

**FACTORS ASSOCIATED WITH DELAYED
SPUTUM SMEAR CONVERSION AMONG
ORANG ASLI WITH PULMONARY
TUBERCULOSIS IN MALAYSIA
FROM 2016 TO 2020**

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UNIVERSITI SAINS MALAYSIA

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By

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LIST OF SYMBOLS

$>$	More than
$<$	Less than
$\geq$	More than and equal to
$\leq$	Less than and equal to
$\%$	Percentage
N	Population size
n	Sample size
m	Ratio between two groups
α	Alpha
β	Beta
$\&$	And

LIST OF ABBREVIATIONS

AdjOR	Adjusted odds ratio
AdjRR	Adjusted relative risk
AFB	Acid-fast bacili
BCG	Bacillus Calmette–Guérin
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRP	C-Reactive protein
DOSM	Department of Statistic Malaysia
DOTS	Directly observed treatment, short-coursed
EPTB	Extrapulmonary tuberculosis
FBC	Full blood count
HIV	Human Immunodeficiency Virus
JAKOA	Jabatan Kemajuan Orang Asli
LFT	Liver function test
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug resistance tuberculosis

MTB C&S	<i>Mycobacterium tuberculosis</i> culture & sensitivity
MOH	Ministry of Health
MyTB	Tuberculosis Information System Malaysia
NGO	Non-governmental organisation
OR	Odds ratio
RBS	Random blood sugar
ROC	Receiver operating characteristic
RR	Relative risk
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
WHO	World Health Organization

ABSTRAK

Faktor-faktor Yang Berkaitan Kelambatan Penukaran Sapuan Kahak Dalam Kalangan Orang Asli di Malaysia dari 2016 sehingga 2020

Latar belakang: Tuberkulosis (TB) masih menjadi cabaran kepada kesihatan awam sedunia. Pelbagai usaha telah dibuat bagi membanteras TB, akan tetapi hasilnya masih tidak seperti dijangkakan. Pendekatan berfokus diperlukan supaya tiada yang terpinggir termasuklah kumpulan rentan seperti Orang Asli. Masyarakat peribumi yang lain di dunia mengalami kejadian penyakit TB dan kelambatan penukaran sapuan kahak yang lebih tinggi berbanding populasi umum. Penyelidikan terhadap masalah tersebut dalam kalangan Orang Asli adalah terhad, seterusnya menyukarkan usaha membanteras TB dalam kalangan mereka. **Objektif:** Kajian ini adalah bertujuan untuk mengukur peratusan TB pulmonari, menentukan ciri-ciri TB pulmonari sapuan positif, dan faktor-faktor yang berkaitan dengan kelambatan penukaran sapuan kahak dalam kalangan Orang Asli di Malaysia dari tahun 2016 sehingga 2020. **Metodologi:** Satu kajian kohort retrospektif telah dilakukan bermula Disember 2020 sehingga Mei 2021 menggunakan data surveilans MyTB. Kesemua kes berdaftar TB dalam kalangan Orang Asli bagi tempoh kajian dilakukan analisa deskriptif. Kemudian, kes TB pulmonari sapuan positif dikenalpasti dan disusuli sehingga akhir fasa intensif. Anggaran saiz sampel yang diperlukan adalah 445. Data berkenaan umur, jantina, suku kaum, lokasi kediaman, tahap pendidikan, pendapatan isi rumah, status merokok, kencing manis, status HIV, parut vaksin BCG, kategori rawatan, sapuan kahak pra-rawatan, x-ray dada pra-rawatan dan kepatuhan rawatan dikumpul menggunakan proforma dan dianalisa menggunakan perisian SPSS ver. 26. Kaedah regressi logistic mudah dan berganda digunakan bagi menentukan faktor-faktor berkaitan kelambatan

pertukaran kahak dalam kalangan Orang Asli. **Keputusan:** Terdapat 808 kes Orang Asli di Malaysia dari 2016 sehingga 2020 yang didiagnosa TB. 725 kes adalah TB pulmonari dan 572 (78.9%) kes daripadanya adalah TB pulmonari sapuan positif. Hanya 487 kes daripada TB pulmonari sapuan positif yang memenuhi kriteria kajian pada akhir fasa intensif dianalisa. Daripada jumlah tersebut, 93 (19.1%) kes berlaku kelambatan penukaran sapuan kahak. Min (SD) umur bagi TB pulmonari sapuan positif adalah 39.20 (16.33) tahun, kebanyakan adalah lelaki (63%), suku Senoi (54.9%), menetap di luar bandar (88.1%), berpendidikan formal (60.4%) dan hidup di bawah paras kemiskinan (97.1%). Faktor-faktor signifikan yang berkaitan kelambatan penukaran sapuan kahak adalah perokok (AdjOR: 3.25; 95% CI: 1.88, 5.59), diabetes mellitus (AdjOR: 12.84; 95% CI: 6.33, 26.06), dan jangkitan HIV (AdjOR: 9.76; 95% CI: 3.01, 31.65). **Rumusan:** TB pulmonary adalah TB yang paling kerap terjadi dalam kalangan Orang Asli dan kejadian ini adalah sama dengan masyarakat peribumi lain di seluruh dunia. Pendekatan yang bersasar dan strategi yang berfokus terhadap pesakit TB pulmonary sapuan positif Orang Asli dengan faktor perokok, diabetes mellitus dan jangkitan HIV hendaklah diambil kira oleh pihak berkepentingan bagi mengelakkan kejadian kelambatan penukaran sapuan kahak. Dengan tindakan yang efektif, penularan TB dapat dikurangkan, seterusnya dapat merealisasikan sasaran 'End TB'.

