ORIGINAL ARTICLE

Drug-resistant tuberculosis in Malaysia: Prevalence, characteristics, and treatment outcomes

Mohd Fahmin Kamarul Zaman, MPH[1], Mohd Yusof Sidek, MCommMed (Occupational Health)[1], Nik Rosmawati Nik Husain, PhD[1], Zamzurina Abu Bakar, Fellowship of Respiratory Medicine (Malaysia)[2]

[1]Department of Community Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [2]Institute of Respiratory Medicine, Kuala Lumpur, Malaysia

ABSTRACT

Introduction: Drug-resistant tuberculosis (DR-TB) poses a serious global health threat, leading to high morbidity and mortality rates. Malaysia has witnessed an increase in DR-TB cases, necessitating research into trends and characteristics. This study aims to determine the prevalence and describe the characteristics and treatment outcomes of DR-TB cases in Malaysia from 2016 to 2020.

Materials and Methods: A retrospective record review was carried out, utilising secondary data obtained from the TB registry of Selangor and Wilayah Persekutuan Kuala Lumpur. All registered DR-TB cases between 2016 and 2020 that met the study criteria were analysed descriptively using SPSS software version 27.

Results: Of 443 cases of registered DR-TB over 5 years, 430 cases fulfilled the study criteria. The prevalence of DR-TB increased from 0.27 to 1.79 per 100,000 population between 2016 and 2020. The average age was 40.96 years, majority were males (70.7%), Malaysian (79.3%), with Malays comprising 50.2%. Most patients had up to secondary school education (51.9%), married (57.0%), employed (53.3%) and 34.9% were smokers. For clinical characteristics, 23.5% had diabetes, and 10.9% were HIV-positive. Retreatment cases accounted for half the total, and 83.9% had positive smear results. Minimal chest X-ray lesions were observed in 54.4% of cases. The majority (66.7%) received supervised treatment from healthcare providers after being diagnosed with DR-TB, and 37.4% had more than one anti-TB resistance. Favourable treatment outcomes were observed in 56.7% of cases, while 42.1% had unfavourable outcomes, mainly due to loss to follow-up (49.7%), death (42.6%) and treatment failure (7.7%).

Conclusion: The rising cases of DR-TB call for comprehensive public health interventions and stakeholder commitment to reduce its occurrence and transmission. These findings provide valuable guidance for policymakers in strengthening DR-TB control and prevention strategies.

KEYWORDS:
Tuberculosis, drug-resistant, prevalence, outcomes, Malaysia

INTRODUCTION

Malaysia is an intermediate tuberculosis (TB) burden country, with a TB notification rate ranging from 10 to 99 cases per 100,000 population.[1] The Ministry of Health (MOH) Malaysia developed the National Strategic Plan for Tuberculosis Control (2016–2020) to support the goal of eliminating TB by 2035, aligned with the WHO End TB Strategy. However, the rise of drug-resistant tuberculosis (DR-TB) has become a significant challenge despite the disease being treatable and preventable. According to WHO Consolidated Guidelines on TB, DR-TB is defined as TB disease caused by Mycobacterium tuberculosis (MTB) strains that are resistant to standard TB medications.[2] Mutations in MTB led to the development of resistance, causing specific treatments or medications to lose their effectiveness against the pathogen.[3] The current categorisation of DR-TB introduced by WHO in 2021 includes isoniazid-resistant tuberculosis (HR-TB), rifampicin-resistant tuberculosis (RR-TB), multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), along with the addition of pre-extensively drug-resistant tuberculosis (pre-XDR TB).[4–5] Compared to the previous classification, where all categories are not mutually exclusive, the current system now includes HR-TB and introduces the new category of pre-XDR TB.[6,7] Globally, almost half a million people developed RR-TB, of which 78% progressed to MDR-TB, with countries like India, China and the Russian Federation bearing significant burdens.[8,9] The Global Burden of Disease study from 2017 indicates that the incidence of MDR-TB showed a significant upward trend worldwide between 1990 and 1999, with the overall age-standardised incidence rate (ASIR) increasing at an average annual rate of 17.63%.[10] However, research and published data on MDR-TB in Malaysia are scarce. The Malaysian Ministry of Health reported 192 cases of DR-TB in 2019.[11]

Treating patients with DR-TB is more complex, costly and time-consuming than patients with susceptible TB strains. Additionally, DR-TB commonly has toxicity and adverse effects from the anti-TB regimen instituted.[12] Inappropriate treatment regimes, poor quality of drugs, concomitant medical diseases and non-adherence to medications are significant determinants of drug resistance, leading to high mortality rates and substantial financial consequences.

