ASSESSMENT OF RISK FACTORS ASSOCIATED WITH MORTALITY AND DEVELOPING DRUG RESISTANT TUBERCULOSIS IN HOSPITAL PULAU PINANG, MALAYSIA: A RETROSPECTIVE STUDY

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by

ASEEL REZEQ ALI YAGHI

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AFB	Acid-fast bacilli
ADA	Adenosine Deaminase
AMs	Alveolar macrophages
CKD	Chronic kidney disease
COPD	Chronic obstruction pulmonary disease
CXR	Chest radiograph
DOTS	Directly Observed Treatment, Short-course
DST	Drug sensitivity test
DM	Diabetes mellitus
EPTB	Extrapulmonary TB
FLD	First-line anti-TB drugs
HPP	High power field
HPP	Hospital Pulau Pinang
HCV	Hepatitis c virus
HBV	Hepatitis B virus
HAART	Highly Active Anti-retroviral Therapy
HIV	Human immunodeficiency virus
H	Isoniazid
LPA	Line Probe Assay
MDR-TB	Multidrug-resistant tuberculosis
NAAT	Nucleic Acid Amplification Test
NTP	National Tuberculosis Program
PTB	Pulmonary TB
QoL	Quality of life

R	Rifampicin
SLE	Systemic lupus erythematosus
S	Streptomycin
SLD	Second-line anti-TB drugs
TB	Tuberculosis
Z	Pyrazinamide

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PENILAIAN FAKTOR RISIKO YANG BERKAIT DENGAN KEMATIAN DAN PEMBENTUKAN TUBERKULOSIS RINTANG DRUG DI HOSPITAL PULAU PINANG, MALAYSIA: SEBUAH KAJIAN RETROSPEKTIF

ABSTRAK

Di peringkat global, Malaysia diklasifikasikan sebagai negara terbeban tuberkulosis (Tibi) pertengahan. Peningkatan kadar kematian dan kemunculan Tibi kerintangan ubat (MDR-TB) memainkan peranan utama dalam menyebabkan hasil rawatan yang tidak berjaya dalam kalangan pesakit Tibi. Walaupun terdapat usaha nasional untuk mengawal Tibi di negara ini, tetapi tidak banyak yang diketahui mengenai hasil pengurusan dan rawatan pesakit MDR-TB di Malaysia serta faktor risiko kematian dalam kalangan populasi Tibi. Bagi tujuan ini, seramai 351 pesakit tibi, termasuk 26 pesakit MDR-TB yang dirawat di klinik dada Hospital Pulau Pinang telah dimasukkan dalam kajian retrospektif ini. Rekod perubatan pesakit Tibi telah dikaji semula dan ciri-ciri sosiodemografi, klinikal dan mikrobiologi pesakit telah diekstrak ke lembaran pengumpulan data yang direka oleh pasukan doktor, ahli farmasi dan penyedia kesihatan. Jenis analisis regresi logistik dan Cox dilakukan menggunakan SPSS versi 23. Dalam kalangan pesakit MDR-TB, 21 (80.8%) mencapai hasil rawatan yang berjaya dan 5 (19.2%) meninggal dunia. Dalam analisis regresi Cox, Tibi berulang (p-value= 0.044, HR= 3.035, 95%CI= 1.028 – 8.957), penggunaan alkohol (p-value= .000, HR= 7.591, 95%CI= 3.097 – 18.610) dan tidak berkahwin (p-value= 0.000, HR= 6.817, 95%CI= 2.599 – 17.879) muncul sebagai faktor risiko pembangunan MDR-TB. Penukaran kahak smear pada bulan kedua rawatan telah dicapai pada 145 (71.4%) pesakit dan 41 (20.1%) pesakit Tibi paru-paru positif (PTB) mengalami penanguhan penukaran kahak smear selepas dua bulan rawatan. Dalam

analisis regresi logistik, beban tinggi bacilli cepat asid (AFB) (p-value= 0.010, HR= 8.526, 95%CI= 1.652 - 44.012) dan virus hepatitis B reaktif (HBV) (p-value= .007, HR= 9.033, 95%CI= 1.827 - 44.669) secara bebas dikaitkan dengan penukaran kahak smear yang tertangguh selepas bulan kedua rawatan. Kadar kematian adalah 22.5%, di mana 73 pesakit TB yang mudah terdedah ubat meninggal dunia semasa rawatan anti-TB. Analisis regresi Cox menunjukkan bahawa ketagihan dadah (p-value= 0.034, HR= 1.836, 95%CI= 1.019 – 3.309), tahap sel darah putih yang tinggi (p-value= 0.000, HR= 1.102, 95%CI= 1.057 – 1.148) dan urea (p-value= 0.002, HR= 1.029, 95%CI= 1.011 – 1.047), dan tahap platelet yang rendah (p-value= 0.000, HR= .996, 95%CI= 0.995 - 0.998) dan albumin (p-value= .006, HR= .964, 95%CI= 0.940 - 0.990) adalah sebagai faktor risiko yang ketara untuk kematian di kalangan pesakit TB. Tambahan pula, kadar kejayaan yang dicapai dalam kalangan pesakit kajian adalah (69.8%), di mana 245 (75.4%) satu (0.3%) 171 (70.0%) pesakit telah sembuh dan 74 (30.0%) pesakit menyelesaikan rawatan anti-TB mereka. Analisis regresi logistik multivariable menunjukkan terapi kombinasi dos tetap 4 ubat (isoniazid, rifampicin, pyrazinamide dan ethambutol) (p-value= .015, OR= 1.560, 95%CI= 1.089 – 2.235) sebagai satu-satunya peramal penting hasil rawatan yang berjaya di kalangan pesakit TB. Kesimpulannya, lebih banyak perhatian harus diberikan kepada pesakit yang berisiko tinggi MDR-TB, termasuk penagih alkohol, pesakit dengan TB berulang dan yang tinggal bersendirian. Kadar kematian yang disebutkan di kalangan populasi kajian menghalang mencapai sasaran WHO sebanyak 85% kadar kejayaan, dan kematian lebih cenderung dialami di kalangan penagih dadah dan pesakit dengan sel darah putih yang tidak normal, urea, platelet dan hasil albumin.

