PREVALENCE, MANAGEMENT AND OUTCOME OF MULTIDRUGS RESISTANT TUBERCULOSIS: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

Background: *Multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), is an important obstacle to global TB control. The failure to diagnose and effectively treat MDR/RR-TB patients perpetuate ongoing MDR/RR-TB transmission in the community and can amplify the MDR/RR-TB burden.*

The aim: *The aim of this study to show about prevalence, management and outcome of multidrug resistant tuberculosis.*

Methods: *By the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. This search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed, SagePub, and Sciencedirect were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *Five publications were found to be directly related to our ongoing systematic examination after a rigorous three-level screening approach. Subsequently, a comprehensive analysis of the complete text was conducted, and additional scrutiny was given to these articles.*

Conclusion: *The success of any national program can only be ascertained by studying the outcomes of treatment regimes in patients with MDR-TB enrolled in different DOTS-plus sites of the country.*

Keyword: *Tuberculosis, MDR-TB, management, outcome.*

INTRODUCTION

Globally, tuberculosis is an important disease of public health importance. Its impact is even higher in resource-limited countries which are heavily burdened with overcrowding and lack of medical facilities. The problem is further complicated by the high prevalence of resistance in *Mycobacterium tuberculosis* to first-line antitubercular drugs. The Revised National Tuberculosis Control Programme (RNTCP) under the programmatic management of drug-resistant tuberculosis or directly observed treatment short course chemotherapy plus (DOTS-Plus) strategy has adopted Category IV regimen as the standard of care for the treatment of multidrug-resistant tuberculosis (MDR-TB) since 2007.[1,2]

Tuberculosis (TB) remains one of the most highly prevalent infectious diseases worldwide, with high mortality and morbidity. The emergence of drug-resistant TB has threatened global efforts to eliminate the disease. Viet Nam is a high TB burden country, with associated high rates of multidrug-resistant TB (MDR-TB, defined as TB resistant to at least both isoniazid [INH] and rifampicin [RMP]). In 2013, of an estimated 130 000 new TB cases nationally, 102 196 were notified. The Fourth National Drug Resistance Survey (DRS) in 2011 showed an MDR-TB rate of 4% among new cases and 23% among retreatment cases. Applying the DRS rates to all notified TB cases in 2013, the number of MDR-TB cases was estimated at 5100 per year.[3,4]

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Timely diagnosis, rapid detection of drug resistance, and effective treatment regimens are critical measures for the effective control of MDR. HRM is a rapid molecular diagnostic technique commonly used in clinical settings that can be used for tuberculosis diagnosis and resistance molecular locus detection of first- and second-line anti-tuberculosis drugs. Faced with complex drug-resistant cases, we need more surveillance data to estimate the risk of transmission of drug-resistant TB. Therefore, having an understanding of the prevalence of drug-resistant tuberculosis (DR-TB) in this region can help optimize the utilization of limited resources to control the spread of TB. Based on the results of the HRM test, this study investigated the population characteristics of MDR-TB and the risk factors related to it in this area to provide epidemiological evidence for the management of clinical MDR-TB.[7,8]

Outbreaks of MDR-TB were initially thought to be driven by nosocomial transmission, particularly among HIV-positive patients. One of the largest and best-documented outbreaks occurred in New York in the late 1980s and early 1990s. As DST laboratory capacity improved in resource-limited settings and global drug-resistant TB surveillance efforts grew, it became clear that MDR-TB was increasingly common throughout the world and a growing threat to the general public health.[9,10]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast prevalence, management and outcome of multidrug resistant tuberculosis. It is possible to accomplish this by researching of prevalence, management and outcome of multidrug resistant tuberculosis. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about prevalence, management and outcome of multidrug resistant tuberculosis. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2014, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "prevalence, management and outcome of multidrug resistant tuberculosis." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed, SagePub, and Sciencedirect databases by inputting the words: *(("Tuberculosis"[MeSH Subheading] OR "Multidrug resistant"[All Fields] OR "Prevalence" [All*

