Treatment regimens for rifampicin resistant tuberculosis: highlighting a research gap

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Summary

Treatment guidance for non-multidrug resistant (MDR) rifampicin resistant (RMP-R) tuberculosis (TB) is variable. We aimed to undertake a systematic review and meta-analysis of the randomised controlled trial (RCT) data behind such guidelines to identify the most efficacious treatment regimens. Ovid MEDLINE, the Web of Science, and EMBASE were mined using search terms for TB, drug therapy, and RCTs. Despite 12,604 records being retrieved, only three studies reported treatment outcomes by regimen for patients with non-MDR RMP-R disease, preventing meta-analysis. Our systematic review highlights a substantial gap in the literature regarding evidence-based treatment regimens for RMP-R TB.

Introduction

The World Health Organization (WHO) estimates that, in 2014, 1.1% of tuberculosis (TB) patients had rifampicin resistant (RMP-R) disease without additional resistance to isoniazid (INH) i.e. not multidrug resistant (MDR).[1] This equates to approximately 40,000 notified pulmonary TB patients with RMP-R strains.[1]

Treatment guidance for non-MDR RMP-R TB is diverse. The WHO stated in 2011 that '[t]he detection of rifampicin resistance by Xpert MTB/RIF usually suffices to start a patient on a second-line TB regimen, subject to confirmatory testing in situations with low rifampicin resistance'.[2] In 2003 the American Thoracic Society (ATS) recommended a regimen of INH, pyrazinamide (PZA) and ethambutol (EMB) for nine to 12 months (with the addition of a fluoroquinolone for patients with more extensive disease) for RMP-R TB.[3] UK National Institute for Care Excellence (NICE) guidelines, developed 2012-2015, endorse following WHO MDR-TB treatment guidance.[2;4]

A previous review of 12 British Medical Research Council randomised controlled trials (RCTs) containing patients with drug resistant disease, published by Mitchison *et al*. in 1986, demonstrated that RMP-R was related to worse treatment outcomes.[5] Some of the included patients had MDR disease, however, and no formal meta-analysis comparing the efficacy of different regimens was undertaken.

Given the variability in treatment guidance, we aimed to undertake an up-to-date systematic review and meta-analysis of RCTs of treatment regimens for RMP monoresistant disease.

Study population and methods

Figure 1 and Online Appendix 1 document our literature search. Reference lists of included papers and review articles were also mined. RCTs of antimicrobial regimens for TB patients indexed by 21st January 2015 were included, provided that either treatment outcome or relapses post-treatment could specifically be extracted for patients with RMP monoresistant disease. TB deaths were also extracted. Studies were not excluded by language. HRS screened all of (and H-AH 10% of) the retrieved records. Both reviewers independently undertook the final stage of full text screening and extraction into a standardised pre-designed spreadsheet. Discrepancies were resolved by discussion; other authors were consulted when required. Both reviewers assessed study quality.[6] Studies were deemed to have a high risk of bias from selective reporting if the overall RCT was not of patients with drug resistant strains. The thresholds for the attrition criteria were- ≥10% losses during follow up across all study participants (ignoring exclusions for not fulfilling inclusion criteria), or

≥10% absolute difference in losses between study arms. Where drug resistance was not the primary focus of a study, attrition was assessed for the entire study population.

This review was registered on PROSPERO (CRD42014015025). As this was a systematic review ethical approval and informed consent were not required.

Results

Of 12,604 de-duplicated publications found, only three reported outcomes specifically for patients with RMP monoresistant disease and had more than one such patient in their trial (Table 1, Figure 1). Consensus between the two reviewers on publications for inclusion was 100%. No study focussed solely on the treatment of patients with drug resistant strains or had more than five RMP-R patients for whom outcomes were reported. All studies recruited patients with pulmonary disease and utilised RMP in every treatment arm. None trialled the treatment regimens recommended by the WHO, NICE or ATS. The risk of bias for various quality domains was frequently unknown (Table 1).

The Hong Kong Chest Service study contained two relevant patients for whom outcome data were extractable, one per regimen arm.[7] Both arms treated patients with INH, PZA, RMP, streptomycin (STM) for four months, one with a daily dosing schedule and one thrice weekly. Both patients had negative cultures at the end of chemotherapy, but the individual with daily dosing relapsed post-treatment. Jindani *et al.* contained five patients across two eight month arms of EMB, INH, PZA, RMP followed by EMB, INH (one dosed daily and one with a thrice weekly intensive phase but daily dosing thereafter) and one six month arm of EMB, INH, PZA, RMP followed by INH, RMP (dosed daily).[8] None failed treatment (ascertained by culture status or needing to change treatment) or relapsed post-treatment. The Tuberculosis Research Centre study contained two relevant patients, one in each of two study arms (two six month EMB, INH, PZA, RMP then INH, RMP regimens with two versus three month intensive phases).[9] No unfavourable outcomes (culture status at the end of treatment, treatment change required, clinical deterioration, died of TB) were reported by the end of treatment. Given the small amount of available data meta-analysis of relative regimen efficacy was not possible.