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ABSTRACT

Globally, Malaysia classified as an intermediate tuberculosis (TB) burden country. Increasing mortality rate and the emergence of multidrug-resistant TB (MDR-TB) played the major role in achieving unsuccessful treatment outcomes among TB patients. Despite the national efforts to control TB in the country, but little is known about the management and treatment outcomes of MDR-TB patients from Malaysia as well as the risk factors of mortality among TB population. For this purpose, a total of 351 TB patients, including 26 MDR-TB patients treated at chest clinic of Hospital Pulau Pinang were included in the present retrospective study. Medical records of TB patients were reviewed and sociodemographic, clinical and microbiological characteristics of the patients were extracted to data collection sheet designed by a team of doctors, pharmacists and health providers. Multivariable logistic and Cox regression were performed using SPSS version 23. Among MDR-TB patients, 21 (80.8%) achieved successful treatment outcomes and 5 (19.2%) died. In multivariable Cox regression analysis, relapsed TB (p-value= .044, HR= 3.035, 95%CI= 1.028 – 8.957), alcohol consumption (p-value= .000, HR= 7.591, 95%CI= 3.097 – 18.610) and single marital status (p-value= .000, HR= 6.817, 95%CI= 2.599 – 17.879) emerged as risk factors of MDR-TB development. Sputum smear conversion at second month of treatment was achieved in 145 (71.4%) patients and 41 (20.1%) smear positive pulmonary TB (PTB) patients had delayed sputum smear conversion after two months of treatment. In multivariable logistic regression analysis, High load of acid-fast bacilli

(AFB) (p-value= .010, HR= 8.526, 95%CI= 1.652 - 44.012) and reactive hepatitis B virus (HBV) (p-value= .007, HR= 9.033, 95%CI= 1.827 - 44.669) were independently associated with delayed sputum smear conversion after second month of treatment. Mortality rate was 22.5%, in which 73 drug susceptible TB patients passed away during anti-TB treatment. Multivariable Cox regression analysis showed that drug addiction (p-value= .034, HR= 1.836, 95%CI= 1.019 – 3.309), high levels of white blood cells (p-value= .000, HR= 1.102, 95%CI= 1.057 – 1.148) and urea (p-value= .002, HR= 1.029, 95%CI= 1.011 – 1.047), and low levels of platelets (p-value= .000, HR= .996, 95%CI= .995 - .998) and albumin (p-value= .006, HR= .964, 95%CI= .940 - .990) were as significant risk factors for mortality among TB patients. Furthermore, success rate achieved among study patients was (69.8%), in which 245 (75.4%) one (0.3%) 171 (70.0%) patient were cured and 74 (30.0%) patients completed their anti-TB treatment. Multivariable logistic regression analysis indicated fixed dose combination therapy of 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) (p-value= .015, OR= 1.560, 95%CI= 1.089 – 2.235) as the only significant predictor of successful treatment outcome among TB patients. In conclusion, more attention must be given to the patients at high risk of MDR-TB, including alcohol addicts, patients with relapsed TB and who are living alone. A worth mentioned rate of mortality among the study population hindered achieving WHO target of 85% success rate, and mortalities were more likely to be experienced among drug addicts and patients with abnormal white blood cells, urea, platelets and albumin results.

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB) is among the top ten reasons of death globally, despite the discovery of in-expensive and successful anti-TB therapy (Glaziou et al., 2018). TB is an infectious disease caused by bacillus *Mycobacterium tuberculosis*, it is an airborne disease which spread from infected person to another by air when they sneeze or cough, affecting mainly the respiratory organs and can also affect brain, kidneys, spine, or intestines. TB is one of the most threatening ancient human infections, with genetic evidence dating back over 17000 years (Sandhu, 2011). Worldwide, TB is one of the leading causes of a single infectious agent. Every year, millions of people suffer with TB. In 2019, an estimated 10 million were infected with TB. TB accounted for nearly 1.2 million deaths among human immunodeficiency virus (HIV)-negative population and 208,000 additional deaths among HIV-positive population in 2019 (World Health Organization, 2020). Since the 1940s, when chemotherapy was launched, TB has been declining globally (Chadha, 2009). Although, TB diagnosis and effective treatment have saved an approximated 43.4 million lives worldwide in the last 14 years, the emergence and spread of drug-resistant TB threatens these gains (World Health Organization, 2015). Anti-TB drugs resistance has been studied since the 1940s (Wolinsky et al., 1948). MDR-TB, is defined as "TB caused by a strain of *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin, the two most efficacious and well tolerated first line anti-TB drugs". They first appeared in literature and clinical practice in the early 1990s (Marcos A. Espinal, 2003;Frieden et al., 1995; Kim J. Y. et al., 2003). According to WHO classification, Malaysia is a country with

intermediate TB burden (World Health Organization, 2020). To reduce the burden of TB, a national strategic plan for TB control has been implemented to ensure that all forms of TB can be diagnosed and treated in a timely manner and to prevent the development of drug-resistant TB in the country (Minstry of Health Malaysia, 2016). Nevertheless, TB is a major public health issue because of the high prevalence of TB in the neighboring countries, such as Indonesia and Thailand (Azit et al., 2019). In 2018, 25,173 cases of TB were reported in Malaysia, with an estimated incidence rate of 92/100,000 (cases/population). Worryingly, the mortality rate among TB patients in Malaysia is the highest in comparison to other infectious diseases, denoting that TB transmission is still active in the country (Bainomugisa et al., 2021). Moreover, the dramatic increase in the number of MDR-TB hospitalized patients from 14 cases in 2004 to 370 cases in 2020 has highlighted the need for further research into MDR-TB management and treatment outcomes since the data on MDR-TB outcomes is insufficient (World Health Organization, 2018). Consequently, the current study examined treatment outcomes for tuberculosis and risk factors associated with MDR-TB in Malaysia.

1.2 Drug resistance tuberculosis

Anti-TB drugs resistance is not a new phenomenon. It appeared right after anti-TB drugs were discovered (Crofton & Mitchison, 1948). Resistance may be either primary or secondary. "Drug resistance in a patient who has never received a drug before" is referred to as primary drug resistance (Telenti & Iseman, 2000). Primary drug resistance is thought to be caused by the transmission of non-chromosomal genetic genes known as 'loops' (Cohen et al., 1972). Secondary drug resistance also known as acquired drug. It is referred as “resistance that has occurred within the course

of antimicrobial therapy" (Telenti & Iseman, 2000). In acquired drug resistance, bacteria develop resistance to specific drugs that were sensitive at the initiation of treatment (Telenti & Iseman, 2000).

