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REVIEW ARTICLE

Tuberculosis in Malaysia: disease timeline, epidemiology, control initiatives and outlook

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Abstract
In Malaysia, tuberculosis remains a public health problem despite initiatives in disease control and prevention. This review explores the timeline of pulmonary tuberculosis (PTB) in Malaysia, epidemiology, management and outlook of the disease in the country. PTB was first reported in Malaya in the early 20th century and caused high morbidity and mortality. With the establishment of the National TB Control Program in 1961 and chest clinics in every state general hospital, mortality was successfully reduced. Nonetheless, PTB incidence rate increased steadily after 2011, and Malaysia is currently an endemic country for the disease. Diagnosis for PTB is performed according to the Ministry of Health's *Clinical Practice Guidelines* which include chest X-ray, sputum culture and antibiotic susceptibility testing. Patients are treated according to WHO guidelines. While the country has seen a 0.02% decrease in drug-resistant cases in recent years; two cases of extensively drug-resistant tuberculosis have been reported. All major *Mycobacterium tuberculosis* lineages (Indo-Oceanic; East-Asian (including Beijing), East-African-Indian and Euro-American) have been reported in the country. The Beijing family of strains were found to have a higher prevalence in Peninsular Malaysia compared to Sabah and Sarawak, suggesting divergence of pathogen evolution between the two locations. Most antibiotic-resistant strains were found to harbour mutations in *rpoB, katG, embB* and *pncA*. Increasing usage of molecular platforms and artificial intelligence in diagnostics, apps and alert systems for better surveillance, and implementation of universal coverage in terms of treatment will be important for the country to achieve a tuberculosis-free status in 2035.

Keywords: pulmonary tuberculosis, Malaysia, TB disease timeline, TB epidemiology, *M. tuberculosis* lineages in Malaysia, TB control initiatives

INTRODUCTION

Tuberculosis (TB) is a disease caused by a group of mycobacteria in the *Mycobacterium tuberculosis* (Mtb) complex family that can infect both humans and animals; Mtb *sensu stricto* is the species causing disease in humans.[1,2] The bacteria primarily attack the lungs, causing pulmonary tuberculosis (PTB). It can also infect sites outside the lungs, such as the brain, spine, and bones, causing extrapulmonary tuberculosis. Mtb spreads through respiratory droplets from individuals with PTB when they sneeze or cough. For a healthy individual, Mtb is usually eliminated by the immune system; however, some bacteria may evade this defence and cause latent TB, which can develop into active TB if the immune system weakens.[3,4] This review explores the timeline of PTB in Malaysia, epidemiology, management and outlook of the disease in the country.

Tuberculosis in Malaysia

Malaysia is a country in Southeast Asia, with Peninsular (West) Malaysia located between Thailand and Singapore, and East Malaysia (states of Sabah and Sarawak) located on the island of Borneo. Early cases of TB in Malaysia were not properly documented, but it was speculated that the disease reached Malaya (colonial Malaysia) around the early 20th century during British colonialism.[5] In 1945, PTB was reported to cause more than 3,000 deaths, with more than three-quarters of deaths occurring in the hospital. When PTB patients quadrupled in the ’50s, the number of deaths reached 6,000 a year.[6,7] To counter the onslaught of the disease, the Malaysian government launched the National TB Control Program (NTCP) in 1961, spearheaded by the National TB Centre (now known as The Institute of Respiratory Medicine (IPR)) headquartered in Kuala Lumpur, and established chest clinics in every state general hospital as part of its network. With the launch of this program, the number of deaths due to TB has been successfully reduced to less than 10 deaths per year.[8]

Between the launch of the NTCP and 1997, very few data can be found on TB cases in Malaysia. Sodhy (1964) mentioned that TB distribution was more focused in urban areas[7] and this finding was subsequently supported by multiple studies.[9–11] Between 1977 and 2000, the TB incidence rate (IR) in Malaysia ranged from 55 to 90 cases per 100,000 population, with the majority of cases being PTB.[8]