Fields]) AND ("Management"[All Fields] OR " Outcome"[All Fields]) AND ("Epidemiology"[All Fields]) OR ("Treatment" [All Fields])) used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and cannot have been seen anywhere else.
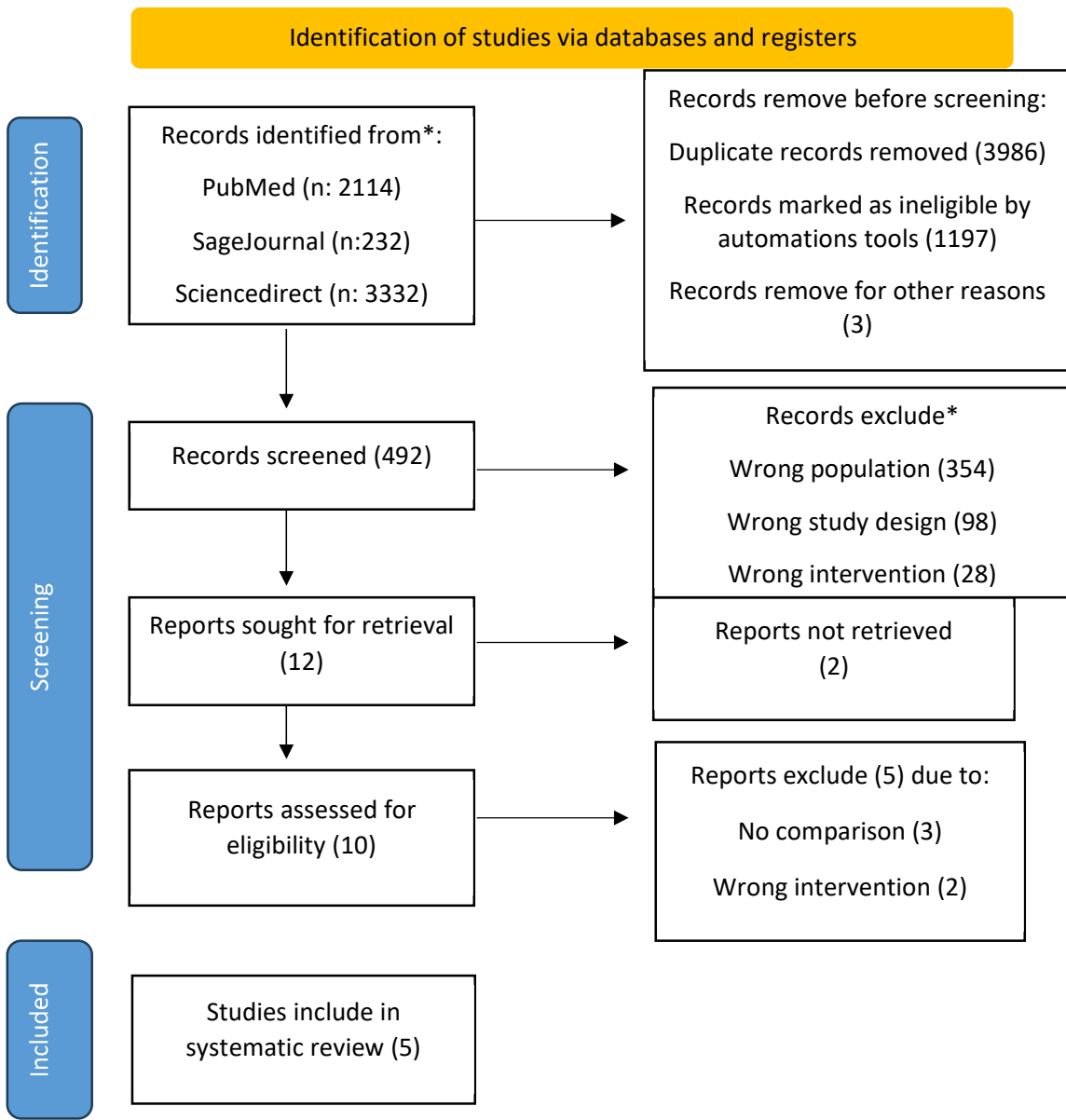

