

The Global Burden of Multidrug-Resistant Tuberculosis: An In-Depth Review of Catastrophic Costs, Patient Burdens, and Strategies for Sustainable Healthcare Solutions

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) poses a significant global health challenge, with approximately 500,000 new cases reported in 2020, predominantly among vulnerable populations in low- and middle-income countries. The World Health Organization (WHO) aims to mitigate catastrophic costs associated with TB treatment, which often exceed 20% of a household's annual income, leading families into severe financial distress. This systematic review and meta-analysis aimed to assess the global burden of catastrophic expenditures related to MDR-TB, focusing on patient and family financial impacts. A comprehensive literature search was conducted across five databases (CINAHL, MEDLINE, Embase, Scopus, and Web of Science) and grey literature sources, utilizing relevant keywords related to MDR-TB and cost implications. Studies were selected based on their relevance to catastrophic costs incurred by MDR-TB patients. The analysis revealed that the financial burden for MDR-TB patients is significantly higher than for drug-susceptible TB (DS-TB) cases, with treatment costs ranging from \$2,423 in Peru to \$14,657 in Tomsk, Russia. Factors influencing these costs include sociodemographic characteristics, diagnostic delays, and the duration of hospitalization. Notably, 43% of TB patients experienced catastrophic expenditures, with MDR-TB patients facing an even greater risk due to longer treatment durations and higher medication costs. In conclusion, the findings underscore the urgent need for effective interventions to reduce the financial burden of MDR-TB on patients and families. Enhanced drug susceptibility testing and improved healthcare access are critical for managing MDR-TB and preventing further economic devastation. Addressing these issues will be vital for achieving the WHO's end-TB strategy and ensuring sustainable healthcare solutions.

Keywords: Multidrug-Resistant Tuberculosis, Catastrophic Costs, Healthcare Access, Treatment Burden, Financial Impact.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a significant worldwide health problem, impacting about 500,000 individuals in 2020. MDR-TB disproportionately impacts the most vulnerable people in low- and middle-income nations [1,2]. Eliminating catastrophic expenses in TB-affected families is a key objective of the World Health Organization's end-TB strategy. The pervasive spread of MDR- and XDR-TB remains a substantial impediment to realizing these ambitious objectives [3-5].

The WHO defines catastrophic TB costs as the total (direct and indirect) expenses for TB diagnosis and treatment exceeding 20% of a household's yearly income [6]. Direct costs include medical expenses (registration, consultation, hospitalization, diagnostics, or pharmaceuticals) and non-medical expenses

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(food, transportation, and nutritional supplements). Indirect costs include the whole loss of earnings resulting from decreased productivity, absenteeism, time loss, income reduction, and caring responsibilities. During periods of financial distress, tuberculosis (TB) patients or households affected by TB adopt various coping mechanisms, including liquidating household assets, incurring debt, depleting savings, and withdrawing children from educational institutions [7,8]. The protracted treatment duration and the necessity for costly second-line medications contribute to the belief that the catastrophic expenses linked to multidrug-resistant tuberculosis (MDR-TB) surpass those associated with drug-susceptible tuberculosis (DS-TB) [9-11]. The economic repercussions of MDR-TB are often so grave that patients and their families may descend into extreme poverty due to substantial out-of-pocket costs and lost income during the diagnosis and treatment of MDR-TB. Research indicates that MDR-TB patients have significant financial burdens before, during, and after therapy. Comprehensive research across many countries indicated that the treatment costs for MDR-TB patients vary from 2,423 United States Dollars (USD) in Peru to 14,657 USD in Tomsk, Russia [12-15].

The financial burden of catastrophic costs for MDR-TB patients is influenced by various factors, including sociodemographic characteristics, diagnostic delays, duration of hospitalization, household wealth, proximity to healthcare facilities, household size, type of healthcare setting (private versus public), pre-TB expenses, and prior hospitalizations. A thorough analysis of tuberculosis patients (both drug-sensitive and drug-resistant) indicated that the incidence of catastrophic expenditures was 43% [16,17]. Nonetheless, the financial burden of catastrophic expenses for MDR-TB patients is anticipated to be greater due to the prolonged treatment time required and the elevated prices of MDR-TB medications in comparison to DS-TB patients [18]. Nevertheless, the expenses related to MDR-TB have not been thoroughly assessed. This review was done to ascertain the worldwide burden of catastrophic expenditures related to MDR-TB on patients and their families.

