THE ASSOCIATION PATTERNS BETWEEN SOCIO-DEMOGRAPHIC, CLINICAL AND TREATMENT- RELATED CHARACTERISTICS IN MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN MALAYSIA

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by

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LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
CI	Confidence interval
DM	Diabetic mellitus
DOTS	Directly Observed Therapy Short Course
HIV	Human immunodeficiency virus
HREC	Human Research Ethics Committee
ID	Identification card
LTBI	Latent tuberculosis infection
MDR-TB	Multidrug-resistant tuberculosis
MOH	Ministry of Health
MREC	Medical Research and Ethics Committee
MTB	Mycobacterium Tuberculosis
OR	Odd ratio
RR-TB	Rifampicin-Resistant tuberculosis
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
TBIS	Tuberculosis Information System
USM	Universiti Sains Malaysia
WHO	World Health Organization

LIST OF SYMBOLS

n	Sample size
μ_{ij}	Expected frequency
π_{ij}	Probability of cell *ij*
π_{i+}	Marginal probabilities of row effect
π_{+j}	Marginal probabilities of column effect
X^2	Pearson chi-square
G^2	Likelihood ratio
$\leq$	Less than or equal to
$>$	More than
df	Degree of freedom
Δ	Difference
r_{ij}	Standardized Pearson residuals
z	z-statistic distribution

POLA HUBUNGAN ANTARA CIRI-CIRI DEMOGRAFI SOSIAL, KLINIKAL DAN RAWATAN TUBERKULOSIS RINTANG PELBAGAI UBAT DI ANTARA PESAKIT DI MALAYSIA

ABSTRAK

Pengenalan: Kemunculan dan peningkatan jumlah tuberkulosis rintang pelbagai ubat (MDR-TB) di seluruh dunia telah menimbulkan ancaman kesihatan awam baru di dalam dan di luar negara. Terdapat beberapa ciri-ciri pesakit yang penting untuk MDR-TB. Walau bagaimanapun, tidak ada kajian yang diterbitkan mengenai hubungan di antara ciri-ciri pesakit MDR-TB di Malaysia.

Objektif: Objektif kajian ini adalah untuk menerangkan ciri-ciri berkaitan demografi, klinikal dan rawatan pesakit MDR-TB di Malaysia dan menentukan hubungan di antara faktor-faktor penyebab MDR-TB.

Metodologi: Analisis data sekunder daripada kajian reka bentuk rentas keratan menggunakan Sistem Maklumat Tuberkulosis (TBIS) Kementerian Kesihatan Malaysia. Ciri-ciri berkaitan demografi, klinikal dan rawatan pesakit MDR-TB diekstrak dari pangkalan data. Analisis log-linear digunakan untuk mengenal pasti pola hubungan di antara ciri-ciri pesakit MDR-TB bersama nisbah odds dan 95% selang keyakinan (SK).

Keputusan: Terdapat 395 kes MDR-TB yang dilaporkan di seluruh Malaysia dari tahun 2012 hingga 2016. Odds pendatang adalah 77% lebih rendah bagi yang berusia tua berbanding muda (nisbah odds = 0.23, 95% SK: 0.11, 0.43). Odds jantina lelaki adalah 2.37 kali bagi yang berusia tua berbanding muda (nisbah odds = 2.37, 95% SK: 1.45, 3.95). Odds jantina lelaki adalah 5.22 kali bagi status HIV positif berbanding status HIV negatif (nisbah odds = 5.22, 95% SK: 1.48, 33.12). Odds sejarah rawatan TB adalah 78% lebih tinggi bagi jantina lelaki

berbanding wanita (nisbah odds = 1.78, 95% SK: 1.13, 2.82) dan 52% lebih rendah bagi status ujian kahak positif berbanding status ujian kahak negatif (nisbah odds = 0.48, 95% SK: 0.30, 0.78)

Kesimpulan: Analisis log-linear menunjukkan bahawa terdapat hubungan di antara kategori umur dan status pendatang, kategori umur dan jantina, jantina dan HIV, jantina dan sejarah rawatan TB, dan sejarah rawatan TB dan status ujian kahak.