Kata kunci: kelambatan penukaran sapuan kahak, TB pulmonari sapuan positif, Orang Asli, peribumi, faktor berkaitan

ABSTRACT

Factors Associated with Delayed Sputum Smear Conversion Among Orang Asli in Malaysia from 2016 to 2020

Background: Tuberculosis (TB) remains a challenge for public health worldwide. Enormous efforts have been made in fighting TB, but the outcome still below the expectation. The approach needs to be focused so that no one leaves behind, including vulnerable groups such as Orang Asli. Indigenous groups worldwide have a higher TB incidence and associated with delayed sputum smear conversion than the general population. There is a limited study to understand this situation among Orang Asli, hence dampening efforts in combatting TB among them. **Objective:** The current study aimed to measure the proportion of pulmonary TB, describe the characteristics of smear positive pulmonary TB and determine factors associated with delayed sputum smear conversion among Orang Asli in Malaysia from 2016 to 2020. **Methodology:** A retrospective cohort study was conducted in December 2020 until May 2021 utilised MyTB data. All registered TB among Orang Asli within the study period were included for the descriptive analysis. Then, the smear positive pulmonary TB was enrolled and followed until the end of the intensive phase. The estimated sample size needed was 445. Data on age, sex, tribes, location of residence, education level, household income, smoking status, diabetes mellitus, HIV status, BCG vaccination scar, treatment category, pre-treatment sputum smear, pre-treatment chest x-ray and treatment adherence were collected using the proforma and were analysed with SPSS ver. 26 software. A simple and multiple logistic regression was used to determine factors associated with delayed sputum smear conversion among Orang Asli. **Results:** There were 808 cases of Orang Asli in Malaysia from 2016 to 2020 diagnosed with

TB. Out of 725 cases of pulmonary TB, 572 (78.9%) were smear positive pulmonary TB. Only 487 cases of smear positive pulmonary TB fulfilled the study criteria at the end of the intensive phase and included for further analysis. Of that, 93 (19.1%) cases were delayed sputum smear conversion. The mean (SD) age of smear positive pulmonary TB among Orang Asli was 39.20 (16.33) years, most were male (63%), Senoi tribe (54.9%), living in the rural area (88.1%), had formal education (60.4%) and living below the poverty line (97.1%). Factors significantly associated with delayed sputum smear conversion were smokers (AdjOR: 3.25; 95% CI: 1.88, 5.59), diabetes mellitus (AdjOR: 12.84; 95% CI: 6.33, 26.06), and HIV infection (AdjOR: 9.76; 95% CI: 3.01, 31.65). **Conclusion:** Pulmonary TB was the commonest type of TB reported among Orang Asli and are comparable to those of indigenous people worldwide. Targeted approaches and focused strategies towards pulmonary TB Orang Asli who are smokers, diabetic and HIV infection should be adopted by stakeholders to tackle delayed sputum smear conversion. With effective measures, the transmission of TB can be reduced, thus realising the End TB target.

Keywords: delayed sputum smear conversion, smear positive pulmonary TB, Orang Asli, indigenous, factors associated

CHAPTER 1

INTRODUCTION

1.1 Overview of tuberculosis

Tuberculosis (TB) is still relevant and remains a significant disease even though it has been documented since an ancient period. According to the World Health Organization [WHO] (2020b), TB has caused 1.5 million people to die yearly, making TB a leading cause of death globally. Despite enormous challenges brought by the COVID-19 pandemic, the efforts in fighting TB should be continued and intensified. The burden of the disease varies across the continents, with the global average being around 130 new cases per 100,000 annually. Most TB cases are in South – East Asia, where Malaysia is located, followed by Africa, Western Pacific, and small percentages in Eastern Mediterranean, the Americas, and Europe (WHO, 2020a). Efforts in combating the disease were made for decades, but the outcome is still below expectation. There are several challenges faced by the authority which significantly delay the progress to end TB. The Ministry of Health Malaysia [MOH] (2016), reported that the number of TB cases in Malaysia had successfully reduced from 350 cases per 100,000 in 1961 to 100 cases in 1980. However, the cases since then have remained unchanged, with the current annual incidence estimated at 92 per 100,000 in 2019, positioned Malaysia as an intermediate TB burden country (WHO, 2020a).

TB is caused by *Mycobacterium tuberculosis*. The pathogenicity of bacteria is unique, where it infects pulmonary or extrapulmonary sites (Aliyu, 2014). Most TB cases are pulmonary TB, which involve the lungs, accounting for 85% of total notified