The IR of TB in Malaysia displayed a downward trend during the early 2000s (2000–2010), with an average of 71 cases per 100,000 population (FIG 1). However, the trend reversed from 2011, with a rise in TB IR observed until 2014. Between 2015 and 2020, the IR remained steady at an average of 92 cases per 100,000 population. Alarmingly, TB IR reached a four-decade high in both 2021 and 2022, with respective rates of 97 and 113 cases per 100,000 population. The increment of TB IR was also seen internationally in 2021, a year after the start of the COVID-19 pandemic, possibly due to the pivoting of most resources towards pandemic mitigation. Subsequently, with a notification rate of more than 100 cases per 100,000 population, Malaysia is currently an endemic country for TB.[12,13]

FIG 1. Trend for TB IR per 100,000 population per year from 2000 – 2022.[12]

FIG 2 and 3 show the number of cases and IR of each state in Malaysia from 2018 – 2022. Sabah (22.05%), Selangor (20.63%), and Sarawak (11.39%) had the most cases, while Labuan (0.46%), Perlis (0.56%) and Melaka (2.0%) recorded the lowest number. Nonetheless, by IR, the top contributors of TB rate notifications are Sabah, Labuan and Kuala Lumpur.[14–18] Sabah makes up only 11% of the Malaysian population of 33.5 million[19,20]; however, the state represents approximately 14.78% of total national TB IR, with Kota Kinabalu, Semporna and Pitas being hotspots due to urbanization and border porosity.[21]