This article was accepted: 08 September 2024
Corresponding Author: Mohd Yusof Sidek
Email: dryusofs@usm.my

Therefore, Malaysia has outlined several strategic interventions to combat DR-TB effectively. Among these, Strategy 4 focusses on strengthening the programmatic management of DR-TB. This strategy aims to enhance early detection, improve patient management, update national guidelines and ensure the availability of resources and training. Key activities under Strategy 4 include the implementation of rapid diagnostic tools, mandatory notifications and comprehensive guidelines for patient management and surveillance.[1] Despite these proactive strategies, there remains a significant gap in assessing the actual burden of the disease. A lack of understanding of the characteristics and insights into the DR-TB burden could exacerbate the DR-TB crisis, leading to increased mortality and economic strain on both the healthcare system and affected individuals. Therefore, this study aims to assess the burden and describe the characteristics of DR-TB patients in Malaysia for 5 years. The findings would contribute to formulating targeted interventions and refining strategies to combat the challenges associated with DR-TB.

MATERIALS AND METHODS

Study Setting and Participants Selection

A cross-sectional study was conducted from December 2022 to May 2023 using secondary data from the Ministry of Health Malaysia's (MOH) National Tuberculosis Registry (NTBR). The study included DR-TB cases registered in NTBR and residing in Selangor and Wilayah Persekutuan Kuala Lumpur (WPKL), Malaysia. To ensure the accuracy of data analysis for DR-TB treatment outcome, cases with missing or incomplete data exceeding 30%, change of diagnosis, or transfer out of the study area were excluded. According to the notification and reporting of DR-TB cases by the MOH, DR-TB is classified based on drug sensitivity testing (DST) in clinical isolates confirmed as MTB. There are five types: isoniazid-resistant tuberculosis (HR-TB) entails resistance to isoniazid alone, with confirmed rifampicin susceptibility in vitro; MDR-TB manifests as resistance to at least both isoniazid and rifampicin; Pre-XDR-TB encompasses MDR/RR-TB and resistance to any fluoroquinolone; extensively drug-resistant tuberculosis (XDR-TB) includes MDR/RR-TB and resistance to any fluoroquinolone plus at least one additional Group A drug; rifampicin-resistant tuberculosis (RR-TB) indicates rifampicin resistance using phenotypic or genotypic methods, potentially with other anti-TB drug resistance, encompassing monoresistant, polyresistant, MDR or XDR. In previous years, the definition of DR-TB included categories such as monodrug and polydrug resistance, which were not mutually exclusive and primarily focused on resistance to the first-line drugs isoniazid and rifampicin, classifying cases as MDR-TB. However, in this current study, we adopted the updated classification from the WHO Global TB Report 2021, which streamlines DR-TB into five distinct categories as previously mentioned, including the updated definition of XDR-TB and the introduction of pre-XDR-TB.

Sample size determination and sampling method

The sample size was calculated using a single proportion formula with a web sample size calculator (https://wnariffin.github), considering an 80% power of the study and 5% type I error rate. The proportion of MDR-TB in Sabah, Malaysia, was used as a reference (0.003), along with a precision of 0.0015. Additionally, 10% of the potential for missing or incomplete data was considered. Since the population of Selangor is approximately 7 million, and WPKL is around 2 million, the estimated sample size was deemed acceptable. Meanwhile, the two independent proportions formula was used to calculate the sample size of DR-TB cases to be included when assessing for characteristics and treatment outcomes. A total of 444 cases were needed. Therefore, no sampling was conducted due to the limited number of cases, and all 430 DR-TB cases registered in the NTBR of Selangor and WPKL from January 2016 to December 2020, that met the study criteria were included in the analysis.

Data collection

Data were collected from two primary sources: the NTBR and the line listing of DR-TB cases. NTBR is a centralised electronic TB information system used by healthcare professionals at various levels of the healthcare system in Malaysia. It contains comprehensive details on TB cases and contacts, including sociodemographic, clinical, laboratory, treatment and follow-up information. The line listing of DR-TB cases is a data comparison to the registered cases in NTBR and includes data from the TB Information System (TBIS) 10G and DRTBIS 50A-1. TBIS 10G provides information on TB cases that have failed first-line treatment and contributing factors, while DRTBIS 50A-1 is used for the registration of all DR-TB cases, regardless of whether treatment has been initiated.

Data extraction was guided by a proforma checklist, focusing on sociodemographic characteristics, social history (smoking history), clinical characteristics and treatment outcomes. Sociodemographic features included age, sex, nationality, ethnicity, level of education, marital status and employment status. Clinical aspects covered comorbidities (diabetes mellitus and HIV), the treatment category, either new or retreatment, smear positivity, chest x-ray results, directly observed treatments (DOTS) supervision and the category of DR-TB. Treatment outcomes are either cured, completed, failed, death, loss to follow-up, not evaluated and treatment success. Population density data for Selangor and Wilayah Persekutuan Kuala Lumpur were obtained from the Department of Statistics Malaysia's (DOSM) website to calculate the prevalence of DR-TB.