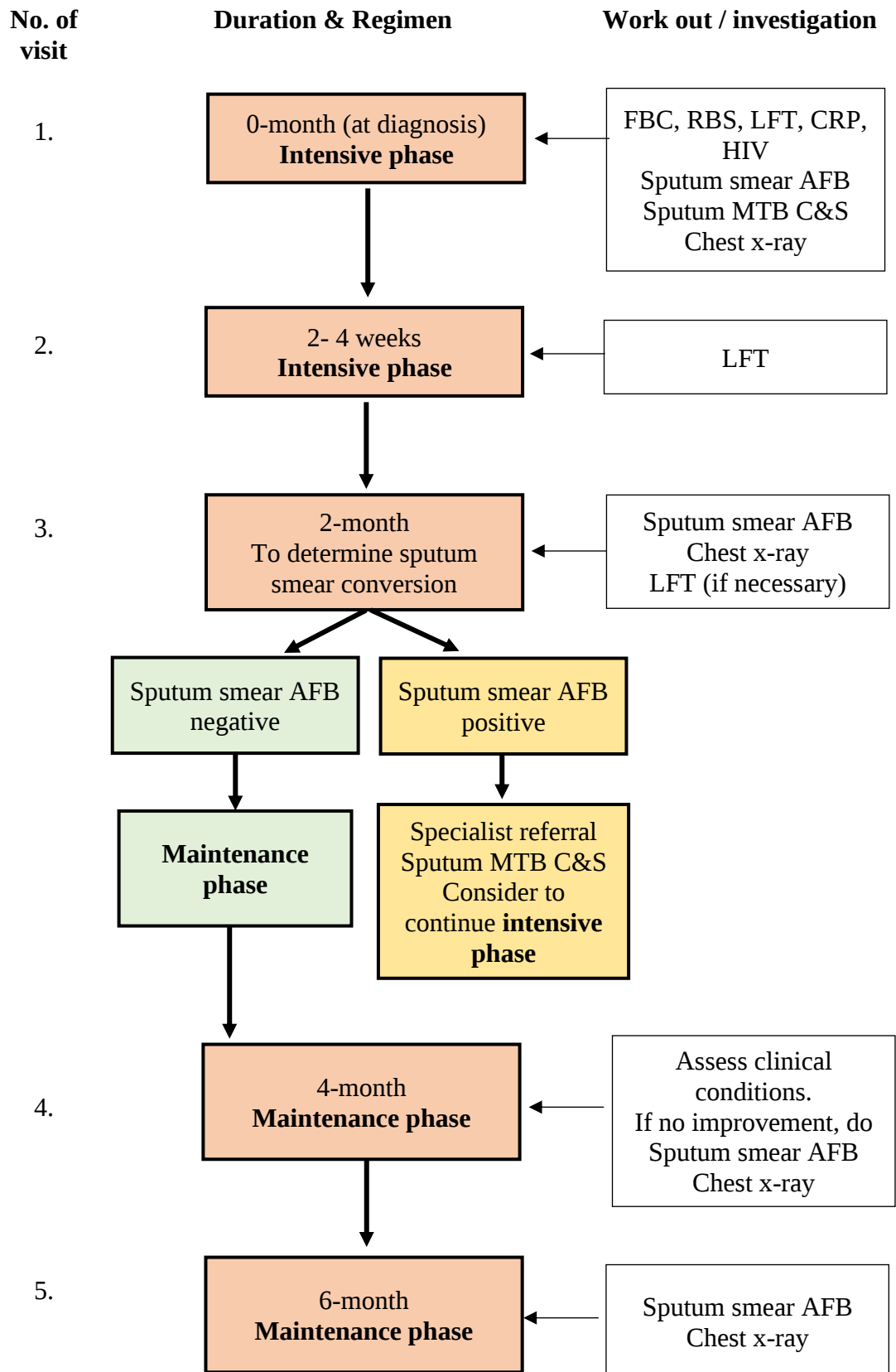
cases, while the remaining 15% are extrapulmonary TB (EPTB) (WHO, 2020a). The infection disrupts the lungs' parenchyma and causes structural changes, that demonstratable by a chest x-ray. While in EPTB, it infects anatomical sites other than the lungs or as a disseminated disease. It can affect organs such as the pleura, abdominal organs, genitourinary tract, lymph nodes, skins, joints, and bones or meninges (Lee, 2015).

Pulmonary TB is further classified by sputum smear status. The presence of *Mycobacterium tuberculosis* is observed as Acid Fast Bacilli (AFB). The sputum result will determine the type of pulmonary TB, either smear positive or smear negative pulmonary TB (MOH, 2012). Smear positive is contagious and accounting for 55% of pulmonary TB cases (WHO, 2020a). Because of that, smear positive pulmonary TB patient is hazardous and become a potential source of infection in the community. A smear positive pulmonary TB patient can infect 15 persons a year (WHO, 2020c). The disease is transmitted via droplets and airborne from the throat and lungs. The fatality rate among untreated pulmonary TB patients, either smear positive or negative was reported up to 20% over ten years (Tiemersma *et al.*, 2011). Despite efficacious pharmacotherapy and a comprehensive national TB programme, up to 25% of pulmonary TB patients remain smear positive at the end of the intensive phase. Delayed sputum smear conversion at the end of the intensive phase is associated with poor treatment outcomes such as failed treatment, required prolonged follow-up and higher mortality rate (Djouma *et al.*, 2015)

1.2 Sputum smear conversion

Providing an effective pulmonary TB treatment is one of the main core strategies in the national TB programme. A newly diagnosed pulmonary TB patient is recommended to comply six months treatment regimen. The treatment should be under Directly Observed Treatment, Short-course (DOTS) for daily drugs administration, which involves two months of the intensive phase and four months of the maintenance phase (MOH, 2012). The patient will receive four drugs daily during the intensive phase, consisting of Ethambutol, Isoniazid, Rifampicin, and Pyrazinamide. The course followed with two drugs daily during the maintenance phase, which consists of Isoniazid and Rifampicin.

The patients are required to follow up periodically to assess the treatment response, such as clinical sign and symptoms, weight changes, adverse drug reactions, blood investigations, sputum smear conversion and chest x-ray. It is recommended to do so at two, four, and six months after the treatment is initiated. Specifically for the monitoring of sputum conversion, a repeat sputum smear is done at two months for all pulmonary TB cases, either smear positive or smear negative, after the treatment initiated (MOH, 2012). With a recommended treatment, it is expected that 85% of smear positive pulmonary TB patients have sputum smear conversion and clinically improved at the end of the intensive phase (MOH, 2016). However, if the smear remains positive at the end of the intensive phase, patients are required for specialist referral and repeat sputum smear AFB and sputum MTB C&S at three months (MOH, 2012). The flow chart for recommended six months of treatment of pulmonary TB is shown in **Figure 1.1**.