Identification of studies via databases and registers

| Identification | Records identified from*:
PubMed (n: 2114)
SageJournal (n:232)
Sciencedirect (n: 3332) | → | Records remove before screening:
Duplicate records removed (3986)
Records marked as ineligible by automations tools (1197)
Records remove for other reasons (3) |

Records screened (492) → Records exclude*
Wrong population (354)
Wrong study design (98)
Wrong intervention (28)

Reports sought for retrieval (12) → Reports not retrieved (2)

Reports assessed for eligibility (10) → Reports exclude (5) due to:
No comparison (3)
Wrong intervention (2)

Studies include in systematic review (5)

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable

for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

Using reputable resources like Science Direct, PubMed, and SagePub, our research team first gathered 5678 publications. A thorough three-level screening strategy was used to identify only five papers as directly relevant to our ongoing systematic evaluation. Next, a thorough study of the entire text and further examination of these articles were selected. Table 1 compiles the literature that was analyzed for this analysis in order to make it easier to view.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Lecai, J et al., 2023[11]	China	The clinical data of 261 MDR-TB patients treated as outpatients in Shenzhen, China during 2010–2015 were collected and analyzed retrospectively.	261	Of 261 MDR-TB patients receiving ambulatory treatment, 71.1% (186/261) achieved treatment success (cured or completed treatment), 0.4% (1/261) died during treatment, 11.5% (30/261) had treatment failure or relapse, 8.0% (21/261) were lost to follow-up, and 8.8% (23/261) were transferred out. The culture conversion rate at 6 months was 85.0%. Although 91.6% (239/261) of patients experienced at least one adverse event (AE), only 2% of AEs caused permanent discontinuation of one or more drugs. Multivariate analysis showed that previous TB treatment, regimens containing capreomycin and resistance to FQs were associated with poor outcomes, while experiencing three or more AEs was associated with good outcomes.
Panford, V et al., 2022[12]	Ghana	A retrospective, cross-sectional analysis.	159	Out of 159 patients included in the analysis, 86 (54.1%) were declared cured, 28 (17.6%) completed their treatment successfully, 6 (3.8%) were declared treatment failure, 12 (7.5%) were lost to follow-up and 27 (17.0%) died. The overall treatment success rate was 71.7%. Patients who were female (adjusted OR (AOR)=1.27, 95% CI: 1.18 to 1.39, p=0.023), younger (AOR=0.53, 95% CI: 0.19 to 2.11, p=0.012), had a higher level of education (AOR=1.12, 95% CI: 0.65 to 1.90, p=0.034), had a baseline body mass index of 18.5 kg/m^2 or above (AOR=1.57, 95% CI: 1.23 to 2.47, p=0.011) and those who did not have a history of TB (AOR=0.47,

				95% CI: 0.10 to 0.75, p=0.028) were more likely to have successful MDR-TB treatment outcomes.
Soeroto, AY et al., 2021[13]	Indonesia	This was a retrospective cohort study of multidrug-resistant tuberculosis patients treated with longer regimen at Hasan Sadikin General Hospital from January 2015 to December 2017.	492	A total of 492 patients were enrolled during the study period. Fifty percents multidrug-resistant tuberculosis patients had successful treatment outcome. Age ≤45 years, male, normal body mass index, no previous tuberculosis treatment, culture conversion ≤2 months, acid fast bacilli sputum smear ≤+1 were independent factors associated with increased treatment success. Sputum culture conversion ≤2 months was the major factor affecting successful outcome (RR 2.79; 95% CI: 1.61–4.84; p-value<0.001). Human Immunodeficiency Virus infection, chronic kidney disease, and cavitary lesion were independent risk factors for unfavourable outcome.
Sharma, N et al., 2020[14]	India	A retrospective record-based study (2009-2014) was conducted in three major drug resistance TB treatment centres of Delhi.	2958	A total of 2958 MDR-TB patients were identified from the treatment cards, of whom 1749 (59.12%) were males. The mean (±standard deviation) age was 30.56±13.5 years. Favourable treatment outcomes were reported in 1371 (53.28%) patients, but they showed a declining trend during the period of observation. On binomial logistic regression analysis, patients with age ≥35 yr, male sex and undernourishment (body mass index <18.5) at the time of treatment initiation had a significantly increased likelihood of unfavourable MDR-TB treatment outcome (*P*<0.001).
Tembo, BP & Malangu, NG., 2019[15]	South Africa	A retrospective review of medical records of suspected drug resistant tuberculosis patients receiving care at public health facilities in Botswana was conducted from January, 2013 and December, 2014.	2568	A total of 2568 TB patients receiving care at public health facilities in Botswana and meeting the inclusion criteria were enrolled in this retrospective study. These included 917 (35.7%) new TB cases and 1651 (64.3%) of previously treated TB cases. The sample was predominantly male accounting for 1317 (51.3%) while female cases constituted 1159 (45.1%), giving a male/female ratio of 1.14: 1. Most cases were adult

