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Mini Review

Prevalence of Multi-Drug Resistant Tuberculosis in the Dominican Republic: A Systematic Literature Review, 2024

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Abstract

Objective: This systematic review assessed available published data related to the prevalence of multidrug-resistant tuberculosis (MDR-TB) in the Dominican Republic (DR). The prevalence of MDR-TB in the DR is among the highest in the Americas. To better understand the barriers associated with increasing rates of MDR-TB, a focused effort must be made in the identification of the actual rates of MDR-TB present in the DR. As of 2024, there remains much variability in the limited amount of published data regarding the actual rates of MDR-TB in the DR. ***Methods:*** A database search was conducted in Medline via PubMed, Cochrane Library, CINAHL Plus Full Text via EBSCOhost, and Web of Science for manuscripts published through January 2024 using keywords "Multi-Drug-Resistant Tuberculosis" in combination with "Dominican Republic." In addition, Google Scholar was referenced to capture "grey literature." Studies published in English estimating the rate of MDR-TB or extensively resistant TB rates were included. The study protocol was registered at PROSPERO (CRD42024529219). Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies. ***Results:*** Sixteen published papers were eligible for full article review. Four of these met the selection criteria for the final analysis. The reported MDR-TB rates ranged from 5% to 15% for new cases and 30% to 44% for previously treated TB cases. ***Conclusions:*** The wide variations in the prevalence of MDR-TB may be related to varying methods used for rate calculations. Our findings show limited data from the DR on national MDR-TB rates.

Keywords: ***Dominican Republic; multidrug resistant tuberculosis; extensively drug-resistant tuberculosis; prevalence; incidence; cumulative incidence.***

Introduction

The emergence of drug-resistant strains of *Mycobacterium tuberculosis* is a serious public health threat. Multidrug-resistant tuberculosis (MDR-TB) is defined as TB caused by strains of *Mycobacterium tuberculosis* that are resistant at least to isoniazid and rifampicin [1]. MDR-TB spreads through person-to-person transmission and mismanagement of tuberculosis (TB) treatment [1]. Although curable and preventable, treatment of MDR-TB in some countries is becoming more difficult. Often, treatment options are limited, expensive, and have adverse side effects for the patient. Risk factors for increased MDR-TB infection include previously unsuccessful TB treatment, interruption of TB treatment, inappropriate TB treatment regimen and duration, previous TB treatment in a hospital, and living in a region with high TB prevalence [1]. In addition, the costs associated with drug-resistant TB (MDR- and XDR-TB) have been shown in other countries to far outweigh those of drug-responsive TB despite a much lower number of reported cases globally [2,3].

In 2022, WHO reported that worldwide, 3.3% of new TB cases and 17% of previously treated TB cases were MDR/rifampin-resistant (RR)-TB [4]. The 2018 WHO Global report provided extensive data on anti-TB drug resistance, which was systematically collected and analysed from 160 countries [5]. The report included data for 91 nations that have continuous surveillance systems based on routine diagnostic drug susceptibility testing of *Mycobacterium tuberculosis* isolates obtained from all TB patients as well as data for 69 countries that rely on epidemiological surveys of bacterial isolates collected from representative samples of patients [5]. From 2018-2022, the expansion of treatment enrolment for MDR-TB/RR-TB patients was not successful in meeting the global targets set by the United Nations (UN) high-level meeting [4]. The most recent data shows that only 55% of patients diagnosed with MDR-TB are enrolled in treatment protocols, suggesting issues with global underdiagnosis and underreporting [4]. Despite the value of these surveillance data, the actual global burden of MDR and extensively drug resistant (XDR) TB is not clear; large gaps remain for some of the most affected areas.

TB occurs all over the world; however, the Dominican Republic (DR) has among the highest TB and MDR-TB burden in the Americas. Published MDR-TB data from the DR are limited and conflicting. One potential source of these limitations is the high degree of variability in the methods of data collection due to limitations of resources in countries such as the DR. To improve early TB detection, treatment, and policy planning, an accurate estimate of the prevalence of MDR-TB is essential. Thus, we performed a systematic literature review to assess the published rates of MDR-TB in the DR.

