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Treatment outcomes of Multi drug resistant and Rifampicin resistant Tuberculosis in LMIC: A Systematic Review

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Abstract
Background: *Despite extensively drug-resistant tuberculosis (XDR TB) being recognised as a major public health concern that threatens global TB control, the treatment outcomes of MDR/RR TB in Low Middle Income Countries have not been explored sufficiently. The overarching objective of this systematic review will be to assess, synthesize and augment the best available evidence on treatment outcomes among MDR/RR-TB patients in a LMIC between the years 2010 and 2019. It is envisaged that this systematic review will provide evidence on treatment outcomes in DR-TB patients in LMIC which will be used for policy formulation and the strenghtening of the Programmatic Management of Drug Resistant TB (PMDT) practice in developing countries.*
Methods: *A systematic review of published literature was conducted. Original studies were identified using the databases MEDLINE®/PubMed®, Cochrane, and Google Scholar. Heterogeneity across studies was assessed using the Cochran's Q test and I 2 statistic. Pooled estimates of treatment outcomes were computed using the random effect model.*
Results:*The systematic review illuminated that 6502 patients had treatment outcomes reported, with 60.5% meeting the definition of successful treatment outcome.Treatment outcomes are substantially worse in patients with MDR/RR-TB as compared to patients who received standardised regimens for drug susceptible-TB. The default rate was 15%; 13% of the patients died, while 6% failed treatment.The systematic review notedthat patients who received a later generation fluoroquinolones would have a 39.5% increase in favourable outcomes, compared with those who did not receive later-generation fluoroquinolones.*
Conclusion: *High proportions of patients had poor treatment outcomes and treatment success rate was higher in studies that reported on individualised treatment regimens. However, the lack of significant associations of treatment outcomes with certain regimens reflects the incomplete reporting in most studies and limitations of pooling the data rather than the lack of differences in efficacy of regimens or drugs. In most of the studies evidence or information about treatment regimens is poorly reported, with data gaps on drugs used initially and in the continuation phase.*

Keywords: *Treatment outcomes, Multi drug resistant TB, Rifampicin resistant Tuberculosis, Extensive Drug Resistant tuberculosis,*

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I. Background

Extensively drug-resistant tuberculosis (XDR TB) is a major public health concern that threatens global TB control[30].Multidrug-resistant TB (MDR TB) is caused by *Mycobacterium tuberculosis* that shows resistance to isoniazid and rifampicin, and XDR TB includes additional resistance to any fluoroquinolone and a second-line injectable drug(Ibid).Drug-resistant TB (X*DR-TB, MDR TB,)* has emerged globally with the World Health Organization (WHO) estimating that there were about 558,000 multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) patients globally in the year 2017, but only 29% (twenty-nine percent) were notified. The 2018 global TB report has shown that only 55% (fifty-five percent) of patients initiated on MDR/RR-TB treatment outcomes had successful treatment outcomes. This is against a background of WHO recommendations of 20-24 month standardised second line drug (SLDs) regimen for treatment of MDR/RR-TB patients in resource-limited settings and the target of achieving a 75-90% treatment success rate (i.e.cured or treatment completed). It is also estimated that 3.5% of new TB cases and 18% of previously treated TB patients had MDR/RR-TB in 2017 [30].

However,the evidence base illuminates that MDR/RR-TB treatment outcomes vary by factors specific to individual patients and are also related to TB program implementation[11-12].Patient-level characteristics like HIV-coinfection, alcohol and substance use, smoking and low body mass index have been found to be associated with unsuccessful treatment outcomes. Programmatic characteristics like delay in treatment initiation, duration of treatment, type of drug sensitivity testing, individualized treatment regimens and use of directly observed therapy have also been found to be associated with adverse MDR/RR-TB treatment outcomes.[11-12]. It is against this background and the paucity of evidence on the treatment outcomes of Multi-drug resistant and Rifampicin resistant Tuberculosis in Low Middle Income Countries (LMIC),this systematic review seeks to assess, collate and synthesize the best available evidence that will strengthen the Programmatic Management of Drug Resistant TB (PMDT) practice in developing countries and proffer policy recommendations and strategies.

II. Methodology

Systematic review methodology was used for this study. Systematic review is defined as an appraisal and synthesis of research papers, articles, reports and other literature sources using a rigorous and clearly documented methodology in both the search strategy and the inclusion and exclusion criteria of literature [20].They are designed to provide a complete, exhaustive summary of current evidence relevant to a research question.Backward snow-balling and meta-analysis methodological strategies were also used in this systematic review.

