MODELING THE IMPACT OF TUBERCULOSIS CONTROL MEASURES IN A HIGHLY ENDEMIC AND AN OVERCROWDED PRISON

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2017

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DESSERTATION SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICAL SCIENCE

FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR

2017

UNIVERSITY OF MALAYA

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ABSTRACT

Globally, the prevalence of tuberculosis (TB) is up to 100 times higher in closed settings such as prisons compared to the general population. Despite this, effecive TB interventions are rarely deployed in prisons in low and middle-income countries where the burden of TB is highest. Our aim was to explore the impact of introducing interventions to reduce the transmission of TB in an overcrowded prison in Malaysia. We used a deterministic transmission model to simulate the effects of three TB control strategies and evaluate their impact on the predicted prevalence of active TB over a ten-year period. In the first set of simulations, in which the current environmental situation (degree of cell crowding and ventilation rate) of the prison was held constant, we investigated the effects of isoniazid preventive therapy (IPT) and anti-tuberculosis treatment (ATBT), independently or as a combined strategy. We susbsequently repeated the simulations assuming improved environmental conditions. We also simulated the effect of prolonging IPT beyond the normal 6-months regimen, to 12 and 36 months. Our model showed that implementing either the ATBT or the combined IPT and ATBT strategy reduced the current 8% prevalence of active TB to below 2.5%, whereas implementing IPT alone increased the projected prevalance to 15%. After successful IPT treatment, reinfection compromises the effectiveness of IPT, irrespective of the treatment regime duration. Reducing overcrowding from six to four inmates per cell and increasing the ventilation rate from 2 to 12 air changes per hour improved IPT effectiveness by reducing the prevalence of active TB to 8% after ten years. To achieve control in such a high TB burden setting, there is an urgent need to implement effective TB interventions, like intensified TB case finding, IPT and environmental changes in the Malaysian prison.

ABSTRAK

Di peringkat global, kelaziman batuk kering (TB) adalah 100 kali lebih tinggi dalam persekitaran tertutup seperti penjara berbanding populasi awam. Walaupun begitu, kawalan TB yang efektif jarang dilaksanakan di penjara terutamanya penjara di negara-negara yang berpendapatan rendah atau sederhana di mana beban TB adalah sangat tinggi. Matlamat kami adalah meneroka dengan menggunakan model matematik, impak kawalan TB dalam penjara yang sesak di Malaysia. Kami menggunakan model transmisi dinamik berketentuan untuk mensimulasikan tiga strategi kawalan TB dan menilai impak strategi ini terhadap kelaziman aktif TB yang diramalkan dalam tempoh sepuluh tahun. Dalam set pertama simulasi, di mana keadaan alam sekitar semasa (tahap kesesakan sel dan kadar pengudaraan) penjara tidak diubah, kami menyiasat impak terapi pencegahan isoniazid (IPT) dan rawatan anti-batuk kering (ATBT), sebagai strategi yang digabungkan atau secara berasingan. Kemudian, simulasi yang sama diulang tetapi dengan keadaan alam sekitar penjara yang lebih baik. Seterusnya, kami juga menyiasat impak IPT sekiranya diberi lebih dari regimen normal iaitu 12 dan 36 bulan. Model kami menunjukkan bahawa ATBT sahaja atau strategi gabungan IPT dan ATBT mengurangkan prevalen aktif TB dari 8% ke 3% dalam tempoh sepuluh tahun, manakala strategi IPT sahaja meningkatkan prevalence ke 15%. Selepas tempoh rawatan IPT selesai, jangkitan semula (reinfection) kompromi keberkesanan IPT, tidak kira tempoh rawatan. Mengurangkan kesesakan daripada enam kepada empat penghuni setiap sel dan meningkatkan kadar pengudaraan 2 ke 12 perubahan udara sejam boleh membaiki keberkesanan IPT dengan mengurangkan prevalen aktif TB kepada 8 % selepas sepuluh tahun. Untuk mengawal TB dalam persekitaran yang endemik, terdapat langkah-langkah yang perlu dilaksanakan segera, ini termasuklah mempergiatkan pencarian kes TB, IPT dan memperbaiki keadaan alam sekitar dalam sistem penjara Malaysia.

ACKNOWLEDGEMENT

Firstly, I would like to give thanks to God Almighty, that despite the many challenges in completing this dissertation, it was successfully possible through His enormous blessing.

I would like to express deepest gratitude to my supervisors, Prof Dr Adeeba Kamarulzaman and Prof Dr Nor Azina Ismail, for their full support, expert guidance, understanding and encouragement throughout my study and research. Without their incredible patience and timely wisdom and counsel, my thesis work would have been a frustrating and overwhelming pursuit.

A special thanks to Dr Haider Al-Darraji for without his persistent help and guidance, this dissertation would not have been possible. I am deeply grateful to Dr Scott McDonald and Mr Kwesi Apenteng for your full support and guidance in introducing me to the world of infectious disease modelling. Also, a special thanks to Dr Karina Razali for her insight with the study.

Finally, I would like thank my husband, my parents and my family for their unconditional love and support during the last three years; I would not be able to complete this dissertation without your continuous love and encouragement. This dissertation is dedicated to them and especially to my precious son, Abraham Emmanuel.