1.3 Mechanism of drug resistance in *Mycobacterium tuberculosis*

Antimicrobial agents, which are used to treat infections, can actively inhibit or kill microorganisms. Antimicrobial resistance occurs by the interruption or disruption of one or more steps required for antimicrobial action (Drake, 1999). Several mechanisms causing the resistance include the production of proteins that alter the antimicrobial's binding site, enzymes that destroy it, proteins that reduce its permeability, and changes to the antimicrobial's metabolic pathway within the bacteria, reducing its efficacy (Dever & Dermody, 1991) (Hawkey, 2000).

Drug resistance in *Mycobacterium tuberculosis* is primarily mediated by spontaneous chromosomal mutations (David, 1970;Kochi et al., 1993;Telenti & Iseman, 2000). As the chromosomal mutations occur spontaneously, transition from isoniazid-susceptible *Mycobacterium tuberculosis* to a population resistant to isoniazid might take 5,000 to 10,000 years (David & Newman, 1971), implying that mycobacterial resistance in the existence of three effective anti-TB drugs is extremely unlikely. However, suboptimal treatment regimen, mono-therapy, irregular intake of drugs, low drug penetration due to empyema and extensive cavitation amplify the afore-mentioned mutations (Zhang & Yew, 2009). Under such selective pressure, genetic mutants being naturally resistant to the given antibiotic thrive, giving rise in the conversion of drug-susceptible TB to mono-resistant TB (Mitchison, 1954). When genetic mutants that are naturally resistant to the given drug are exposed to a second course of therapy with yet another anti-TB drug, they emerge as dominant strains,

resulting in poly-resistant strains, including MDR-TB strains ((Rattan et al., 1998;Zhang & Yew, 2009).

1.4 Epidemiology of TB and multidrug resistant TB

1.4.1 Global epidemiology

WHO classified world countries according to TB burden into; high, intermediate and low burden. The 30 countries with the highest TB burden accounted for 87% of the world cases; eight of the high burden countries, including India, China, Indonesia, Philippines, Nigeria, South Africa, Pakistan, and Bangladesh accounted for roughly 70% of the total (World Health Organization, 2020). Large drop in TB cases was reported globally in 2020, referred mainly to COVID-19 pandemic. Number of people newly diagnosed with TB dropped by 18% from 7.1 million in 2019 to 5.8 million in 2020, globally (World Health Organization, 2020). The increased mortality among TB patients from 1.2 million in 2019 to 1.4 million in 2020 is the immediate cause of the large drop in TB incidence. The WHO regions of South-East Asia (44%), Africa (25%), and the Western Pacific (18%) represented the majority of the estimated number of cases (World Health Organization, 2020).

According to Global TB report 2019, it is estimated that a total 465, 000 new MDR-TB cases emerged globally with an estimated proportion of 3.3% of new cases and 18% of previously treated TB cases. Thirty MDR-TB high burden countries accounted for more than half of the estimated MDR-TB cases in 2019. Nearly 50% of global cases were in India (27%), China (14%) and the Russian Federation (8%). Among notified pulmonary TB (PTB) cases, India has the highest estimated MDR-TB cases (124,000) followed by China (65,000). Among new cases, the MDR-TB were highest in Belarus (38%) followed by Russian Federation (35%). Among retreatment

TB cases, the percentages with MDR-TB were highest in Somalia (88%) followed by Russian Federation (71%) (World Health Organization, 2019).

Although the number of TB deaths reported annually before 2020 was falling globally, the decline is not fast enough to reach the End TB Strategy target, that is a 35% reduction between 2015 and 2020. WHO reported only 14% decrease in mortality rate between 2015 and 2020 (World Health Organization, 2020). In 2019, nearly 1.2 million deaths (range 1.1-1.3 million) among HIV-negative people and 208,000 deaths (range 177,000-242,000) among HIV-positive people were attributed to TB (World Health Organization, 2020). Regionally, South-East Asia accounted for the greatest HIV negative/TB deaths, in which 632,000 (range 593,000-671,000) deaths were reported, followed by Africa that recorded 378,000 (range 313,000-448,000) deaths in 2019. In the same year, WHO reported an estimated number of 84,000 (range 78,000-91,000) deaths in Western Pacific, 76,000 (range 65,000-87,000) deaths in Eastern Mediterranean, 20,000 (range 20,000-21,000) deaths in Europe and 17,000 (17,000-18,000) deaths in the Americas (World Health Organization, 2020). Approximately 86% of the global TB related mortality is reported in the high TB burden countries, where 1 million (range 966,000-1.1 million) patients infected with TB passed away in 2019. The majority of TB deaths were recorded in India, 436,000 (range 404,000-469,000) TB patients died in 2019. Furthermore, 127,000 (range 74,000-195,000) TB deaths reported from Nigeria, 42,000 (range 34,000-51,000) from Pakistan, 38,000 (range 24,000-56,000) from Bangladesh and 31,000 (range 28,000-34,000) TB deaths from China in 2019 (World Health Organization, 2020).

1.4.2 Epidemiology of TB and MDR-TB in Malaysia

Malaysia is a Southeast Asian country with an estimated population of 29.7 million people in 2020. Between 2012 and 2019, the incidence rate of TB in the country fluctuated dramatically (World bank, 2021). TB was the second most commonly reported communicable disease since 2001 (Kurniawati et al., 2012). In 2020, Malaysia have a TB incidence rate of 72.4 per 100,000 people according to the latest national reports. There was a reduction of this incidence from 92.00/100,000 in 2016 to 72.4/100,000 in 2020 but it was still below the End TB Strategy target of more than 20% reduction (Ministry of Health Malaysia, 2021). 23,644 cases of TB were reported in 2020, in which 91.7% of them were new cases, 58.0% were smear positive PTB and 32.1% were smear negative PTB. At tertiary care respiratory clinics, 10–14 % of TB cases were classified as extrapulmonary TB (EPTB) (Nissapatorn et al., 2004). Extrapulmonary involvement was found in approximately 14% of PTB patients. EPTB cases with HIV co-infection account for nearly 20% of all cases (Mohammad & Naing, 2004). The incidence of EPTB showed a significant increase from 13.3% in 2015 to 15.7% in 2020 (Ministry of Health Malaysia, 2021).

