3						
RfE-Fq	1	0.3						
RfE	1	0.3						
Total	**374**	**100.0**						

Use of fluoroquinolones

In order to ascertain whether the use of Fqs was unevenly distributed across key clinical and demographic groups, or whether different durations of Fqs were used in these groups, data were further tabulated. The inclusion, but not duration, of Fqs was associated within the presence of additional drug resistance and site of disease (Supplementary File 4 Tables 2 and 3). These two variables were thus included in sensitivity analyses (Supplementary File 8).

Supplementary File 4: continued

Table 2: The inclusion of fluoroquinolones in the treatment regimen, by important clinical and demographic characteristics

594 patients had at least some regimen data (Figure 1); 16 of these did not have information on the inclusion of fluoroquinolones in their regimen and thus 578 remain to examine the usage of this drug. CNS- central nervous system, Fq- fluoroquinolone other than M, M- moxifloxacin, TB- tuberculosis, *19 additional people were missing information on dosing frequency, ±- plus or minus, +ve- positive, -ve- negative

Exposure variables	Total	Fq/M included in regimen (row %)
Age (years)		
18-37	336	136 (40.5)
38-57	179	87 (48.6)
58-77	57	27 (47.4)
≥78	6	1 (16.7)
Site of disease		
Pulmonary ± extrapulmonary, smear +ve	176	90 (51.1)
Pulmonary ± extrapulmonary, smear –ve	147	61 (41.5)
Meningeal TB or other CNS involvement	21	14 (66.7)
Other extrapulmonary	234	86 (36.8)
Any additional drug resistance		
No	534	224 (42.0)
Yes	44	27 (61.4)
Thrice weekly dosing*		
More frequent	497	209 (42.1)
Thrice weekly	62	33 (53.2)
Adherence issues or treatment gaps		
No or unknown	451	187 (41.5)
Not severe or of unknown severity	69	33 (47.8)
Severe	58	31 (53.5)

Table 3: The overall duration of treatment, by important clinical and demographic characteristics

374 patients successfully completed treatment, had full regimen information available, and thus can have overall treatment duration calculated (Table 3). Durations quoted in months. CNS- central nervous system, IQR- inter-quartile range, TB- tuberculosis, *- seven additional people were missing information on dosing frequency, ±- plus or minus, +ve- positive, -ve- negative

Exposure variables	Total	Overall treatment duration (IQR)
Age (years)		
18-37	225	12.0 (9.3-12.2)
38-57	109	11.9 (9.2-12.0)
58-77	36	10.9 (9.2-12.1)
≥78	4	12.0 (11.8-12.2)
Site of disease		
Pulmonary ± extrapulmonary, smear +ve	108	12.0 (9.5-12.2)
Pulmonary ± extrapulmonary, smear –ve	97	11.9 (9.2-12.0)
Meningeal TB or other CNS involvement	8	12.3 (11.9-15.2)
Other extrapulmonary	161	11.8 (9.2-12.2)
Any additional drug resistance		
No	347	11.9 (9.3-12.1)
Yes	27	11.9 (9.2-13.0)
Thrice weekly dosing*		
More frequent	332	11.9 (9.3-12.1)
Thrice weekly	35	11.5 (9.2-12.2)
Adherence issues or treatment gaps		
No or unknown	306	11.9 (9.2-12.1)
Not severe or of unknown severity	37	12.0 (11.5-13.9)
Severe	31	10.6 (9.3-12.6)

Supplementary File 5: Univariable logistic regression of baseline characteristics as a predictor of negative outcomes

Univariable logistic regression of demographic and clinical baseline characteristics as predictors of negative regimen-specific outcomes in patients without additional drug resistance, unless to streptomycin. Each model contains the patients without missing data. CI- confidence interval, CNS- central nervous system, No.- number, OR- odds ratio, p- p-value, TB- tuberculosis, ±- with or without, -ve- negative, +ve- positive