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LIST OF SYMBOLS AND ABBREVIATIONS

ACH	:	Air Changes per Hour
ATBT	:	Anti-Tuberculosis Treatment
α	:	Rate of recovery with treatment
α_n	:	Rate of natural recovery
β	:	Transmission rate
σ	:	Rate of short term or fast progressor develop infectious TB
DFE	:	Disease-free equilibrium
DOTS	:	Directly Observed Treatment Strategy
DOTs	:	Directly Observed Treatment, Short-course
GN	:	Gammaitoni and Nucci
EMB	:	Ethambutol
f	:	Acquired immunity after primary infection
ICRC	:	International Committee of the Red Cross
INH	:	Isoniazid
IPT	:	Isoniazid Preventive Therapy
LTBI	:	Latent Tuberculosis Infection
MA	:	Mass Action Model
MAPTB:		Malaysian Association for the Prevention of Tuberculosis
MDG	:	Millennium Development Goals
MDR	:	Multi-drug resistant
MOH	:	Ministry of Health
NTBIS:		National TB Information System
NTBCP:		National TB Control Programme
RIF	:	Rifampicin
RMR	:	Riley-Murphy-Riley
TB	:	Tuberculosis
TBCTA:		Tuberculosis Coalition for Technical Assistance

τ	:	Rate of recovery with preventive therapy
PLHIV	:	People living with HIV
PWID	:	People who inject drugs
PYZ	:	Pyrazinamide
p	:	proportion of population
r	:	Relapse rate
SIR	:	Susceptible-Infected-Recovered
WHO	:	World Health Organization
μ	:	Death rate
ω	:	reactivation rate
XDR	:	Extensively drug-resistant

LIST OF APPENDICES

CHAPTER 1 : INTRODUCTION

1.1. Introduction

The introduction to the study is divided into six parts. The chapter begins with the research problem that the study intends to address, followed by laying out the scope of research and research objectives. Next the research question is formulated based on the research objectives, and the rationale for conducting the research provided. The chapter ends by stating the relevance and significance of this study in relation to broader trends in the Malaysian context.

1.2. Research Problem

Closed settings such as prisons present a special challenge for national tuberculosis (TB) control programmes. Poor environmental conditions, such as overcrowding and inadequate ventilation; a high prevalence of individuals at high risk for TB, such as people who use drugs and alcohol; being homeless; a history of past incarceration; existing comorbidities; and lack of access to medical services contribute to the high prevalence of TB in prisons (Baussano et al., 2010; Getahun, Gunneberg, Sculier, Verster, & Raviglione, 2012; Moller, Gatherer, & Dara, 2009). It has been estimated that the prevalence of TB in prisons is up to 100 times higher than that in the general population (World Health Organization, 2000). Recent reports from Malaysian prisons have shown an astoundingly high prevalence of latent TB infection (LTBI) among HIV-infected and non-HIV infected inmates in two prisons in Malaysia (Al-Darraji, Kamarulzaman, & Altice, 2014; Margolis, Al-Darraji, Wickersham, Kamarulzaman, & Altice, 2013). In a further study, undiagnosed active TB was reported at 8 per cent among 442 inmates in the same prison, 62 times higher than the estimated prevalence for the general population (Al-Darraji, Altice, & Kamarulzaman, 2016) . The same prison is also currently

overcrowded and has a daily census of 4,200 inmates, operating at 120 per cent of its maximum capacity of 3,500 (Al-Darraji et al., 2014).

Transmissions of TB which occur in prison do not stop within the prison walls as a large proportion of inmates' cycle in and out of prison on a regular basis. Inmates who are incarcerated for a short period of time and who do not receive adequate treatment may transmit the infection upon their return to the community (Barbour, Clark, Jones, & Veitch, 2010). In a recent systematic review by Baussano et al., a significant incidence of TB cases in the general population was attributable to TB exposure within prison, accounting for 1 in 11 TB cases in high-income countries and 1 in 16 cases in low to middle income countries (Baussano et al., 2010). Additionally, the high rate of TB within prisons may occur to facility staff members who are in close daily contact with inmates. It was estimated that, for each percentage increase in the incarceration rate, there was a 0.34 per cent increase in TB incidence in the population (Stuckler, Basu, McKee, & King, 2008).

Guidelines addressing the control of TB in closed settings have been released by the World Health Organization (WHO) and Tuberculosis Coalition for Technical Assistance (TBCTA) and International Committee of the Red Cross (ICRC) (Dara, Kimerling, Reyes, & Zagorskiy, 2009; World Health Organization, 2000, 2009). Core services to be provided include provision of effective anti-tuberculosis treatment (ATBT) for active cases and isoniazid preventive therapy (IPT) for latently infected individuals. Other recommended control measures are intensified case finding for new and transferred inmates, contact investigation and infection control by managerial, administrative and environmental interventions (Dara et al., 2009; World Health Organization, 2000, 2009).

Isoniazid preventive therapy prescribed for a minimum duration of six months, is an effective preventive tool which can halt the progression of latent TB to active disease among HIV-infected and non-HIV infected individuals (Akolo, Adetifa, Shepperd, & Volmink, 2004; Smieja, Marchetti, Cook, & Smaill, 2000). In a highly endemic setting, prolongation of IPT to 36 months or longer has been shown to have durable effectiveness in preventing TB, particularly in those with a positive tuberculin skin test (Martinson et al., 2011; Samandari et al., 2011).