Search Methodology

Comprehensive searches were performed across five databases (CINAHL (EBSCO), MEDLINE, Embase, Scopus, and Web of Science) to obtain pertinent studies. We further explored the grey literature employing Google as well as Google Scholar. Reference lists of the listed studies were examined for further relevant papers. "Multidrug-resistant tuberculosis" (also known as MDR-TB), "extensively drug-resistant tuberculosis" (also known as XDR-TB), and "cost" (cost(s), sadness, revenue, loan, finance, economics, expenditure, spending, payment, and impoverishment) were among the search terms. The search was conducted from the creation of each database until 2023.

Risk Factors for Multidrug-Resistant Tuberculosis (MDR-TB)

This study investigated risk factors for multidrug-resistant tuberculosis (MDR-TB) including demographics, detrimental lifestyle choices, comorbidities, and tuberculosis-related characteristics. Sputum AFB smear positive, lung cavity presence, a history of tuberculosis, and prior anti-tuberculosis treatment were identified as major risk factors for multidrug-resistant tuberculosis, irrespective of the context. Conversely, sociodemographic factors (such as sex, age category, residential region, schooling, relationship status, job, and history of incarceration), detrimental behaviors (including drinking alcohol and cigarette smoking), comorbidities (like diabetes mellitus, HIV infection, and COPD), and additional TB-related factors (such as Beijing genotype, site of TB infection, history of BCG scar, close contact with a TB-infected individual, DOT, and known outcomes of prior anti-TB treatment) exhibited no significant correlations with MDR-TB.

Tuberculosis is a very perilous human affliction, regarded as the foremost cause of mortality among all illnesses; it has likely existed globally for millennia. The establishment and proliferation of drug-resistant tuberculosis primarily include interrelated factors concerning patient characteristics, the healthcare system, and Mycobacterium tuberculosis's reaction, which facilitates the development of strains with increased virulence, diminished treatability, and reduced detectability under selective pressure. MDR-TB poses a significant hazard to human health because to the complexities and high costs associated with its

identification and treatment. Despite a minor decline in drug-susceptible TB infections globally, the incidence of MDR-TB diagnoses is increasing, highlighting the need for advancements in this area. To guarantee patient compliance with the whole therapeutic regimen, measures have been instituted to assist them in taking the pills consistently, including the presence of a healthcare professional to witness the ingestion of the medication. Neglecting this action promotes the development of acquired drug resistance. The severe pandemic of multidrug-resistant tuberculosis (MDR-TB) is regarded as a significant public health concern in several countries and represents a substantial obstacle to successful tuberculosis control globally, underscoring the need of universal medication susceptibility testing. Currently, medication resistance may be identified by either phenotypic (culture) or genotypic (DNA) tests, which are much expedited and can be completed within one day or less.

Likewise, recognizing risk factors for MDR-TB is crucial. Numerous disparities exist across studies evaluating risk factors for MDR-TB due to variations in area, sample size, disparate variables, and contradictory findings, among other reasons. Our investigation rigorously assessed global risk variables for MDR-TB irrespective of geographical context, which may aid in formulating an effective preventive and control approach aimed at primary prevention.