Statistical Analysis

IBM SPSS version 27 was used for data entry and analysis. The data was cleaned once it was entered. A preliminary data description was performed to discover any missing values. The data set was reviewed for inaccuracies and corrected as necessary. To calculate the prevalence of DR-TB, the below formula was used, and the results are expressed over 100,000 population.

$$\text{Prevalence} = \frac{\text{Total number of DR-TB cases in Selangor and WPKL in a given year}}{\text{Total population in Selangor and WPKL in a given year}} \times 100{,}000$$

A descriptive analysis was conducted on the patients' characteristics and treatment outcomes. Categorical data is expressed as frequency and percentage, while normally distributed numerical data is expressed as mean and standard deviation (SD). Treatment outcomes were categorised into unfavourable or favourable outcomes. Favourable treatment outcomes include cases categorised as cured and treatment completed. Unfavourable outcomes encompass cases designated as treatment failure, death, and loss to follow-up.[6]

RESULTS

Prevalence rate of DR-TB cases

During a 5-year period from 2016 to 2020, 443 cases of DR-TB were notified and registered for the first time in the NTBR database for Selangor and WPKL. After excluding 13 cases due to missing data, diagnostic changes or transfer out of the study area, 430 cases met the study criteria. The yearly number and calculated prevalence rate of DR-TB cases in Selangor and WPKL from 2016 to 2020 are shown in Table I. Over 5 years, there was a gradual increase in the number of DR-TB patients. The prevalence rate of DR-TB shows a steady rise, climbing from 0.27 in 2016 to 1.79 in 2020.

DR-TB treatment outcomes

Within this group, there were 244 cases with favourable treatment outcomes, 181 with unfavourable outcomes, and five with ongoing treatment, constituting 56.7%, 42.1% and 1.2% of the total, respectively. Figure 1 depicts that among the 181 cases of unfavourable treatment outcomes in DR-TB patients, the majority were due to loss to follow-up (49.7%), followed by death (42.6%), and a smaller proportion resulted from treatment failure (7.7%).

Characteristics of DR-TB cases

For sociodemographic characteristics, the ages of individuals diagnosed with DR-TB ranged from 26 to 56 years old, with a mean of 40.96 (SD = 15.04) years. Meanwhile, the bulk of the cases were males, with 304 cases (70.7%), while Malaysians predominated with 341 cases (79.3%), with 216 cases (50.2%) being Malays. Furthermore, the majority of the patients had education up to secondary school (51.9%), married (57.0%) and employed (53.3%), as presented in Table II. Smokers constitute one-third of total DR-TB cases (34.9%).

Meanwhile, for clinical characteristics, among patients with DR-TB, 23.5% had diabetes, and 10.9% were HIV-positive. The treatment category almost equally represented new cases and retreatment cases. These findings also imply that the majority of DR-TB patients (83.9%) showed positive smear results, while 15.6% were negative and a small percentage (0.5%) did not undergo smear testing, potentially influencing their treatment outcomes. Regarding chest x-ray results, most DR-TB patients (54.4%) had minimal lesions, 41.2% showed moderate to far advanced lesions and 4.4% had no lesions. Among DR-TB cases, the majority were MDR/Pre-XDR/XDR-TB, followed by HR-TB and RR-TB. DOT supervision from healthcare workers was received in two-thirds of the cases (66.7%) after being diagnosed as DR-TB. Family members also played a significant role in providing supervision but to a lesser extent. A small number of patients received no monitoring or supervision other than the two categories mentioned. Further details on the clinical characteristics of DR-TB cases are summarised in Table III.

DISCUSSION

Individuals from marginalised communities are disproportionately affected by DR-TB.[13] They often face challenges such as adverse drug reactions, high treatment costs, social stigma and discrimination. These factors, along with clinical considerations, significantly impact treatment outcomes. Addressing this issue is crucial, given the global concern about the low rate of favourable outcomes in DR-TB cases. Therefore, this study was designed to determine the prevalence rate and to describe the sociodemographic and clinical characteristics of DR-TB cases, providing valuable insights for our national TB policy-making efforts.

Prevalence of DR-TB

The current study, based on data from the NTBR, revealed an increase in the prevalence of DR-TB cases in Selangor and WPKL, ranging from 0.27 to 1.79 per 100,000 population. Selangor, with a population of 6.9 million, is the state with the greatest Malaysian population composition, at 21.6% in 2020, and has a population density of 880 people per square kilometre. In comparison, WPKL, with a population of 1.9 million, has the highest population density in Malaysia, with 8,045 people per square kilometre.[14] The low number of cases observed during the initial 2-year period of the study could have led to an underestimated prevalence rate in these two states, attributed to the low number of DR-TB cases being notified and registered in the NTBR database during that time. International studies reported the DR-TB prevalence within the range of 3–5%. For instance, Amin et al.[15] reported a prevalence of 3.8% in Ethiopia, while Al Ammari et al.[16] and Sambas et al.[17] reported rates of 4.4% and 5.0%, respectively, both from Saudi Arabia. Additionally, from 2010 to 2012, the prevalence of DR-TB at one hospital in Bangkok, Thailand, was found to be 2.6%.[18] Locally, Goroh et al.[19] found that MDR-TB prevalence was 0.3% of TB cases. The study used a retrospective record review of 33,193 TB cases from the NTBR database reported in Sabah, Malaysia, between 2012 and 2018.