1.3. Scope of Research

The study focuses on the provision of treatment and preventive therapy as well as improving environmental conditions as the TB intervention strategies to reduce TB transmission in a highly endemic and overcrowded prison. The study also explores the effectiveness of IPT beyond recommended minimum duration. The study uses a dynamic transmission model methodology to estimate the effectiveness of these strategies in this setting.

1.4. Research Objectives

This study has the following objectives:

1) To investigate the impact of ATBT and IPT on active TB prevalence in a highly endemic and overcrowded prison
2) To explore the impact of improving air ventilation and overcrowding on active TB prevalence in a highly endemic and overcrowded prison
3) To explore the effect of prolonging the provision of IPT beyond the minimum duration of six months

1.5. Research Questions

The high prevalence of TB among inmates in a highly endemic and overcrowded prison led to primary questions of whether introducing TB interventions in this setting would reduce the incidence of TB among inmates. Secondly, would changing the current conditions by improving the ventilation and reducing the overcrowding in the prison affect the effectiveness of TB interventions implemented in the prison? Thirdly, given the evidence of increased IPT effectiveness in similar settings elsewhere, would prolonging IPT beyond the minimum duration improve the effectiveness of TB interventions? To answer these research questions, a dynamic transmission model was developed to simulate the different TB intervention strategies at the current and improved conditions of the prison.

1.6. Research Rationale

Despite the high prevalence of TB that has been recorded in Kajang prison, measures to reduce the infection rate are not currently being practiced in this prison (Al-Darraji et al., 2014; Margolis et al., 2013). Most inmates present to the clinic with advanced disease as symptoms of infectious TB can be very mild and take months to develop. Delay in seeking treatment among infectious inmates would result in the spread of the TB bacteria to other inmates in the prison and the general population. Using dynamic transmission model, this study hopes to demonstrate the different strategies of TB interventions in reducing TB transmission among inmates in an overcrowded prison. The study which was designed to identify the most effective intervention strategy would help prison officials to implement appropriate interventions for this population in this setting which can eventually prevent further transmission to the general population.

1.7. Relevance and Significance

This timely study will provide supporting evidence and recommendations to policymakers and relevant stakeholders such as the Prison Department and Ministry of Health (MOH) on the importance of improving access to medical care in prisons to ensure adequate treatment for those infected with TB. Such measures will not only lead to better health for the inmates, but may also play an important public health role in controlling the burden of TB within prisons and, ultimately, the general population.

CHAPTER 2 : LITERATURE REVIEW

2.1 Introduction

This literature review is intended to illustrate the current burden of TB in prisons, a summary of recommended TB infection control measures for high burden prison settings and to contextualize the risk of TB among inmates and its impact to the general population. The review begins with an overview of the history of TB which would inform the reader that TB is an ancient disease and the discovery of effective treatment but is yet challenged with the new resurgence of the disease including increasing resistance to standard treatment. The review proceeds with an illustration of the current global burden of TB and in the Malaysian context including the burden of TB in Malaysia's prison setting. This is followed by an overview of the WHO strategy on TB control which is the Directly Observed Treatment Strategy (DOTS) and available international guidelines in TB infection control for closed settings. Next, the risk of TB transmission before, during and after imprisonment is described. The review ends with the context of the risk of TB in prison and its impact to the community.

2.2 History of Tuberculosis

Studies suggest that TB has been present for at least 150 million years (Hayman, 1984). Evidence of TB in humans dated back to 2400-3400 B.C where the skeletal spine of the remains of Egyptian mummies were found to be consistent with tubercular decay. It was not until 1882, when Robert Koch made pertinent discoveries on TB that significantly contribute to the control and elimination of the deadly disease (Daniel, 1982). Koch's discovery of the tubercle bacillus as the causative agent of the disease and its way of spreading had significantly helped in stopping the spread of the disease and marks the beginning of TB control and prevention (Cambau & Drancourt, 2014; Clayson,

1957). His attempts in finding treatment for tuberculosis have led to rapid development in latent TB diagnostic tool (Cambau & Drancourt, 2014). In 1921, Albert Calmette and Camille Gue´rin, developed an attenuated strain of live bovine bacillus as a vaccine against tuberculosis (Calmette, Guerin, & Weill-Halle, 1924). The vaccine which is called the Bacille Calmette-Gue´rin (BCG), has greatly reduced the number of meningitis cases among infants and incidence of military disease (Aronson, Aronson, & Taylor, 1958).

Since that discovery by Robert Koch, TB has been identified as a disease caused by a bacteria called Mycobacterium tuberculosis and it is a communicable disease. This means that the disease is transmitted through air that if a person with active TB coughs, sneezes, spits or even talk, another person can become infected if they are exposed to them on daily basis such as by living or working in close quarters (Centers for Disease Control and Prevention, 2012). According to WHO, the majority of the TB cases reported were pulmonary TB (World Health Organization, 2016). However, the bacteria can result in infections involving any site of the body including kidney, spine and brain. This type of infection is classified as extra-pulmonary TB. Some studies have suggested that extra-pulmonary TB may vary according to geographic location and population (Ilgazli, Boyaci, Basyigit, & Yildiz, 2004; Musellim, Erturan, Sonmez Duman, & Ongen, 2005; Noertjojo, Tam, Chan, & Chan-Yeung, 2002; Yang et al., 2004) .