(Source: Clinical Practice Guidelines Management of Tuberculosis, 3rd Edition, 2012)

Figure 1.1: Flow chart for the recommended six-month treatment of pulmonary TB

Sputum smear conversion is the recommended indicator by WHO in monitoring patient progress and a performance indicator for the national TB control programme. It is defined as a percentage of the patients who converted sputum smear at the end of the intensive phase among the patients who have identified sputum smear positive at the pre-treatment stage (WHO, 2017). The target for sputum conversion rate is above 85%, where Malaysia achieved in the past few years (MOH, 2018). However, some numbers had persistent smear positive that required attention. Patients with delayed sputum smear conversion are significantly related to poor treatment outcomes, affecting the cure rate (Jayakody *et al.*, 2013). In addition, the later event will lead to a high secondary attack in the community, which later causes a continuous burden to public health.

Many studies were conducted to explain the factors that determine the delay in sputum smear conversion. Immunocompromised conditions such as uncontrolled diabetes mellitus, renal failure, malignancy, anaemic and HIV infection are strongly related to delay in sputum conversion (Behnaz *et al.*, 2015; Nagu *et al.*, 2014; Singla *et al.*, 2013). Following that, an intensified efforts have been made in focusing these groups. However, few factors that confined to the particular background that varied between countries and locality are still not well explored, such as geographical area, ethnicity, and vulnerable groups.

Most studies on factors associated with delayed sputum smear conversion worldwide were limited to the general population. A few studies involved vulnerable groups like indigenous people, such as Canada, Australia and Brazil (Croda *et al.*, 2012; Dehghani *et al.*, 2018; Wilson *et al.*, 2019). In Malaysia, a study on this issue was limited to the general population and primarily involved patients in Penang and

Kuala Lumpur (Atif *et al.*, 2014; Shariff and Safian, 2015). A limited study involving Orang Asli or other indigenous groups in Malaysia.

1.3 Orang Asli - a vulnerable group for TB infection and delayed sputum smear conversion

Orang Asli is regarded as an indigenous people living across the Peninsular of Malaysia. According to the Department of Orang Asli Development [JAKOA] (2018, 2020), the community is making up 0.5% of Malaysia's population with 178,197 people, living in 853 villages, in which 525 villages (61.5%) are located in the suburban area while the remaining 328 villages (38.5%) located in the rural area. They consist of three main tribes, Senoi, the largest tribe, followed by Melayu Proto and Negrito. Orang Asli has an ancient history with prehistoric migration into Peninsular Malaysia and has shown distinctive origin based on their genotype studies, which link to different indigenous peoples in Papuans, Australia, Southern China, Indians, and Africans (NurWaliyuddin *et al.*, 2015). Indigenous people in many countries are identified as vulnerable groups with generally poor health conditions compared to the general population and receive a lack of essential health services and infrastructure (Cheng *et al.*, 2014).

Even though nowadays, the Orang Asli community has been given better attention from the government and local authorities regarding access to healthcare, education, communication and other basic facilities, they are still regarded as vulnerable groups. They are struggling in socio-economic and health due to circumstances with the social determinants of health (Shah *et al.*, 2018). The Economic Planning Unit Malaysia [EPU] (2020) reported that most of them still live below the

poverty line and 33% of them living in hard-core poverty, a much higher than the national level, at 0.7%. These conditions have led to poor health outcomes, resulting in a higher incidence of infectious disease than the general population (Hussin *et al.*, 2020; Wong *et al.*, 2019).

Several studies conducted among indigenous worldwide found that they have an unacceptably high TB incidence compared to dominant populations (Cunha *et al.*, 2014). Besides that, indigenous TB patients were associated with poor treatment outcome. Indigenous people in Amazons, Brazil, Colombia as well as in low TB burden countries like Canada and Australia have higher TB morbidity and mortality than the general population (Castro *et al.*, 2016; Donnan *et al.*, 2017; Hernández Sarmiento *et al.*, 2013; Larcombe *et al.*, 2012). In conclusion, there are many unresolved health issues involving Orang Asli, such as malnutrition; a chronic infection that leads to anaemia; high prevalence of smokers and alcoholism; as well as poor health-seeking behaviour that all these could impact the national TB control programme, including risk for delayed sputum smear conversion in this community (Zerbini *et al.*, 2017; Zubaidah, 2018). Therefore, these health determinants in Orang Asli become a unique challenge for the national TB control program and need further explorative and epidemiological study.

1.4 Problem statement and study rationale

Several studies worldwide have found that a significant percentage of TB patients among indigenous people have delayed sputum smear conversion compared to the general population. Delayed sputum smear conversion has been shown to contribute to the treatment failure, developing drug resistance, mortality and continue

transmitting the disease in the community (Basham *et al.*, 2019; Bouti *et al.*, 2013; Gunda *et al.*, 2017). Orang Asli in Malaysia shared almost similar characteristics with indigenous people from other countries and is regarded as a vulnerable group for TB infection and poor treatment outcome. However, there are limited studies on sputum smear conversion rate and factors associated with it among them. Hence, it is challenging for health providers and policymakers to understand the situation and provide effective TB control and management involving Orang Asli.

With the adoption of the 2030 Agenda by the United Nations Development Programme [UNDP] (2018), it is to ensure that no one will leave behind and endeavour to reach the furthers behind first, to achieve the Sustainable Developmental Goals (SDG). Hence, this study is vital to look at Orang Asli from Malaysia's perspective and develop a foundation for future references in improving and recommending the National TB program for effective intervention measures.

1.5 Research questions

1. What is the proportion of pulmonary TB among Orang Asli with TB in Malaysia from 2016 to 2020?
2. What are the characteristics of smear positive pulmonary TB among Orang Asli in Malaysia from 2016 to 2020?
3. What factors are associated with delayed sputum smear conversion among Orang Asli with smear positive pulmonary TB in Malaysia from 2016 to 2020?