Exposure variables	Negative outcome		
	No.	Row %	OR [95% CI], p-value
Overall	84	100.0	-
Year			
2009	16	11.7	p=0.91
2010	14	11.9	0.84 [0.38-1.89]
2011	19	13.5	0.99 [0.47-2.09]
2012	20	16.0	1.22 [0.58-2.58]
2013	15	14.3	1.12 [0.51-2.47]
Missing	0	-	-
Sex			
Male	45	11.8	p=0.12
Female	39	15.9	1.47 [0.90-2.40]
Missing	0	-	-
Age (years)			
18-37	43	12.0	p=0.23
38-57	32	16.1	1.58 [0.93-2.68]
58+	9	14.5	1.40 [0.62-3.19]
Missing	0	-	-
UK born			
No	63	12.7	p=0.16
Yes	20	16.5	1.57 [0.85-2.91]
Missing	1	12.5	-
Ethnic group			
White	15	15.5	p=0.40
Black African	13	10.4	0.55 [0.23-1.29]
Black Other	7	15.6	0.87 [0.31-2.45]
Indian subcontinent	33	12.2	0.63 [0.29-1.34]
Other	16	18.8	1.08 [0.47-2.49]
Missing	0	0.0	-
Social risk factors			
No or unknown	69	13.5	p=0.91
One or more ever	6	16.2	1.15 [0.43-3.08]
One or more current	9	11.4	0.89 [0.40-1.98]
Previous TB diagnosis			
No	77	13.4	p=0.10
Yes	5	25.0	2.82 [0.89-8.94]
Missing	2	6.5	-
Inpatient			
No	55	13.0	p=0.38
Yes	28	14.7	1.26 [0.75-2.13]
Missing	1	7.1	-
Site of disease			
Pulmonary ± extrapulmonary, smear +ve	30	15.5	1.47 [0.76-2.83]
Pulmonary ± extrapulmonary, smear –ve	19	11.9	p=0.45
Meningeal TB or other CNS involvement	5	20.8	2.19 [0.66-7.23]
Other extrapulmonary	30	12.0	1.10 [0.58-2.10]
Missing	0	-	-
Part of outbreak			
No	70	14.0	p=0.85
Yes	9	13.8	0.92 [0.41-2.10]
Missing	5	8.3	-

Supplementary File 6: Isoniazid resistance mutations

Isoniazid resistance mutations among the 161 strains that underwent successful genotyping and their associated degree of phenotypic resistance to isoniazid. No.- number.

	Total	Phenotype					
		Highly resistant		Resistant		Borderline	
Genotype		No.	Row %	No.	Row %	No.	Row %
ahpC_C-72T	1	1	100.0	0	0.0	0	0.0
fabG1_C-15T	79	63	79.7	10	12.7	6	7.6
inhA_I194T/fabG1_C-15T	1	1	100.0	0	0.0	0	0.0
inhA_I21T/fabG1_C-15T	1	1	100.0	0	0.0	0	0.0
inhA_S94A/fabG1_C-15T	1	1	100.0	0	0.0	0	0.0
katG_S315T/N	72	72	100.0	0	0.0	0	0.0
katG_S315T/fabG1_C-15T	5	5	100.0	0	0.0	0	0.0
katG_S315T/fabG1_G-17T	1	1	100.0	0	0.0	0	0.0
Total	161	145	90.1	10	6.2	6	3.7

Supplementary File 7: Multivariable logistic regression of treatment regimen as a predictor of negative outcomes- isoniazid resistance genotype included

Multivariable logistic regression of treatment regimen as a predictor of negative regimen-specific outcomes in patients without additional drug resistance, unless to streptomycin, taking into account Hr resistance genotype. Model contains 115 patients and adjusted for all variables in the table, in addition to sex, age, ethnic group and previous TB treatment. *strata perfectly predicts the outcome, CI- confidence interval, E- ethambutol, Fq- fluoroquinolones, H- isoniazid, m- months, M- moxifloxacin, OR- odds ratio, p- p-value, R- rifamycin, TB- tuberculosis, Z- pyrazinamide

Exposure variables	**OR [95% CI], p-value**
Regimen	
[H]RfZE	p=0.42
[H]RfZE-Fq/M	0.57 [0.14-2.28]
Thrice weekly dosing	
More frequent	p=0.26
Thrice weekly	3.15 [0.43-23.11]
Phenotype	
Highly resistant	p=0.78
Resistant	1.99 [0.10-37.81]
Borderline, sensitive or results not logged	2.56 [0.14-47.85]
Genotype	
fabG1 C-15T	p=0.31
katG S315T/N	2.06 [0.48-8.83]
Multiple/other	*

Supplementary File 8

In order to assess the impact of any documented treatment non-adherence on the regimen-outcomes relationship, thrice weekly treatment was swapped for an adherence variable within the multivariable model. Evidence for effect modification between regimen and adherence was not detected. The inclusion of this variable did not have an appreciable impact on the effect estimate for treatment regimen (0.90 [0.50-1.63], 0.73; Supplementary File 8 Table 1). When individuals with any drug resistance pattern were included in the model the effect estimate also remained largely unaltered (0.98 [0.55-1.76], 0.94; Supplementary File 8 Table 2).