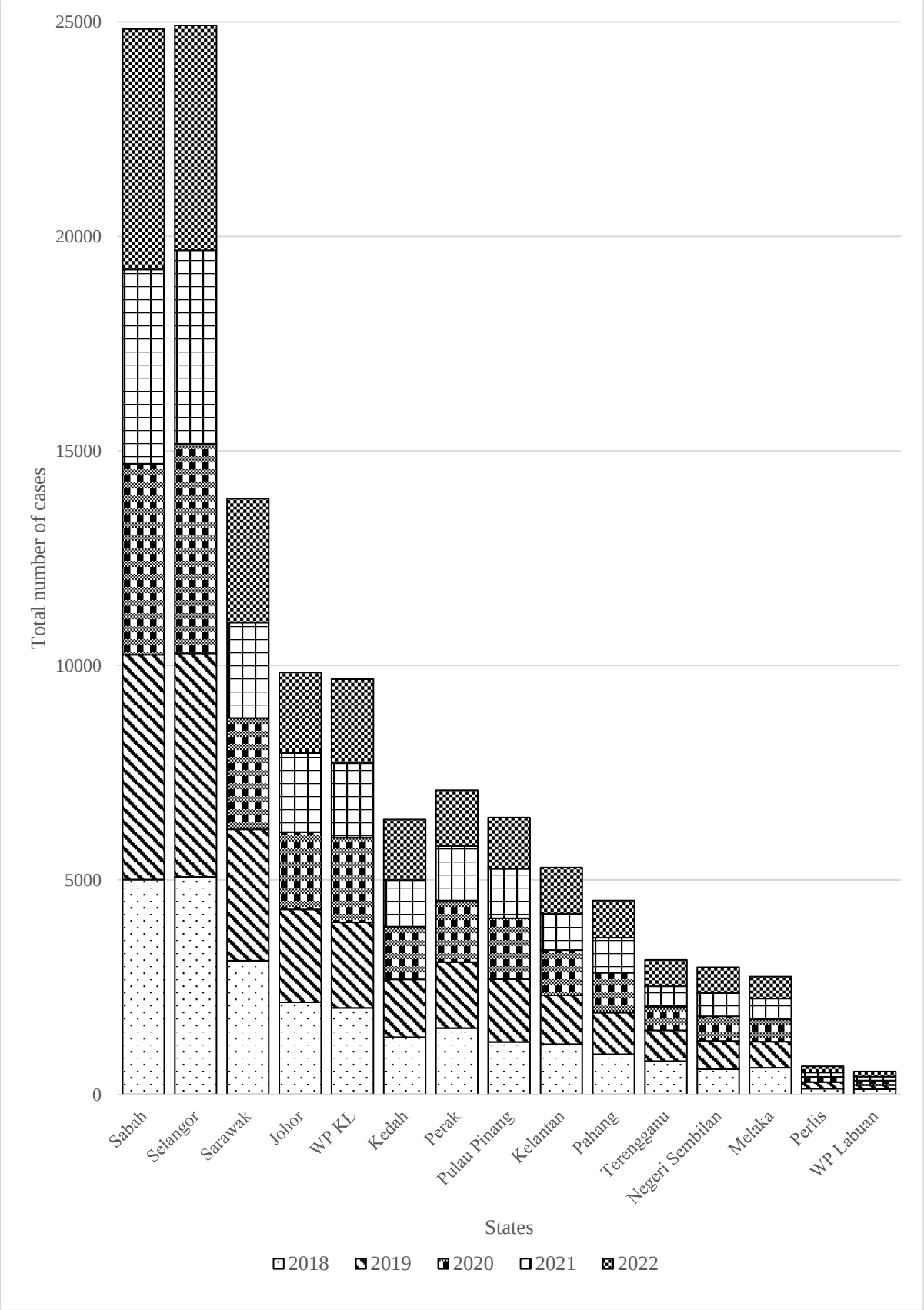

FIG 2. TB cases by state from 2018 – 2022.[14–18]

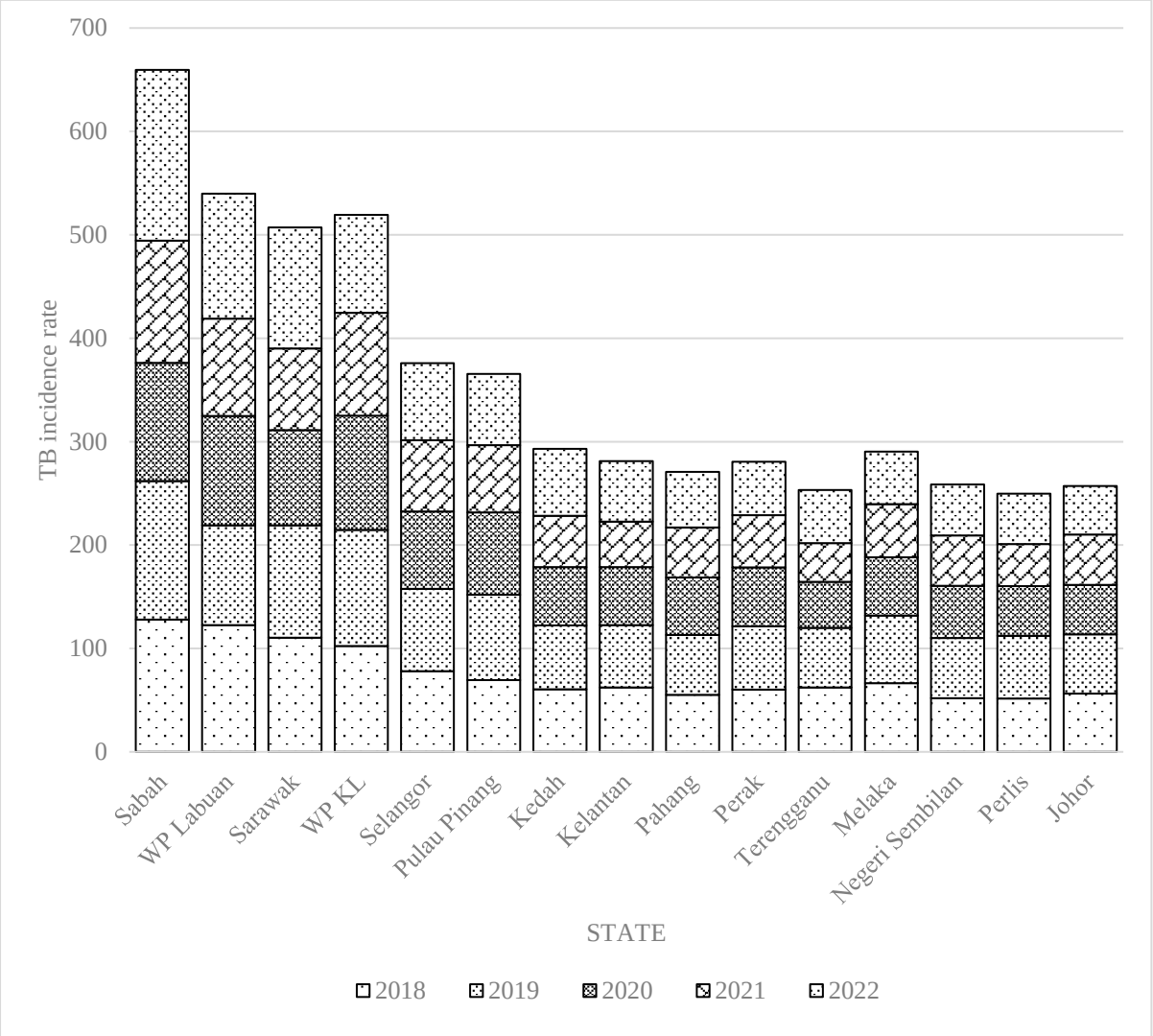

FIG 3. TB IR by state from 2018 – 2021.[14–18]