WHO reported a high incidence of TB in neighbouring countries; in Indonesia an estimated incidence of 845,000 (range 770,000-923,000) patients and 570,000 (range 404,000-764,000) patients in Thailand in 2019. Moreover, high rates of TB related mortality were recorded in these countries; 92,000 (range 86,000-98,000) deaths among HIV-negative TB patients in Indonesia as well as 9600 (range 7100-12,000) deaths in Thailand in 2019 (World Health Organization, 2020). Therefore, the impact of high TB burden in the neighboring countries was observed in a_markable increase in death cases from 1,696 in 2015 to 2,320 cases in 2020, giving a mortality rate of 7.1 per 100,000 (Ministry of Health Malaysia, 2021). Despite not being one of

the 30 high-burden countries, Malaysia's treatment outcome rate falls short of the WHO's standard (≥90%), where 81% TB treatment success rate was reported in 2017. 370 cases of MDR-TB were reported in the country in 2017, accounted for 1.5% of new cases and 3.1% of previously treated cases (World Health Organization, 2018).

In 2017, 97 cases of MDR-TB were enrolled in TB treatment out of a total of 370 cases. The treatment success rate of MDR-TB cohort felt from 62% in 2013 to 41% in 2017 (World Health Organization, 2018).

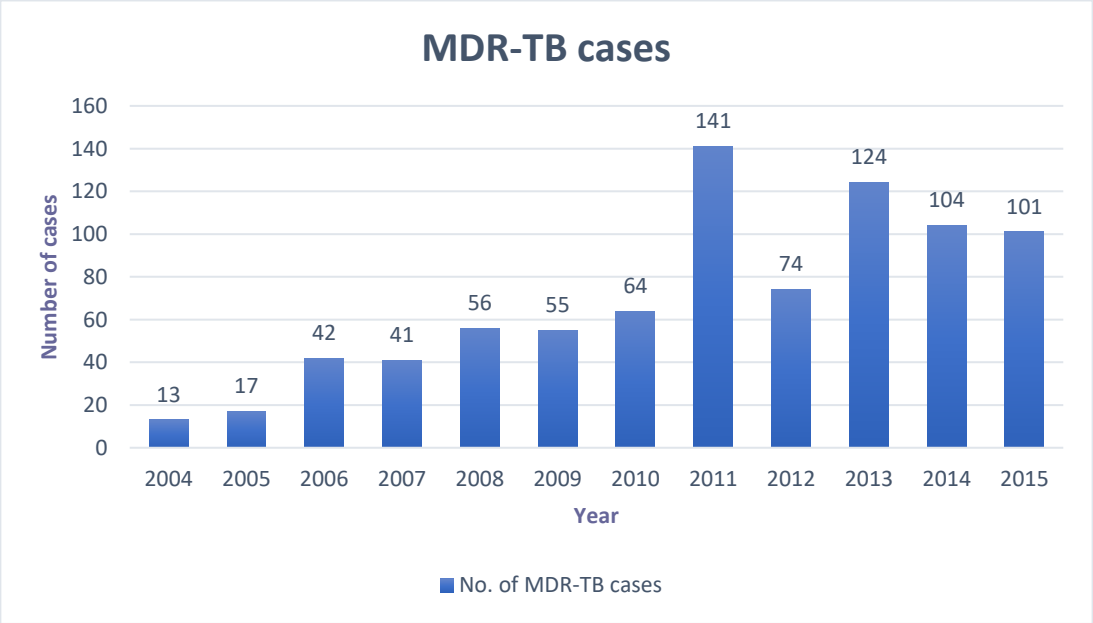

Figure 1.1 Cases of MDR-TB, Malaysia (2004-2015) (Ministry of Health Malaysia, 2021)

1.5 Management of TB and MDR-TB in Malaysia

1.5.1 Pulmonary TB and Extrapulmonary TB

Adult patients with active PTB typically present with a history of productive cough, haemoptysis, loss of appetite, unexplained weight loss, fever, night sweats and fatigue. However, the typical symptoms may be absent in the immunocompromised or elderly patients. According to national guidelines, full history and clinical examination

for patients with suspected TB referred to a tertiary care hospital is a must. Initially, patients suspected for TB submit at least two sputum specimens for smear microscopy to confirm the presence of AFB and perform a chest radiograph (CXR). Once PTB diagnosis confirmed, patients must have mycobacterial culture performed at the initial visit to look for drug-susceptibility pattern. It is to confirm the presence of *Mycobacterium tuberculosis* and to exclude drug (Ministry of Health Malaysia, 2021).

Patients suspected for EPTB undergo several tests to confirm the diagnosis, including mycobacterial culture and molecular tests, which are specific tests but not sensitive for the detection of EPTB. Patients must submit tissue specimens (cerebrospinal fluid, urine, lymph node aspirate or tissue, pericardial fluid, or bone and joint tissue) to GeneXpert to confirm the diagnosis. GeneXpert MTB/RIF assay which is a nucleic acid amplification assay detects *Mycobacterium tuberculosis* and resistance to *rifampicin* in less than 2 hours (1-2 days). Patients suspected to have pleural TB, adenosine Deaminase (ADA) test can be used as adjunct in the diagnosis workup. Computed tomography scan and/or magnetic resonance imaging should be use in the diagnosis in TB of central nervous system (Ministry of Health Malaysia, 2021). According to WHO and Malaysian national tuberculosis guidelines, treatment of TB is divided into: intensive phase and maintenance phase (Ministry of Health Malaysia, 2021)(World Health Organization, 2014). Figure 1.2 illustrate the duration of PTB and EPTB treatment and the regimens used in intensive and maintenance phase of treatment.