The observed rise in reported DR-TB cases after 2018 may reflect changes in reporting criteria rather than a true increase in incidence. Reporting is based on administrative instructions from the Disease Control Division rather than being mandated by law, so the reported numbers may not accurately represent the actual number of cases. Initially, the 2013 instructions required reporting only MDR-TB and XDR-TB. These criteria were expanded in 2018 to include more detailed reporting for MDR and XDR-TB and were further refined in 2020 to include HR-TB.[11] Improved notifications and documentation practices via state line listing and regular updates between district health offices and treatment centres ensure accurate surveillance. The national TB surveillance system, reinforced by the NTBR electronic TB information system introduced in 2012, supports this enhanced monitoring. Additionally, better programmatic management of DR-TB, as outlined in the National Strategic Plan's fourth

Table I: Prevalence of DR-TB cases in Selangor and WPKL from 2016 to 2020

Year	No. of population	No. of DR-TB cases	Prevalence of DR-TB* (95% CI)
2016	8,060,000	22	0.27 (0.19, 0.45)
2017	8,170,000	44	0.54 (0.39, 0.74)
2018	8,270,000	101	1.22 (0.99, 1.49)
2019	8,290,000	115	1.39 (1.18, 1.72)
2020	8,290,000	148	1.79 (1.55, 2.14)

*Prevalence over 100,000 population

Table II: Sociodemographic characteristics of DR-TB cases in Selangor and WPKL from 2016 to 2020 (n = 430)

Variables	Mean (SD)	Frequency (%)
Age* (years)	40.96 (15.04)	
Sex		
Female		126 (29.3)
Male		304 (70.7)
Citizenship		
Malaysian		341 (79.3)
Non-Malaysiana		89 (20.7)
Races		
Malay		216 (50.2)
Chinese		61 (14.2)
Indian		51 (11.9)
Others		102 (23.7)
Level of education		
No formal education		93 (21.6)
Primary		35 (8.1)
Secondary		223 (51.9)
Tertiary		79 (18.4)
Marital status		
Single		157 (36.5)
Married		245 (57.0)
Divorcee		28 (6.5)
Employment status		
Unemployed		201 (46.7)
Employed		229 (53.3)
Smoking status		
No		280 (65.1)
Yes		150 (34.9)

*Mean (SD)
[a]Indigenous peoples, Bumiputera Sabah and Sarawak, Non-Malaysian

strategy, has further contributed to improved detection and reporting of cases.

The rising trend of DR-TB in Malaysia is partly due to advancements in laboratory testing. GeneXpert testing, introduced in 2009, has revolutionised TB diagnostics with its Xpert MTB/RIF assay, which provides results in under 2 hours with high sensitivity (91% for culture-positive cases and 95.1% for rifampicin resistance).[20] Although GeneXpert testing has improved DR-TB detection, expanding its coverage is essential, as a significant portion of cases were not tested by culture, and culture positivity was low (26% among pulmonary cases).[19] Furthermore, in high HIV and TB prevalence settings, this testing has significantly enhanced the detection of active pulmonary TB, particularly among HIV-infected high-risk individuals.[21]

Treatment outcomes of DR-TB cases

This study found that 56.7% of DR-TB cases ended up with favourable treatment outcomes. Meanwhile, of the 181 cases of unfavourable treatment outcomes among DR-TB patients, the majority was attributed to loss to follow-up (49.7%), followed by death (42.6%), with a smaller proportion resulting from treatment failure (7.7%). In another study conducted in Vietnam by Wrohan et al.[22], among the 211 cases that experienced unfavourable treatment outcomes, loss to follow-up was also the most prevalent at 50.7%, followed by treatment failure at 25.6% and death at 23.7%. The observation that loss to follow-up has the highest percentage among unfavourable treatment outcomes in this study raises several critical considerations. Loss to follow-up might reflect challenges related to treatment adherence.[23]

Factors such as socioeconomic status, access to healthcare, patient education and support systems could contribute to individuals discontinuing their treatment prematurely.[7]

Table III: Clinical characteristics of DR-TB cases in Selangor and WPKL from 2016 to 2020 (n = 430)

Variables	n (%)
Diabetes mellitus	
No	329 (76.5)
Yes	101 (23.5)
HIV status	
Negative	383 (89.1)
Positive	47 (10.9)
Treatment category	
New cases	217 (50.5)
Retreatment cases	213 (49.5)
Smear positivity	
Negative	67 (15.6)
Positive	361 (83.9)
Not done	2 (0.5)
Chest x-ray	
No lesion	19 (4.4)
Minimal	234 (54.4)
Moderate/far advanced	177 (41.2)
DOT supervision	
Healthcare workers[a]	287 (66.7)
Family members	124 (28.8)
No supervision/others[b]	19 (4.5)
Category of DR-TB	
HR-TB	148 (34.4)
RR-TB	121 (28.2)
MDR/Pre-XDR/ XDR-TB	161 (37.4)

[a]including virtual DOT
[b]DOT by other than healthcare workers and family members
DOT = Directly observed treatmen