Clinical manifestations of PTB in Malaysia

Individuals with active PTB exhibit a variety of debilitating symptoms. The most common symptom is a persistent cough that lasts more than three weeks, sometimes accompanied by blood. Other frequent symptoms include chest pain, fatigue or weakness, fever, night sweats, loss of appetite, and sudden weight loss.[22] A retrospective study by the IPR reported similar clinical manifestations of PTB in Malaysian patients, including cough, fever, sputum production, lymphadenopathy and chest infiltrates, as observed in patients from other countries.[23–25]

PTB diagnosis in Malaysia

The Malaysian Ministry of Health (MOH) plays a crucial role in ensuring standardized and effective diagnosis of TB through the established Clinical Practice Guidelines – Management of Tuberculosis Fourth edition.[26] These guidelines outline a multi-pronged approach to identify TB cases, particularly PTB.

In symptomatic patients, the initial step for diagnosis involves collection of sputum samples (gastric aspirate or nasopharyngeal aspirate for children). The sputum will be stained for acid-fast bacilli, prior to mycobacterial culture using the Löwenstein–Jensen medium. Cultures are then incubated for a maximum of eight weeks. Concurrently, chest X-rays will be conducted for adults, as this remains the primary modality used in Malaysia to support the diagnosis and management of PTB. For paediatric patients, tuberculin skin tests and the Interferon Gamma Release Assay (IGRA) will be carried out; though, diagnosis is usually difficult due to non-specific clinical symptoms and the limited utility of tuberculin skin testing that relies on the reaction of the immune system.[27] Upon positive identification of Mtb growth, drug-susceptibility tests via BACTEC MGIT will be conducted to guide treatment.

In recent years, the GeneXpert MTB/RIF assay (Cepheid, USA) may be used (especially in private medical centres[28]) when TB is suspected in sputum smear-negative cases. The RIF assay detects the presence of Mtb and identifies potential resistance to rifampicin at the same time. Nonetheless, the cost of the test remains challenging for many patients from the lower-income community,[29] who unfortunately has a higher risk for the disease. In some hospitals, the lateral flow urine lipoarabinomannan assay is offered to detect PTB in HIV-positive adults, making diagnosis in this high-risk population safer. Once PTB is diagnosed in Malaysia, the case must be notified to the MOH via the District Health Office.[26]

PTB Treatment in Malaysia

TB causes considerable morbidity and mortality.[30] Nonetheless, the disease can be treated with antibiotics, provided that patients comply with their prescribed treatment regime.[31] TB treatment in Malaysia is prescribed according to the WHO guidelines. Patients who are drug-susceptible are treated with four different kinds of antibiotics, namely rifampicin, isoniazid, ethambutol and pyrazinamide. They are required to take these antibiotics daily for the course of six months, with two months of intensive phase that consists of all four antibiotics, and four months of continuation phase with isoniazid and rifampicin. It is important for patients to take their medications daily to stop the growth and eliminate Mtb in their body, and to prevent from relapsing.[32]

Nevertheless, treatment in Malaysia is not without its challenges, such as delays in the diagnosis of smear-negative PTB, extrapulmonary TB and TB in children. There are also cases of treatment default and non-adherence.[26] For drug-resistant patients, the treatment requires knowledge on the resistance profile of the strains that are infecting the individual (refer Table 1).