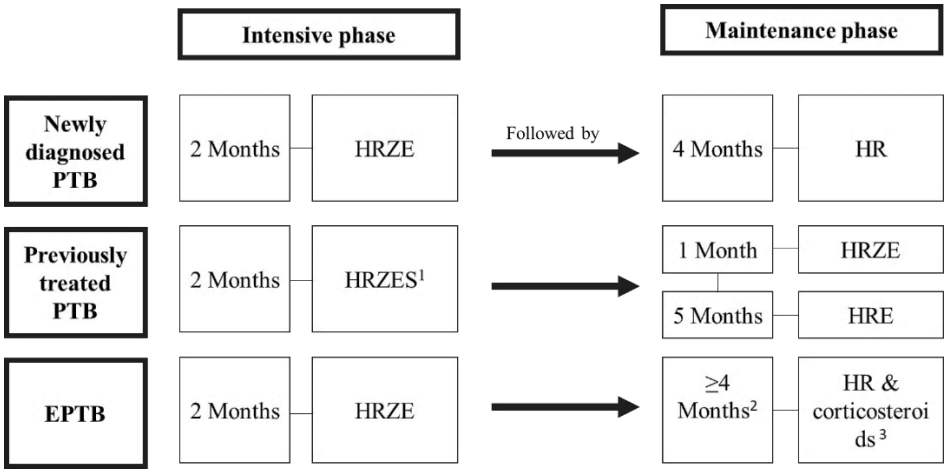

Figure 1.2 Duration of treatment and regimens used in TB treatment course

[1] H, Isoniazid; R, Rifampicin; Z, Pyrazinamide; E, Ethambutol; S, Streptomycin.
[2] 6-9 months maintenance phase for TB bone and joints; 9-12 months for TB meningitis; 6 months for other sites of EPTB.
[3] Corticosteroids recommended for TB meningitis and pericarditis.

DRUG	RECOMMENDED DOSES			
	Daily		3X a week	
	Dose (range) in mg/kg body weight	Maximum in mg	Dose (range) in mg/kg body weight	Maximum in mg
Isoniazid (H)	5 (4 - 6)	300	10 (8 - 12)	900
Rifampicin (R)	10 (8 - 12)	600	10 (8 - 12)	600
Pyrazinamide (Z)	25 (20 - 30)	2000	35 (30 – 40)*	3000*
Ethambutol (E)	15 (15 - 20)	1600	30 (25 – 35)*	2400*
Streptomycin (S)	15 (12 - 18)	1000	15 (12 – 18)*	1500*

Figure 1.3 Doses of anti-TB drugs used in the treatment of PTB* (Ministry of Health Malaysia, 2021).

*Only daily anti-tuberculosis regimen should be used throughout the treatment of PTB. Fixed-dose combination is preferred over separate drug formulation in the treatment of PTB.

1.5.2 Multidrug resistant Tuberculosis (MDR-TB)

Multidrug-resistant tuberculosis (MDR-TB), defined as "TB caused by *Mycobacterium tuberculosis* strain that is resistant to the most two effective first line anti-TB drugs (FLD), both isoniazid and rifampicin (Marcos A. Espinal, 2003).

According to Malaysian national guidelines, patients suspected to have MDR-TB should be initially evaluated for the presence of AFB and *rifampicin* resistance by using smear microscopy and Xpert *Mycobacterium tuberculosis* (MTB)/RIF assay. If patient was previously exposed to fluoroquinolones, Line Probe Assay (LPA) is rapid molecular diagnostic technique based on polymerase chain reaction (PCR) used to detect resistance to isoniazid & rifampicin. Upon positive sputum smear microscopy and rifampicin resistance, patient should be enrolled for MDR-TB treatment with empirical treatment regimen, and the specimen sample should be sent to a reference laboratory for culture and drug sensitivity test (DST) against both FLD and second line anti-TB drugs (SLD) (LJ Media and Automated/liquid media). Upon reception of DST results, patients should be switched from empirical regimen to standardized or DST based individualized regimen (Ministry of Health Malaysia, 2016).

National guidelines have outlined the following general principles for MDR-TB treatment: i) treat the patients with at-least four likely effective SLD plus pyrazinamide ii) avoid drugs for which resistance crosses over iii) eliminate the drug not safe for the patient iv) remain ready to prevent, observe and manage adverse effects for each selected drug v) each drug in an MDR-TB regimen is given as DOT throughout the treatment.

The intense phase and the continuing phase are the two phases of MDR-TB treatment. The intensive phase refers to the period a patient is on injectable SLD. Sputum culture conversion, defined as "two consecutive negative sputum cultures taken at least 30 days apart following an initial positive culture and should be continued for at least eight months with a minimum of six months after sputum culture conversion," guides the duration of the intensive phase. Other clinical markers, such as weight gain, resolution or improvement of respiratory problems, and/or pulmonary

lesions, can be taken into account when determining the duration of the intensive phase. Only the injectable SLD is stopped during the maintenance phase, and the patient continues to take the same oral medications as at the end of the intense phase. A new MDR-TB patient should be treated for at least 20 months after culture conversion, and for at least 18 months beyond that. (NTP, 2012). (Figure 1.4) illustrate the duration of MDR-TB treatment and the regimens used in intensive and maintenance phase of treatment. Table 1.1 shows the drugs used in the treatment of MDR-TB and their categories according to WHO guidelines and the recommended doses.

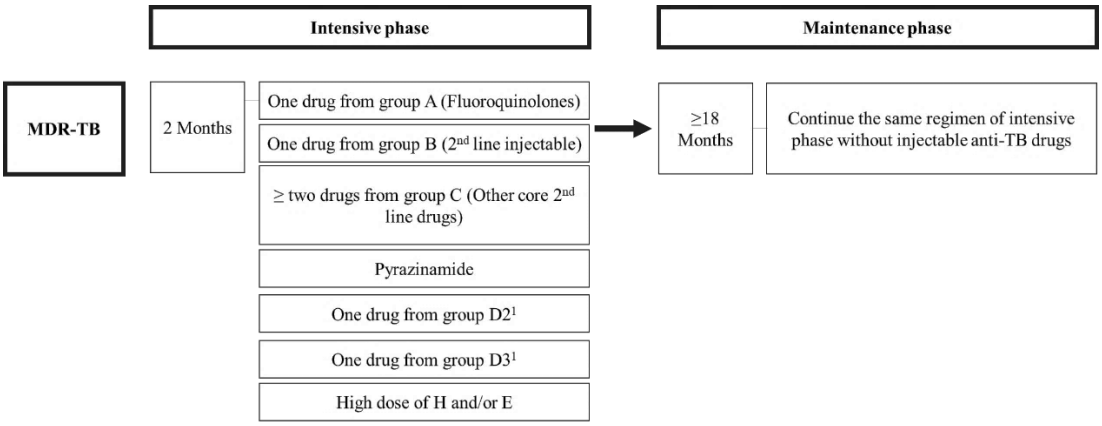

Figure 1.4 Duration of treatment and regimens used in MDR-TB treatment course

[1] Drugs from group D2 and D3 used when it is not possible reach five effective anti-TB drugs from group A-C, to bring the total to five.

