

**TREND AND FACTORS ASSOCIATED WITH
DELAYED SPUTUM CONVERSION AMONG
ELDERLY WITH SMEAR-POSITIVE
PULMONARY TUBERCULOSIS
IN PENINSULAR MALAYSIA
FROM 2015 – 2024**

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UNIVERSITI SAINS MALAYSIA

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FROM 2015 – 2024**

by

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**Thesis submitted in fulfilment of the requirements
for the degree of
Master of Public Health**

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Alhamdulillah, with the grace of Allah SWT, I have successfully completed this dissertation entitled “*Trends and Factors Associated with Delayed Sputum Conversion Among Elderly with Smear-Positive Pulmonary Tuberculosis in Peninsular Malaysia from 2015 to 2024.*”

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TABLE OF CONTENTS

ACKNOWLEDGEMENT	ii
TABLE OF CONTENTS	iii
LIST OF TABLES	vii
LIST OF FIGURES	viii
LIST OF SYMBOLS	ix
LIST OF ABBREVIATIONS	x
LIST OF APPENDICES	xii
ABSTRAK	xiii
ABSTRACT	xv
CHAPTER 1 INTRODUCTION	1
1.1 Overview of tuberculosis	1
1.2 Confronting tuberculosis in an ageing Malaysia	3
1.3 Sputum conversion as a key treatment indicator	5
1.4 Problem statement and study rationale	7
1.5 Research questions	9
1.6 Research objectives	10
1.6.1 General objective	10
1.6.2 Specific objectives	10
1.7 Research hypothesis	10
CHAPTER 2 LITERATURE REVIEW	11
2.1 Overview of delayed sputum conversion (DSC) among the elderly	12
2.2 Factors influencing delayed sputum conversion (DSC) among the Elderly ..	15
2.2.1 Sociodemographic factors	15
2.2.1(a) Sex	15
2.2.1(b) Ethnic	16

2.2.1(c)	Occupation	17
2.2.1(d)	Educational level	17
2.2.1(e)	Residency area	18
2.2.2	Clinical factors	19
2.2.2(a)	Diabetes mellitus	19
2.2.2(b)	Anaemia	20
2.2.2(c)	Chronic obstructive pulmonary disease (COPD)	21
2.2.2(d)	Human immunodeficiency virus (HIV)	21
2.2.2(e)	BCG scar	22
2.2.2(f)	Chest X-ray findings	23
2.2.2(g)	Bacillary load	24
2.2.2(h)	Body Mass Index (BMI)	24
2.2.2(i)	Case category	26
2.2.3	Treatment-related factors	27
2.2.3(a)	Adherence to medication (DOTS)	27
2.2.3(b)	DOTS supervision	27
2.2.3(c)	History of TB treatment	28
2.2.4	Lifestyle factors	29
2.2.4(a)	Smoking	29
2.2.4(b)	Alcoholic	30
2.2.4(c)	Substances misuse	30
2.3	Conceptual framework	32
CHAPTER 3 METHODOLOGY		33
3.1	Study area	33
3.2	Study design	34
3.3	Study duration	35
3.4	Study population	35

3.4.1	Reference population.....	35
3.4.2	Source population.....	35
3.4.3	Sampling frame.....	35
3.4.4	Study criteria.....	35
3.5	Sample size estimation.....	36
3.6	Sampling method and subject recruitment.....	40
3.7	Study tools.....	40
3.7.1	National Tuberculosis Registry (NTBR) database.....	40
3.7.2	Structured proforma checklist.....	41
3.8	Operational definitions.....	42
3.9	Data collection method.....	46
3.10	Data analysis.....	46
3.11	Ethical considerations.....	48
3.12	Study flowchart.....	49
CHAPTER 4 RESULTS.....		51
4.1	Trends of delayed sputum conversion (DSC) from 2015 to 2024.....	51
4.2	Sociodemographic characteristics.....	52
4.3	Clinical, treatment and smoking characteristics.....	53
4.4	Simple logistic regression analysis.....	55
4.5	Multiple logistic regression analysis.....	59
CHAPTER 5 DISCUSSION.....		61
5.1	Trends of delayed sputum conversion (DSC) (2015–2024).....	61
5.2	Factors associated with delayed sputum conversion (DSC).....	67
5.2.1	Residency area.....	67
5.2.2	Diabetes mellitus.....	70
5.2.3	Pre-treatment chest X-ray.....	73
5.2.4	Case category.....	77

5.2.5	DOTS adherence	80
5.2.6	Smoking status	84
5.2.7	Factors not associated with DSC.....	87
5.3	Model performance of multiple logistic regression	90
5.4	Strengths of study	92
5.5	Limitations of study	93
CHAPTER 6 CONCLUSION AND RECOMMENDATION		95
6.1	Conclusion.....	95
6.2	Recommendations	96
6.2.1	Strengthening TB care service delivery and treatment support	96
6.2.2	Innovative and community-based strategies	98
6.2.3	Future research directions	100
REFERENCES.....		101
APPENDICES		119

LIST OF TABLES

	Page
Table 3.1: Sample size calculation for objective 2.....	39
Table 4.1: Proportion of DSC among elderly patients with smear-positive pulmonary TB in Peninsular Malaysia from 2015 to 2024 (n=15736).....	51
Table 4.2: Sociodemographic characteristics according to sputum smear conversion of smear-positive PTB among elderly in Peninsular Malaysia from 2015-2024 (n=1620)	53
Table 4.3: Clinical, treatment-related and smoking characteristics according to sputum smear conversion of smear-positive PTB among elderly in Peninsular Malaysia from 2015-2024 (n=1620)	54
Table 4.4: Factors associated with delayed sputum smear conversion among elderly with smear-positive PTB in Peninsular Malaysia using simple logistic regression (n=1620).....	57
Table 4.5: Factors associated with delayed sputum smear conversion among elderly with smear-positive PTB in Peninsular Malaysia using multiple logistic regression (n=1620)	60

LIST OF FIGURES

	Page
Figure 1.1: TB cases and TB Notification rate (NR) for Malaysia from 2015 to 2020.....	2
Figure 1.2: Growth of older people in Malaysia, 1950–2100	4
Figure 1.3: TB incidence rate by age group, United States, 1993-2022.....	7
Figure 2.1: Conceptual framework for factors associated with sputum smear conversion among elderly with smear-positive PTB	32
Figure 3.1: Map of Malaysia – Peninsular and East Malaysia	33
Figure 3.2: Flowchart of study sampling method and subject recruitment from the NTBR database, 2015–2024	50
Figure 4.1: Proportion of DSC among elderly patients with smear-positive pulmonary TB in Peninsular Malaysia from 2015 to 2024 (n=15736).....	52

LIST OF SYMBOLS

%	Percentage
=	Equal sign
\geq	Greater than or equal to
N	Total population size
n	Sample size
m	Ratio between two groups
α	Alpha level
β	Beta level
&	And