Population-level data as early as 1850's in England and Wales as well as in the United States from 1804 to 1950 showed that the TB epidemic has a very slow dynamic and takes years to grow to show any symptoms of TB illness (Blower et al., 1995; Myers, 1965). People can be infected with TB but do not manifest any symptoms of TB illness; these were identified as latent infection or what is commonly known as the latent TB infection (LTBI) individuals. The natural history of TB demonstrated that after exposure to TB bacteria, only 5 to 10 per cent progress to active TB with a higher likelihood within the first two years after infection (Chaisson, 2007; Ozcaglar, Shabbeer, Vandenberg,

Yener, & Bennett, 2012). The remaining 90 to 95 per cent stayed at latent stage with a small proportion of them (5 to 10%) having a lifetime risk of developing active TB (Hauck, Neese, Panchal, & El-Amin, 2009; P. L. Lin & J. L. Flynn, 2010). The WHO estimated that nearly one-third of world population has latent TB (World Health Organization, 2016).

However people with compromised immune systems such as people living with HIV, malnutrition or diabetes, or people who are using tobacco or drugs have greater risk of developing active TB (Alavi-Naini, Sharifi-Mood, & Metanat, 2012; Alcaide et al., 1996; Altet-Gomez, Alcaide, Godoy, Romero, & Hernandez del Rey, 2005; Crump et al., 2015; Garcia-Basteiro et al., 2015; Li, Zhao, & Zhao, 2015; Meijerink et al., 2015; Ronacher et al., 2015; Shanmuganathan & Subramaniam, 2015) . A study among people who injects drug (PWID) found that those with HIV positive status are at 30 per cent greater risk of developing active TB (Selwyn et al., 1989).

When recently infected or latently infected individuals develop active TB, they begin to show symptoms of TB illness and are able to spread the disease to another person especially amongst those with pulmonary TB. The risk of transmission in those with extra-pulmonary TB is minimal (Inoue, Koyasu, & Hattori, 2011). Symptoms of pulmonary TB illness include cough that lasts two weeks or longer, coughing up blood or sputum (phlegm), pain in the chest, fever, chills, night sweats, fatigue and weight loss. These symptoms may appear trivial for many months. Often this causes delay in seeking treatment which results in exposure of more individuals with TB bacteria. Without proper treatment, active TB can result in death with a mortality rate that has been described at 21 per 100,000 population in 2014 (World Health Organization, 2016).

Streptomycin, the first effective antibiotic against TB bacteria was first developed in 1944 (Daniel, 1982, 2006). This discovery was followed by isoniazid (INH) the first oral mycobacterial drug in 1952. However it was not until 1957 when the most effective first-

line anti-TB drug, rifampicin (RIF) was discovered that cure is possible for the TB infected person. With the availability of treatment, the number of TB cases was significantly reduced until the late 1980s when the resurgence of TB claimed many lives due to the rise of drug-resistant strains and the spread of HIV/AIDS (Paolo & Nosanchuk, 2004; World Health Organization, 2002).

2.2 Epidemiology of Tuberculosis

2.2.1 Global Burden of Tuberculosis

In the recent Global TB report released by WHO, the overall TB cases worldwide were reported to be slowly declining at an average rate of 1.5 per cent annually since 2000 (World Health Organization, 2016). It was estimated that between 1990 and 2015, mortality rate and prevalence rate fell by 47 and 42 per cent respectively. Since then, an estimated 43 million lives have saved. Based on this, the WHO announced that the 2015 Millennium Development Goal (MDG) of halting and reversing TB incidence has been successfully achieved. However, despite the availability of effective anti-TB medications, unacceptably high number of people continue to die from TB. In 2014, 1.5 million lives were lost due to TB disease (World Health Organization, 2016). TB cases is reported from all regions in the world but the burden of TB is highest in South-East Asia and Western Pacific regions which account for 58 per cent of the global TB burden in 2014 (World Health Organization, 2016). The African region accounted for a quarter of total cases but the most severe burden with more than double the global average of 133 per 100,000 population (World Health Organization, 2016).

In 2014, the WHO estimated that there were 9.6 million incident cases including 1.2 million HIV positive individuals infected with TB. However, only 64 per cent of the estimated TB cases were notified and newly diagnosed or were already on treatment. The other 3 million "missing" cases highlight that major efforts are needed to ensure all cases

are detected, notified and treated. Although according to the WHO report, the treatment success rate continued to be high at 86% among all new TB cases, higher levels of resistance and poor treatment outcome are of major concern (World Health Organization, 2016). The percentage of new TB cases with multi-drug resistant TB (MDR-TB) in 2014 was 3.3 per cent and has not changed compared to recent years. It was estimated that 190,000 people died of MDR-TB (World Health Organization, 2016). Further to that, 20 per cent of previously treated TB cases were estimated to have MDR-TB. It was also estimated that about 9.7 per cent of MDR-TB patients have extensively drug resistant TB (XDR-TB).

2.2.2 Epidemiology of Tuberculosis in Malaysia

Malaysia, an upper-middle income country located in the Asia Pacific region, has an intermediate burden of TB. The prevalence of TB is less than 1 per cent among general population, the notification rate of TB is increasing from 65 per 100,000 populations in 2000 to 89 per 100,000 populations in 2015 (World Health Organization, 2016) . It is also the second most common communicable disease after dengue and the leading cause of mortality among all communicable diseases in Malaysia (5.37 per 100,000 populations) (Ministry of Health, 2014). Cases of MDR-TB remained below 1 per cent except in 2011 when MDR-TB cases were reported to be 1.3 per cent of all notified cases (Ministry of Health, 2012).