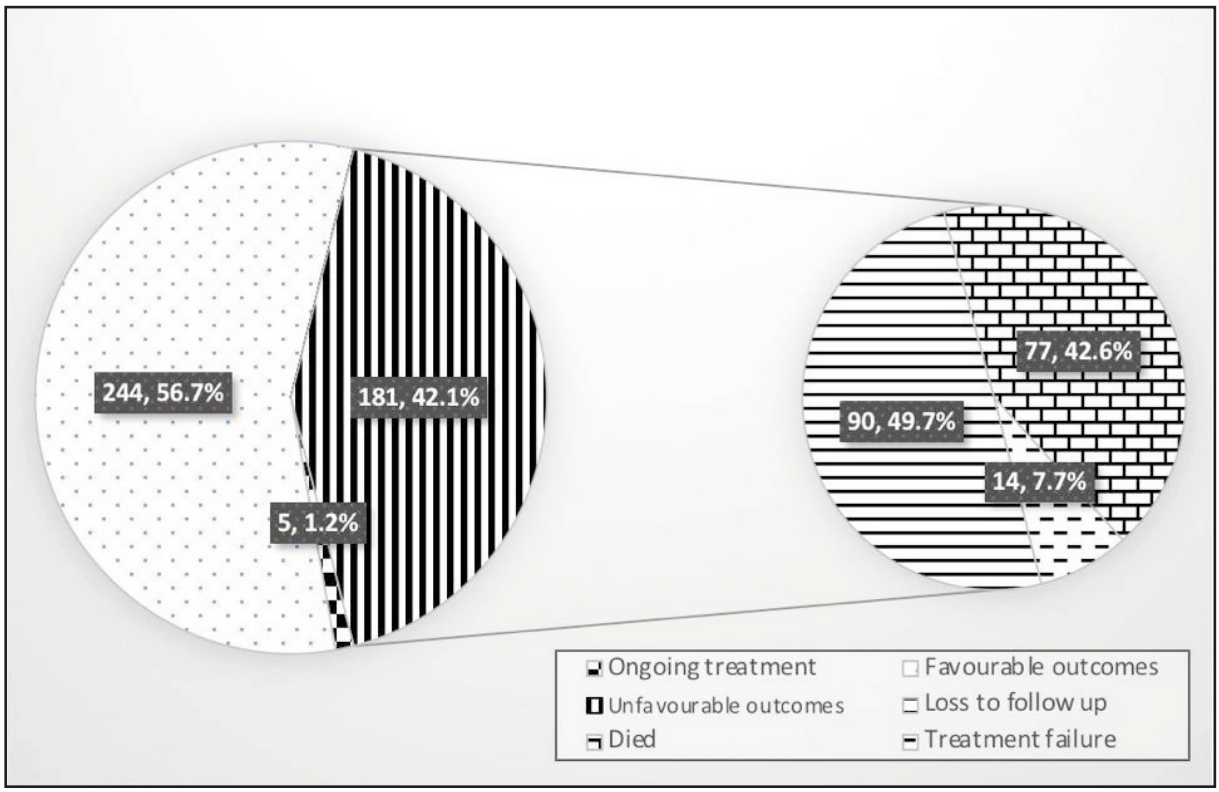

Fig. 1: Categories of treatment outcomes among DR-TB cases in Selangor and WPKL from 2016 to 2020

Suboptimal treatment not only jeopardises patient outcomes but also heightens the risk of disease transmission and the emergence of further drug resistance.[24] The stigma associated with TB and its treatment, along with societal attitudes towards the disease, could deter patients from continuing treatment.[25] DR-TB is more challenging to treat than drug-sensitive TB due to the longer and more expensive therapy required, along with potentially adverse side effects.[7] Therefore, strategies such as decentralising treatment services, providing financial support for transportation or treatment costs and establishing support groups should be considered.

Sociodemographic characteristics of DR-TB cases

This study found that DR-TB cases in Malaysia primarily affected adults aged 26 to 56 years, with a mean (SD) of 40.96 (15.04) years, potentially due to workplace transmission, impacting productivity and causing financial strain. Males were predominantly affected, consistent with earlier studies in Saudi Arabia,[16] Vietnam,[22] and China.[26] Males are considered at higher risk compared to females, probably due to their vulnerability and risk in terms of underlying comorbidities such as HIV infection, diabetes mellitus and chronic obstructive pulmonary disease (COPD), which are predominant in males; behavioural risk factors like smoking, illicit drug and alcohol abuse;[27,28] socio-cultural factors, for example occupational-related factors in certain male-predominant professions such as mining and construction;[15,29] and also health-seeking behaviour patterns as most male patients delay seeking treatment, resulting in delayed diagnosis and treatment initiation.[30] Malaysians comprised the majority, while Burmese and Indonesians predominate for non-citizens as a result of the influx of foreign workers in various industries.[31] Illegal or unpermitted foreign employees without proper health screening and the presence of refugees and asylum seekers complicate the situation. Regarding education, most of the cases (51.9%) had received education up to the secondary school, and 21.6% had no formal education, a finding similar to that reported by Liew et al.[32] Despite Malaysia's high literacy rate of 95.10% in 2017, the low post-secondary education enrolment (16-17%) raises concerns about educational access and attainment.[33] Health literacy impacts treatment adherence, disease awareness, health-seeking behaviour and socio-economic status.