Table 1.1 Doses of anti-TB drugs used in the treatment of MDR-TB (Ministry of Health Malaysia, 2016)

Group	**Drug name (abbreviation)**	**Recommended dose** **Daily dose (mg/kg body weight)**
Group A. Fluoroquinolones	Levofloxacin (Lfx)	7.5-10 once daily
	Moxifloxacin (Mfx)	400 mg once daily
Group B. Second line Injectable drugs	Amikacin (Am)	15–20 once daily
	Capreomycin (Cm)	15–20 once daily
	Kanamycin (Km)	15–20 once daily
	Streptomycin (S)*	12–18 once daily
Group C. Other core second line drugs	Ethionamide /Prothionamide (Eto/Pto)	500-750 mg/day in 2 divided doses
	Cycloserine / Terizidone (Cs/Trd)	500-750 mg/day in 2 divided doses
	Linezolid (Lzd)	600 mg once daily
	Clofazimine (Cfz)	200–300 mg (2 first months) then 100 mg once daily
Group D. Add-on drugs (not part of the core MDR-TB regimen)	D1 Pyrazinamide (Z)	20-30 once daily
	Ethambutol (E)	15-25 once daily
	High-dose isoniazid (Hh)	16-20 once daily
	D2 Bedaquiline (Bdq)	400 mg once daily for 2 weeks then 200 mg 3 times/week
	D3 p-aminosalicylic acid (PAS)	8 gm/day in 2 divided doses
	Imipenem-cilastatin (Ipm)	1000 imipenem/1000 mg cilastatin twice daily
	Meropenem (Mpm)	1000 mg three times daily (alternative dosing is 2000 mg twice daily)
	Amoxicillin-clavulanate (Amx-Clv)	80 mg/kg/day in 2 divided doses

* used as replacement when amikacin, capreomycin or kanamycin are not available

TB management globally comes under the umbrella of DOTS (directly observed treatment short course) program. DOTS is a standardized short-course technique for diagnosing and curing primary tuberculosis. It is not solely a pharmacotherapeutic solution to TB patients, but also a public health services

management technique that includes policy-making, case identification by quality-assured bacteriology, short-term chemotherapy, patient compliance surveillance, appropriate medical supply, and sound monitoring systems (Sandhu, 2011). In Malaysia, DOTS program has been adopted by Ministry of Health since 1984 and TB treatment with DOTS strategy has been proven to be a successful, innovative and effective approach for controlling TB epidemic (World Health Organization, 1999).

The idea from introducing DOTS program is to help patients complete their anti-TB therapy course as quickly as it is possible, without unnecessary interruptions, to prevent the spreading of TB infection from patient to another, to decrease the risk of developing drug-resistant TB that results from erratic or incomplete treatment and to avoid unsuccessful TB treatment outcomes including treatment failure and relapse. For the reason of the inability to predict if the patients will take the prescribed medications correctly as directed, DOTS program was implemented to enhance patients' adherence to the medication course. Studies show that 86-90% of patients receiving anti-TB treatment under DOT complete the therapy, in comparison to 61% for those on self-administered therapy (Minnesota Dept. of Health, 2022).

1.6 Problem statement

TB continue to be a global health issue, even though the global incidence has declined in the latest few years. In Malaysia, the current incidence of TB is 92 per 100,000 population and 7.1 per 100,000 population TB death rate yearly, which creates a significant national health problem (Ministry of Health Malaysia, 2021). TB is concomitant with a breakdown in the immune system that clarifies an established link between active TB disease and non-communicable diseases (Diabetes mellitus (DM)) as well as communicable diseases (Human immunodeficiency virus (HIV), HBV and

Hepatitis C virus (HCV)) that may significantly weaken the immune system. In the current era, TB itself impacts humans' life negatively and its burden could be doubled with the association of other comorbidities in developing countries, including Malaysia (Bates et al., 2015).

Previous studies have reported sputum smear conversion at second month of treatment as a predictor of successful outcomes, whereas delayed conversion after second month with prolonged treatment duration and unsuccessful treatment outcomes, but there is a scarcity in the published information regarding the predictors of delayed sputum smear conversion in Malaysia.

Although recent studies have reported different associated factors with unsuccessful TB treatment outcomes, few studies have figured out the effect of laboratory values on anti-TB treatment outcomes, specially mortality. Literature shows lack evidences on this association and possible mechanisms. The increasing rate of mortality among TB population in Malaysia opposing the global decrease in the overall rate, triggering the need for further research to find out factors associated with the mortality among TB patients and possible explanations.

Furthermore, drug resistant TB have emerged as another TB-related health issue undermine the global and national efforts to control TB spread. The number of MDR-TB cases in Malaysia are increasing significantly. Few published studies evaluated the occurrence, management and treatment outcomes among MDR-TB patients (Minstry of Health Malaysia, 2016). Therefore, the purpose of the current study was to evaluate the treatment outcomes and its associated factors in TB and MDR-TB patients in Malaysia.

1.7 Rationale of the study

Evaluating the management and treatment outcomes of patients is an effective tool for analyzing the efficacy of a program (Leimane, et al., 2005). The current study evaluated the management and treatment outcomes of TB and MDR-TB patients. The study conducted at Hospital Pulau Pinang might assess the efficacy of national TB control program, and enable the program managers to identify the problems.

The present study by evaluating i) predictors of delayed sputum smear conversion ii) management and risk factors for MDR-TB, iii) treatment outcomes and risk factors for unsuccessful outcomes among drug-susceptible TB, and iv) predictors of successful treatment outcomes among TB patients, might help clinicians to recognize high risk groups. Providing special attention and enhanced clinical management to patients with identifiable risk factors might improve treatment outcomes.

The present study evaluated the drug resistance pattern among MDR-TB patients. It would assess the suitability of the guidelines that recommend empirical regimen for the management of MDR-TB. It will help in optimizing the individualized empirical drug therapy.

1.7.1 General objective

To examine the factors associated with TB treatment outcomes and the emergence of MDR-TB among study population.