Search and selection strategy

Using the search strategy described in Table 1, we identified studies that reported the treatment outcomes of Multi drug resistant (MDR) and Rifampicin resistant tuberculosis in Low-Middle income countries, Developing countries, least developed countries. We searched databases such as PubMed, EMBASE, Medline, Web of Science, Cochrane databases. The search range/ limitation was from 2010 to 2019. Only articles in English language were accessed.Keyword and title search of Web of Science was performed using the terms tuberculosis, TB, tb, multiple drug resistant, multiple drug resistance, multi-drug resistance, multi-drug resistant, multi-drug-resistant, drug resistant, MDR, MDRTB, extensively drug resistant, XDRTB.Backward snowballing and meta-analysis was conducted on all systematic reviews, randomised control trials,cohort studies which were relevant to the study. Grey literature such as Word Health Organisation reports, United Nations reported were also considered in this study.

Selection of Studies and Inclusion and Exclusion Criteria

The studies accessed from the literature search were checked by title, abstract and citation. Relevant articles were reviewed by title, abstract and full text.

Exclusion criteria were as follows: articles written in other languages which is not English, exclusive useof first-line therapy in the treatment protocol, single studies, opinion papers, articles published from 2010 and below. For further information find below PRISMA table.

Characteristics of Included Studies

The studies selected for this study were systematic reviews and meta-analysis, randomised control trials, observational studies, case control study, cross sectional survey, retrospective review of TB treatment, retrospective record review. All of the studies were published in English with study populations varying from 46 to 1,369 and undertaken between 2010 and 2019.

Operational Definition

Treatment outcomes of MDR-TB aredefined based on the WHO guidelines, as follows:

- Cured: defined as a patient who had completed treatment according to program protocol and who has been consistently culture-negative (with at least five results) for the final 12 months of treatment.
- Treatment completed: defined as a patient who had completed treatment according to program protocols, but does not meet the definition of "cured" because of a lack of bacteriological results.
- Died: defined as a patient who died for any reason during the course of TB treatment.
- Treatment failed: if two or more of the five cultures recorded in the final 12 months of treatment were positive, or if any one of the final three cultures was positive.
- Lost to follow-up: defined as a patient whose TB treatment was interrupted for two or more consecutive months for any reason.
- Transferred out: defined as a patient who had been transferred to another reporting and recording unit, and for whom the treatment outcome was unknown. For the purposes of this review, those cured or who

completed their treatment was categorized as successful treatment outcomes, whereas the others were categorized as unsuccessful treatment outcomes.[22]