A comparison of five years reported TB cases between states in Malaysia demonstrated that there is an increasing trend in the majority of the states. Sabah recorded the highest cases of TB and remained so in the last five years, followed by Selangor and Sarawak (Figure 2.1). The TB notification rate for specific age group was also found to be increasing over time and predominantly occurring among the elderly population (Figure 2.2).

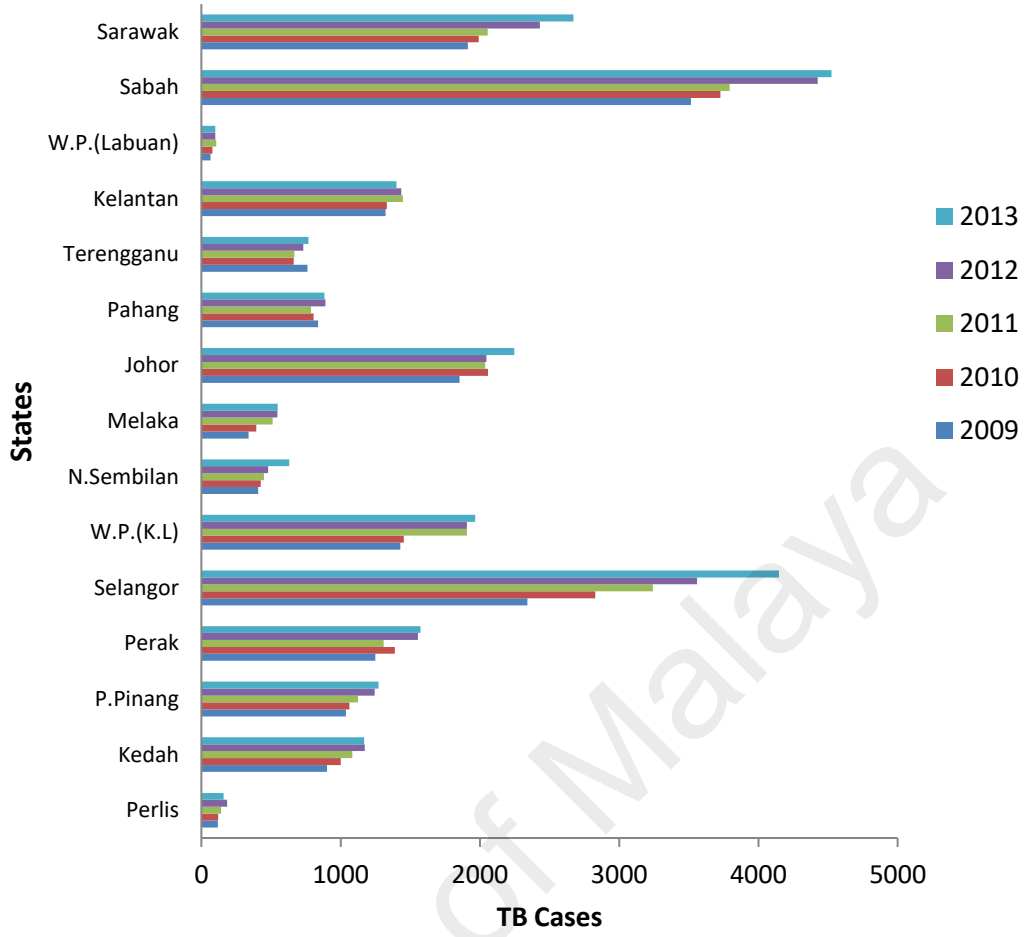
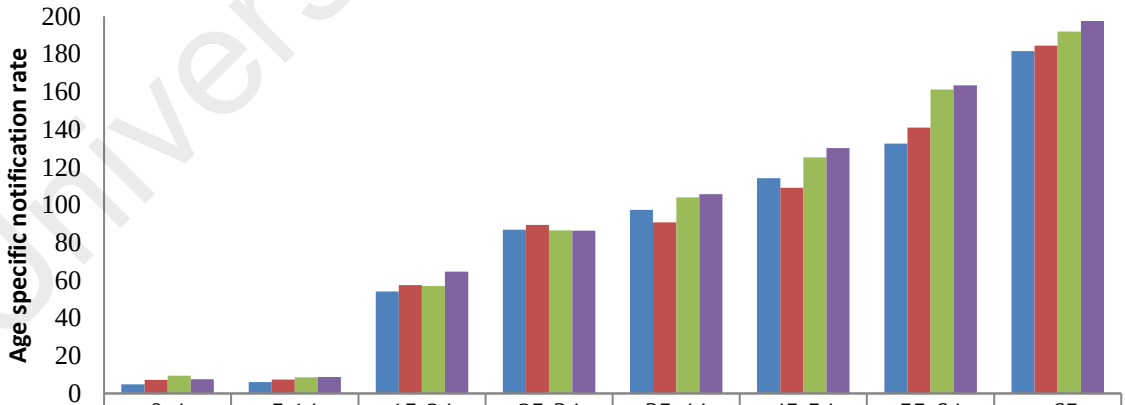