Table 1. Drug-resistant classification of Mtb based on their resistance profile.[33,34]

Classification of drug-resistant Mtb	Definition
Mono-resistant	Resistant towards one of the first-line drugs
Isoniazid-resistant (Hr-TB)	Resistant towards isoniazid only
Rifampicin resistant (RR)	Resistant towards rifampicin
Poly drug-resistant	Resistant towards two or more of the first-line drugs, not including isoniazid and rifampicin
Multidrug-resistant (MDR)	Resistant towards at least rifampicin and isoniazid
Pre-extensive drug-resistant (Pre-XDR)	Resistant towards rifampicin, isoniazid and at least one fluoroquinolone (levofloxacin/moxifloxacin)
Extensive drug-resistant (XDR)	Resistant towards rifampicin, isoniazid, at least one fluoroquinolone and at least one other drug in 'Group A' (bedaquiline/linezolid)

Based on the 2022 update of the WHO operational handbook on tuberculosis for drug-resistant treatment, it is recommended that for patients with MDR/RR-TB that is susceptible or having unknown resistance towards fluoroquinolones to be administered a six-months or 26-week regime of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM). If the infecting strain was found to be resistant, or developed resistance towards moxifloxacin during treatment, the drug may be dropped in the regime, while the other drugs in the BPaL regime is continued. Patients may also opt for the nine-months all oral regime, consisting of bedaquiline, levofloxacin/moxifloxacin, clofazimine, pyrazinamide, ethambutol, high-dose isoniazid and ethionamide, if the Mtb is resistant towards rifampicin and susceptible towards fluoroquinolones. The longer MDR/RR-TB treatment regime (Table 2) should only be use for patients that would not benefit from either BPaLM/BPaL or all oral regimes.[33,34]

Table 2. Treatment grouping and antibiotics recommended by WHO in the longer MDR/RR-TB treatment regime.[33,34]

Treatment regimen	Antibiotics
Group A: Include all three antibiotics	Levofloxacin *or* moxifloxacin Bedaquiline Linezolid
Group B: Addition of one or both antibiotics	Clofazimine *or* cycloserine Terizidone
Group C: Add to complete the regime and when medications from Group A and B could not be used	Ethambutol Delamanid Pyrazinamide Imipenem-cilastatin *or* meropenem Amikacin *or* (streptomycin) Ethionamide *or* prothionamide P-aminosalicyclic acid

In general, less Malaysian citizens were reported to develop moderate or advanced illness ($p<0.0001$) compared to non-citizens when a chest X-ray has been performed for the patient.[21] This was most probably due to the free treatment for TB provided for Malaysians once the disease is diagnosed. Thus, treatment success rate for Malaysians has been higher compared to undocumented Malaysians or non-citizens.[35] This implicates the importance of public health measures in controlling the disease.

Intriguingly, in another study, Malaysians were reported to have a greater mortality risk from the disease compared to economic migrants in the country; authors conclude that this observation may be due to under-reported cases and deaths attributable to PTB among the migrant community compared to Malaysians.[36] Comparatively, Malay Malaysians had a higher mortality risk among TB/HIV co-infected patients,[37] though, intriguingly, Chinese and Indian Malaysians had a higher tendency to develop MDR-TB (OR 6.23, CI 95% 2.24 – 9.68; OR 3.17 CI 95% 1.04 – 9.68).[38]

TB antibiotic resistance in Malaysia

In Malaysia, the resistance of DR-TB strains towards antibiotics poses a multidimensional challenge to tuberculosis control and management. Susceptibility testing of Mtb isolates varies among healthcare facilities; nonetheless, specific resistance patterns have been observed, indicating the circulation of various DR-TB strains in the country. Based on the Global Tuberculosis Report,[39] Malaysia reported a 0.02% decrease in new DR-TB cases, where the prevalence of MDR/RR-TB is still low in Malaysia. However, Mtb resistance towards isoniazid and rifampicin has become a major concern worldwide, including in Malaysia. FIG 4 shows the trend of DR-TB cases from 2018 to 2022 in Malaysia. While the number of cases for RR-TB showed a steady decline, the number of HR-TB cases showed an alarming increase. These findings are corroborated by studies from multiple countries.[40–42] The rising trend of Hr-TB could be attributed to a lack of focus on identifying and managing isoniazid resistance, potentially leading to the development of MDR-TB.