LIST OF ABBREVIATIONS

AdjOR	Adjusted Odds Ratio
AdjHR	Adjusted Hazard Ratio
AdjRR	Adjusted Risk Ratio
AFB	Acid-Fast Bacilli
AI	Artificial Intelligence
AUC	Area Under Curve
BCG	Bacillus Calmette-Guérin (vaccine)
BMI	Body Mass Index
CB-DOT	Community-Based Directly Observed Treatment (Short-course)
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus Disease
CT	Computed Tomography
DM	Diabetes Mellitus
DOSM	Department of Statistics Malaysia
DOTS	Directly Observed Treatment, Short-course
DSC	Delayed Sputum Conversion
DST	Drug Sensitivity Test
HbA1c	Glycated Haemoglobin
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IP	Intensive Phase
KOSPEN	Komuniti Sihat Pembina Negara (Healthy Communities, Building the Nation)
MDR-TB	Multidrug-Resistant Tuberculosis
MOH	Ministry of Health
NCD	Non-Communicable Disease
NSPTB	National Strategic Plan for TB
NTBR	National Tuberculosis Registry
OR	Odds Ratio
PTB	Pulmonary Tuberculosis

ROC	Receiver Operating Characteristic
RR	Relative Risk
TB	Tuberculosis
WHO	World Health Organisation

LIST OF APPENDICES

- | | |
|------------|---|
| Appendix 1 | Proforma checklist |
| Appendix 2 | National Medical Research Register (NMRR), Ministry of Health Malaysia approval letter |
| Appendix 3 | Human Research Ethics Committee, Universiti Sains Malaysia (USM) approval letter |
| Appendix 4 | Permission to use NTBR data from TB & Leprosy Sector, Disease Control Division, Ministry of Health application letter |
| Appendix 5 | ROC Curve Figure from SPSS output |

**TREND DAN FAKTOR-FAKTOR YANG BERKAIT DENGAN
KELEWATAN PENUKARAN SAPUAN KAHAK DALAM KALANGAN
WARGA EMAS DENGAN TUBERKULOSIS PULMONARI SMEAR
POSITIF DI SEMENANJUNG MALAYSIA
DARI TAHUN 2015 - 2024**

ABSTRAK

Latar Belakang: Tuberkulosis (TB) kekal sebagai isu kesihatan awam yang mencabar di Malaysia, khususnya dalam kalangan warga emas yang lebih terdedah akibat faktor penuaan, penyakit komorbid dan cabaran sosioekonomi. Kelewatan penukaran kahak, iaitu keputusan ujian sapuan kahak yang masih positif selepas fasa rawatan intensif dua bulan, merupakan petunjuk awal terhadap tindak balas rawatan yang kurang memuaskan, kebolehhangkitan yang berpanjangan serta risiko kerintangan ubat. Walau bagaimanapun, kajian yang memfokuskan kepada warga emas di Malaysia masih terhad. **Objektif:** Kajian ini bertujuan untuk menilai trend kelewatan penukaran kahak dan mengenal pasti faktor-faktor yang berkaitan dalam kalangan pesakit tuberkulosis pulmonari (PTB) smear positif yang berumur 60 tahun dan ke atas di Semenanjung Malaysia bagi tempoh 2015 hingga 2024. **Metodologi:** Reka bentuk kajian perbandingan keratan rentas ini menggunakan data sekunder daripada pangkalan data National Tuberculosis Registry (NTBR). Bagi analisis trend, semua 15,736 pesakit PTB smear positif warga emas yang didaftarkan dari tahun 2015 hingga 2024 telah dianalisis. Seramai 1,620 pesakit (810 kes dengan kelewatan penukaran kahak dan 810 kes tanpa kelewatan) telah dipilih melalui pensampelan rawak berstrata mengikut tahun pendaftaran kes. Analisis deskriptif serta regresi logistik mudah dan berganda dijalankan menggunakan perisian SPSS versi 29. **Keputusan:** Prevalens keseluruhan kelewatan penukaran sapuan kahak ialah 8.83%,

dengan peningkatan ketara dari 6.87% (2015) kepada 12.95% (2024). Analisis deskriptif menunjukkan majoriti pesakit berumur 60–74 tahun (82.6%), lelaki (74.0%) dan berbangsa Melayu (66.5%). Komorbid utama yang dilaporkan adalah diabetes mellitus (43.7%) dan status merokok (34.0%). Faktor-faktor signifikan kepada kelewatan penukaran sapuan kahak berdasarkan regresi logistik berganda termasuk tempat tinggal luar bandar (AdjOR=1.49, 95% CI: 1.20–1.84), diabetes mellitus (AdjOR=1.30, 95% CI: 1.05–1.61), lesi paru-paru teruk pada radiograf dada (AdjOR=3.31, 95% CI: 1.50–7.32), kes TB ulangan (AdjOR=1.77, 95% CI: 1.12–2.78), pematuhan DOTS yang rendah (<80%) (AdjOR=3.63, 95% CI: 2.20–5.99) dan status perokok semasa (AdjOR=1.28, 95% CI: 1.02–1.60). Model akhir menunjukkan keupayaan diskriminasi sederhana (AUC = 62.3%). **Kesimpulan:** Kelewatan penukaran kahak dalam kalangan pesakit PTB warga emas di Malaysia semakin meningkat, terutamanya selepas tahun 2020, dan ianya dipengaruhi oleh pelbagai faktor seperti sosiodemografi, klinikal, rawatan dan gaya hidup. Penemuan ini menekankan keperluan pelaksanaan intervensi berfokus untuk memperkukuh sokongan pematuhan rawatan, khususnya dalam kalangan pesakit diabetes, kes ulangan, dan pesakit yang tinggal di luar bandar. Pelaksanaan DOTS berasaskan komuniti (CB-DOTS), pemeriksaan saringan radiologi, dan program berhenti merokok yang menyeluruh adalah kritikal untuk meningkatkan kadar penukaran kahak dan menyokong pencapaian sasaran *National Strategic Plan to End TB 2021–2030*.