Figure 2.1: Distribution of TB cases by state (2009-2013) (Source: Ministry of Health, 2014)



	0-4	5 14	15-24	25-34	35-44	45-54	55-64	>65
2010	4.8	6.1	54	86.9	97.4	114.1	132.5	181.5
2011	7.3	7.4	57.5	89.3	90.7	109	141	184.4
2012	9.4	8.6	57	86.4	103.9	125.2	161.1	191.9
2013	7.6	8.8	64.6	86.3	105.7	130.1	163.3	197.4

Figure 2.2: Age specific notification rate per 100,000 (2010-2013) (Source: Ministry of Health, 2014)

The WHO estimated that the incidence rate of TB in Malaysia would be decreasing over time. However, contrary to those estimates (Figure 2.3), the notification rate in Malaysia has been found to be increasing from 65 per 100,000 populations in 2000 to 81 per 100,000 populations in 2013 (Ministry of Health, 2012). There are several possible explanations for the rise in the incidence of TB which includes improvement in the reporting of TB cases as a result of nationwide increase in the capacity of diagnostic laboratories and treatment centre (Ministry of Health Malaysia, 2014). Studies conducted in the Malaysian setting suggested that multiple contributing factors influence the increase in the TB incidence in Malaysia. These factors include the increase in comorbidities (TB-diabetes mellitus and TB-HIV) among Malaysians (Mohammad & Naing, 2004; Nissapatorn et al., 2005; Sulaiman et al., 2013; Venugopalan, 2004) and the implication of the influx foreign workers into the country (Liew S.M. et al., 2014). Nonetheless, TB control strategy in Malaysia heavily relies on passive surveillance and hence the current number may reflect an underreporting of the actual occurrence cases of TB in the country.

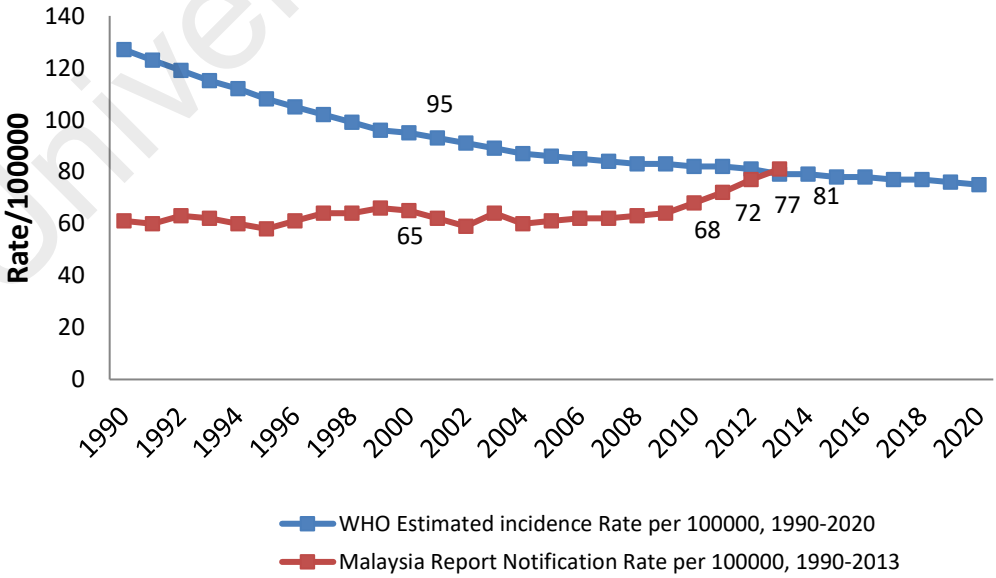


Figure 2.3: Notification rate of TB in Malaysia (1990-2013) against WHO estimated incidence (Source: Ministry of Health, 2014)

2.2.3 Epidemiology of Tuberculosis in Malaysian Prisons

TB prevalence in prisons is estimated to be up to 100 times higher compared to that of the general population (World Health Organization, 2000). An evaluation of the TB control programme in 2001 found that the prevalence of TB among HIV individuals in Selangor's prison and drug rehabilitation centres is as high as 11.7 per cent (Venugopalan, 2004). A recent cross-sectional study in Kajang Prison found that LTBI based on turbeculin skin test (TST) reactivity was as high as 84.7 and 92.5 per cent among HIV-infected and HIV-uninfected inmates, respectively (Al-Darraji et al., 2014). A further cross-sectional study conducted in Pengkalan Chepa prison which also used the TST method, reported similar findings of high prevalence of LTBI among HIV-infected (83.6 per cent) and HIV-uninfected inmates (91.5 per cent) (Margolis et al., 2013). Other low and middle income countries such as Brazil (73 per cent) and Lebanon (45 per cent) also reported high prevalence of LTBI in prisons (Adib, Al-Takash, & Al-Hajj, 1999; Nogueira, Abrahao, & Galesi, 2012). However, compared to these countries, Malaysia reported the highest LTBI prevalence in prison.

In an intensified TB case finding study in Kajang prison, using a single GeneXpert, previously undiagnosed active TB prevalence among HIV-infected inmates was 12 percent. The overall TB prevalence including previously diagnosed active TB among HIV-infected inmates was 16.7 per cent (Abed Al-Darraji, Abd Razak, Ng, Altice, & Kamarulzaman, 2013). The overall TB prevalence was one of the highest reported prevalence of active TB, 152 times higher than the estimated prevalence for general population.