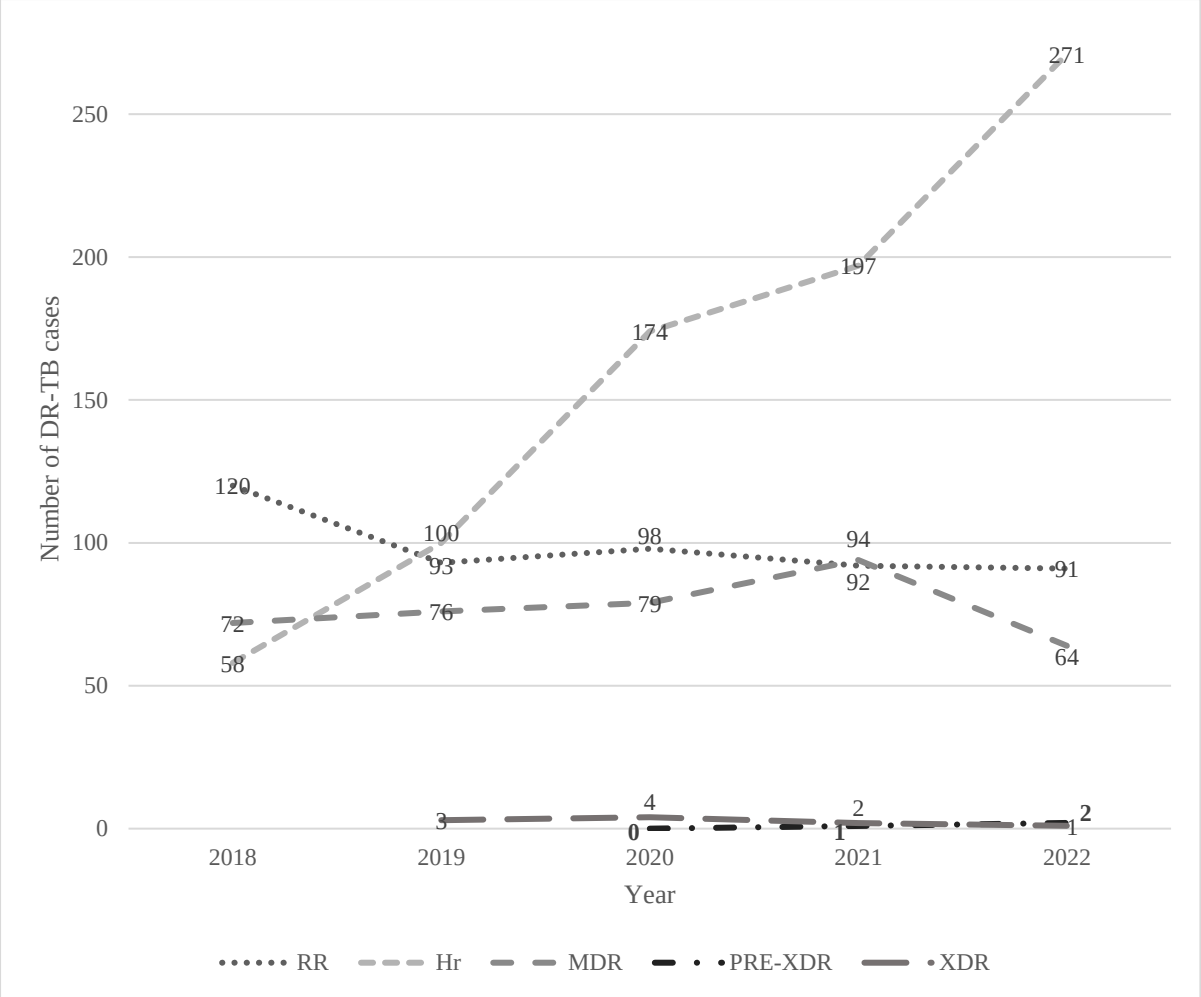

FIG 4. Trend of DR-TB cases in Malaysia, 2018 - 2022 (Unpublished data from MOH).

In addition to MDR-TB, Malaysia has also recorded cases of XDR-TB. One case was reported in Universiti Malaya Medical Centre Kuala Lumpur; while another was reported in Queen Elizabeth Hospital in Kota Kinabalu, Sabah. Both strains were reported to be resistant to rifampicin, isoniazid, streptomycin, kanamycin and ofloxacin, but susceptible towards para-amino salicylate sodium.[43,44]

Mtb genotypes and lineages reported in Malaysia

Mtb lineages that cause diseases in humans include those from lineages 1, 2, 3, 4, 7, 8 and 9, with lineages 1 - 4 included in the six major global Mtb complex lineages. These lineages are associated with the geographical origin of ancestral Mtb strains, with lineage 1 as Indo-Oceanic (IO); lineage 2 as East-Asian (including Beijing) (EA), lineage 3 as East-African-Indian (EAI); and lineage 4 as Euro-American (EuA). Mtb from lineage 1 is considered 'ancient', while the other Mtb lineages are considered 'modern' in evolution.[2] The basis for these lineages were firstly established using large sequence polymorphisms[45] and spoligotyping.[46] More recently, an SNP barcode for Mtb genotyping and also whole genome sequencing (WGS) are now commonly used[47] to determine Mtb lineage.