Clinical Characteristics of DR-TB Cases

This study identified 23.5% of DR-TB patients as diabetics, and 10.9% were HIV-positive. Comparing this finding with another local study by Elmi et al.,34 the results were 26.7% and 5.7%, respectively. Another study in Saudi Arabia involving 2098 patients from the MDR-TB and RR-TB categories revealed an even lower percentage of DR-TB with diabetes mellitus and HIV-positive individuals (12.7% and 2.1%, respectively).[16] The variations could be due to differences in study populations, locations and changes in the HIV epidemic over time. The comorbidities can significantly impact the treatment outcomes of DR-TB in terms of a weakened immune system, leading to more severe disease, an increased risk of treatment failure, and higher mortality.[7] Managing concurrent DR-TB, HIV or diabetes is challenging due to potential drug interactions and adherence complexities, which require vigilant monitoring. Diabetes increased the likelihood of contracting TB by two- to three-fold when compared to non-diabetic controls. In addition, weakened immunity in individuals with diabetes may lead to the emergence of active TB from latent infection.[28] Therefore, early detection through HIV testing in new TB patients and TB screening in newly diagnosed HIV patients, as recommended by the National TB Control Programme, may improve treatment outcomes. The study also highlighted the importance of smear status in diagnosing DR-TB, with 83.9% of cases being smear-positive. Positive AFB smears, often indicating high mycobacterial loads, were associated with severe disease and unfavourable outcomes.[18] Smear positivity was identified as an independent risk factor for MDR-TB among previously treated patients, as reported by Law et al.[35] Despite aligning with MOH policy, the accuracy of DST for some anti-TB medications remains imperfect.[1] In fact, almost 20% of cases with smear-negative TB and no sputum were diagnosed as DR-TB in this study, underlining the challenges in diagnosing TB, possibly due to immunosuppression, early illness, or poor specimen quality.[36]

Regarding CXR findings, while 54.4% of cases had minimal lesions, a normal CXR can still be observed in approximately 4-5% of patients. Trained personnel interpreting CXRs significantly improved TB detection by 1.23-fold (95% CI: 1.02,1.48).[37] While the severity of CXR abnormalities may indicate disease progression and potential drug resistance, it is not the sole determinant; individuals' factors such as immune status and comorbidities also contribute.38 Meanwhile, for the type of drug resistance, WHO monitors and reports two main categories, which are MDR and RR-TB. In this study, MDR-TB predominates the DR-TB category with 156 cases (36.3%), followed by HR-TB (n = 148, 34.4%), and RR-TB (n = 121, 28.2%). The analysis also showed four cases of pre-XDR-TB and one case of XDR-TB. Elmi et al.[34] also highlighted that rifampicin had the highest degree of resistance, followed by isoniazid. The widespread use of rifampicin since its introduction in 1971, especially in the context of isoniazid-resistant organisms, has contributed to this rise in resistance.[39] As a result, the growing number of patients resistant to both isoniazid and rifampicin. Similar trends have been observed in other countries like Pakistan and Vietnam, where MDR/RR-TB accounts cases are prevalent.[22] Last but not the least, DOT is a critical element of TB treatment, where anti-TB medicine consumption is directly monitored by healthcare workers, trained family members or, in specific locations, trained community volunteers or a non-governmental organisation (NGO). It ensures patients take prescribed medications correctly, enhancing compliance. DOT was reportedly practised in Malaysia at 97% (93% to 100%).40 In our study, the majority of the cases (66.7%) were supervised by healthcare workers, including virtual DOT, followed by family members (28.8%) and others (1.4%). Sadly, 3.0% of cases had no DOT supervision from any of the personnel mentioned above or organisations. Lack of supervision led to unfavourable outcomes, emphasising the importance of consistent DOT throughout the treatment.

Limitations and recommendations for future studies

Despite the encouraging findings, a few limitations were encountered during this study. The assumed coverage of the

NTBR database would ideally be 100% of all TB cases within the studied region. However, given the limitations and challenges of data collection, entry errors, especially by a new or untrained user, and potential inconsistencies, achieving true 100% coverage and accuracy might not be guaranteed. As mentioned above, some necessary variables that can contribute extra knowledge about DR-TB are not available in NTBR. In addition, the number of cases couldn't reach the calculated sample size due to the small number of cases in the early 2 years of the study period. Therefore, all DR-TB cases with unfavourable treatment outcomes were considered. Proper documentation and improvement in DR-TB notification only started in 2018 through a clear written circular from MOH, with dedicated staff taking care of data at the state level in the TB Unit.

To improve DR-TB control across Malaysia, it is recommended to enhance the surveillance by strengthening our laboratory capacity and integrating advanced diagnostic tools such as GeneXpert for early detection. Additionally, focused research should be conducted to identify socioeconomic, environmental, and healthcare-related factors contributing to the rise in DR-TB cases. Capacity-building programs should also be implemented to improve healthcare professionals' ability to diagnose and manage DR-TB effectively.