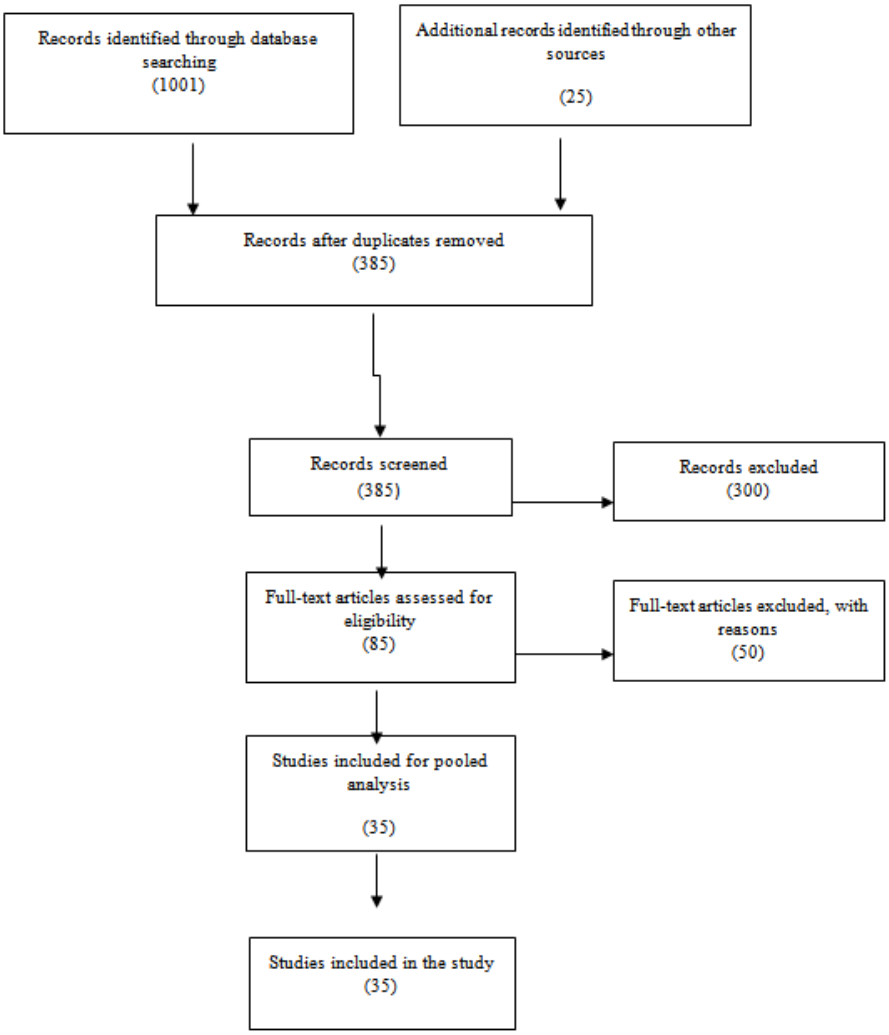
III. Data Analysis

The pooled analysis and estimates of MDR-TB treatment was determined using the random effects model (Dersimonian Laird for random effects meta-analysis). This also involved summarising and analysing the proportion of patients/ participants who experienced favourable outcomes and unfavourable outcomes. With the proportions of treatment outcomes of 95% confidence intervals (CIs). The heterogeneity of outcomes within and between articles were assessed using the Cochrane Q test. Sensitivity analyses were performed to eliminate duplicate studies which may include participants/patients who had been described in the previously published reports.

IV. Results

We identified a total of 1001(one-thousand and one) original articles in databases such as MEDLINE®/PubMed®, Cochrane, and Google Scholar. Twenty five (25) additional articles were identified through other sources such as conference proceedings, World Health TB reports and programme reports. Of these, three-hundred and eighty five (385) articles were screened and assessed after duplicates were removed. Using the inclusion and exclusion criteria, three hundred articles were excluded for the study, the exclusion reasons were as follows: not targeting MDR-treatment outcomes, population focus was on high income countries, the sample size was not representative (*less than 10 patients/participants with MDR-TB),* failure to report on standard outcomes, language restrictions (*not English),* exclusive use of first-line therapy in the treatment protocol, single studies, opinion papers, articles published from 2010 and below. Thirty-five studies were included for the final analysis. Find below Prisma Flow Diagram for further illustrations.

Figure 1: PRISMA Flow Diagram



Treatment Outcomes

Description

The pooled treatment outcomes were analysed from thirty-five (35) studies in ten countries, which reported on treatment outcomes for a total six-thousand five hundred and two (6502) patients/participants. All thirty-five (35) studies used the World Health Organisation standard of definition of cure ofat least five consecutive negative cultures during the last twelve (12) months of treatment. All patients met the definition of infection with MDR/RR-TB. The mean age of participants ranged from 25.5 to 50.5years. In the studies reviewed, the patients were reportedly treated for MDR/RR-TB in hospital locations and ambulatory basis. Find below Table 1 the characteristics of studies included in the review.

Table 1 Characteristics of studies included in the review

Study area	Study period	Study design	Study population	No. of patients and # of studies for SR
Nigeria	2016	Retrospective review of TB treatment		1070
South-East Nigeria	2019	Retrospective Analysis on Treatment Outcome	PTB patients	1070
Western India	2015	Prospective cohort study	MDRTB	145
South Ethiopia	2017	Retrospective cohort study		-
Swaziland	2010	Cross-sectional survey		988
South Korea	2015	Systematic review principles and approaches		422
Mozambique	2012	National Drug Resistance Survey		_
Swaziland	2019	Case Control Study		400
Ethiopia	2019	Retrospective study		385
South Africa and Northern Ethiopia	2011- 2015	Five retrospective analysis		1850
South Africa	2014	Systematic Review		45 studies were considered
South Africa	2018	Retrospective Medical Record Review		86
Ethiopia	2018	Systematic Review		34 studies were considered in the final analysis
Karakalpakstan, Uzbekistan	2011	Cohort Study		487
South Africa	2012	Systematic Review		Twelve studies, 3489 patients
South Africa	2013	Systematic Review		36 studies were considered
Myanmar	2015	Cohort study includes record review		261 patients
Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan	2018	Retrospectively reported and compared the DR-TB treatment outcomes		1,369
South Ethiopia	2017	Retrospective cohort study		154
Low income countries	2014	Systematic Review		20 studies were considered
Low Income Countries	2013	Systematic Review		560
Low Income Countries	2014	Analysis of individual patient data assembled from 31 previously published cohort studies of patients with MDR and XDR tuberculosis		8955
Ethiopia	2015	Hospital based retrospective study		380
South Africa	2013	Retrospective medical record review		86
Low Middle Income Countries	2011	Systematic Review		25 studies were considered

- *SR- Systematic Review*

Treatment Outcomes

The systematic review illuminated that 6502 patients hadtreatment outcomes reported, with 60.5% meeting the definition of successful treatment outcome. Similar to previous studies the pooled overall success rate of MDR/RR-TB patients was 64% and this is below the WHO target of 75-90%. The default rate was 15%, 13% of the patients died, 6% failure rate as illustrated in Table 3.Treatment outcomes were substantially worse in patients with XDR-TB and in patients who received standardise regimens for MDR-TB.Thelowest cure rate

(21%) was in a South African study. The results of this study revealed that a high proportion of patients had poor treatment outcomes.