Kata kunci: Kelewatan penukaran kahak, tuberculosis dalam kalangan warga emas, TB paru-paru, sapuan kahak positif, faktor yang berkaitan, trend, Semenanjung Malaysia

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ABSTRACT

Background: Tuberculosis (TB) remains a major public health concern in Malaysia, with the elderly population disproportionately affected due to age-related immunosenescence, comorbidities, and social vulnerabilities. Delayed sputum conversion (DSC), defined as the persistence of sputum smear positivity beyond the two-month intensive phase, is a critical marker of poor treatment response, ongoing infectiousness, and increased risk of drug resistance. Despite these concerns, research on DSC among Malaysia's elderly remains limited. **Objectives:** This study aimed to examine trends and identify factors associated with DSC among elderly patients (aged ≥ 60 years) with smear-positive pulmonary TB (PTB) in Peninsular Malaysia from 2015 to 2024. **Methods:** A comparative cross-sectional study was conducted using secondary data from the National Tuberculosis Registry (NTBR). For trend analysis, all 15,736 elderly smear-positive PTB cases registered from 2015 to 2024 were included. For analytical purposes, 1,620 patients (810 with DSC and 810 with timely conversion) were selected via proportionate stratified random sampling. Descriptive analysis as well as simple and multiple logistic regression were conducted using SPSS Version 29. **Results:** The overall prevalence of DSC among elderly patients was 8.83%, with a notable increase from 6.87% in 2015 to 12.95% in 2024. Descriptive analysis showed that most patients were aged 60–74 years (82.6%), male (74.0%), and of Malay ethnicity (66.5%). Diabetes mellitus (43.7%) and smoking (34.0%) were common comorbidities. Multiple logistic regression identified significant predictors of

DSC: rural residency (AdjOR=1.49, 95% CI: 1.20–1.84), diabetes mellitus (AdjOR=1.30, 95% CI: 1.05–1.61), advanced chest X-ray lesions (AdjOR=3.31, 95% CI: 1.50–7.32), relapse TB cases (AdjOR=1.77, 95% CI: 1.12–2.78), poor DOTS adherence (AdjOR=3.63, 95% CI: 2.20–5.99), and current smoking (AdjOR=1.28, 95% CI: 1.02–1.60). The final model showed modest discrimination (AUC = 62.3%).

Conclusion: DSC among elderly TB patients in Malaysia has shown a rising trend, particularly after 2020, and is influenced by a combination of sociodemographic, clinical, treatment-related, and lifestyle factors. These findings call for targeted interventions to strengthen adherence support, especially among diabetics, relapse cases, and rural residents. Implementation of community-based DOTS (CB-DOTS), enhanced radiographic screening, and integrated tobacco cessation programs are critical to improving bacteriological response and achieving national TB control targets under the National Strategic Plan to End TB 2021–2030.

Keywords: Delayed sputum conversion, elderly tuberculosis, pulmonary TB, Smear-positif, factors associated, Trend, Peninsular Malaysia

CHAPTER 1

INTRODUCTION

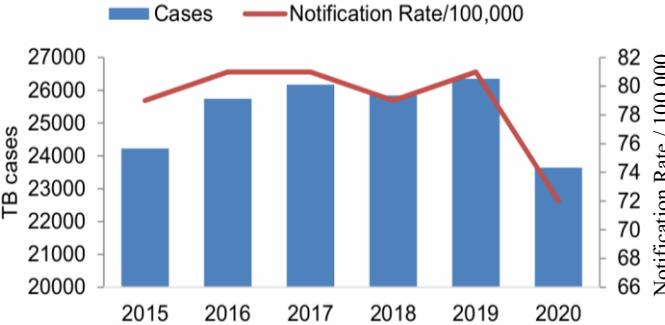
1.1 Overview of tuberculosis

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium *Mycobacterium tuberculosis* that primarily targets the lungs but also affects multiple extrapulmonary sites such as the lymph nodes, bones, kidneys and central nervous system (Pai *et al.*, 2016). TB remains an endemic disease and a significant global public health challenge, including in Malaysia. People with active pulmonary tuberculosis (PTB) spread through airborne droplets expelled during coughing, sneezing, speaking or singing. These tiny droplets, which contain *Mycobacterium tuberculosis*, can stay in the air and be inhaled by others, causing latent or active infection (WHO, 2025).

Individuals with a competent immune system, the infection may be contained as latent TB infection (LTBI) without symptoms. However, individuals with weakened immunity such as the elderly, malnourished or those with comorbid conditions like diabetes mellitus or human immunodeficiency virus (HIV) are at higher risk of developing active TB disease, characterised by persistent cough, weight loss, night sweats and haemoptysis (Lonnroth *et al.*, 2009).

According to the World Health Organisation (WHO, 2025), TB remains one of the leading causes of death from infectious diseases, with an estimated 10 million people continuing to fall ill with TB every year. Alarmingly, TB incidence has been rising since 2021, largely due to disruptions in TB services during the COVID-19 pandemic. In 2023 alone, an estimated 10.8 million people developed TB and approximately 1.25 million lives were lost to the disease (WHO, 2025). Malaysia reflects the global challenge of TB, where the disease remains a significant public health concern. Classified as an upper-

moderate TB burden country, Malaysia reports an annual notification rate of 50 to 99 cases per 100,000 population (MOH, 2021b). The trend of TB cases in Malaysia from 2015 to 2020 reflects the continued challenge of TB control, with fluctuating case numbers and notification rates. As shown in **Figure 1.1**, TB cases peaked between 2016 and 2019, with notification rates exceeding 80 per 100,000 population, before a marked decline occurred in 2020, likely influenced by reduced healthcare access and service disruptions during the COVID-19 pandemic. Although significant progress has been made in TB diagnosis and treatment, the disease remains endemic and continues to heavily impact vulnerable populations such as the elderly and individuals with underlying health conditions.



(Source: National Strategic Plan to End TB 2021-2030, MOH, 2021b)

Figure 1.1: TB cases and TB Notification rate (NR) for Malaysia from 2015 to 2020

In line with the WHO’s End TB Strategy, Malaysia has set national targets under the National Strategic Plan to End TB 2021–2030, using 2015 as the baseline year. These targets include achieving a 90% reduction in TB incidence, a 95% reduction in TB-related mortality and the elimination of catastrophic health expenditure due to TB by 2030 (MOH, 2021b). Achieving these goals requires intensive and targeted interventions, particularly among high-risk groups such as individuals with HIV, malnutrition, diabetes,

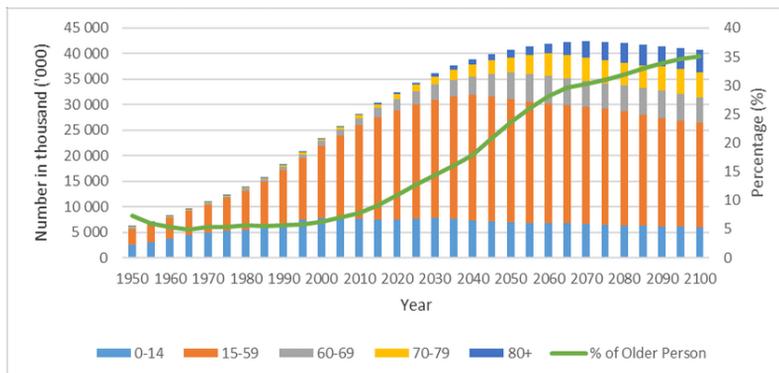
smoking, alcohol use and especially the elderly (Lonnroth *et al.*, 2009). As TB incidence remains significantly higher and healthcare systems continue to recover from the impact of the COVID-19 pandemic, immediate action is crucial to expedite improvements towards national and global TB elimination agendas.