Kata kunci : Penyakit rintang pelbagai ubat, tuberkulosis, analisa log-linear, hubungan di antara faktor

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ABSTRACT

Introduction: The emergence and increasing number of multidrug-resistant tuberculosis (MDR-TB) worldwide have posed new threats to public health locally and globally. There are a number of important patient's characteristic for MDR-TB. However, there are no studies published about association between the characteristics of MDR-TB patient in Malaysia.

Objective: The objective of this study was to describe the socio-demographic, clinical and treatment related characteristics of MDR-TB patients in Malaysia and to determine the association patterns between the characteristics of MDR-TB patients in Malaysia

Methods: Analysis of secondary data from a cross-sectional design study on registry of Tuberculosis Information System (TBIS) of Ministry of Health Malaysia. Socio-demographic, clinical and treatment related characteristics of MDR-TB patient were extracted from the databases. Log-linear regression was used to identify association patterns between the characteristics with odd ratios and 95% confidence interval.

Results: There were 395 cases of MDR-TB reported across Malaysia from 2012 to 2016. Odds of immigrant were 77% lower in old age than young age (OR = 0.23, 95% CI: 0.11, 0.43). Odds of male gender were 2.37 times in old age group than young age group. (OR = 2.37, 95% CI: 1.45, 3.95). Odds of male gender were 5.22 times in HIV positive status group than negative HIV status (OR = 5.22, 95% CI: 1.48, 33.12). Odds of previous TB treatment were 78% higher in male than female (OR = 1.78, 95% CI: 1.13, 2.82) and 52% lower in positive sputum status than negative sputum status (OR = 0.48, 95% CI: 0.30, 0.78).

Conclusion: Log-linear analysis revealed that there are association between age category and immigrant status, age category and gender, gender and HIV, gender and history of previous TB treatment, and history of previous TB treatment and sputum status.

Keywords: Multidrug-resistant, tuberculosis, log-linear analysis, association between characteristics

CHAPTER 1

INTRODUCTION

1.1 Tuberculosis

Tuberculosis (TB) has existed since 1800s and remains a major global health problem and burden (Keshavjee and Farmer, 2012; Frieden *et al.*, 2014; World Health Organization, 2016). More than 10 million new cases reported in 2015 and almost two million deaths due to TB with about 2 to 3 billion people latently infected despite the fact that TB is curable. (World Health Organization, 2016). Figure 1.1 shows 60% of the new cases are contributed by these countries: India with the highest numbers, followed by Indonesia, China, Nigeria, Pakistan and South Africa. In order to meet their first milestone of the End TB Strategy, WHO has set up a target of reduction of 4% to 5% annually worldwide by 2020. However, the rate of decline persisted at 1.5% from 2014 to 2015 with major steps need to be done in TB prevention and care worldwide especially in these countries (World Health Organization, 2016).