1.7.2 Specific objectives

i. To evaluate drug resistance pattern by DST and contributing factors associated with developing MDR-TB among TB patients.

ii. To determine the clinical outcomes of tuberculosis treatment in drug susceptible and MDR-TB patients.

iii. To determine the risk factors for mortality among drug-susceptible TB patients.

iv. To evaluate the factors associated with delayed sputum smear conversion after 2 months of treatment among drug-susceptible TB patients.

v. To determine the predictors of successful treatment outcomes among drug-susceptible TB patients.

CHAPTER 2

LITERATURE

Global picture of TB burden reflects a decrease in the incidence of TB but not enough to reach the target of WHO (≥35% reduction), showing that the transmission of the disease still active. Also, a dramatic increase in mortality rate in 2020 has arose, challenging the efforts made to control TB spread nationally and globally. The published literature referred the high rates of death among TB patients to co-morbid diseases, such as HIV, DM, HBV and HCV as well as several sociodemographic and clinical factors (World Health Organization, 2014).

Furthermore, MDR-TB constitutes another major global obstacle when seeking to eliminate tuberculosis (TB), and is also a significant public health problem (Y. Kang et al., 2021). Treatment is challenging; long-term use of SLD that are more toxic and less effective than first line drugs is essential (Bastos et al., 2017). Treatment outcomes remain unsatisfactory, the proportion of MDR-TB patients in a 2021 global cohort who successfully completed treatment was only 57%, which trigger the need for further researches to determine the reasons behind MDR-TB occurrence and poor treatment outcomes (World Health Organization, 2014).

2.1 Drug resistant pattern

Drug resistant pattern of *Mycobacterium tuberculosis* varied between countries and the information regarding the MDR-TB are scarce, as the global pattern of MDR-TB is not well known. Mesfin and colleagues, 2018, conducted a cross-sectional study from June/2015 to December/2016, for the aim of investigating the drug resistant patterns among MDR-TB suspected patients in Addis Ababa, Ethiopia. Patients'

related characteristics and sputum samples were collected from 358 MDR-TB suspected patients. Sputum samples were analyzed by using Ziehl-Neelsen technique, GeneXpert MTB/RIF assay and data were analyzed by SPSS version 23. Out of 358 patients, 226 patients had positive *Mycobacterium tuberculosis* culture, of them 133 (58.8%) were males. DST results showed a majority of 122 (54%) patients resistant to any FLD, among them 110 (48.7%) patients resistant to isoniazid, 94 (41.6) to streptomycin, 89 (39.4%) to rifampicin, 72 (31.9%) to ethambutol, and 70 (30.9%) to pyrazinamide. A total of 89 (39.4%) patients diagnosed with MDR-TB, where 52/89 (58.4%) were resistant to all FLD.

Another cross-sectional study took place in Guizhou, China in 2019, to determine the drug resistant pattern of *Mycobacterium tuberculosis* isolates and to investigate MDR-TB trends in a central hospital in Guizhou between 2008-2015. The clinical isolated were collected from PTB patients registered between Jan/2013 till Dec/2015 to analyze the resistant pattern against FLD and SLD followed by a comparison with two previously published studies. Out of 462 isolates collected, 77 (16.7%) showed resistant to rifampicin, 96 (20.8%) to isoniazid, 59 (12.8%) to ethambutol and 79 (17.1%) to streptomycin. Sixty-six (14.3%) patients diagnosed with MDR-TB. In addition, 85 (18.4%) were resistant to one of the fluoroquinolones drugs and 37 (10.2%) were resistant to one of the injectable SLD. The trend of drug resistant TB has declined from 2008-2015 at the hospital site (Lan et al., 2019).

2.2 Risk factors for development of MDR-TB

The emergence and prevalence of drug-resistant TB has a strong relation with the past and present management of TB and it can be avoided by successful treating of drug-susceptible TB. Risk factors for drug-resistance can be divided in two categories: factors associated with selection of resistance in the community and factors related to the patients' conditions that appear to make some of them more vulnerable to resistance (Caminero, 2010).

2.2.1 Previous treatment

Previous exposure to anti-TB treatment is a proved risk factor for the emergence of drug-resistant TB as well as unsuccessful MDR-TB treatment outcomes. (Iradukunda et al., 2021) conducted a case-control study in Burundi, a sub-Saharan African country to identify the key factors influencing MDR-TB among patients infected with TB and to predict the probability of MDR-TB occurrence among drug susceptible TB patients and the associated factors. A total number of 180 TB patients, 60 cases and 120 controls were included in the study took place in Kibumbu Sanatorium and Bujumbura anti-tuberculosis centres from 1st August 2019 to 15th January 2020. Patients with a history of TB treatment were at two times higher risk to have MDR-TB than patients receiving TB treatment for the first time. The complete absence of isoniazid resistance test in the country as well as treatment of all RR-TB patients as MDR-TB patients were the main limitations. More addition, the study suffered from small sample size due to the nature of conditions under study.

2.2.2 Treatment adherence

Many people find difficulties to complete their anti-TB treatment due to the long duration of treatment course, which is a key barrier to eradicating the disease (Cuneo & Snider Jr, 1989). Poor treatment adherence can result in prolonged infectiousness, drug resistance, TB relapse, or even death. Mohd Shariff and collegues, 2016, investiagted the contributing factors of the development of MDR-TB among TB patients through an unmatched case-control study of patients received anti-TB treatnment from April 2013 until April 2014. A total of 150 patients with confirmed TB diagnosis, 30 local (malay) MDR-TB cases and 120 drug-susceptible TB controls were included in the study carried out at the Institute of Respiratory Medicine located in Jalan Pahang, Kuala Lumpur, Malaysia. The results showed patients non-adherent to the prescribed treatment were at 4 times higher risk and patients treated previously with anti-TB drugs at 8 times morelikely to develop MDR-TB. The study was conducted in one govermental center and did not include patients treated in private sector, for that the results could not be generalized. Also the study included only local TB patients excluding TB patients from other countries received their treatment in Malaysia (Mohd Shariff et al., 2016b).