Discussion

This systematic review, which sought to assess the relative efficacy of different treatment regimens for RMP monoresistant TB disease, highlights a substantial gap in the literature, perhaps because such studies are perceived as challenging or relatively low priority. This is

despite our extending and updating of the work of Mitchison *et al*. from 1986, which included only two patients with RMP monoresistance.[5]

Our inclusion criteria were limited to RCTs; observational studies can provide useful information in the absence of adequately powered trials. A literature search (Online Appendix 2) undertaken on the 11th of January 2016 identified very few relevant observational publications. For example, Meyssonnier *et al*. undertook a retrospective cohort study of treatment regimens and outcomes for non-MDR RMP-R in France, 2005-2010; with only 49 patients few conclusions could be drawn.[10] Such studies are more subject to bias than RCTs, and frequently insufficient for the formulation of evidence-based guidance.

It is unclear if current WHO guidance results in over-treatment of non-MDR RMP-R disease; indeed, it may be appropriate if weaker regimens are inadequate. Lengthy treatments with unpleasant adverse events can reduce patient adherence, increasing the likelihood of further drug resistance and onward transmission to others. Therefore, given the duration and toxicity of MDR-TB regimens, minimising unnecessary exposure of non-MDR RMP-R patients to such treatments, whilst ensuring an effective cure, is a priority.

Conclusions

To provide a solid scientific foundation for global treatment guidance, and given current data sparsity, we recommend that a properly powered RCT is undertaken to answer unresolved questions concerning the efficaciousness of different treatment regimens for RMP monoresistant disease.

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Author contributions

HRS and IA conceived and designed the work. HRS acquired the data and drafted the original manuscript. All authors contributed to the analysis and interpretation of the data, revision of the manuscript for intellectual content, and gave their approval of the manuscript.

Conflict of interests

HRS declares funding from the National Institute for Health Research (NIHR), UK during the conduct of the study; and, outside of the submitted work, grants and personal fees from Otsuka Pharmaceutical, non-financial support from Sanofi, and other support from the World Health Organization (WHO). RH declares funding from the NIHR, UK during the conduct of the study. H-AH reports funding from Engineering and Physical Sciences Research Council during the conduct of the study. All other authors have nothing to disclose.

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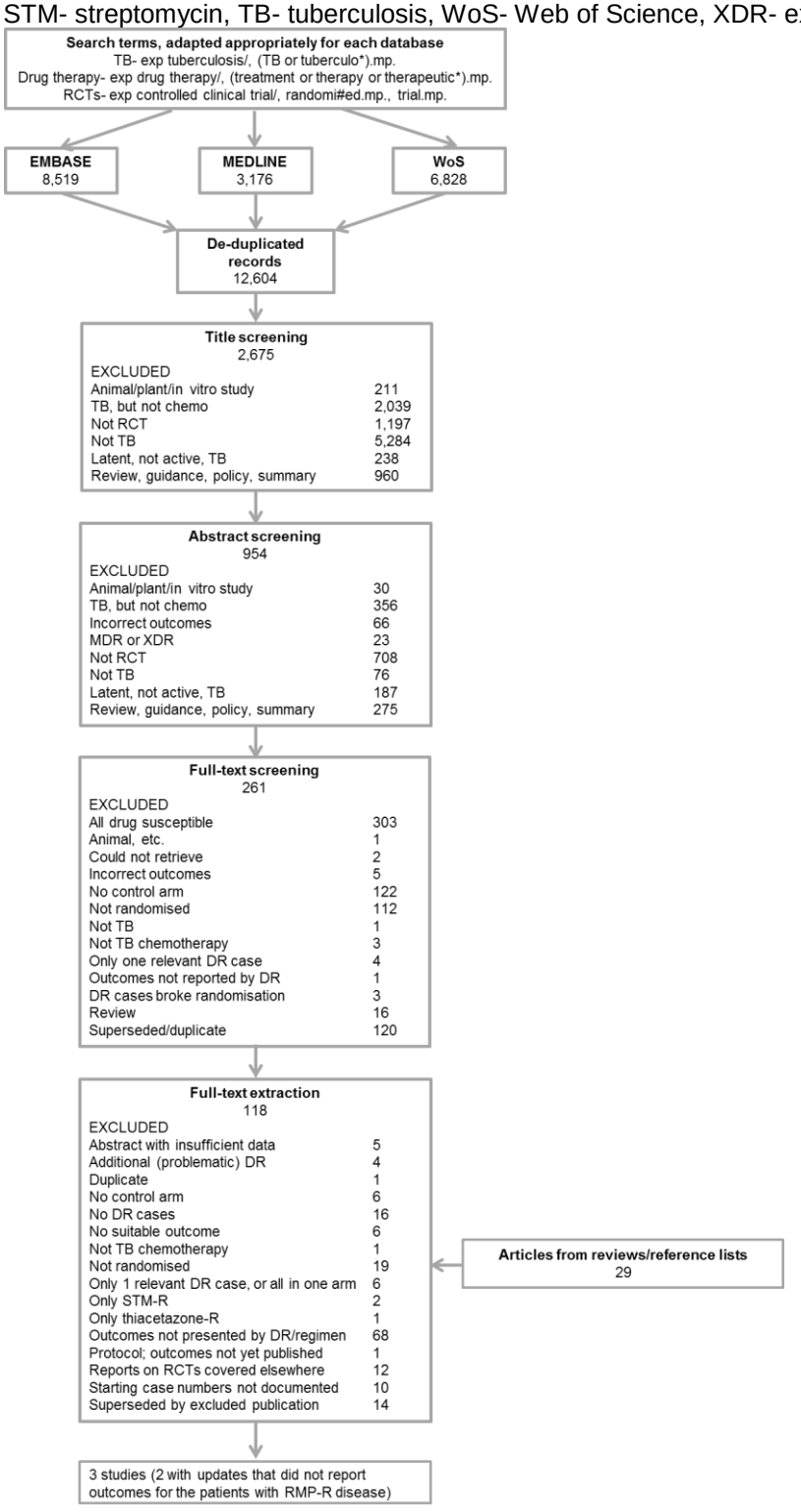
Table 1: Studies fulfilling the inclusion criteria