Methods

In February 2024, a database search was conducted in Medline via PubMed, Cochrane Library, CINAHL Plus Full Text via EBSCOhost, and Web of Science were searched for relevant articles using variations of the keywords "Tuberculosis or Drug Resistance or Multi-Drug Resistant Tuberculosis or Extensively Drug-Resistant Tuberculosis" in combination with "Dominican Republic or Hispaniola or West Indies." To capture "grey" literature, Google Scholar was also searched with a limitation of the first 100 records. The protocol for this systematic review was registered at PROSPERO (CRD42024529219). A detailed database search strategy is provided in supplementary 1. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA) statement [6]. The initial search of all databases, after deleting duplicates, yielded 875 records. Two independent assessors reviewed the records by title/abstract using the data management software, Rayyan® (Rayyan Systems Inc.) [7], with 16 records meeting the selection criteria for a full-text article review. The investigators examined the full reports regarding the inclusion and exclusion criteria. Of the 16 articles, 4 were accepted for evaluation. The results of the search strategy are indicated by a flowchart in **Figure 1**. In addition, risk of bias assessment was performed using the Joanna Briggs Institute (JBI) tool for prevalence studies (**Table 1**). Two independent assessors (KM and CW) performed the critical appraisal of the studies, with any disagreements being resolved by a third assessor who is an expert in the field (MC).

No filters were used during the search. Briefly, the inclusion criteria included studies published in English and conducted in the DR on estimating the rate of MDR-TB, and studies that reported outcomes as prevalence, incidence, or cumulative incidences for multi- or extensively drug-resistant strains of TB were included for the review. Studies published on data from outside the DR and that did not report on outcomes of prevalence, incidence, or cumulative incidence were excluded.

Figure 1: PRISMA Flow Diagram

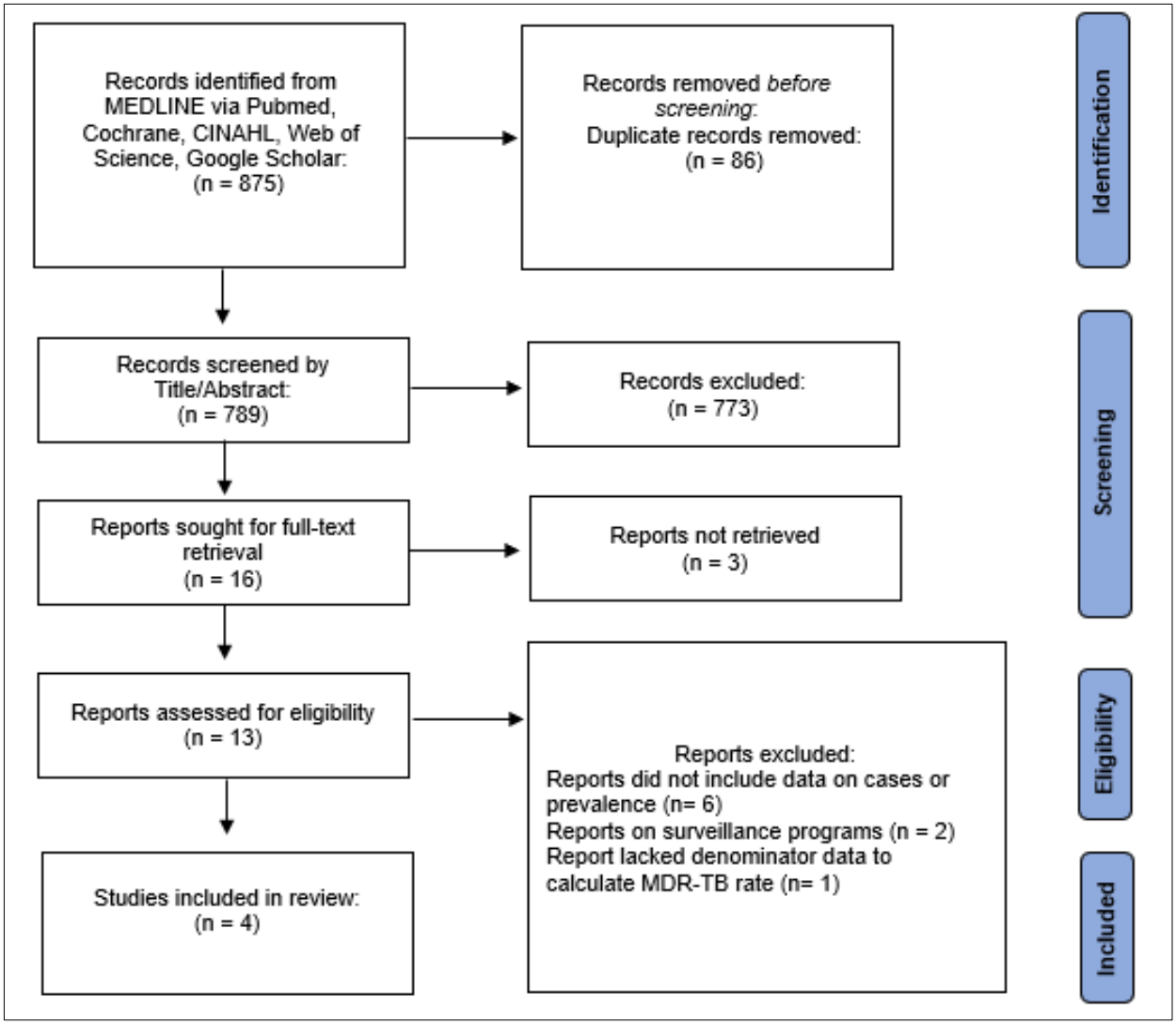

Figure 1: This diagram depicts the systematic process used in implementing the search strategy and article inclusion. The systematic process included identification, screening, and eligibility phases for producing the study results.