1.6 Research objectives

1.6.1 General objective

To study the characteristics of smear positive pulmonary TB and factors associated with delayed sputum smear conversion among Orang Asli in Malaysia from 2016 to 2020

1.6.2 Specific objectives

1. To determine the proportion of pulmonary TB among Orang Asli with TB in Malaysia from 2016 to 2020
2. To describe the characteristics of smear positive pulmonary TB among Orang Asli in Malaysia from 2016 to 2020.
3. To determine factors associated with delayed sputum smear conversion among Orang Asli with smear positive pulmonary TB in Malaysia from 2016 to 2020.

1.7 Hypothesis

There are significant associations between sociodemographic, lifestyle and clinical characteristics with delayed sputum smear conversion among Orang Asli with pulmonary TB in Malaysia

CHAPTER 2

LITERATURE REVIEW

Smear positive pulmonary TB is the most infectious and contagious form of TB. If left untreated, the disease will be transmitted to the community. Prevention and control for TB are challenging for public health due to prolonged incubation period, stigmatisation in the community, and poor accessibility to health care in certain groups (Daftary *et al.*, 2017; Lönnroth *et al.*, 2017). In addition to that, TB patients need to be supervised according to the recommended guidelines throughout the treatment course to ensure a favourable outcome. A delayed sputum smear conversion at the end of the intensive phase reflects a suboptimal TB programme and it is associated with many factors.

A number of literatures were searched to understand the epidemiology of TB in Orang Asli and other indigenous people locally and globally as one of the recognised vulnerable group in TB transmission. Further searched more focus on delayed sputum smear conversion among Orang Asli, a basis for this study to explore this issue. Literature was searched using the journal search engine, mainly were PubMed, Scopus, Science Direct, Web ISI, Springer link and Google Scholar. Recent literature was selected with keywords such as delayed sputum smear conversion, persistent sputum smear positive, poor TB outcome, factors associated, Orang Asli, aborigine and indigenous. Several searching strategies were applied by using Boolean operators like “AND”, “OR” and “NOT”.

2.1 The burden of TB among Orang Asli

TB has become a burden to the community and country in terms of economic costs as well as clinical consequences. Poorly treated TB patients will burden more to the public health due to prolonged treatment and disease transmission in the community. A number of studies on TB among general populations in Malaysia were widely published. However, the literature on TB in Orang Asli hardly found. TB in Orang Asli has been documented and focused on by the government for a long time since before the pre-independence era (Paul, 1936). However, the issue remains until today, and the agenda is continuing to be prioritised in the national TB programme (Lye *et al.*, 2019).

Orang Asli possessed a higher risk of disease transmission due to their social and cultural background, such as social gathering, overcrowding houses and other social determinants of health (Abdullah *et al.*, 2016; Mas *et al.*, 2021). It was documented in 1999 that the incidence of TB among Orang Asli in the state of Perak was 240 per 100,000 populations, which were 5.5 times higher than the state general population at that time (Jeyakumar, 1999). A more recent study conducted in the Kinta District, Perak, reported that TB incidence was highest among Orang Asli compared to the general population (Othman *et al.*, 2006). The situation was similar to other natives in Malaysia, where Kadazan, Dusun and Murut in Sabah, and natives in the longhouse in Sarawak showed higher incidence compared to the general population. A combination of these natives reported notification rate was 221 per 100,000 population compared to the non-natives notification rates, which was 100 per 100,000 population in year 2000 (Dony *et al.*, 2004). However, there was a limited study to truly understand the current epidemiology of TB among Orang Asli in Malaysia.

Pulmonary TB is the most common type of TB in the general population, where most of them were smear positive pulmonary TB (MOH, 2016). A number of studies on indigenous people worldwide showed that the prevalence of pulmonary TB was higher compared to the general population. A cross-sectional study involving 1071 rural tribes TB patients in Madhya Pradesh, India, found that 76.9% of them were pulmonary TB. The prevalence of pulmonary TB in this community was found to be 3294 per 100,000 population, a much higher than the general population, which was 160 per 100,000 population (Rao *et al.*, 2015). A retrospective study in Daurados, Brazil, involving the indigenous community found that the TB notification was 673 per 100,000 population compared to the general population, which was 41 per 100,000 population. It was found that 90% of TB cases in the community was pulmonary TB (Croda *et al.*, 2012). A similar finding was also shown by a prospective study among 20,556 rural tribes in Western Kenya where 123 were diagnosed TB, making prevalence as 598 per 100,000 population than the general population, which was 233 per 100,000. Pulmonary TB made up 78% of total TB cases in the community (Hoog *et al.*, 2011).

The situation was similar in developed countries such as Australia and Canada where TB incidence was higher than in the general population. A report from the Public Health Agency of Canada [PHA] (2014), stated that the TB incidence among North American Indian and Inuit tribes were respectively 198.6 and 22.2 per 100,000 population. The national incidence figure was lower, which was 4.7 per 100,000 population. A retrospective study using secondary data from 2006 until 2016 in Far North Queensland, Australia, involving the Torres Strait tribe found that the incidence rate was 54.3 per 100,000 population than the national rate, which was 5.3

per 100,000 population. It was found that 63% of the cases involved pulmonary TB (Wilson *et al.*, 2019).