1.2 Confronting tuberculosis in an ageing Malaysia

The demographic shift towards an ageing population in Malaysia is expected to have significant implications for public health, particularly in the management of chronic and infectious diseases such as TB. According to the Department of Social Welfare Malaysia (2021) and the United Nations (1982), those aged 60 years and older are defined as elderly. The ageing process is often accompanied by physiological changes, multiple comorbidities and reduced social support that significantly impact disease susceptibility, treatment response and healthcare utilisation (Massie and Staude, 2024). As shown in **Figure 1.2**, the proportion of older persons has been steadily increasing since the 1990s and is projected to rise sharply in the coming decades. By 2030, it is estimated that 15% of the Malaysian population, equivalent to approximately 5.8 million individuals, will be aged 60 years and above. This percentage is expected to continue increasing, reaching over 35% by the year 2100 (Pazim, 2019).

This demographic transition indicates that as the elderly population grows, Malaysia is expected to face a rising burden of TB, since older adults have persistently recorded the highest TB incidence among all age groups (CDC, 2023). The elderly are at a higher risk of developing TB and experiencing complications throughout the treatment regimen. Elderly individuals experience declines in immune function, along with comorbidities such as diabetes mellitus, chronic lung disease, and cardiovascular conditions, which complicate both the diagnosis and management of TB. Additionally,

TB symptoms in older adults are often atypical or masked by other conditions, resulting in delayed diagnosis and initiation of treatment (MOH, 2021a).



(Source: Pazim, *The Relationship between intergenerational transfers, co-residence and labour participation among older people in Malaysia*, 2019)

Figure 1.2: Growth of older people in Malaysia, 1950–2100

Treatment adherence is another critical challenge among this group. Polypharmacy, cognitive decline and inadequate treatment literacy may contribute to missed doses, adverse drug reactions or early cessation of therapy (Siddiqui *et al.*, 2010; Wang *et al.*, 2025). Limited mobility and lack of caregiver support lead to challenges in their regular follow-up and treatment adherence (Horvat *et al.*, 2024). Several studies support these concerns. For instance, a study conducted in Sabah, Malaysia, revealed that 16% of elderly TB patients experienced delayed sputum conversion (DSC) (Khor *et al.*, 2023). Similarly, research from rural Tanzania reported that 20% of elderly patients faced DSC after two months of treatment (Gunda *et al.*, 2017). These findings highlight the increased vulnerability of the elderly to TB and reinforce the urgent need for targeted, age-specific strategies to enhance treatment outcomes in this high-risk population.

1.3 Sputum conversion as a key treatment indicator

Sputum-smear conversion is widely recognised as an indicator of treatment success for patients with smear-positive PTB. It refers to the change from a positive to a negative sputum smear for *Mycobacterium tuberculosis* at the end of a two-month intensive phase after the initiation of anti-TB treatment. The World Health Organisation (WHO) recommends sputum conversion monitoring as an essential component of TB management due to its ability to demonstrate bacterial load reduction and reflect the effectiveness of medical therapy (WHO, 2025).

The mechanism of sputum conversion in pulmonary tuberculosis is primarily driven by the bactericidal effects of first-line anti-TB medications and the host's immune response. During the intensive phase of treatment, isoniazid and rifampicin rapidly eliminate actively replicating *Mycobacterium tuberculosis*, leading to a substantial reduction in bacillary load. Pyrazinamide enhances this effect by targeting semi-dormant bacilli within acidic environments, such as necrotic lesions, while ethambutol prevents the emergence of resistance and supports overall drug efficacy. Collectively, these agents contribute to the early conversion of sputum from smear- or culture-positive to negative, which is a key indicator of treatment response and decreased infectiousness (WHO, 2020).

Globally, many high-burden TB countries use sputum conversion rates as key performance indicators within their national TB programs. Countries with high TB burdens such as India, South Africa and Ethiopia routinely monitor sputum smear results at the end of the second month of treatment to guide clinical decisions and evaluate the effectiveness of their programme (Chakrabarti *et al.*, 2012; Mlotshwa *et al.*, 2016; Asemahagn, 2021). The preference for sputum conversion as a treatment indicator is

Commented [ZZ1]: Review conversion.

DONE

because of its practicality, low cost and reliability, especially in resource-limited settings (Liu *et al.*, 2022). It provides a more objective measure compared to clinical symptoms or radiographic changes, which may be subjective or delayed (Azarkar *et al.*, 2016). Furthermore, studies have validated sputum conversion as a strong predictor of long-term treatment outcomes, making it a valuable tool for both clinicians and policymakers (Liu *et al.*, 2022).

Early sputum conversion not only signifies individual clinical improvement but also indicates reduced infectivity, which helps to reduce transmission of TB in the community (Azarkar *et al.*, 2016). However, DSC has often been associated with higher risks of treatment failure, relapse and mortality. Djouma *et al.* (2015) found that patients with DSC were 11 times more likely to experience treatment failure (adjOR=11.2, 95% CI: 3.5-35.2) and almost four times more likely to die (adjOR=3.7, 95% CI: 1.5-9.0), while Dembele *et al.* (2007) observed a significant difference in cure rates between patients with timely conversion (90%) and those with delays (74.3%) ($p < 0.001$).

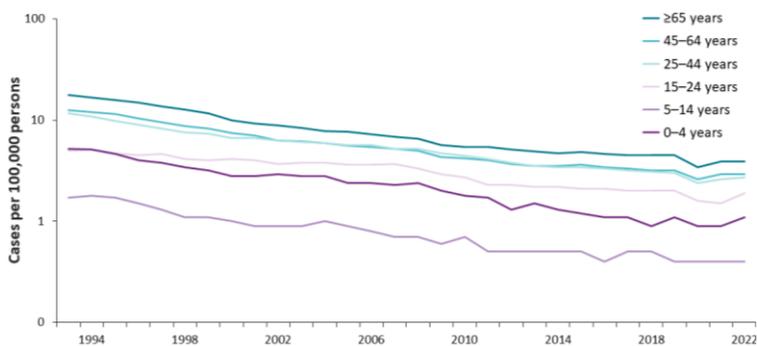
In addition to these clinical consequences, DSC is increasingly recognised as an early indicator of potential multidrug-resistant tuberculosis (MDR-TB) (Anwar *et al.*, 2018; Pang *et al.*, 2024). MDR-TB is a form of TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to rifampicin and isoniazid therapy. When drug resistance is unrecognised and ineffective regimens are continued, this can result in prolonged infectiousness, further transmission of MDR-TB and increased clinical and financial burdens to the healthcare systems (Anwar *et al.*, 2018).