				patients with a mean age of 40.8 years (range 1 to 88 years. Of the cases included in the study, the majority of the patients 1471 (57.3%) resided in urban/peri-urban areas of the country. Overall HIV prevalence in the study population was 55.5%. Overall, multidrug/ rifampicin - resistance among suspected drug resistant tuberculosis patients in Botswana were found in 139 (5.4%) cases with 1.3% among new cases and 7.7% among previously treated tuberculosis patients. Being a previously treated tuberculosis patient and having a positive smear were found to be factors associated with the prevalence of multidrug/rifampicin-resistant tuberculosis ($p < 0.05$). However, age, sex, living in urban area and HIV status were not associated with this disease ($p > 0.05$).

Lecai, J et al., 2023 showed good success rates and early culture conversion were achieved in MDR-TB patients with SLID-based conventional long regimens under a fully ambulatory model during the GFP in Shenzhen. These findings support WHO recommendations that MDR/RR-TB patients should be treated as outpatients. However, we believe that the high success rates with the ambulatory based, conventional regimens in Shenzhen were likely attributable to the high quality of care that integrated sustained access to affordable drugs, well-implemented DOT, ample patient support and active monitoring and proper management of AEs. These aspects should be emphasized when implementing the newer, WHO recommended, all-oral MDR-TB treatment regimens.[11]

Panford, V et al., 2022 showed MDR-TB continues to pose a great threat to the elimination of TB due to the increasing incidence and mortality rate recorded each year worldwide. The main objective of this study was to determine treatment outcomes of MDR-TB and associated factors among patients with TB in the Ashanti Region, Ghana. The findings have demonstrated that favourable treatment outcomes for patients with MDR-TB could be achieved in a resource-limited country. Although the recommended WHO target was not met, the current result (71.7% treatment success rate) is still commendable considering all the challenges associated with TB treatment in Ghana. The study has provided useful information that could inform policy decisions on strategies to improve MDR-TB management in the Ashanti Region and the country as a whole. Although several studies have assessed treatment outcomes of drug-susceptible TB in Ghana, very little has been done in the aspect of MDR-TB. We, therefore, recommend further studies in this area to bridge the dearth of information on MDR-TB treatment outcome and its associated factors in the country.[12]

Soeroto, AY et al., 2021 showed Male, age ≤45 years, normal BMI, sputum culture conversion ≤2 months, AFB smear ≤+1 and no previous TB treatment were factors independently increase treatment succes, with the major factor was sputum culture conversion ≤ 2 months. On the other hand HIV, CKD, and presence of cavitary lesions were risk factors of unfavourable outcome. These factors should always be considered in managing TB-MDR/RR patients with longer regimen.[13]

Sharma, N et al., 2020 showed the treatment outcomes in drug-resistant TB patients may be influenced by the factors affecting their drug adherence including socio-economic status and the presence of adverse drug reactions and these variables need to be accurately recorded. Since undernutrition (low pre-treatment BMI) was found to be a predictor of unfavourable drug-resistant TB treatment outcomes, BMI variable (height and weight) should be correctly recorded in the treatment cards.[14]

Tembo, BP & Malangu, NG., 2019 showed revealed important information on the current prevalence and factors associated with the prevalence of MDR/RR-TB in Botswana. Based on the results obtained, this study has demonstrated low levels of MDR/RR–TB in Botswana. History of previously anti-TB treatment and a positive smear were the only statistically significant factors associated with the prevalence of MDR/RR-TB. Therefore, strategies in controlling MDR/RR-TB should emphasize on effective implementation of DOTS strategy, continuous surveillance of drug

resistance, prevent the development of new cases of MDR/RR-TB and to treat existing patients. Further interventions should focus on strengthening TB infection control activities.[15]