All major Mtb lineages (IO, EA, EAI and EuA) have been reported in Malaysia.[48,49] One of the earliest reports on Mtb genotypes in Malaysia was performed via spoligotyping by IPR on 439 strains collected from various states of Malaysia between 1993 and 1994.[50] At the time, the

Beijing (EA) family of strains was found to have a higher prevalence in Peninsular Malaysia but not in Sabah and Sarawak, suggesting that Mtb evolution is divergent between Peninsular and East Malaysia. About a decade later, a multicentre study on 51, 22, 18 and 12 MDR strains isolated from the Philippines, Vietnam, Indonesia and Malaysia, respectively, between the years of 1996 to 2006 was published.[51] Spoligotyping identified most of the strains used in this study to be from the EAI (n = 41, 39.8%) or Beijing (n = 32, 31.1%) families; however, specific information about the country from where each strain was isolated from was not mentioned in the report. The study also reported *rpoB 531* (rifampicin resistance) and *katG 315* (isoniazid resistance) mutations in more than 50% of the EAI and Beijing strains. With spoligotyping, another 36 and 184 Mtb strains isolated between 2009 and 2013 from Kuala Lumpur and Kelantan, respectively, also showed dominance of EAI (56.4%), followed by Beijing (28.6%). The investigators observed slightly higher antibiotic resistance in Beijing strains compared to the ones from EAI; however, the difference was not significant.

Subsequently, whole genome analysis of 15 MDR-TB strains isolated from several states in Peninsular Malaysia during the same period (between 2009 and 2012) revealed that the majority (n = 11, 73.3%) of the strains were of the EA lineage; three were IO (27.3%), while one (9.1%) strain was EuA.[52] Most strains harboured *rpoB* and *katG* mutations; two strains harboured the G7362C and G9304A mutation in *gyrA* (fluoroquinolone resistance), respectively. In another WGS study on 23 Mtb isolated in 2017 found a slightly higher prevalence of IO strains (n = 11, 47.83%), followed by EA (n = 8, 34.78%), EAI (n = 3, 13.04%) and EuA (n = 1, 4.35%)[48]. Of note, 50.0% of the strains in Fakhruzzaman et al.'s study was also MDR-TB, harbouring 26 SNPs in nine resistance-associated genes towards 10 different TB antibiotics. A subsequent larger study on 56 Mtb isolates collected throughout 2017 and 2019 from central Peninsular Malaysia reported dominance of the EA strains (N = 40, 71.43%), followed by smaller frequencies of IO (N = 10, 17.86%), EuA (N = 5, 8.93%) and EAI (N=1, 1.79%). Interestingly, these were also mostly antibiotic-resistant Mtb strains (N = 54, 96.4%) with mutations in *rpoB*, *katG*, *embB* (ethambutol resistance) and *pncA* (pyrazinamide resistance).[53]

For East Malaysia, a recent study conducted in Sabah on 208 strains isolated from 2012 – 2017 reported a higher prevalence of IO (n = 195, 93.8%), compared to EA (n = 8, 3.8%) and EuA (n = 5, 2.4%). The higher prevalence of IO strains at Sabah compared to Peninsular Malaysia might be due to the closer proximity of the state to the Philippines, where the IO lineage has been reported to be dominant.[54] As the investigators also collected information on the TB patients' characteristics, they found higher rates of culture conversion failure in patients infected with EA strains, even though majority of the tested strains (n = 193, 93%) were phenotypically susceptible to all first-line TB antibiotics. This suggests the EA strains in Sabah have greater virulence compared to the other lineages.