In Malaysia, sputum smear conversion is also monitored as part of the National Strategic Plan for Tuberculosis Control. The Malaysian Ministry of Health (MOH) recommends routine sputum smear examination at the end of the intensive phase (2

months of treatment with ethambutol, isoniazid, rifampicin and pyrazinamide), followed by another examination at the end of the continuation phase (4 months of treatment with isoniazid and rifampicin) to evaluate treatment response (MOH, 2021b). Studies conducted in Malaysia have confirmed its reliability as an indicator of treatment success, especially in identifying patients at risk for delayed response, including the elderly (Khor *et al.*, 2023). Therefore, increasing focus on sputum conversion can enhance early detection of treatment complications such as MDR-TB and facilitate timely interventions in TB care management.

1.4 Problem statement and study rationale

The persistently highest incidence rate of TB among the elderly demands urgent, focused research and intervention. As illustrated in **Figure 1.3**, the United States shows older age groups have consistently recorded the highest TB incidence rates compared to all other age groups over the past three decades (CDC, 2023).



(Source: Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD and TB Prevention, Centers for Disease Control and Prevention)

Figure 1.3: TB incidence rate by age group, United States, 1993-2022

Despite medical advancements in the treatment of PTB, a significant proportion of the elderly, continue to experience DSC. This delay not only indicates a suboptimal response to therapy, but may also serve as an early warning sign of underlying or emerging drug resistance (Anwar *et al.*, 2018; Pang *et al.*, 2024). Early detection of MDR-TB is crucial to prevent the continued use of ineffective regimens, which can lead to the amplification of drug-resistant strains and increase the risk of ongoing TB transmission within the community.

Smear-positive PTB patients with a high bacillary load are estimated to infect up to 15 individuals annually if not promptly treated (Gunda *et al.*, 2017). Consequently, sputum conversion rates serve as a crucial marker for evaluating both individual treatment outcomes and the broader public health impact of TB control strategies. In a large-scale study of 95,189 adult PTB patients in Brazil, failure to achieve sputum conversion was associated with a twofold increase in the likelihood of unfavourable treatment outcomes (adjusted OR=2.06, 95% CI: 1.97–2.16) (do Socorro Nantua Evangelista *et al.*, 2018).

The implications of DSC are not limited to clinical prognosis. Patients with DSC often require extended treatment durations, which impose greater financial costs on healthcare systems and contribute to increased patient morbidity (Khor *et al.*, 2023). The healthcare system in Malaysia is under increasing pressure to address age-related challenges in the administration of TB due to the ageing population. In Malaysia and throughout the Southeast Asia-Pacific region, there is a notable lack of published research that specifically addresses the factors that contribute to DSC among elderly TB patients, despite these growing concerns.

In response to the lack of research focusing on the elderly and factors contributing to DSC in older patients, we conducted this study to examine the trends and investigate the factors that influence sputum smear conversion, with the goal of empowering and improving current treatment practices. The findings of this study will provide essential baseline data that can guide policymakers in enhancing treatment protocols and improving surveillance systems. By prioritising specific interventions and developing tailored guidelines for elderly high-risk TB patients, we aim to improve treatment outcomes, reduce mortality rates, minimise the risk of drug-resistant TB and lower healthcare costs.

1.5 Research questions

1. What are the trends of delayed sputum conversion (DSC) among elderly patients with smear-positive PTB in Peninsular Malaysia from 2015 to 2024?
2. What are the factors associated with delayed sputum conversion (DSC) among elderly patients with smear-positive PTB in Peninsular Malaysia from 2015 to 2024?

1.6 Research objectives

1.6.1 General objective

To study the trends of delayed sputum conversion (DSC) and its associated factors among the elderly with smear-positive PTB in Peninsular Malaysia from 2015 to 2024.

1.6.2 Specific objectives

1. To describe the trends of delayed sputum conversion (DSC) among the elderly with smear-positive PTB in Peninsular Malaysia from 2015 to 2024.
2. To determine the associated factors with delayed sputum conversion (DSC) among the elderly with PTB in Peninsular Malaysia from 2015 to 2024.

1.7 Research hypothesis

There are significant associations between sociodemographic, clinical or lifestyle factors with delayed sputum smear conversion among the elderly with smear-positive pulmonary tuberculosis in Peninsular Malaysia from 2015 to 2024.

CHAPTER 2

LITERATURE REVIEW

This chapter provides a comprehensive review of existing literature on delayed sputum conversion (DSC) among the elderly patients with smear-positive pulmonary tuberculosis (PTB). The literature review aims are to critically synthesise the epidemiological patterns, risk factors, comorbidities and treatment outcomes related to DSC, particularly in older populations. By incorporating both global and Malaysian evidence, this chapter establishes a strong theoretical and empirical foundation for the present study.

A systematic and targeted literature search was conducted to ensure the inclusion of high-quality, relevant and up-to-date sources. Multiple academic databases were used, including PubMed, Scopus, ScienceDirect, Web ISI, Springer link, Google Scholar and Web of Science, focusing on peer-reviewed journal articles, official reports, WHO documents and relevant grey literature. Boolean operators (AND or, NOT) were applied to refine search results and ensure comprehensive coverage.

Key search terms included combinations such as “delayed sputum conversion” AND “elderly tuberculosis,” “smear-positive pulmonary TB” AND (“treatment outcome” OR “sputum conversion”) and “pulmonary tuberculosis” AND (“older adults” OR “geriatric” OR “aged 60 and above”). Additional combinations such as “predictors” OR “risk factors” AND “sputum non-conversion” were also used. The inclusion criteria were limited to studies published between 2000 and 2024, written in English and addressing either elderly populations (typically defined as aged 60 and above) or studies with age-disaggregated TB treatment outcomes.

2.1 Overview of delayed sputum conversion (DSC) among the elderly

Delayed sputum conversion (DSC) refers to the failure of sputum smear-positive PTB patients to achieve smear negativity by the end of the intensive treatment phase, typically within 60 days. As the global population ages and the burden of tuberculosis (TB) increasingly shifts toward older adults, understanding the age-specific patterns and consequences of DSC has become essential to achieve TB control targets. Globally, the prevalence of DSC ranges from 7% to over 30%, with high rates reported among elderly and drug-resistant TB cases. For example, a hospital-based study in Gujarat, India, reported a 34.9% prevalence of DSC among the elderly (Vora *et al.*, 2016), while Uganda documented a 32% rate among MDR-TB patients (Izudi *et al.*, 2020).

In Malaysia, the prevalence of DSC varies considerably across population subgroups and geographic regions. In Sabah, a study among smear-positive PTB patients receiving care at government health facilities reported a prevalence of 8.8% (Khor *et al.*, 2023). Among the aboriginal Orang Asli population in Peninsular Malaysia, the prevalence was substantially higher at 19.1% (Ibrahim *et al.*, 2022). In Pulau Pinang, an observational study conducted between 2016 and 2018 among inpatients at a tertiary hospital recorded a DSC prevalence of 30.5%, significantly exceeding rates observed in other population groups (Bhatti *et al.*, 2021).