Results

For the final analysis, we included four papers published between 1998 and 2016 (**Table 2**). Only one is a national survey [8] to estimate MDR-TB prevalence in the DR. These articles described various methodological approaches, the most common was a retrospective cohort study (n=2) [9,10]. There were also a cross-sectional survey with interviews (n=1) [11], and a multi-step proportional weighted approach (n=1) [8]. Two studies examined MDR-TB across several countries and used a proportionate cluster sampling technique in the DR [10,11]. The samples collected varied in size, ranging from 337 to 420 MDR-TB cases. All four studies reported on previously treated and new cases of MDR-TB and found differing rates. Three papers reported the prevalence rate [8,10,11], and one reported incidence [9].

For critical appraisal of included studies, a risk of bias assessment is presented in Table 1. 2 of the 4 studies reported a retrospective cohort study design; therefore, the assessment of the sampling method as well as the response rate in these studies was reported as not applicable (**Table 1**). All studies identified the sample population adequately and demonstrated consistency in testing and validation of the condition (**Table 1**). Two reports of unclear were noted in the assessment, as subgroup identification within the sample population was not available (**Table 1**).

In 1998, Espinal and colleagues [8] found MDR-TB rates of 15.5% for new cases and 29.9% for previously treated tuberculosis cases. In 2000, Espinal and colleagues [10] reported 5% MDR-TB among new cases and 5% MDR-TB among previously treated tuberculosis cases. They also found that in the DR, 30.3% of new tuberculosis cases were resistant to at least one drug, and, for previously treated tuberculosis cases, 12.6 % were resistant to at least one drug [10]. Pablos-Mendez [11] found 14.9% MDR-TB among new cases in the DR and 29.9% MDR-TB among previously treated TB cases. They also reported that among new cases, 1.3% were resistant to all four drugs and that, among previously treated TB cases, 6% were resistant to all four drugs [11]. In 2016, Mercado [9] reported 44% of MDR-TB among previously treated TB patients in the DR.

Table 1: Joanna Briggs Institute (JBI) tool for critical appraisal of prevalence studies.

	Espinal, 1998 [8]	Pablos-Méndez, 1998 [11]	Espinal, 2000 [10]	Mercado, 2016 [9]
Was the sample frame appropriate to address the target population?	Yes	Yes	Yes	Yes
Were study participants sampled in an appropriate way?	Yes	Yes	NA	NA
Was the sample size adequate?	Yes	Yes	Yes	Yes
Were the study subjects and the setting described in detail?	Yes	Yes	Yes	Yes
Was the data analysis conducted with sufficient coverage of the identified sample?	Yes	Yes	Unclear	Unclear
Were valid methods used for the identification of the condition?	Yes	Yes	Yes	Yes
Was the condition measured in a standard, reliable way for all participants?	Yes	Yes	Yes	Yes
Was there appropriate statistical analysis?	Yes	Yes	Yes	Yes
Was the response rate adequate, and if not, was the low response rate managed appropriately?	Yes	Yes	NA	NA

Table 2: Summary data for included studies reporting MDR-TB rates in the Dominican Republic

Article	Study Design	Sampling Method	Sample Size	MDR-TB Rate Outcome Data
Espinal, 1998 [8]	Nationwide survey	Multi-step proportional weighted sampling	420	New cases: 15.5%; previously treated TB cases: 29.9%
Pablos-Méndez, 1998 [11]	Cross-sectional surveys and surveillance report	Proportionate cluster sampling	303	New cases: 14.9%; previously treated TB cases: 29.9%; Resistance to all 4 drugs was 1.3% among new cases and 6.0% among previously treated TB cases
Espinal, 2000 [10]	Retrospective cohort study	Proportionate cluster sampling	373	Both new and previously treated TB cases: 5%; Resistance to at least 1 drug was 30.3% among new cases and 12.6% among previously treated TB cases
Mercado, 2016 [9]	Retrospective cohort design	Previously treated TB cases records	427	Previously treated TB cases: 44%