2.3 The Directly Observed Treatment Strategy (DOTS)

In 1993, the WHO declared TB to be a global emergency (Grange & Zumla, 2002; World Health Organization, 2002). To control the growing epidemic, the WHO adopted the Directly Observed Treatment, Short-course (DOTS) strategy which was initially modeled based on TB control programmes in African countries from the late 1980s (World Health Organization, 2002). The strategy was further developed and it was launched on a global scale in 1995 as a WHO recommended strategy for TB control. DOTS has five main components including political commitment with increased and sustained financing, case detection through quality assured bacteriology, standardized treatment with supervision and patient support, an effective drug supply and management system and the final component is the monitoring and evaluation system and impact measurement (Murali & Sajjan, 2002; World Health Organization, 2002).

With continuous research and development, it was recognized that several anti-TB treatment (ATBT) needed to be used together for treatment for TB. Currently, the WHO recommended treatment for new cases of drug-susceptible TB is a six-month regimen, combination of four first-line drugs: INH, RIF, ethambutol (EMB) and pyrazinamide (PYZ) (World Health Organization, 2016). The treatment for MDR-TB is longer and requires more expansive and toxic drugs. The current regimens recommended for most patients with MDR-TB last 20 months. However, WHO reported that the treatment success remained low (World Health Organization, 2016).

Another approach of containing TB transmission is to eliminate the TB bacteria among latently infected people. Following the discovery of INH, for decades monotherapy with this drug was shown to effectively prevent development of TB disease (Lobue & Menzies, 2010; D. Menzies, Al Jahdali, & Al Otaibi, 2011). In preventing and reducing the burden of TB infections in people living with HIV (PLHIV), the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recommended Isoniazid

Preventive Therapy (IPT) as a key public health intervention for the prevention of TB among PLHIV in 1998. IPT taken for 6 to 12 months, is well-recognized to significantly reduce the risk of progression of LTBI to active TB disease (World Health Organization, 2011). Two meta-analysis published in 2000 and 2004 found that IPT is an effective preventive tool in individuals with (36 per cent) and without (60 per cent) HIV-infection (Akolo et al., 2004; Smieja et al., 2000). But, in a recent study of adults with HIV in Botswana where TB is highly endemic, it was found that prolongation of IPT to 36 months or longer has been shown to have durable effectiveness in preventing TB, particularly in those with a positive tuberculin skin test (Samandari et al., 2011).

However, worldwide IPT implementation has been very slow and has been impeded by several barriers including lack of an accepted approach to exclude active TB disease and restricted access to isoniazid for fear of the development of drug resistance (World Health Organization, 2011). By the end of 2009, it has been estimated that globally only 8 per cent of (85,000 of 1.1 million) PLHIV received IPT (World Health Organization, 2011). In response to this, the WHO/UNAIDS has recently re-conceptualized the existing policy on IPT by providing updated guidance and recommendations for national TB and AIDS programmes in particular for resource-constrained settings based on new evidence taking into consideration the changing context of HIV and TB prevention, treatment and care (World Health Organization, 2011).

2.4 Tuberculosis Control Measures in Closed Setting

In 1998, the WHO and International Committee of the Red Cross (ICRC) released a guideline addressing the control of TB in prison and other incarcerated settings such as detention center of asylum seekers and remand centers (World Health Organization, 1998). This first guidelines by WHO and ICRC were designed not only to provide recommendations to national prison authorities on how to establish TB control in prison

but it was also an important advocacy tool which highlights to policymakers the need to control TB in prison. The guidelines demonstrated the high burden of TB in prisons, the potential for spread to the wider community and the importance of political commitment for effective TB control in prisons. However, some recommendations for TB control were not specific and limited. For example, the case-finding approaches were focused only on identifying those suspected of having TB who presented to health services and were screened for TB. It did not provide recommendations on how screening for TB should be implemented effectively in prison setting.

Following these guidelines, WHO released another manual in 2000. The manual is primarily for programme managers to implement the control of TB infection in prisons (World Health Organization, 2000). The technical manual comprehensively illustrated the three components in TB control which include medical interventions, environmental and administrative measures. In overcrowded prisons and those with high prevalence of TB, the manual recommends active case-finding screening that is effectively linked with treatment provision. In 2009, WHO produced another guideline on WHO policy on TB infection control in health-care facilities, congregate settings and households. However, much of the focus was for health-care and households setting. The guidelines for congregate setting were briefly summarized at managerial activities, administrative and environmental control levels as well as personal protection.

In the same year, Tuberculosis Coalition for Technical Assistance (TBCTA) and International Committee of the Red Cross (ICRC) released guidelines for TB control in prisons (Dara et al., 2009). The guidelines expand on the problems of TB-HIV co-infection and multidrug-resistant TB (MDR-TB) and contain updated information on diagnostic and treatment approaches. The guidelines recommended that an effective and strong TB infection control in prison should cover four important areas; organizational, administrative, environmental and personal protection control measures.

In 2014, the WHO Regional Office for Europe published a report on Prisons and Health that outlines important measures to improve the overall health and well-being of prisoners. The guidelines suggested the formation of integrated healthcare services for communicable diseases such as HIV, TB and viral hepatitis; non-communicable diseases such as cardiovascular diseases, cancers and diabetes, mental health and oral health of prisoners. The report also discussed behavioural risks among prisoners such as drug, alcohol and tobacco use and outlined evidence-based interventions to address these behavioural risks. For TB control in prison, this report included the most recent diagnostic technology such as GeneXpert and strongly recommended its use in high burden settings.