This prolonged infectiousness poses a critical threat in high-burden settings, as it facilitates ongoing transmission and undermines TB control efforts. Moreover, DSC is associated with a higher risk of developing multidrug-resistant TB (MDR-TB), primarily due to the extended exposure of *Mycobacterium tuberculosis* to subtherapeutic drug levels, which fosters resistance selection (Kusmiati *et al.*, 2020; Suryana *et al.*, 2022). The emergence of MDR-TB further complicates treatment due to

the requirement for longer, more toxic, and less effective drug regimens, ultimately increasing healthcare costs and burdening national TB programmes (Hoffner, 2016; Akalu *et al.*, 2023).

Evidence consistently shows that the elderly face a significantly higher risk of DSC and its associated adverse outcomes. In Sabah, Malaysia, a retrospective study by Mokti *et al.* (2021) found that individuals aged 60 and above had more than twice the odds of experiencing DSC compared to younger adults (AdjOR=2.1, 95% CI: 1.1–4.0, $p=0.03$). Similar findings were reported in Brazil, where patients over 65 had increased odds of unfavourable TB outcomes, including DSC (AdjOR=1.13, 95% CI: 1.04–1.23, $p<0.01$) when compared to those aged 15–24 years old (do Socorro Nantua Evangelista *et al.*, 2018). In Thailand, Satung *et al.* (2016) reported a significantly higher risk of DSC among elderly patients when compared to the younger age group of 18–30 years (AdjRR=1.41, 95% CI: 1.04–1.91), while Banu Rekha *et al.* (2007) in India, observed that both delayed sputum and culture conversion were significantly associated with patients aged over 45 years ($p=0.03$) and ($p=0.01$), respectively.

Beyond delays in microbiological clearance, ageing is also associated with increased mortality during TB treatment. In Southern Ethiopia, Dangisso *et al.* (2014) found that patients aged above 65 were nearly four times more likely to die during treatment than younger individuals (AdjOR=3.86, 95% CI: 2.94–5.10). In Cameroon, Djouma *et al.* (2015) reported that DSC significantly increased the odds of treatment failure (AdjOR=12.4, 95% CI: 4.0–39.0) and mortality (AdjOR=3.6, 95% CI: 1.5–9.0). Similarly, a study by (Nakamura *et al.*, 2022) in Japan revealed that conversion delays beyond 90 and 120 days were strongly associated with increased in-hospital mortality

(AdjHR=0.424, 95% CI: 0.252–0.712) and (AdjHR=0.333, 95% CI: 0.195–0.570) respectively, when compared to patients who converted within 60 days.

Global evidence further supports these associations. In Japan, Komiya *et al.* (2020) found that the elderly (median age 82 years) with high pre-treatment smear grades, elevated C-reactive protein (CRP) levels and poor performance status were more likely to experience non-conversion at two months. In Portugal, Mota *et al.* (2012) showed that patients aged ≥ 50 had significantly higher odds of persistent smear positivity compared to those aged < 50 years (OR=4.4, 95% CI: 1.5-13.3). Similarly in Malaysia, Khor *et al.* (2023) reported that elderly patients aged ≥ 60 had elevated odds of DSC compared to those aged 18–59 years (AdjOR=4.303, 95% CI: 1.41–13.18). Collectively, these studies consistently highlight the strong association between ageing and DSC across various settings.

2.2 Factors influencing delayed sputum conversion (DSC) among the Elderly

2.2.1 Sociodemographic factors

2.2.1(a) Sex

Multiple studies have consistently demonstrated that male gender is significantly associated with DSC among TB patients, including the elderly. In Thailand, Satung *et al.* (2016) reported that male sex was independently linked to DSC at the end of the intensive phase (adjRR=1.36, 95% CI: 1.12–1.64). Similarly, Azarkar *et al.* (2016) found that the mean time to sputum smear conversion was significantly longer among males (mean = 2.29 months, SD = 1.23) compared to females (mean = 1.74 months, SD = 0.85), with a statistically significant difference ($p=0.046$). In Taiwan, Feng *et al.* (2012) reported that male patients had a lower two-month sputum culture conversion rate than female (78.8% vs. 89.3%, $p=0.002$). Reinforcing these findings, Mota *et al.* (2012) identified male gender as an independent predictor of persistent smear positivity after two months of intensive phase (OR=10.8, 95% CI: 1.3–91.1).

Further supporting this association, Gunda *et al.* (2017) in a rural Tanzanian study, found that male patients were significantly more likely to experience DSC (OR=8.2, 95% CI: 1.0–64.7, $p=0.046$), particularly among those aged over 50 years. This emphasises the compounded vulnerability of elderly men to DSC due to age-related health challenges.

However, contradictory evidence exists. A study by Krishnamoorthy *et al.* (2024) in South India reported that females had a significantly higher likelihood of persistent sputum positivity at the end of the intensive phase (OR=6.77, $p=0.003$), with the direct effect of being female also reaching statistical significance (OR=3.42,

$p=0.03$). These findings suggest that gender-related disparities in treatment response may vary across different populations and warrant context-specific interpretation.

2.2.1(b) Ethnic

Ethnicity has emerged as an important determinant of DSC, reflecting a complicated relationship among genetic predispositions, healthcare access, sociocultural influences and socioeconomic conditions. In the Malaysian context, Ibrahim *et al.* (2022) reported that among indigenous groups, the elderly individuals from the Melayu Proto subgroup had a significantly higher likelihood of experiencing DSC compared to their Senoi counterparts (OR=1.78, 95% CI: 1.09–2.98). Supporting this observation, Kenangalem *et al.* (2013) found that 88% of Papuan patients in Indonesia achieved culture conversion after the intensive phase, compared to only 70% of non-Papuan patients ($p=0.02$). Similarly, Chakrabarti *et al.* (2012) reported that tribal populations in India exhibited significantly higher sputum conversion rates than non-tribal groups ($Z = 2.28$, $p<0.05$), suggesting a potential protective influence of genetic or culturally mediated factors in certain ethnic groups.

In contrast, findings from high-income countries highlight persistent ethnic disparities in TB outcomes. A large-scale study in the United States by Regan *et al.* (2024) revealed that non-Hispanic Black individuals had a 27% higher risk of experiencing adverse TB outcomes, including DSC, compared to non-Hispanic Whites (AdjRR=1.27, 95% CI: 1.22–1.32). Similarly, American Indian or Alaska Native individuals had a 24% increased risk (AdjRR=1.24, 95% CI: 1.12–1.37), while Hispanic individuals had a 20% higher risk (AdjRR=1.20, 95% CI: 1.14–1.27). These findings highlight the enduring impact of racial and ethnic disparities on TB treatment outcomes, even in settings with advanced healthcare infrastructure.