Author	Country of study	First year of recruitment	Regimens with which resistant patients were treated	Outcomes for rifampicin monoresistant patients		Quality assessment: risk of bias from…					
				Treatment outcome reported?	Relapse reported?	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Attrition	Selective reporting
HKCS[7]	Hong Kong	1978	HRSZ	Yes	Yes	Unknown	Unknown	Unknown	Unknown	High	High
Jindani[8]	Benin, China, Guinea, Mozambique, Nepal, Tanzania	1998	EHRZ/EH, EHRZ/HR	Yes (but combined with relapse)	Yes (but combined with treatment outcome)	Low	Low	High	High	High	High
TRC[9]	India	1990	EHRZ/HR	Yes	No	Unknown	Unknown	Unknown	Unknown	High	High

Table of included publications after the extraction stage. Quality assessment (risk of bias) utilised the framework of Higgins *et al.*[6] XX/YY- indicates drugs present in initiation (X) versus continuation (Y) phase, E- ethambutol, H- isoniazid, HKCS- Hong Kong Chest Service, R- rifampicin, S- streptomycin, TB- tuberculosis, TRC- Tuberculosis Research Centre Madras, Z- pyrazinamide

Figure 1: Selection of papers for inclusion

Selection strategy for systematic review. At full text extraction stage 'not randomised' relates to the functionality of randomisation for patients with DR disease (randomisation may have been broken). 'Only STM-R' and 'Only thiacetazone-R' criteria refer to studies documenting outcomes specifically for patients with STM or thiacetazone resistant disease but not a relevant resistance pattern for this review. DR- drug resistance, MDR- multidrug resistant, R- resistant, RCT- randomised controlled trial, RMP- rifampicin, STM- streptomycin, TB- tuberculosis, WoS- Web of Science, XDR- extensively DR



ONLINE APPENDIX 1: Search strategy for randomised controlled trials

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and **Ovid MEDLINE(R)**

#1	exp Tuberculosis/	
#2	(TB or tuberculo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
#3	1 OR 2	
#4	exp Drug Therapy/	
#5	(treatment or therapy or therapeutic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	
#6	4 OR 5	
#7	exp controlled clinical trial/	
#8	exp Randomized Controlled Trial/	
#9	randomi#ed.mp.	
#10	trial.mp.	
#11	7 OR 8 OR 9 OR 10	
#12	**3 AND 6 AND 11**	

Web of Science

#1	(Tuberculosis[MeSH Terms]) OR TB OR tuberculo*	~619,973
#2	(Drug Therapy[MeSH Terms]) OR treatment OR therapy OR therapeutic*	~21,168,564
#3	(Controlled Clinical Trial[MeSH Terms]) OR (Randomized Controlled Trial[MeSH Terms]) OR randomized OR randomised OR trial	~3,704,538
#4	**1 AND 2 AND 3**	**6,828**

Embase Classic+Embase

#1	exp tuberculosis/	
#2	(TB or tuberculo*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	
#3	1 OR 2	
#4	exp drug therapy/	
#5	(treatment or therapy or therapeutic*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	
#6	4 OR 5	
#7	exp controlled clinical trial/	
#8	randomi#ed.mp.	
#9	trial.mp.	
#10	7 OR 8 OR 9	
#11	**3 AND 6 AND 10**	

ONLINE APPENDIX 2: Search strategy for observational studies

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and **Ovid MEDLINE(R)**

#1	exp Tuberculosis/	168,941
#2	(TB or tuberculo*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	232,853
#3	1 OR 2	234,398
#4	exp Drug Therapy/	1,142,884
#5	(treatment or therapy or therapeutic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	5,148,843
#6	4 OR 5	5,591,774
#7	exp Rifampin/	15,838
#8	(rifampicin or rifampin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	25,143
#9	7 OR 8	25,143
#10	exp Drug Resistance/	875,289
#11	resistan*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1,026,177
#12	10 OR 11	857,222
#13	**3 AND 6 AND 9 AND 12**	**2,415**