2.2.3 Human immunodeficiency virus (HIV)

HIV reduces immunity, predisposes patients to infections and activates latent one. HIV co-infection in TB patients has significantly increased the risk for developing MDR-TB. Workicho and collegues, 2017, conducted a case-control study for the aim of identifying the risk factors for MDR-TB among TB patients. The study was carried out in St. Peter's TB Specialized Hospital, Addis Ababa, Ethiopia, the only health care center where treatment for MDR-TB was provided for patients from all states of

Ethiopia. Among all TB patients who were treated and followed up, 180 patients, 90 MDR-TB cases and 90 non-MDR-TB controls were included in the final analysis. Interviews were conducted with the participants in the study using a pretested structured questionnaire and medical records of the patients were reviewed. Multivariable logistic regression results indicted history of previous TB treatment and being HIV infected as independent predictors of MDR-TB. Patients coinfected with HIV were three times more likely to develop MDR-TB than non-HIV patients. The study was conducted at time there was no treatment center other than the study site, so the information needed to understand the drug resistant situation at the country was limited (Workicho et al., 2017).

2.2.4 Diabetes mellitus

Diabetes mellitus (DM) also found to be a risk factor for the emergence of MDR-TB as well as for unsuccessful treatment outcomes among drug susceptible and MDR-TB patients (Alisjahbana et al., 2007;Kang et al., 2013). A case-control study conducted by Baghaei and colleagues, 2016 aimed to determine the effect of DM on anti-tubercular drug resistance in new TB cases. The study included 124 TB patients who were registered and hospitalized from May 2013 to October 2013 at the National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Iran, divided in to 62 newly diagnosed TB patients with diabetes as cases and 62 newly diagnosed TB patients without diabetes as controls. DM was a significant factor associated with resistance to any anti-TB drug, new TB patients with diabetes were at approximately 5 times greater risk to develop drug resistance, particularly MDR-TB than new TB patients without diabetes. The small sample size in both case and control group limited

further assess to other risk factors related to drug resistance occurrence (Baghaei et al., 2016).

2.2.5 Alcohol consumption

Alcohol consumption is one of patients' lifestyle factor showed to have relation with the occurrence of drug resistance TB. Desissa and colleagues, 2018 designed a case-control study for the purpose of assessing the predicted factors associated with the emergence of MDR-TB among patients under MDR-TB treatment course. The study conducted from February 2016 to April 2016 at two community hospitals in Ethiopia, where 219 patients were included, 73MDR-TB cases and 146 non-MDR-TB controls. Primary data was collected through an interviewer-administered structured questionnaire and data from clinical records was collected by using a checklist. Patients previously treated with anti-tubercular drugs were at higher odds of developing MDR-TB as well as alcoholic patients were 4 times more likely to develop MDR-TB than non-alcoholic patients. The study had limitations summarized in unidentified factors proved to be associated with the development of MDR-TB such as HIV co-infection due to small sample size and because some of the information collected was dependent on the study participants' recall capacity, there could have been recall bias in the study (Desissa et al., 2018).

2.2.6 Marital status

Marital status as a sociodemographic characteristic found to be related with the emergence of MDR-TB. Despite the fact that there is no biological relation between the marital status of the patients and TB, single people are at increased hazard to be infected with TB or MDR-TB strains compared with married ones (Mohd Shariff et

al., 2016b).Age and gender have contradicted reported association with the occurrence of MDR-TB (Gao et al., 2016;Mulu et al., 2015;Workicho et al., 2017;Zhao et al., 2012).

2.3 Clinical outcomes

Important indicators for assessing the effectiveness of the national tuberculosis control program include monitoring the results of TB treatment and fully understanding the causes of unfavorable treatment outcomes. Therefore, Atif and colleagues, 2018, conducted a retrospective cohort study to identify the outcomes of TB treatment among a population of PTB patients and the risk factors associated with unsuccessful treatment. The study was carried out at the Bahawal Victoria Hospital (BVH) in southern Punjab, Pakistan. Patients' related sociodemographic and clinical characteristics were collected from their medical records and analyzed by SPSS version 21.0. A total of 969 TB patients' files were reviewed and 690 PTB patients were included in the final analysis. Majority of patients were male and aged between 15-24 years old. At the end of anti-TB course, 163 (67.3%) confirmed cured and 4 (1.7%) patients completed their treatment. On the other hand, 10 (4.1%) patients failed the treatment, 38 (15.7%) default treatment and 18 (7.4%) passed away. Multiple logistic regression model indicated relapsed TB cases, smokers and patients with positive sputum at second month of treatment at higher risk to achieve unfavorable TB treatment outcomes.

Another study was conducted in Taiz and Alhodidah, Yemen for the aim of identifying the factors related to unfavorable TB treatment outcomes. Prospectively, patients newly diagnosed with positive smear PTB were followed up at the two centers from Apr/2014 to Mar/2015 and their information were obtained on standardized forms.

Patients' related data were analyzed by PASW version 22.0. Out of 273 cases included, 227 (83.1%) success the treatment, where 46 (16.9%) achieved unsuccessful outcomes. Among 46 patients, 29 (10.6%) loss the follow up, 6 (2.2%) transferred out, 6 (2.2%) failed the treatment and 5 (1.8%) died. Multivariate logistic regression analysis showed that female gender, illiterate status, and comorbid diseases were significantly associated with unsuccessful treatment outcomes (Jaber et al., 2017).

2.4 Mortality rate among TB patients

Although the number of TB deaths reported annually is decreasing globally, the rate of decrease is not fast enough to meet the End TB Strategy's 35% reduction target between 2015 and 2020. Only a 14% decrease in mortality rate was reported by the WHO between 2015 and 2020(World Health Organization, 2020). In 2019, TB claimed the lives of nearly 1.2 million HIV-negative people (range 1.1-1.3 million) and 208,000 HIV-positive people (range 177,000-242,000) (World Health Organization, 2020).

South-East Asia, in which Malaysia is part, had the highest number of HIV negative/TB deaths, with 632,000 (range 593,000-671,000) deaths reported in 2019, followed by Africa with 378,000 (range 313,000-448,000) deaths. In 2019, 1 million (range 966,000-1.1 million) patients infected with TB died in high TB burden countries, accounting for roughly 86% of global TB-related mortality. The majority of TB deaths occurred in India, with 436,000 (range 404,000-469,000) patients died in 2019 (World Health Organization, 2020).

Malaysia is a Southeast Asian country with a population of 29.7 million people in 2020, according to estimates. The incidence rate of TB in the country fluctuated