2.2.1(c) Occupation

Occupation may influence delayed sputum conversion both as a sociodemographic factor and as a proxy for workplace-related exposures. From a sociodemographic perspective, individuals employed in blue-collar jobs were found to have significantly higher odds of DSC compared to those in white-collar professions (AdjOR=1.9, 95% CI: 1.3–2.8, $p=0.001$) (Bhatti *et al.*, 2021). In contrast, workplace conditions such as poor ventilation, exposure to airborne particulates, and physically demanding environments may impair lung function and immune response, thereby slowing bacteriological clearance during treatment (Hammouri *et al.*, 2024).

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A more specific occupational risk was identified in a study assessing two-month culture conversion, where individuals engaged in “social service jobs”, primarily motorbike passenger riders were three times more likely to remain culture-positive compared to those in formal professional roles (RR=3.0, 95% CI: 1.11–8.19, $p=0.031$) (Atwine *et al.*, 2017). These findings indicate that individuals employed in informal and high-contact occupations demonstrated higher rates of DSC, potentially due to increased environmental exposure and inconsistent treatment adherence as reported by the study authors.

2.2.1(d) Educational level

Educational level is a key factor influencing health literacy and treatment adherence. In TB care, low education may limit a patient’s understanding of the disease, medication schedules and the importance of completing treatment. These limitations can lead to DSC, especially in older adults. In Malaysia, access to education has improved significantly. As of 2018, enrolment rates reached 85.4% for early childhood, 97.8% for primary, 95.3% for lower secondary and 87.2% for upper secondary levels. Tertiary

enrolment exceeded 40%, supported by a centralised and federally managed education system (Tee, 2023).

However, disparities persist. Several studies support the link between low education and DSC. In Indonesia, Wardani and Wahono (2019) found that patients with lower education were five times more likely to have DSC (OR=5.313, 95% CI: 1.711–16.503). A local study by Mokti *et al.* (2021) showed that illiterate individuals had three times the odds of experiencing DSC compared to those with formal education (OR=3.0, $p<0.01$). These findings suggest that limited education reduces understanding of TB care and the importance of treatment adherence.

2.2.1(e) Residency area

Residency in rural area has been identified as a significant factor associated with DSC among TB patients. Several studies have demonstrated that individuals residing in rural settings are more likely to experience delayed treatment response compared to those in urban settings.

In Malaysia, Ibrahim *et al.* (2024) reported a higher DSC rate of 19.1% among aboriginal populations, most of whom resided in rural settings. This rate was considerably higher than the national average. Similarly, Kayigamba *et al.* (2012) found that patients treated in rural health facilities were more likely to experience low sputum conversion rates compared to urban facilities ($p=0.001$). In their multivariable analysis, rural facility was the only independent factor associated with poor conversion outcomes ($p=0.001$). In northwestern Tanzania, Gunda *et al.* (2017) reported a DSC rate of 8.3% among patients residing in rural areas. Advanced age and high initial smear grades, both common in rural populations were identified as contributing factors.

Contrasting findings have also been documented. In the Sidama Zone of southern Ethiopia, Dangisso *et al.* (2014) observed a slightly higher treatment success rate patients residing in rural areas compared to those in urban areas (AdjOR=1.11, 95% CI: 1.03–1.20). In contrast, Tessema *et al.* (2009) reported significantly lower treatment success rates in rural areas (16.2%) compared to urban areas (42.0%) ($p<0.001$), highlighting inconsistencies across settings. These findings reflect variability in healthcare access, service delivery and patient characteristics, as reported by the respective authors.

2.2.2 Clinical factors

2.2.2(a) Diabetes mellitus

Diabetes mellitus (DM) has been widely reported as a factor associated with DSC among patients with PTB. Several studies have demonstrated that the presence of DM is significantly linked to prolonged sputum smear positivity following the intensive phase of treatment. In Turkey, Guler *et al.* (2007) reported that DM was significantly associated with DSC (OR=2.39, 95% CI: 1.04–5.48, $p=0.04$). In Malaysia, Shariff and Safian (2015) found that patients with DM were four times more likely to remain smear-positive after the intensive phase compared to non-diabetic individuals (OR=4.00, 95% CI: 1.61–9.96).

Ibrahim *et al.* (2022), in another Malaysian study, reported a markedly increased risk of DSC among diabetic patients (AdjOR=12.84, 95% CI: 6.33–26.06, $p<0.001$). Similarly, Baskaran *et al.* (2022) observed a significant association between DM and DSC in a primary care setting in Pahang (AdjOR=1.52, 95% CI: 0.04–0.18, $p=0.011$). Asemahagn (2021) reported consistent findings in Ethiopia, where diabetic TB patients had more than twice the odds of experiencing DSC compared to non-diabetic counterparts (AdjOR=2.11, 95% CI: 1.18–4.20). However, not all studies observed a

statistically significant association. Khor *et al.* (2023), in a retrospective analysis conducted in Sabah, Malaysia, reported no significant association between DM and DSC after adjusting for potential confounders. Collectively, these studies suggest that diabetes mellitus is a potential factor in DSC among TB patients, although the strength of the association varies across different study settings and populations.

2.2.2(b) Anaemia

Anaemia has been identified as a comorbid condition associated with DSC in patients with PTB. According to WHO criteria, anaemia is defined as a haemoglobin concentration <13.0 g/dL in men and <12.0 g/dL in non-pregnant women, although thresholds may vary across countries and populations (WHO, 2011, 2023). One of the earliest findings was reported by Morris *et al.* (1989), who identified anaemia as one of the clinical factors associated with DSC. More recent evidence from Tanzania by Nagu *et al.* (2014) supported this association, demonstrating that anaemic patients were three times more likely to experience DSC compared to non-anaemic individuals at two months of treatment (RR=3.05, 95% CI: 1.11–8.40, $p=0.030$).

Furthermore, Nagu *et al.* (2014) observed that the risk of DSC increased with the severity of anaemia (P for trend < 0.01), suggesting a dose-response relationship. This indicates that anaemia, especially in its more severe forms, may significantly impair early bacteriological clearance during TB therapy. Additional evidence was provided by Agrawal *et al.* (2017), who found that 12% of sputum-positive TB patients with anaemia experienced DSC after two months of treatment. The study also noted that the severity of anaemia influenced outcomes, with patients suffering from severe iron deficiency anaemia being more likely to have DSC. These findings highlight the potential role of anaemia as a clinical risk factor for DSC.

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2.2.2(c) Chronic obstructive pulmonary disease (COPD)

Chronic lung diseases have been linked to DSC in TB patients due to impaired clearance of *Mycobacterium tuberculosis* during the treatment. In Ankara, Turkey, (Guler *et al.*, 2007) reported that patients with extensive lung disease had significantly higher odds of persistent sputum smear positivity at the end of the intensive phase (OR=13.44, 95% CI: 5.89–30.67, $p<0.001$). In Thailand, the presence of cavitary lesions was significantly associated with a reduced likelihood of sputum conversion at two months, indicating a higher risk of DSC when compared to patients without cavitary lesions (AdjRR=0.79, 95% CI: 0.67–0.93) (Satung *et al.*, 2016).