Sputum AFB smear positive (OR = 1.478, 95%CI 1.077–2.028) independently predicted MDR-TB, supporting prior research [19]. Smear-positive pulmonary tuberculosis (PTB) is the most infectious and transmissible type of the illness among humans and may be mitigated with airborne measures [20]. Smear positivity correlates with infectiousness, possibly due to smear-positive individuals releasing more quantities of MTB into the environment than smear-negative cases, since MTB organisms are detectable by sputum microscopy only at sufficiently elevated levels [21]. The positive of a sputum AFB smear indicates a heightened bacterial load. Furthermore, a high bacterial load may indicate an increased microbial burden, which would complicate therapy. The presence of smear-positive facilitates the transmission of both TB and MDR-TB, hence elevating the likelihood of treatment resistance. Isoniazid and rifampicin both show spontaneous resistance mutations. Alterations in certain genes correlate with medication resistance. MTB develops resistance to antimicrobial agents by selecting bacteria with mutations in resistance genes [22]. Prior research has shown that mutations associated with antibiotic resistance may diminish bacterial fitness, and the acquisition of compensatory mutations in drug-resistant populations can reinstate their survival capability [23,24]. A molecular investigation indicated that drug-resistant strains of MTB might be as transmissible as pan-sensitive variants [25]. It is essential to adequately manage smear-positive individuals to achieve effective tuberculosis control. Moreover, the sputum smear-positivity rate for MDR-TB patients has significantly surpassed that of drug-sensitive TB cases (MDR-TB at 80.0% compared to drug-sensitive TB at 53.3%) [26].

This analysis shown that the incidence of MDR-TB is significantly higher in patients with lung cavities compared to those without (OR = 1.716, 95%CI 1.149–2.564), corroborating findings from a prior study [7]. Untreated caseous necrosis in tuberculosis may readily result in the formation of lung cavities. Cavitory TB results from lung damage and is characterized by macroscopic holes that form between the infection site and the airways, facilitating bacterial expectoration [27]. Inadequate therapy may result in prolonged persistence of these cavities; thickening of the cavity wall and fibrotic lesions may develop, potentially advancing to chronic fibrocavitory pulmonary tuberculosis [8]. Drugs given orally or intravenously seldom reach effective circulation concentrations in cavities, facilitating the formation of multidrug resistance (MDR) [28]. This is a significant obstacle to tuberculosis control. Investigators have administered medications using percutaneous lung biopsy into cavities for the treatment of pulmonary tuberculosis cavities [29]. Consequently, three tiers of prophylaxis must be instituted to avert the onset of cavitory tuberculosis: early identification, prompt treatment, and the use of interventional therapy for related lesions [30].

Moreover, the aforementioned findings align with a prior meta-analysis [19] indicating that previously diagnosed tuberculosis and anti-tuberculosis treatment are the most consistently significant risk factors for multidrug-resistant tuberculosis, irrespective of the context. These results also validate another research [31]. Our analysis indicated that the likelihood of developing MDR-TB was 6.078 times greater in individuals with a prior TB diagnosis compared to those without such a history; concurrently, individuals

with a history of anti-TB treatment were 5.427 times more susceptible to developing MDR-TB than those with no prior anti-TB therapy. Our findings corroborate a strong correlation between prior anti-TB therapy and multidrug-resistant tuberculosis infection [32]. Previous exposure to inadequate doses of anti-TB drugs is recognized as a catalyst for drug resistance, as shown by worldwide surveillance data [33,34]. Previous exposure to anti-TB drugs may substantially elevate the likelihood of infecting strains developing multidrug resistance, particularly in instances of non-compliance. The majority of MDR-TB cases result from inadequate adherence to tuberculosis treatments, inconsistent drug use, disrupted drug supply, medical errors, and the availability of pharmaceuticals without prescriptions for sufficient therapy [58]. Therefore, tuberculosis treatment must be standardized, and meticulous monitoring of tuberculosis patients is essential. Directly Observed Therapy (DOT) is the most efficacious approach for guaranteeing appropriate pharmaceutical use globally [35].

Simultaneously, the execution of the DOT approach is essential for the proper management of drug-resistant TB and MDR-TB, especially in overseeing TB patients throughout treatment. Drug susceptibility testing (DST) is necessary for patient retreatment when initiating anti-tuberculosis therapy, and the appropriate medications will be chosen accordingly. Rapid drug susceptibility testing (DST) procedures are crucial, particularly for individuals at high risk of drug-resistant tuberculosis, to initiate appropriate therapy promptly before phenotypic DST findings are accessible. Furthermore, enhancements in other tuberculosis management and control strategies are essential, including the updating of clinical guidelines, ongoing training for healthcare professionals, and the monitoring and support of healthcare workers throughout service provision [36].