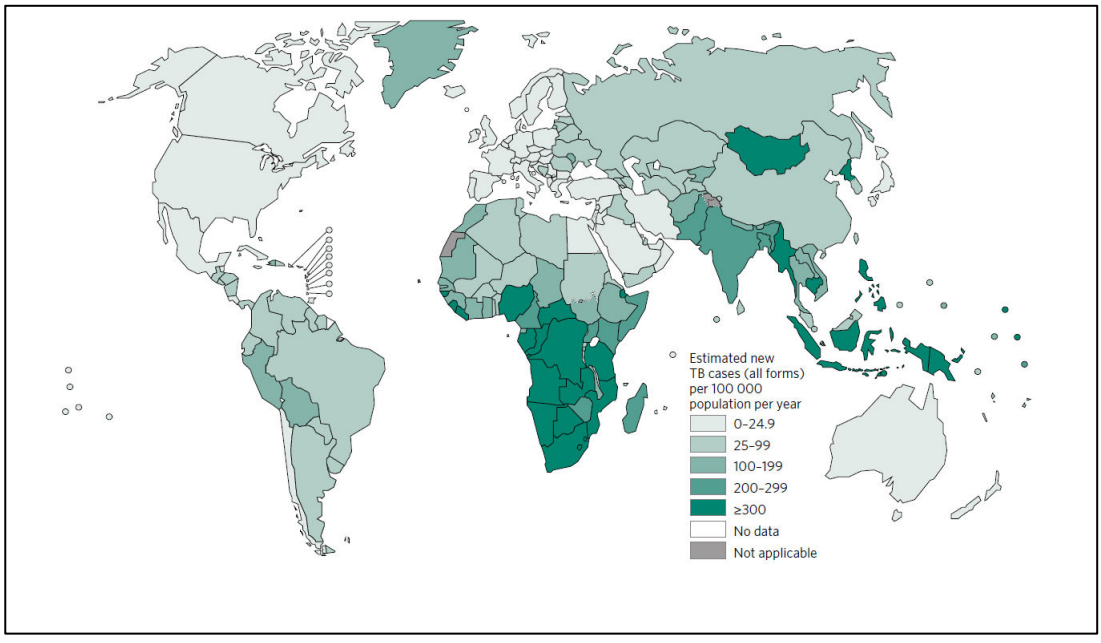

Figure 1.1 The estimated TB incidence rate in 2015

Tuberculosis is caused by the rod-shaped, non–spore-forming, aerobic bacterium *Mycobacterium tuberculosis* (MTB) (Knechel, 2009; Keshavjee and Farmer, 2012). It is transmitted via small airborne droplets and usually formed by the action of talking, coughing, sneezing or even singing by an individual with pulmonary or laryngeal tuberculosis (Knechel, 2009; Turner and Bothamley, 2015). The presence of MTB in the lungs leads to respiratory system infection causes pulmonary tuberculosis and the bacterium may also spread to other organs in the body and thus causing extrapulmonary tuberculosis (Knechel, 2009).

Majority of those who inhaled the droplets containing MTB would develop an effective acquired immune response leading to successful inhibition of MTB growth and thus leads to bacteria becoming latent; this is called latent TB infection (LTBI) (Fogel, 2015). They do not transmit the disease to others nor present any symptoms (Cruz-Knight and Blake-Gumbs, 2013). On the other hand, those with active TB have primarily respiratory symptoms such as cough, chest pain and haemoptysis and systemic symptoms such as fever, night sweat and weight loss (Knechel, 2009; Maher, 2009; Zaman, 2010).

For treatment of a new case, an intensive regimen of a total of six months is recommended (Fox *et al.*, 1999). Daily dose of isoniazid, rifampicin, pyrazinamide and streptomycin (or ethambutol if streptomycin is contraindicated) is given for two months and followed by four-month maintenance regimen of daily isoniazid and rifampicin. By giving medications and monitoring the patients directly via Directly Observed Therapy Short Course (DOTS) programme, it can ensure better success rate of eliminating the disease by more than 85% (Blumberg *et al.*, 2005; World Health Organization, 2016).

1.2 Multidrug-resistant Tuberculosis

However, the emergence and increasing number of multidrug-resistant tuberculosis (MDR-TB) worldwide have posed new threats to public health locally and globally (Dheda *et al.*, 2017). Based on Global Tuberculosis Report in 2016, almost half a million-people developed MDR-TB and in Malaysia, MDR-TB cases are accounted for 3.1% in previously treated TB cases (World Health Organization, 2016).

MDR-TB can be defined as MTB with resistance to at least two most powerful first-line anti-TB drugs which are rifampicin and isoniazid (McBryde *et al.*, 2017). The resistance may arise either by transmission of MDR strain by infected person to another, or by insufficient treatment of individual who has been infected with non-resistant strain or only one single drug resistant (Faustini *et al.*, 2006). The inadequate drug treatment will allow the growth of small number of resistant MTB by spontaneous mutation and subsequently leads to MTB being resistance to many drugs (Faustini *et al.*, 2006).

1.3 Epidemiology of MDR-TB

1.3.1 Global Situation

In 2016, WHO estimated incidence cases of MDR-TB to be approximately 490,000. As depicted in Figure 1.2, the South-East Asia, Europe and Western Pacific regions contribute 37%, 23% and 18% respectively of the total global new cases of MDR-TB. These three regions contribute the largest number of MDR-TB incidence globally.