DISCUSSION

The theme of World tuberculosis (TB) day of the year 2022 was - "Invest to end TB. Save lives." This message reflects the utmost importance of fighting against TB, one of the topmost infectious killers in the world. It has been appraised that 997500 incidence TB cases among pediatric folk. Among them, 481000 and 516500 cases were 0-4-years and 5-14-years old, respectively, in 2019. Another study reported a shortfall of comprehensive data on epidemiology and DR-TB portrayal among childhood TB cases. One more investigation revealed that laboratory MDR-TB global prevalence was 3.2% among the pediatric group. The Coronavirus disease (COVID-19) pandemic has reversed the progress achieved by several TB control programs worldwide, and the fight against TB has been set back by several years.[16,17]

MDR-TB is a major threat to global TB control strategies. HIV co-infection MDR-TB did not get key attention until recently in East Africa, where the tuberculosis prevalence and risk factors are highest. MDR-TB, despite being nearly 100% curable, cure rates remain below 100% in practice even in high-income settings, also it is one of the main public health problems that is most-frequently the cause of death among immune suppressed persons. One-third of the world's population is infected with tuberculosis. The presence of the drug-resistant gene in *Mycobacterium tuberculosis* is the major challenge of controlling TB. MDR (resistance to at least both to first-line anti-TB drugs such as isoniazid and rifampicin) TB occurred among 3.6% and 18% of new and previously treated TB cases, respectively (5.6% among all cases). Treatment of MDR-TB requires long time with a combination of second-line anti-TB drugs; most of them are less effective, has a considerable rate of adverse effects, and more expensive than first-line drugs.[18–20]

The emergence of drug-resistant TB, multidrug-resistant TB (MDR TB) and extensively drug-resistant TB poses a significant worldwide threat to the control and treatment of the disease. As defined by the WHO, MDR TB demonstrates resistance to at least both of isoniazid and rifampicin; extensively drug-resistant TB demonstrates additional resistance to any fluoroquinolone and to at least one second-line injectable agent (capreomycin, kanamycin, amikacin). The increasing proportion of resistant cases is contributing to a risk to public health, with significant morbidity and mortality on a global level, and a significant challenge to public health in industrialized countries.[21,22]

Treatment of MDR-TB can take up to two years with drugs that are poorly tolerated and difficult to monitor. Moreover, the treatment outcomes of patients with MDR-TB are generally poor. Several factors have an impact on the outcomes of the treatment given for MDR-TB. Social and financial hardships, including undernutrition, enhance vulnerability to tuberculosis and challenge the process and the outcomes of the treatment given for the disease. Co-morbidities with MDR-TB, including HIV, malignancies, diabetes mellitus and chronic renal failure are risk factors for death among patients with MDR-TB. Moreover, adverse drug reactions from second-line drugs and MDR-TB associated stigma have a negative impact on the outcomes of the treatment given for MDR-TB. Without addressing these factors, the mere provision of free drugs may not directly lead to optimum treatment outcomes of patients treated for the disease.[23–25]

To optimize treatment outcome among DR-TB patients, special attention should be given to patients with MDR-TB, homelessness, substance abuse, as well as miliary and CNS-TB. Admission of these patients to a modern TB centre may be an option to intensify the treatment and monitoring of these high-risk patients. It can also prevent further development of drug resistance and transmission of tuberculosis in the community. The treatment management for these patients should not only focus on medical support but also on social support. Treatment should not only be seen from the perspective of delivery to the patients but should also be seen from a comprehensive care perspective that should consider the patient's ability to take medicine, to make a right life choice, and the treatment should support their circumstances to ensure an adherence to the treatment and an improvement in the quality of life.[26]

CONCLUSION

The success of any national program can only be ascertained by studying the outcomes of treatment regimes in patients with MDR-TB enrolled in different DOTS-plus sites of the country.

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