After finding a potential association between drug resistance and site of disease with the use of Fqs (Supplementary File 4 Table 2), *post hoc* these variables were also included the main multivariable model. No discernible difference in the odds of a negative outcome between the two regimens was detected (0.96 [0.51-1.83], 0.91).

Table 1: Sensitivity analysis- multivariable logistic regression of treatment regimen as a predictor of negative outcomes (adherence included)

Multivariable logistic regression of treatment regimen as a predictor of negative regimen-specific outcomes in patients without additional drug resistance, unless to streptomycin, adjusted for all variables in the table. Sensitivity analysis adjusting for adherence to treatment instead of thrice weekly dosing. Model contains 453 patients. CI- confidence interval, E- ethambutol, Fq- fluoroquinolones, H- isoniazid, m- months, M- moxifloxacin, OR- odds ratio, p- p-value, Rf- rifamycin, TB- tuberculosis, Z- pyrazinamide

Exposure variables	**OR [95% CI], p-value**
Regimen	
[H]RfZE	p=0.73
[H]RfZE-Fq/M	0.90 [0.50-1.63]
Adherence issues or treatment gaps	
No or unknown	p=0.22
Not severe or of unknown severity	2.02 [0.90-4.52]
Severe	0.82 [0.31-2.17]
Phenotype	
Highly resistant	p=0.32
Resistant	0.62 [0.17-2.28]
Borderline, sensitive or results not logged	2.01 [0.71-5.68]
Missing	
Sex	p=0.14
Male	1.52 [0.87-2.65]
Female	
Age (years)	
18-37	1.08 [0.71-1.66]
Per 20 year increase	
Ethnic group	
White	0.38 [0.14-1.00]
Black African	0.34 [0.09-1.36]
Black Other	0.52 [0.23-1.19]
Indian subcontinent	1.02 [0.42-2.48]
Other	
Previous TB diagnosis	
No	2.70 [0.67-10.78]
Yes	p=0.73

Table 2: Sensitivity analysis- multivariable logistic regression of treatment regimen as a predictor of negative outcomes (all patterns of drug resistance included)

Multivariable logistic regression of treatment regimen as a predictor of negative regimen-specific outcomes, adjusted for all variables in the table (including the presence of additional drug resistance). Sensitivity analysis including all individuals, regardless of drug resistance status. Model contains 459 patients. CI- confidence interval, E- ethambutol, Fq- fluoroquinolones, H- isoniazid, m- months, M- moxifloxacin, OR- odds ratio, p- p-value, Rf- rifamycin, TB- tuberculosis, Z- pyrazinamide

Exposure variables		**OR [95% CI], p-value**
Regimen		
	[H]RfZE	p=0.94
	[H]RfZE-Fq/M	0.98 [0.55-1.76]
Thrice weekly dosing		
	More frequent	p=0.01
	Thrice weekly	3.09 [1.31-7.33]
Phenotype		
	Highly resistant	p=0.68
	Resistant	0.62 [0.19-2.02]
	Borderline, sensitive or results not logged	1.17 [0.39-3.49]
Sex		
	Male	p=0.00
	Female	2.25 [1.28-3.95]
Age (years)		
	18-37	p=0.71
	Per 20 year increase	1.09 [0.70-1.69]
Ethnic group		
	White	p=0.08
	Black African	0.36 [0.13-0.97]
	Black Other	0.32 [0.09-1.17]
	Indian subcontinent	0.57 [0.24-1.35]
	Other	0.99 [0.39-2.52]
Previous TB diagnosis		
	No	p=0.03
	Yes	4.54 [1.22-16.83]
Any additional drug resistance		
	Absent	p=0.59
	Present	1.19 [0.64-2.21]