	Sample Size	**Successful outcome** (n)	**Unsuccessful Outcome**		
			Default	Death	Failure
	178	123	32	16	10
	651	429	74	136	19
	29	12	6	2	1
	75	55	16	7	2
	40	25	5	4	6
	10	6	1	3	2
	128	77	23	25	5
	68	26	17	9	8
	117	71	16	18	12
Summary	130%	64%	15%	13%	6%
95% CI	-	59-71	12-19	9-18	3-11
pvalue		0.0002	0.0382	<0.0001	

Table 3: Summary of Outcomes at the End of Treatment

This systematic review concurs with other studies on treatment outcomes being substantially worse in patients with MDR/RR-TB as compared to patients who received standardised regimens for drug susceptible-TB[11-17].There is also limited evidence that evaluates, assess studies on the treatment of MDR/RR-TB with focus on the efficacy and effectiveness of the directly observed treatment but however this systematic review reaffirms two critical outcomes of MDR/RR-TB which are severe drug-related adverse eventsand end of treatment outcomes.

The systematic review notedthat patients who received a later generation fluoroquinolones would have a 39.5% increase in favourable outcomes, compared with those who did not receive later-generation fluoroquinolones. This re-establishes previous studies[14]. However, this poses the clinical question, as it suggests that the addition of a later-generation fluoroquinolone, even in the presence of representative fluoroquinolone resistance, might significantly improve outcomes (Ibid). However, these findings can reaffirm the potential importance of fluoroquinolones in the treatment of MDR/RR-TB.

With regard to treatment models, at least eight (eight) studies utilized an individualized regimen and four studies utilized a standardized regimen as illustrated in **Table2.** Treatment duration was expressed in different ways and varied between studies, with the overall treatment duration of between 18-24 months.

Table 2 Summary Description of the treatment in the included studies

Model*	Treatment duration (months)	Drugs in regimen†	DOTS location	Provider of DOTS
I	18-24	n/a	Local health centre	Nurse
S	6-9	6,4	Decentralized clinics	Health Workers
S	≥18	5,4	Outpatient	Household member, Private Health Worker
I	10-24	n/a	Health centre or patient home	Household member/ local nurse
S	23 *median* (0 · 4-35 · 9) *median* 6 (5-9)	Median 6 (5-9	Outpatient	Household member
I	8-12, 16-24	≥5	Peripheral health centre or patient home	Local nurse
S	18-24	5,4	Village health centres, clinics or hospital	Health worker
S	≥6, ≥18	6	Local health centre, or patient home	Local nurse
I	≥24	5,3	-	
S	≥6, ≥18	5, ≥2	-	
S	24	5, 4	-	

**I = Individualized, S = Standardized. ‡ Duration of intensive phase and continuation phase are separated by a comma. Duration symbolises length of treatment. † Number of drugs in intensive and continuation regimens separated by a comma.*

V. Discussion

The results of this systematic review revealed that high proportions of patients had poor treatment outcomes and treatment success rate was higher in studies that reported on individualised treatment regimens.Standardised treatment ensures that all patients with MDR-TB receive the same treatment regimens involving a common drug susceptibility test (DST) of the prevalent MDR-TB strains. However, one of the major weakness/limitation was the incomplete reporting in most studies. At least one-third of studies revealed adequate information about drug susceptibility testing and laboratory methods for diagnosis. In most of the studies evidence or information about treatment regimens is poorly reported, with data gaps on drugs used initially and in the continuation phase and the duration of these two important phases.

The poor outcomes in MDR/RR patients is consistent with the findings of previous meta-analyses [7-11].This systematic review further reaffirms that fifteen years (15) after the first report of XDR-TB in Ethiopia and South Africa there has been no major advance in MDR/RR-TB.

VI. Conclusion

There has been insurmountable interest in the last ten years (10) to use evidence synthesis tools such as systematic review in reporting published experience in MDR/RR-TB this has been affected by studies methodological limitations and incomplete reporting on MDR/RR-TB. As previous studies have proffered, they is need for multi-lateral and bilateral support to treatment and adverse events, diagnostics. Robust and stronger study designs which include patient data-meta-analysis, randomised control trials, registry trials might assist in developing safer and effective treatment for MDR/RR-TB.

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