Many studies also discovered that indigenous people worldwide have a lower conversion sputum rate compared to the general population. A retrospective cohort study in Brazil using national surveillance data showed that their indigenous groups showed lower sputum conversion rates leading to poor treatment outcome (Do *et al.*, 2018). The situation in developed countries such as Canada also showed similar results, where the Inuit tribe had a 77% sputum conversion rate at the end of the intensive phase, which was lower than the national target. Intensified efforts by the local authorities were made by focusing on these (Nguyen *et al.*, 2003). There are limited data on the sputum smear conversion among Orang Asli in Malaysia. However, a number of studies have shown that Orang Asli had genetic links to other indigenous tribes from Africa, Indonesia, Australia, India as well as China which can be hypothesised similar findings with delayed sputum smear conversion (Aghakhanian *et al.*, 2015; Norhalifah *et al.*, 2016; NurWaliyuddin *et al.*, 2015).

2.2 Factors associated with delayed sputum smear conversion among Orang Asli in Malaysia

Several past studies documented many factors associated with delayed sputum smear conversion. The factors are categorised into sociodemographic, lifestyle and clinical characteristics.

2.2.1 Sociodemographic characteristics

a) Age

Age is a vital factor in determining health status. Extreme age groups such as infants, toddlers and the elderly were generally susceptible to the infections due to poor immunological and delayed treatment response (Giefing-Kröll *et al.*, 2015). A retrospective study involving 136 smear positive pulmonary TB in Portugal has shown that age 50 years old and above were 4.4 times more likely to be associated with delayed sputum smear conversion at the end of the intensive phase (AdjOR: 4.40, 95% CI 1.5, 13.3; $p=0.008$) (Mota *et al.*, 2012). A similar finding was found by a retrospective cohort study using secondary data, involving 19,165 smear positive pulmonary TB patients in Eden district, South Africa that the patient's age above 60 years old was likely for delayed sputum smear conversion. Multivariate analysis was shown that patients aged above 60 years old had 4.56 times more likely associated with delayed sputum smear conversion compared to the younger age group (AdjOR: 4.56, 95% CI 1.79, 11.60; $p=0.001$) (Mlotshwa *et al.*, 2016).

However, a cross-sectional study conducted in 2017 in rural Tanzania shown a contrast finding where the younger population, aged below 50 years old has shown to be significantly associated with delayed sputum smear conversion. A multiple logistic regression analysis was found that age group below 50 years old patients were 6.7 times more likely to have delayed sputum smear conversion at the end of the intensive phase (AdjOR: 6.70, 95% CI 1.90, 23.00; $p=0.003$) (Gunda *et al.*, 2017).

b) Sex

Being a male was reported to be more at risk of TB than females due to biological factors such as sex hormones and social activities, which engage more in high-risk activity. A similar study also discovered That male is a predictor for delayed sputum smear conversion (Nhamoyebonde and Leslie, 2014). Another prospective study among 85 smear positive pulmonary TB in Birjand Tuberculosis Centre, Iran, found that male had a longer time for sputum smear conversion. The study found that male had a mean (SD) of 2.29 (1.23) month for sputum smear conversion compared to 1.74 (0.85) among female ($p=0.04$). A similar finding was found in a retrospective cohort study involving 19,165 smear positive pulmonary TB patients in South Africa where being a male had 1.44 times likely associated with delayed sputum smear conversion than female (AdjOR: 1.44, 95% CI 1.27, 1.63; $p<0.001$)

However, a retrospective cohort study conducted in 7 years period involving 228 pulmonary TB patients in Beleng, Cameroon, has shown that no significant difference between sexes for delayed sputum smear conversion (Djouma *et al.*, 2015). A similar finding also was found in a study in Manitoba, Canada, involving 149 First Nations tribe TB patients, where no significant difference between sexes for delayed sputum smear conversion and treatment outcome (Basham *et al.*, 2019).

c) Tribes

In terms of tribes among indigenous people, several studies that documented varied TB varied and sputum smear conversions between tribes. A report in Canada stated that three large tribes in Northern America had different TB incidence and treatment outcome. Inuit tribe had the lowest sputum smear conversion at the end of the intensive phase, which was 67 to 77% compared to American Indian and Metis (PHA, 2014).

A study among different indigenous tribes in Madhya Pradesh, India, has found that the Saharia tribe had the highest TB incidence in the state and poor treatment outcome including delayed sputum smear conversion at two-month of the intensive phase. The study related the situation due to biological differences in TB susceptibility. There were several tribes in Madhya Pradesh, India, and the results for delayed sputum smear conversion between tribes were varied (Rao *et al.*, 2015). However, the explanation for the association between tribes and delayed sputum smear conversion was inconclusive and yet to explore.

d) Location of residence

Most of the Orang Asli resides in a rural area. Many studies from Canada, Australia, South Africa, and Taiwan has shown that indigenous tribes mostly were living in a rural or remote area (Chen *et al.*, 2014; Dehghani *et al.*, 2018; Wilson *et al.*, 2019). Rural or remote areas are commonly associated with poor accessibility towards health care and other social determinants of health. A study involving 5702 TB patients in Iran has shown that location of residence had significantly associated with diagnosis delay ($p < 0.001$). A study in Anhui, China, among 148 TB patient has shown significant treatment outcome among rural and urban patients. The study found that patients living in rural area were likely to have poor treatment outcome. It was related to poor health delivery, such as lack of equipment at the rural clinics and poor TB awareness among rural patients (Li *et al.*, 2013).

However, contradicted findings were shown by several studies in indigenous groups in Brazil. A retrospective study conducted at a different state in Brazil showed that rural, suburban and urban resident had no association with TB treatment outcome. (Cunha *et al.*, 2014; Kolte *et al.*, 2020).

e) Education level

Most of Orang Asli received lower education level, and a significant number has not received a formal education. A review study has shown that only 39.1% of Orang Asli schoolchildren completed primary school and only 30% of these finish secondary schools. It was also reported that more than half of late adult did not receive a formal education (Sawalludin *et al.*, 2020). This situation was similarly seen among indigenous tribes in Taiwan, where almost half of those who finished primary school enrolled on secondary school (Liu *et al.*, 2014). A case-control study among 93 pulmonary TB patients in Lampung, Indonesia among smear positive pulmonary TB has found that lower education patients had 5.31 times likely associated with delayed sputum smear conversion than higher education patients (AdjOR: 5.31, 95% CI 1.71, 16.50; $p=0.004$) (Wardani and Wahono, 2017).