Discussion

The review results are based on four peer-reviewed articles published in the English language. Two of these articles were published more than ten years ago. The reported MDR-TB rates ranged from 5% to 15% for new cases and 30% to 44% for previously treated TB cases. The wide variations of prevalence of MDR-TB may be related to varying methods used for data collection and to procedures for monitoring of MDR-TB in the DR. Estimating the burden of disease on a national basis requires systems that are standardized to ensure reliable and valid data. In 2016, the proportion of MDR/RR-TB among TB patients averaged from 4.1% for new cases, to 19% among the retreatment cases on a global level [9]. The proportion of MDR-TB in the DR is higher compared to the global rates, and the rate is rising. The rise of MDR-TB cases in any country indicates a poor national TB control program [12]. MDR-TB is a manmade health problem. It is difficult and expensive to treat an MDR-TB case compared to a TB case, with costs-per-patient estimates in countries such as Peru and Russia ranging from 2434 United States dollars (USD) to 14,657 USD [13]. In addition, the MDR-TB treatment duration is longer, the drugs are more toxic and less effective compared to standard treatment of TB, and only have a success rate of roughly 60% [14]. Prompt identification, timely diagnosis, and appropriate treatment of TB cases are the most important measures to prevent further increases of MDR-TB cases. Accurate data on the national MDR-TB burden are necessary for resource allocation and policy development for MDR-TB prevention, control, and management. These results will be useful for coordinating patient care across various clinical settings, for estimating costs related to diagnosis and treatment, and for estimating additional resources needed for surveillance and patient monitoring. These results may also be utilized as a tool for making

clinical decisions. During our literature review, we noted a lack of reporting and focus on the topic of MDR-TB incidence and prevalence in the DR. There were only a few studies on MDR-TB in the DR, and most of the published manuscripts were based on old data and on a proportionate sampling method as part of multi-national studies. Only one study, conducted in 1998, was based on a national survey.

The allocation of additional resources for estimating the MDR-TB rate based on regional data will be essential for the national response to MDR and XDR-TB problems. Accurate regional and national data are needed, but resources are limited, requiring targeted intervention programs for efficiency. There are logistical and methodological constraints for accurate estimation of MDR-TB cases in the DR [15]. Incidence-based surveillance may underestimate the MDR-TB cases due to transmission. Estimation of the proportion of incident drug-resistant TB cases due to acquired resistance is more difficult to capture because resistance among retreatment cases is due to both acquisition and transmission.

Most resource-limited countries, such as the DR, report MDR-TB rates using estimates of either the incidence or prevalence of drug resistance from a subset of cases in a community. A problem is that the sample may not be randomly chosen from all cases with respect to drug resistance. Further, in many of these countries, there are obstacles and resource limitations for random sampling methods.

On a global scale, roughly 2 out of every 3 persons with drug-resistant TB goes undetected [16]. With the advent of more recent molecular and computational techniques such as Gene Xpert, whole genome sequencing, and Myc-TB, patients with drug-resistant TB can be identified much faster compared to traditional methods of testing. While the implementation of these techniques is not feasible in many areas, they are essential to the development of low-cost assays for MDR-TB detection for dissemination in areas where resources are scare. Since 2016, progress has been made in the capital, Santo Domingo, on identification and diagnosis of MDR-TB by implementing the Gene Xpert-based diagnosis of MDR-TB. It is important that the island county establish a nationwide MDR-TB identification and diagnosis system based on expanding the Gene Xpert-based surveillance or by strengthening national network of properly equipped laboratories with trained personnel and a fully functioning national reference laboratory. These are necessary to ensure access to quality-assured sputum smear microscopy, culture, and drug-susceptibility testing.

Our review included only studies published in the English language in peer-reviewed journals. Any studies published in other languages or not in peer-reviewed journals were not included in this review. We acknowledge this limitation of our study.

Conclusion

Recent MDR-TB data based on national surveillance is needed for accurate estimation of the national MDR-TB burden, and epidemiological studies are recommended for better understanding of the transmission dynamics, risk factors, and interventions strategies for controlling or eliminating MDR-TB from the DR. Among the limited available data on estimating an accurate rate of MDR-TB in the DR, there are varying types of sampling methods which may further impact the visibility of the actual burden of MDR-TB. This has negatively impacted the opportunity to provide cost-effective prevention and treatment strategies to those who need it the most. The results of this systematic review highlight the need for focused effort on improving barriers to accurate data collection and dissemination of appropriate treatment for new and existing MDR-TB cases throughout the DR. Renewed efforts towards improving reporting and estimating rates, along with the utilization of improved molecular technologies have an immense potential to lower the physical, emotional, and economical burden produced by MDR-TB within the DR.

Data Availability

All data has been made available in Figure 1 and Tables 1 and 2. The search strategy utilized for this systematic review is outlined in 'Research Material' file uploaded.

Conflict of Interest

All authors declared no conflict of interest.

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