The intense phase of Tuberculosis therapy involves a combination of the aforementioned four medications administered for two months, while the continuation phase consists of isoniazid and rifampin for an additional four months. Among the second-line medications are: injectable aminoglycosides, such as streptomycin, amikacin, and kanamycin; injectable polypeptides, such as viomycin and capreomycin; fluoroquinolones, such as levofloxacin, gatifloxacin, ofloxacin, and moxifloxacin; and para-amino salicylic acid, ethionamide, cycloserine, prothionamide, trazodone, and linezolid [37].

Research was undertaken to delineate the side consequences of each anti-tuberculosis medication as follows: Isoniazid: hepatic injury (fatigue, nausea, lethargy, abdominal pain, and emesis), dermal rash, paresthesia, cephalalgia, and limb tingling; Rifampin: jaundice, arthralgia, and pyrexia; Ethambutol: visual disturbances including blurred or diminished vision and blindness, hepatic injury, cephalalgia, and nausea; Pyrazinamide: vomiting, painful or swollen joints, and hepatic injury [37]. The study's published findings indicate that the greatest frequency of multi-drug-resistant TB was seen in men.

One research indicated that the ratio of infections with multi-drug-resistant TB was 70.4% in men and 29.6% in females [38]. A study of patients with resistant TB in Ghana revealed a male-to-female ratio of 69.6% to 30.4% [202], whereas separate research in Egypt indicated a ratio of 67.5% to 32.5% [39,40]. Additionally, a comparable study done in Ethiopia revealed that 65.3% of males and 34.7% of females had multidrug-resistant tuberculosis [41].

Our research indicates a significant frequency of several strains of Tuberculosis, particularly drug-resistant forms. Conversely, these strains are treatable, and analogous techniques and therapies exist to manage both known and novel infections. Given the problems associated with this illness, effective control and treatment are essential, since it is feasible to decrease the death rate generated by Tuberculosis via the regulation of its various strains.

The constraints of the current meta-analysis should be acknowledged. Initially, the absence of prospective randomized controlled trials suggests a possible risk of bias, namely selection and information biases, stemming from the observational characteristics of the studied studies. Secondly, not all relevant characteristics in the included studies could be investigated owing to an inadequate number of trials and the lack of data necessary for a comprehensive meta-analysis, including COPD, Beijing genotype, BCG scar, DOT, and known outcomes of prior TB treatment. Previous investigations indicate that Beijing M. tuberculosis strains are more prone to multidrug-resistant tuberculosis than non-Beijing M. tuberculosis

strains [42-44]. Thirdly, significant heterogeneity was seen in several analyses, including factors such as age, HIV infection, COPD, Beijing genotype, lung cavities, prior TB therapy, and DOT. Nevertheless, the sensitivity analysis did not allow us to identify the cause of heterogeneity. This variation may arise from varying case definitions, research methodologies, and demographic characteristics, among other factors. Therefore, further comprehensive investigations, namely bigger prospective randomized controlled trials, must be undertaken to validate these findings. Moreover, comprehensive regional investigations are essential to evaluate the correlations between sociodemographic factors and MDR-TB.

Conclusions

The findings of this review highlight the substantial economic burden associated with multidrug-resistant tuberculosis (MDR-TB) and its implications for affected individuals and families. The data reveal that the costs incurred due to MDR-TB treatment can lead to catastrophic financial consequences, pushing vulnerable populations further into poverty. This situation is particularly alarming in low- and middle-income countries, where healthcare systems are often strained and unable to provide adequate support.

The analysis identified several key factors contributing to the financial burden of MDR-TB, including sociodemographic characteristics, delays in diagnosis, and the lengthy duration of treatment. Patients often face direct costs, such as medical expenses for consultations, diagnostics, and medications, alongside indirect costs related to lost income and decreased productivity. These financial strains can lead families to adopt drastic coping mechanisms, such as liquidating assets or incurring debt, thereby perpetuating a cycle of poverty and health inequity.