However, a study conducted in Malaysia gives contradicted result, where most of delayed sputum smear conversion were those with secondary education level, followed by primary and tertiary. Further analysis was shown that education level was not associated with delayed sputum smear conversion (Shariff and Safian, 2015).

f) Employment status

A prospective study conducted among 54 smear positive pulmonary TB in rural Nepal has shown that different occupations had different mean time for sputum smear conversion. Labour workers had longer sputum smear conversion, 58.2 days compared to office workers, which took 48 days (Shrestha *et al.*, 2018).

However, a cross-sectional study in Northwest Ethiopia involving 520 pulmonary TB showed that different occupation types had no association with delayed

sputum smear conversion (Kassa *et al.*, 2021). A similar finding was shown by a study involving 52 smear positive pulmonary TB in Lithuania that employment status was not significantly associated with delayed sputum smear conversion (Musteikienė *et al.*, 2017).

g) Household income

The findings for household income with delayed sputum smear conversion were varied. A prospective cohort study involving 833 pulmonary TB patients in Yunnan, China, has discovered that patients with low income were 4.7 times more likely for delayed sputum smear conversion than high-income patients (AdjOR: 4.70, 95% CI 1.80, 12.30; $p=0.002$) (Hua *et al.*, 2011).

Meanwhile, several studies conducted in Indonesia and Bangladesh found household income was not a contributing factor for delayed sputum smear conversion (Flora *et al.*, 2013; Wardani and Wahono, 2017).

2.2.2 Lifestyle characteristics

a) Smoking status

Many studies have found that smoking was a significant risk factor for delayed sputum smear conversion. A retrospective study conducted in Kamataka, South India, involving 233 smear positive pulmonary TB was found that smoker patients had 2.18 times likely for delayed sputum smear conversion than non-smoker patients (AdjOR: 2.18, 95% CI 1.13, 4.61; $p=0.040$) (Anandaraj *et al.*, 2017). Besides that, a prospective study involving 360 smear positive pulmonary TB across Brazil, Iran was found that

active smoker patients were 2.28 times more likely for delayed sputum smear conversion compared to never smoke patients (AdjOR: 2.28, 95% CI 1.02, 5.33; $p=0.040$) (Maciel *et al.*, 2013). In addition, the immunological study also found that toxic substance in cigarettes cause alveolar epithelial damage and reduce immunological response against *Mycobacterium tuberculosis* (Underner and Perriot, 2012).

b) Alcohol

Alcohol consumption has been associated with delayed sputum smear conversion. A prospective study at Dar es Salam, Tanzania, involving 1,245 smear positive pulmonary TB in 2011 was current alcohol drinker patients were 2.79 times more likely for delayed sputum smear conversion than never drink patients (AdjRR: 2.79, 95% CI 1.50, 4.84; $p=0.001$) (Nagu *et al.*, 2014). A similar finding was found by a prospective cohort study among 228 pulmonary TB in Abbassia, Egypt, that alcohol drinker patients were 2.80 times the risk for delayed sputum smear conversion than non-drinker patients (AdjRR: 2.80, 95% CI 1.10, 6.80; $p=0.040$) (Gadallah *et al.*, 2016).

However, a study in Ethiopia involving 392 pulmonary TB was found out that drinking status was not significant with delayed sputum smear conversion (Yihunie *et al.*, 2018)

c) Substance abuse

Particular substance abuse has been documented for delayed sputum smear conversion among pulmonary TB patients. Multiple logistic regression analysis in a retrospective study involving 5,846 pulmonary TB patients in Spain found intravenous

drug user patients were 7.15 times more likely for delayed sputum smear conversion than non-drug abuser patients (AdjOR: 7.15, 95% CI 4.12, 13.40; $p<0.001$). A similar finding was also documented in a case-control study in Peru, showing that recreational drug user patients were 3.74 times more likely for delayed sputum smear conversion than non-drug user patients (AdjOR: 3.74, 95% CI 1.25, 11.14; $p=0.030$) (Culqui *et al.*, 2012).

2.2.3 Clinical characteristics

a) Nutritional status

Nutritional status is essential for optimal immune and drugs response. This has been documented by many studies. BMI is commonly used to reflect nutritional status. Many studies among indigenous TB patients showed that lower BMI was significantly associated with delayed sputum smear conversion. A study among 218 patients treated at Masan Hospital, South Korea found that patients with BMI less than 18.5 kg/m² were likely associated with delayed sputum smear conversion, compared to patients with BMI 18.5 kg/m² or more (HR: 1.74, 95% CI: 1.01, 3.01, $p=0.047$) (Park *et al.*, 2016). A study in Jakarta, involving 376 pulmonary TB patients was found that patients with BMI less than 16 kg/m² were two times likely associated with delayed sputum smear conversion (Putri *et al.*, 2014)

However, a study among rural tribes in Bengal, India showed no significant association where the patient with BMI less than 16kg/m², BMI with 16-18kg/m² and normal BMI in sputum smear conversion time (Velayutham *et al.*, 2016).

b) Comorbidity – Diabetes Mellitus

Diabetes mellitus is identified as one of the risk factors for delayed sputum smear conversion. Many studies have documented the association between diabetes mellitus and delayed sputum smear conversion as well as poor treatment outcomes. The pathophysiology of poor treatment responses among diabetes mellitus patient had been documented as well. A study in Malaysia involving 150 smear positive pulmonary TB has found that diabetic TB patients were four times more likely for delayed sputum smear conversion at the end of the intensive phase than non-diabetic patients (AdjOR: 4.01, 95% CI: 1.61, 9.96, $p=0.003$).