Further evidence has shown that emphysema, a chronic obstructive lung condition, may also influence treatment response. In a retrospective cohort study conducted in Japan among 124 hospitalized PTB patients who underwent high-resolution CT, Takasaka *et al.* (2020) using a multivariate Cox proportional hazards analysis, found that the presence of emphysema was significantly associated with delayed time to culture conversion compared to patients without emphysema (AdjHR=2.43, 95% CI: 1.18–4.97, $p=0.015$).

2.2.2(d) Human immunodeficiency virus (HIV)

Several studies have demonstrated that HIV-positive individuals are more likely to experience DSC during TB treatment. In Malaysia, Ibrahim *et al.* (2022) found that HIV infection had significantly higher odds of experiencing delayed sputum conversion compared to those without HIV (AdjOR=9.76, 95% CI: 3.01–31.65). Similarly, Asemahagn (2021) in Ethiopia reported that TB patients with HIV co-infection had more than twice the odds of experiencing DSC compared to HIV-negative patients (AdjOR=2.38, 95% CI: 1.20–4.91).

In Thailand, Satung *et al.* (2016) also identified HIV status as a predictor, with an adjusted relative risk (AdjRR=0.89, 95% CI: 0.79–1.00), indicating a lower likelihood of early sputum conversion among HIV-positive individuals. Conversely, a study by Mzinza *et al.* (2015) reported no significant association between HIV infection and 2-month sputum culture conversion, suggesting that the impact of HIV on treatment response may vary by population and setting.

2.2.2(e) BCG scar

The Bacillus Calmette–Guérin (BCG) vaccine is currently the only approved and most widely used tuberculosis vaccine globally. It is routinely administered during infancy and has consistently demonstrated high efficacy in preventing severe forms of tuberculosis in young children, particularly tuberculous meningitis and miliary TB (Trunz *et al.*, 2006; Yuan-Zhi *et al.*, 2021). However, the protective effect of BCG against adult pulmonary TB is limited, and the influence of BCG scarring on treatment outcomes like sputum conversion remains inconclusive.

Despite the limited and uncertain overall protection of BCG in adults, some observational studies have explored its potential influence on treatment response, particularly DSC. In a study conducted in Tanzania among pulmonary tuberculosis (PTB) patients aged ≥ 15 years, Jeremiah *et al.* (2010) reported that the absence of a BCG scar was significantly associated with DSC at the end of the intensive treatment phase (OR=3.35, 95% CI: 1.48–7.58, $p=0.004$). Similarly, Goswami (2016), in a study involving newly diagnosed smear-positive PTB patients aged ≥ 13 years in India, found a significantly higher sputum conversion rate among those with a visible BCG scar (90.9%) compared to those without a scar (63.9%) ($p=0.0013$). These findings suggest a potential protective effect of prior BCG vaccination on early bacteriological response during TB treatment.

2.2.2(f) Chest X-ray findings

Radiographic abnormalities, including cavitary lesions, bilateral opacities and emphysematous changes, have been strongly associated with DSC in PTB. Guler *et al.* (2007) reported that extensive pulmonary disease evident on chest X-ray significantly increased the likelihood of DSC at the end of the intensive phase (OR=13.44, 95% CI: 5.89–30.67, $p<0.001$). Similarly, Ozsahin *et al.* (2011) demonstrated that patients with cavitary disease had a markedly higher proportion of positive sputum cultures after the first month of treatment compared to those without cavitation (53.7% vs. 37.7%). Further supporting this, Hernandez-Romieu *et al.* (2019) found that cavitary lesions detected on computed tomography (CT), especially multiple or large cavities that may be missed on chest X-ray, were significantly associated with delayed sputum culture conversion. Patients with a single cavity had a slower conversion (aHR=0.56, 95% CI: 0.32–0.97), while those with multiple cavities showed an even more delayed response (aHR=0.31, 95% CI: 0.16–0.60).

Mokti *et al.* (2021) in Kota Kinabalu, Sabah aligned with these findings, reporting that advanced chest X-ray findings at baseline were associated with higher odds of DSC (AdjOR=2.67, 95% CI: 1.60–4.50, $p=0.01$). Similarly, Mota *et al.* (2012) observed that bilateral radiographic involvement significantly predicted persistent culture positivity (OR=3.7, 95% CI: 1.5–9.0, $p=0.005$), suggesting that widespread pulmonary damage may impede early bacteriological clearance. In contrast, Satung *et al.* (2016) reported that the presence of cavitary lesions was associated with a significantly lower risk of DSC (AdjRR=0.79, 95% CI: 0.67–0.93). This unexpected finding may reflect contextual differences in clinical management, the timing of diagnosis, or population characteristics, and warrants further investigation.

2.2.2(g) Bacillary load

Higher pre-treatment bacillary load, as indicated by sputum smear grading, has been consistently associated with DSC in patients with PTB. In Bafoussam, Cameroon, Djouma *et al.* (2015) reported that smears graded 2+ and 3+ were independently associated with DSC ($p < 0.01$), highlighting the role of bacterial burden in hindering a timely treatment response. Similar findings were observed in Thailand, where Satung *et al.* (2016) found a significant association between high pre-treatment bacterial grades ($\geq 2+$) and DSC (AdjRR=2.08, 95% CI: 1.74–2.49), compared to patients with lower bacterial grades ($< 2+$).

In Malaysia, Khor *et al.* (2023) reported that patients in Sabah with higher sputum bacillary loads at diagnosis had significantly increased odds of delayed conversion. Specifically, those with a 2+ smear had an adjusted odds ratio (AdjOR) of 5.061 (95% CI: 1.315–19.478, $p=0.018$), while those with a 3+ smear had an AdjOR of 4.992 (95% CI: 1.249–19.947, $p=0.023$), compared to those with scanty or 1+ grading. In Ethiopia, Kumar *et al.* (2023) demonstrated that PTB cases with an initial smear grading of $< 2+$ (scanty or 1+) were 54% less likely to experience delayed conversion than those with $\geq 2+$ grades (AdjOR=0.46, 95% CI: 0.21–0.73). Additionally, Mota *et al.* (2012) found that a higher bacillary load (3+) was strongly associated with persistent smear positivity, with an AdjOR of 11.7 (95% CI: 1.4–100.6), reinforcing the predictive value of bacterial quantification in early treatment phases.

2.2.2(h) **Body Mass Index (BMI)**

Nutritional status, particularly low body mass index (BMI), is a well-established determinant of TB treatment outcomes and has been consistently associated with DSC, especially among the elderly patients. Multiple studies have reported a significant association between underweight BMI and DSC. In Malaysia, Shariff and Safian (2015)

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