CONCLUSION

The study highlights a concerning rise in Drug-resistant tuberculosis (DR-TB) prevalence in Malaysia from 2016 to 2020, increasing from 0.27 to 1.79. Just over half of the patients achieved favourable treatment outcomes, while a significant number faced unfavourable outcomes, primarily due to loss to follow-up and death. Middle-aged males were the most affected, often presenting with comorbidities such as diabetes and HIV. These findings emphasise the critical need for enhanced monitoring, commitment from healthcare workers and family support in treatment supervision. The rising trend of pre-extensively drug-resistant tuberculosis and extensively drug-resistant tuberculosis poses a significant global threat with limited treatment options, highlighting the importance of prevention over treatment alone.

ACKNOWLEDGEMENT

Ethical approval was obtained from the Medical Research and Ethics Committee of the Malaysian Ministry of Health (NMRR ID-23-00038-72L) and the Human Research Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/22110712). The study adhered to the principles outlined in the Declaration of Helsinki and followed the guidelines set forth by the Malaysian Good Clinical Practice Guideline. No subject vulnerability was involved in the study as secondary data was used. We have no conflict of interest to be declared.

The authors would like to thank the Malaysian Association for Prevention of Tuberculosis (MAPTB) for awarding us the research grant (MAPTB/N/GAB/111904). We would also like to thank all the respective personnel from the Selangor State Health Department, Kuala Lumpur and Putrajaya State Health Department, and Institute of Respiratory Medicine, Kuala Lumpur for their assistance during data collection.

REFERENCES

1. Ministry of Health Malaysia. National Strategic Plan for Tuberculosis Control (2016-2020) [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/
2. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment. Drug-resistant tuberculosis treatment. 2022 update [cited Apr 2023]. Available from: https://www.who.int/publications/i/item/9789240063129.
3. Almeida D, Ioerger T, Tyagi S, Li SY, Mdluli K, Andries K, et al. Mutations in pepQ confer low-level resistance to bedaquiline and clofazimine in Mycobacterium tuberculosis. Antimicrob Agents Chemother 2016; 60(8): 4590–9.
4. World Health Organization. Global Tuberculosis Report 2021 [cited Oct 2022]. Available from: https://www.who.int/publications/i/item/9789240037021.
5. World Health Organization. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis [cited Nov 2022]. Available from: https://www.who.int/publications/i/item/9789240018662.
6. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014 and January 2020) [cited Jan 2023]. Available from: https://iris.who.int/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1.
7. Ministry of Health Malaysia. CPG management of drug resistant TB [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Respiratory/CPG%20Management%20of%20Drug%20Resistant%20TB.pdf.
8. World Health Organization. Global Tuberculosis Report 2020 [cited Oct 2022]. Available from: https://iris.who.int/bitstream/handle/10665/336069/9789240013131-eng.pdf?sequence=1.
9. Monedero-Recuero I, Gegia M, Wares DF, Chadha SS, Mirzayev F. Situational analysis of 10 countries with a high burden of drug-resistant tuberculosis 2 years post-UNHLM declaration: progress and setbacks in a changing landscape. Int J Infect Dis 2021; 108: 557–67.
10. Ou ZJ, Yu DF, Liang YH, He WQ, Li YZ, Meng YX, et al. Trends in burden of multidrug-resistant tuberculosis in countries, regions, and worldwide from 1990 to 2017: results from the Global Burden of Disease study. Infect Dis Poverty 2021; 10(1): 24.
11. Ministry of Health Malaysia. Notifikasi dan Pelaporan Kes Drug-resistant TB (DRTB), Disease Control Division. MOH circular (ref. no.: KKM.600-1/3/66 (16)); 2020. [cited Apr 2023].
12. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009; 9(3): 153–61.
13. Spence DP, Hotchkiss J, Williams CS, Davies PD. Tuberculosis and poverty. BMJ 1993; 307(6907): 759-61.
14. Department of Statistics, Malaysia. OpenDOSM [cited Apr 2023]. Available from: http://www.dosm.gov.my/v1/index.php.
15. Amin Z, Mitiku H, Marami D, Shume T, Weldegebreal F. Magnitude of multidrug resistance and associated factors of pulmonary tuberculosis among adult smear positive patients in eastern Ethiopia. Infect Drug Resist 2021; 14: 4493–4500.
16. Al Ammari M, Al Turaiki A, Al Essa M, Kashkary AM, Eltigani SA, Ahmed AE. Drug-resistant tuberculosis in Saudi Arabia: an analysis of surveillance data 2014-2015. Antimicrob Resist Infect Control 2018; 7: 12.
17. Sambas M, Rabbani U, Al-Gethamy MMM, Surbaya SH, Alharbi FFI, Ahmad RGA, et al. Prevalence and determinants of multidrug-resistant tuberculosis in Makkah, Saudi Arabia. Infect Drug Resist 2020; 13: 4031-8.