Outlook of TB management in Malaysia

Malaysia aims to be a TB-free country by the year 2035 with timely diagnosis, accessible treatment and improved surveillance for the disease.[55] To this end, the NTCP includes periodical updates of clinical practice guidelines,[26] development of reference booklets for healthcare providers, improving case detection with contact tracing[56] and active surveillance via the national case-based TB registry (MyTB).[21]

The current protocol for TB diagnosis in Malaysia is still very much dependent on sputum culture and chest X-ray, with some laboratories offering molecular diagnostics on the GeneXpert MTB/RIF platform.[28] Beyond this, a study is currently being conducted by the Ministry of Health (The National Institute of Health, Disease Control Division and IPR) to

evaluate the performance of artificial intelligence software (Putralytica and Qure.ai) for TB diagnosis via chest X-rays.[57] In a separate development, computer-aided diagnosis via DeepPulmoTBNet (DPTBNet) has been developed for reading computerized tomography scans of TB lesions, leading to better segmentation of the disease and improved classification of infected lung cavities.[58]

Once TB has been diagnosed, patients are subjected to antibiotic treatment and monitoring, where patients on a standard regimen start on four antibiotics for two months, followed by two antibiotics for another four months (drug-susceptible TB).[59] The long duration of TB treatment and drug adverse reactions pose significant challenges to the patient and may lead to non-adherence to therapy, affecting clinical outcomes and spawning resistance. Directly observed therapy (DOT) has been initiated to improve treatment adherence; however, this approach may cause stigma, inconvenience and reduced economic productivity.[60] To overcome these challenges, a group of Malaysian researchers have developed and tested the Gamified Real-time Video Observed Therapy (GRVOTS) mobile app, a virtual monitoring system that connects the patient, therapy supervisor and clinic administrator.[61] Interestingly, majority of the patients showed significantly higher treatment adherence scores (95% CI: 7.29,14.46; $p < 0.001$) using the app and successfully reduced patient attrition. Separately, the inclusion of community pharmacists into the DOT programme has been mooted, where monitoring from a community pharmacist that the patient is familiar with may bridge perceived treatment adherence barriers.[62]

TB detection in Malaysia remains low and could be further improved.[63] A study by Rashid et al (2023) explored the potential of using the Autoregressive Integrated Moving Average (ARIMA) model, a time series forecasting method, to predict seasonal trends in TB cases in Malaysia. This approach could be valuable for preparedness efforts by the MOH. The study identified a recurring rise in TB cases during March and December each year; potentially contributing to the seasonal peaks were school holidays and celebrations. The ARIMA $(2,1,1)(0,1,0)_{12}$ model emerged as the most accurate predictor, demonstrating the lowest Mean Absolute Percentage Error (MAPE) and highest R-squared values. By implementing this model, the MOH could gain a six-months window of preparation to address the anticipated rise of new TB cases in Malaysia.[64]

The utilisation of apps such as MySejahtera (https://mysejahtera.moh.gov.my/ms/), initially developed for the nation's COVID-19 home surveillance, disease hotspot alert system and vaccination initiative, can be further improved for systematic tracing and treatment of individuals exposed to TB patients; this strategy may be also useful for the detection and treatment of latent TB infection. Rollout of the National BCG Vaccination Program for newborns and future vaccines, such as the M72/AS01E immunization[65] can be carried out via the app. Importantly, MySejahtera's hotspot alert system allows a community to be aware of any upsurge of active TB cases in the vicinity and adopt preventive measures such as mask-wearing to curb disease transmission. Nevertheless, while proactive case-finding and surveillance are important, the MOH faces challenges in having adequate human resources for the task.[56] Beyond the community, collaboration with The Ministry of Home Affairs and the Malaysian AIDS Council has been carried out to control TB in Malaysian prisons and HIV patients, respectively.

Importantly, as TB is very much associated with poverty and marginalised societies, the establishment of social protection schemes for patients regardless of citizenship will be crucial in eliminating the disease.[66] Even though Malaysia is currently classified as a higher middle-income country, as many as 40% of the bottom 40% of income earners live below the relative poverty line income.[67] In addition, the existence of economic migrant communities in the country complicates the management of TB.[68] Many of the migrant communities originate from high-burden countries; while they are screened to be TB-free when entering the country,

cramped living conditions in migrant worker hostels and accommodation are risk factors for the spread of the disease. Furthermore, cross-border migration influences TB transmission dynamics, raising the possibility of outbreaks and the emergence of DR-TB. Malaysia provides universal access only to its citizens for TB diagnosis and treatment; therefore, legal restrictions frequently impede the capacity of migrant communities to access timely healthcare and comply with TB treatment plans. It will be important for the country to effectively provide social protection coverage via promotion of equity and social justice in the nation, in its effort to reduce and eliminate TB.

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