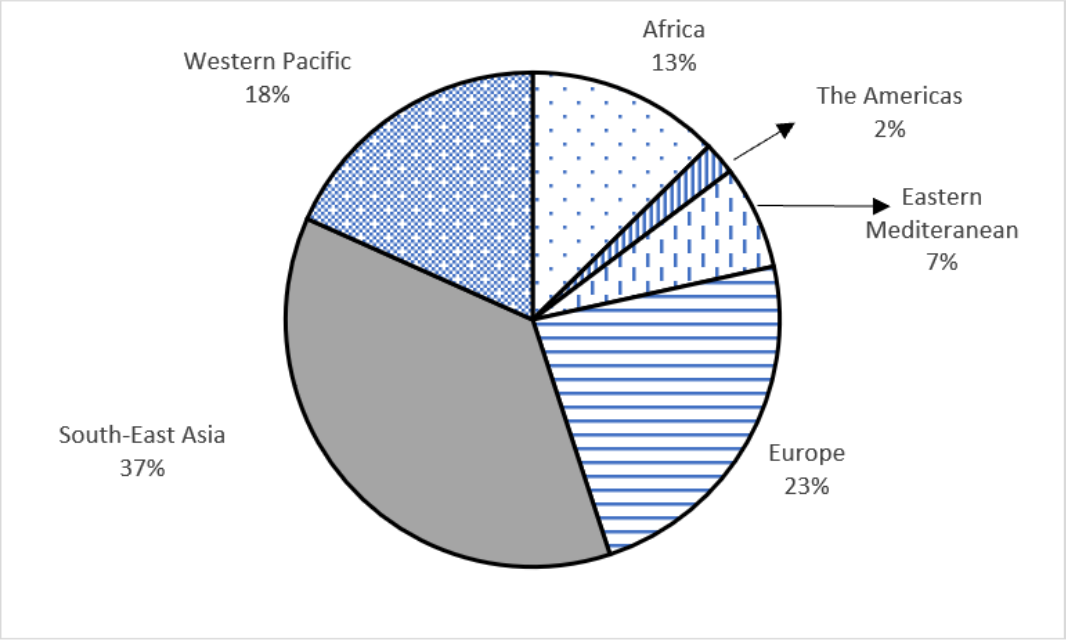

Figure 1.2 Estimated incidence of MDR-TB in 2016 by WHO region(World Health Organization, 2016)

With reference to Figure 1.3, the top three countries with largest number of cases are populous countries led by India with 147,000 cases, followed by China with 73,000 cases and Russian Federation with 63,000 cases which contribute to nearly half of global total.

Moreover, according to a report published in The Lancet Infectious Diseases, the number of MDR-TB are predicted to increase in India, the Philippines, Russia and the South Africa, countries which already have a high burden (Sharma *et al.*, 2017). This is estimated from mathematical model derived from data of WHO reports and drug resistance survey from the respective countries.