18. Jitmuang A, Munjit P, Foongladda S. Prevalence and Factors Associated with Multidrug-Resistant Tuberculosis at Siriraj Hospital, Bangkok, Thailand. Southeast Asian J Trop Med Public Health 2015; 46(4): 697-706.
19. Goroh MMD, Rajahram GS, Avoi R, Van Den Boogaard CHA, William T, Ralph AP, et al. Epidemiology of tuberculosis in Sabah, Malaysia, 2012-2018. Infect Dis Poverty 2020; 9: 1-11.
20. World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational 'how-to' practical considerations. Geneva: World Health Organization 2011. [cited August 2024]. Available from: https://iris.who.int/bitstream/handle/10665/44593/9789241501569_eng.pdf?sequence=1.
21. Al-Darraji HA, Abd Razak H, Ng KP, Altice FL, Kamarulzaman A. The diagnostic performance of a single GeneXpert MTB/RIF assay in an intensified tuberculosis case finding survey among HIV-infected prisoners in Malaysia. PLoS One 2013; 8(9): e73717.
22. Wrohan I, Nguyen TA, Nguyen VN, Nguyen BH, Hoang TTT, Nguyen PC, et al. Predictors of treatment outcomes among patients with multidrug-resistant tuberculosis in Vietnam: a retrospective cohort study. BMC Infect Dis 2022; 22(1): 68.
23. Tola HH, Tol A, Shojaeizadeh D, Garmaroudi G. Tuberculosis treatment non-adherence and lost to follow up among TB patients with or without HIV in developing countries: a systematic review. Iran J Public Health 2015; 44(1): 111.
24. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Healthcare system factors influencing treatment results of MDR TB patients [cited Nov 2022]. Available from: https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/mdr-tb-healthcare-factors-influencing-treatment-results.pdf.
25. Baral SC, Karki DK, Newell JN. Causes of stigma and discrimination associated with tuberculosis in Nepal: a qualitative study. BMC Public Health 2007; 7: 211.
26. Ma JB, Zeng LC, Ren F, Dang LY, Luo H, Wu YQ, et al. Treatment outcomes and risk factors of multidrug-resistant tuberculosis patients in Xi'an China, a retrospective cohort study. Infect Drug Resist 2022; 15: 4947–57.
27. Rajendran M, Zaki RA, Aghamohammadi N. Contributing risk factors towards the prevalence of multidrug-resistant tuberculosis in Malaysia: a systematic review. Tuberculosis (Edinb) 2020; 122: 101925.
28. Molla KA, Reta MA, Ayene YY. Prevalence of multidrug-resistant tuberculosis in East Africa: a systematic review and meta-analysis. PLoS One 2022; 17(6): e0270272.
29. Kaur K, Said S, Norkhadijah S, Lim PY. Risk factors of unfavourable TB treatment outcomes in Hulu Langat, Selangor. Malays J Med Health Sci 2022; 18: 52–60.
30. Johansson E, Long NH, Diwan VK, Winkvist A. Gender and tuberculosis control: perspectives on health-seeking behaviour among men and women in Vietnam. Health Policy 2000; 52(1): 33–51.
31. International Labour Organization. TRIANGLE in ASEAN Quarterly Briefing Note Malaysia July-December 2022 [cited May 2022]. Available from: https://www.ilo.org/wcmsp5/groups/public/---asia/---ro-bangkok/documents/genericdocument/wcms_614381.pdf.
32. Liew SM, Khoo EM, Ho BK, Lee YK, Mimi O, Fazlina MY, et al. Tuberculosis in Malaysia: predictors of treatment outcomes in a national registry. Int J Tuberc Lung Dis 2015; 19(7): 764–71.
33. Ministry of Education, Malaysia. Malaysia Education Statistics [cited Apr 2023]. Available from: https://www.moe.gov.my/en/muat-turun/laporan-dan-statistik/quick-facts-malaysia-education-statistics/563-quick-facts-2018-malaysia-educational-statistics/file.
34. Elmi OS, Hasan H, Abdullah S, Mat Jaeb MZ, Bin Alwi Z, Naing NN. Multidrug-resistant tuberculosis and risk factors associated with its development: a retrospective study. J Infect Dev Ctries 2015; 9(10): 1076–85.
35. Law WS, Yew WW, Chiu Leung C, Kam KM, Tam CM, Chan CK, et al. Risk factors for multidrug-resistant tuberculosis in Hong Kong. Int J Tuberc Lung Dis 2008; 12(9): 1065–70.
36. Ministry of Health Malaysia. Management of Tuberculosis (Fourth Edition) [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/resources/Main%20Banner/2021/Okt/Draft_CPGManagement_of_Tuberculosis(Fourth_Edition)_for_Reviewers.pdf.
37. Abubakar I, Story A, Lipman M, Bothamley G, van Hest R, Andrews N, et al. Diagnostic accuracy of digital chest radiography for pulmonary tuberculosis in a UK urban population. Eur Respir J 2010; 35(3): 689–92.
38. Murthy SE, Chatterjee F, Crook A, Dawson R, Mendel C, Murphy ME, et al. Pretreatment chest x-ray severity and its relation to bacterial burden in smear positive pulmonary tuberculosis. BMC Med 2018; 16(1): 73.
39. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh Jr. CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993; 328(8): 527–32.
40. Ministry of Health Malaysia. Management of Tuberculosis (Third Edition) [cited Oct 2022]. Available from: https://www.moh.gov.my/moh/attachments/8612.pdf.