A similar finding was seen in a retrospective cohort study in Guangzhou, China, involving 1,589 pulmonary TB patients, where analysis was found that underlying diabetes mellitus patients were 3.85 times more likely for delayed sputum smear conversion than non-diabetic patients (AdjRR: 3.85, 95% CI: 2.24, 6.63, $p<0.001$). It was also found that poorly controlled diabetic patients were 2 times more likely for delayed sputum smear conversion than controlled diabetic patients (Mi *et al.*, 2013).

c) Comorbidity – HIV co-infection

Several studies have been conducted among HIV patients for delayed sputum smear conversion. HIV co-infection is a concern among health providers in ensuring good treatment outcomes. However, many studies were discovered that HIV infection has significantly associated with delayed sputum smear conversion. A retrospective study conducted in Rwanda, involving 581 pulmonary TB patients found that HIV co-infected TB patients were 3.43 more likely for delayed sputum smear conversion at

two-month of the intensive phase compared to non-HIV patients (AdjOR: 3.43, 95% CI: 1.69, 6.98, $p<0.001$) (Kayigamba *et al.*, 2013).

Similarly, studies in South Africa and Uganda among pulmonary TB patients with HIV co-infection were significantly associated with delayed sputum smear conversion at the end of the intensive phase, compared to non-HIV patients. (Mlotshwa *et al.*, 2016; Sekaggya *et al.*, 2018)

d) Comorbidity – Anaemia

Anaemia has been identified as a risk for infection including TB (Jonker and Boele, 2014). A retrospective study conducted in Evandro Chagas, Brazil, involving 258 TB patients found that microcytosis of red blood was 2.36 times likely to be associated with delayed sputum smear conversion compared to normocytic red blood cell patients (AdjOR: 2.36, 95% CI: 1.02, 5.44, $p=0.044$) (De Mendonça *et al.*, 2021). A similar study in Tanzania also found that anaemic patients were three times more likely to be delayed sputum smear conversion than non-anaemic patients (Nagu *et al.*, 2014).

However, a case-control study conducted in Haryana, India, involving 100 smear positive pulmonary TB was found that anaemia was not statistically significant for delayed sputum smear conversion (Agrawal *et al.*, 2017)

e) Comorbidity – Chronic obstructive pulmonary disease (COPD)

Chronic respiratory illness has been shown to impair the normal immunological response of lungs towards infection. A study conducted in Iran involving 85 smear positive pulmonary TB has showed that patients with underlying COPD have significantly prolonged the mean (SD) time for sputum smear conversion, which was 3.0 (1.22) months compared to non-COPD patients, which was 1.92 (1.03) months

($p=0.040$) (Azarkar *et al.*, 2016). Another study conducted in Mumbai, India, involving 258 pulmonary TB patients reported that patients with chronic respiratory disease were likely associated with delayed sputum smear conversion than non-respiratory disease patients (Tamhane *et al.*, 2012)

f) BCG vaccination scar

BCG vaccination is beneficial for younger age against severe TB. However, the benefit towards adults is not well established. The findings in Spain among vulnerable groups, involving immigrants and indigenous tribes found no association between BCG history with delayed sputum smear conversion (Godoy *et al.*, 2013).

However, a study conducted in Assam, India involving 102 new smear positive pulmonary TB was found that patients with no BCG scar were significantly associated with delayed sputum smear conversion ($p<0.001$) (Goswami, 2016).

g) Treatment category

At the time of diagnosis, tuberculosis patient will be identified either new case, previously treated or relapse. A retrospective cohort study among 547 smear positive pulmonary TB in Istanbul, Turkey, found that those previously treated for TB were times more likely associated with delayed sputum smear conversion than new case patients ($p<0.016$) (Babalik *et al.*, 2012). This finding was similar to a study in South Delhi, India, where previously treated patients was 4.31 times more likely for delayed sputum conversion than new case patients (AdjOR: 4.31, 95% CI: 1.43, 12.97, $p=0.007$) (Singla *et al.*, 2013).

h) Pre-treatment sputum smear

Sputum smear was assessed at the time of diagnosis before the treatment was started. The sputum was categorised according to the AFB smear result. A retrospective cohort study in Yazd, Iran, involving 211 smear positive pulmonary TB patients reported higher-grade sputum smear at pre-treatment was three times more likely for delayed sputum smear conversion than a low-grade sputum smear (AdjOR: 2.93, 95% CI: 1.28, 6.73, $p=0.011$) (Behnaz *et al.*, 2015). A similar finding was also documented in Portugal where a high-grade sputum smear at pre-treatment associated with prolonged time for sputum conversion than low-grade sputum (Mota *et al.*, 2012).

However, a study in Birjand, Iran showed that pre-treatment sputum smear conversion has no significance for delayed sputum smear conversion (Azarkar *et al.*, 2016).

i) Pre-treatment chest x-ray

A pre-treatment chest x-ray showed to be associated with delayed sputum smear conversion and poor treatment outcome. This association was documented in a study in South Africa where a higher cavity score pre-treatment chest-ray was 1.79 more likely for delayed sputum smear conversion than a lower cavity score (AdjOR: 2.17, 95% CI: 1.29, 3.64, $p=0.010$) (Brust *et al.*, 2013). A similar finding was also found in a study in India where moderate to advanced chest x-ray were significantly associated with delayed sputum smear conversion (Singla *et al.*, 2013).