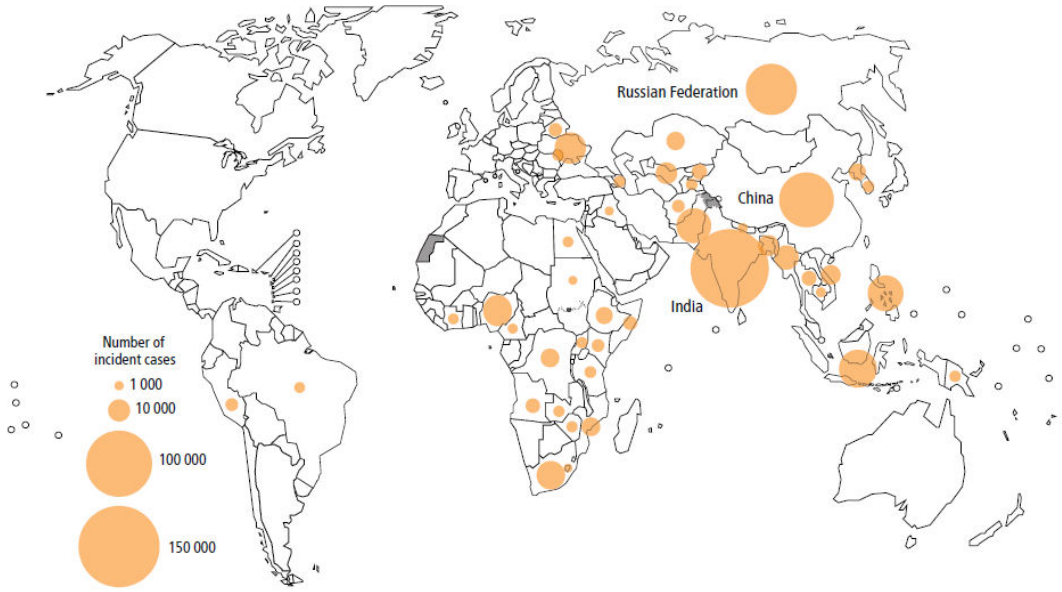

Figure 1.3 The estimated incidence of MDR/RR-TB in 2016 by WHO, for countries with at least 1000 incident cases(World Health Organization, 2016)

Also, there is a wide gap between detection and the start of MDR-TB treatment where only 22% of the estimated incidence of MDR/RR-TB cases started treatment in 2016. Most significantly, closing this wide gap requires progress in a subset of countries especially China and India because both countries are responsible for 39% of the total gaps (World Health Organization, 2017). In addition, it has been estimated by the same governing body that 4.1% of new cases and 19% of previously treated cases have MDR/RR-TB (World Health Organization, 2017).

As mentioned previously, the treatment success rate is quite low for MDR-TB as compared to TB. This is evident in the case of death from MDR/RR-TB where almost 240,000 deaths have been reported in 2016 (World Health Organization, 2017).

1.3.2 Situation in Malaysia

Figure 1.4 reveals that there has been a gradual increase in the number of MDR-TB cases in Malaysia from 2004 till 2010. Then, a sharp rise on the number of cases seen and peaked in 2011 with 141 cases. The figure also shows that in 2015, 101 cases of MDR-TB were reported. The MDR-TB burden for Malaysia in term of its incidence rate is estimated to be 1.8 cases per 100 000 population. Moreover, it has been estimated that 1.5% of new cases and 3.1% of previously treated TB cases have MDR-TB. Furthermore, Malaysia has a lower treatment success rate of 32% as compared to global success rate (54%) based on the cohort study conducted in 2014 (World Health Organization, 2017).

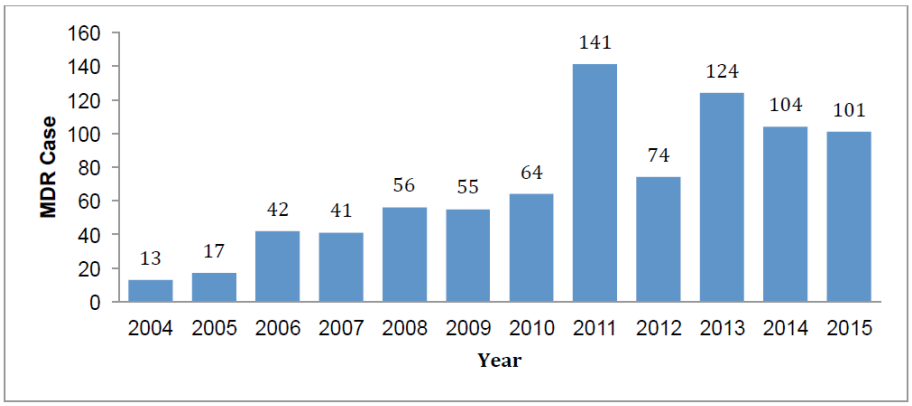

Figure 1.4 MDR-TB Cases in Malaysia from 2004 to 2015(Ministry of Health Malaysia, 2016)

1.4 Tuberculosis Information System (TBIS) Registry

TBIS is an electronic record system that ensures notifications and records of each of TB patient are standardised. This allows continuous monitoring in term of treatment success and overall performance of national TB control programme.

Figure 1.5 shows TB surveillance system in Malaysia. All TB cases including MDR-TB cases must be immediately notified to district, state TB organiser team and TB/Leprosy Sector via