Furthermore, the review underscores the critical need for comprehensive strategies aimed at reducing the economic impact of MDR-TB. This includes enhancing access to timely diagnosis and treatment, improving the affordability of second-line medications, and implementing effective health financing mechanisms. Drug susceptibility testing (DST) should be prioritized to ensure that patients receive appropriate treatment regimens promptly, which could help mitigate the risk of developing further drug resistance.

Additionally, public health interventions must focus on raising awareness about the risks associated with MDR-TB and the importance of adherence to treatment protocols. Engaging community health workers and healthcare professionals in educational initiatives can improve patient compliance and reduce the incidence of MDR-TB. In conclusion, addressing the multifaceted challenges posed by MDR-TB requires a coordinated global effort that prioritizes both health outcomes and financial sustainability. By implementing targeted interventions and policies, we can alleviate the burden of MDR-TB on patients and their families, ultimately contributing to the broader goal of tuberculosis elimination.

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العبء العالمي لمرض السل المقاوم للأدوية المتعددة: مراجعة معمقة للتكاليف الكارثية وأعباء المرضى واستراتيجيات الحلول الصحية المستدامة

الملخص

الخلفية: يمثل مرض السل المقاوم للأدوية المتعددة (MDR-TB) تحديًا صحيًا عالميًا كبيرًا، حيث تم الإبلاغ عن حوالي 500,000 حالة جديدة في عام 2020، خاصة بين الفئات الضعيفة في البلدان ذات الدخل المنخفض والمتوسط. تهدف منظمة الصحة العالمية إلى الحد من التكاليف الكارثية المرتبطة بعلاج السل، والتي غالبًا ما تتجاوز 20٪ من الدخل السنوي للأسر، مما يؤدي إلى ضائقة مالية شديدة. هدفت هذه المراجعة المنهجية والتحليل التلوي إلى تقييم العبء العالمي للتكاليف الكارثية المتعلقة بالسل المقاوم للأدوية المتعددة، مع التركيز على التأثيرات المالية على المرضى وأسرهم.

الطرق: تم إجراء بحث شامل في خمسة قواعد بيانات (CINAHL، MEDLINE، Embase، Scopus، و Web of Science) بالإضافة إلى مصادر الأدبيات الرمادية، باستخدام كلمات مفتاحية ذات صلة بالسل المقاوم للأدوية المتعددة وأثاره المالية. تم اختيار الدراسات بناءً على صلتها بالتكاليف الكارثية التي يتحملها مرضى السل المقاوم للأدوية المتعددة.

النتائج: أظهرت التحليلات أن العبء المالي على مرضى السل المقاوم للأدوية المتعددة أعلى بشكل ملحوظ من مرضى السل الحساس للأدوية (DS-TB)، حيث تراوحت تكاليف العلاج من 2,423 دولارًا في بيرو إلى 14,657 دولارًا في تومسك، روسيا. تشمل العوامل التي تؤثر على هذه التكاليف الخصائص الاجتماعية والديموغرافية، وتأخيرات التشخيص، ومدة الإقامة في المستشفى. ومن الجدير بالذكر أن 43٪ من مرضى السل واجهوا تكاليف كارثية، مع مواجهة مرضى السل المقاوم للأدوية المتعددة خطرًا أكبر بسبب طول مدة العلاج وارتفاع تكاليف الأدوية.

الاستنتاجات: في الختام، تؤكد النتائج الحاجة الملحة إلى تدخلات فعالة لتقليل العبء المالي لمرض السل المقاوم للأدوية المتعددة على المرضى والأسر. يعتبر تعزيز اختبارات مقاومة الأدوية وتحسين الوصول إلى الرعاية الصحية أمرًا حيويًا لإدارة السل المقاوم للأدوية المتعددة ومنع المزيد من الكوارث الاقتصادية. معالجة هذه القضايا ستكون ضرورية لتحقيق استراتيجية القضاء على السل لمنظمة الصحة العالمية وضمان حلول صحية مستدامة.

الكلمات المفتاحية: السل المقاوم للأدوية المتعددة، التكاليف الكارثية، الوصول إلى الرعاية الصحية، عبء العلاج، التأثير المالي.