Based on all of the available guidelines mentioned above, the recommended TB infection controls in prisons are summarized as the following.

2.4.1 Managerial or Organizational Activities of Infection Control

The organizational activities aimed at identifying and strengthening the coordinating body for TB infection control to support and facilitate the implementation, operation and maintenance of TB infection control. The activities include assessing the infection risk of TB in prison, developing policy, budgeting, building human resource capacity, setting up surveillance systems, monitoring and evaluation, enabling and conducting operational research.

2.4.2 Administrative Infection Control

Administrative infection control activities including early diagnosis through screening upon entry and intensified case-finding, isolation of infectious inmates in particular TB suspects and TB patients to be kept separate from HIV-positive inmates and initiation of treatment with minimal delay.

2.4.3 Environmental Infection Control

In prison setting, a minimum of 12 air changes per hour must be maintained to achieve adequate ventilation to reduce TB transmission indoors. A good natural ventilation

system requires large windows. In prison where this may not be feasible, well-designed, well-maintained and correctly operated exhaust fan (mixed-mode ventilation) should be implemented to obtain adequate ventilation. However, in some settings where natural and mixed-mode ventilation may not be achieved due to weather, use of ultraviolet germicidal irradiation (UVGI) could be considered. Room air cleaners with UVGI may provide a less expensive alternative to more expensive environmental control measures that require structural alterations of a facility. Effective use of UVGI ensures that M. tuberculosis, as contained in an infectious aerosol, is exposed to a sufficient dose of ultraviolet-C (UV-C) radiation at 253.7 nanometers to result in inactivation.

2.4.4 Personal Protection Measures

It was recommended that respirators N95 or FFP-II equivalent or higher would provide good protection against TB by filtering out microscopic droplets and aerosols. The use of respirators provides protection for health care workers in close contact with TB patients in particular when health staff are supervising a cough-inducing procedure (e.g.,bronchoscopy) or sputum induction.

2.5 Tuberculosis Control Programme and Policy in Malaysia

At the end of the second world war, tuberculosis was ranked as the biggest single killer in Malaysia (Malaysian Association for the Prevention of Tuberculosis (MAPTB)). The anecdotal information by MAPTB claimed that by 1957, it was estimated that the prevalence of TB was 25 per cent among 5 year old and 75 per cent among 15 year old children (Malaysian Association for the Prevention of Tuberculosis, 2002).

It was only in 1961 that the government introduced the National TB Control Programme (NTBCP) and a team of dedicated physician and nurses was formed at every state in Malaysia (Iyawoo, 2004). This group was known as the TB Managerial Team, responsible for the implementation of TB control activities at the state and district levels.

In 1995, NTBCP was integrated to the Public Health Division, under the Director of Infectious Disease Control of MOH. To enhance the surveillance system for TB in Malaysia, the MOH introduced the National Tuberculosis Information System (TBIS) in 2002. This system links all the primary care at the health clinic to notify any TB cases to the district level and subsequently to the state level. In Malaysia, under the Prevention and Control of Infectious Disease Act 1988 (Act 342) any cases of infectious disease including TB, must be notified to the MOH within a week of diagnosis (Ministry of Health, 2012).

In line with the WHO Global TB Control Targets and Stop TB Partnership, the MOH introduced the National Strategic Plan for TB for 2011-2015. A midterm review of NSP TB highlights some important achievements such as the availability of a strong clinical infrastructure with 534 health centers as case holding centres, online database for TB surveillance, National Reference Laboratory, LED microscopy in 48 per cent of laboratory and 2 units of GeneXpert (Ministry of Health Malaysia, 2014).

2.6 Tuberculosis Intervention in Malaysia's Prison

Despite the high incidence of TB in the prison setting and WHO recommendations on IPT among immunosuppressed individuals, TB interventions in Malaysian prison are non-existent (Margolis et al., 2013). In prison where TB diagnoses is passive, there is a heavy reliance on inmates coming to the clinic with advanced disease as infectious TB symptom can be very mild and take months to develop. Delay in seeking treatment among infectious inmates would result in spreading the TB bacteria to other inmates in the prison and eventually to the community.

2.7 Tuberculosis Risk in Prison

2.7.1 High Risk Populations

In a study by Coninx and colleagues, the high risk of transmission of TB in prisons is likely attributed to the incoming inmate population who are already belong to high risk groups (Coninx, Maher, Reyes, & Grzemska, 2000; World Health Organization, 2007). Many of them come from socioeconomically deprived background and may have unhealthy lifestyle such as alcoholism, smoking and drug use which are associated with higher risk of TB (Valenca et al., 2015). Countries that have a high number of poorer citizens, such as developing countries, often have TB as a leading cause of mortality (World Health Organization, 2016). In Malaysia, a five years retrospective study in a small district found that the increase of TB incidence was more predominant amongst the socioeconomically deprived (Othman N., Abdul Rahman Hairul. Izwan., & Abdul Hadi Hazlee., 2003). Another study among 195 newly diagnosed TB, reported that more than 50 per cent were unemployed with risk factors of smoking or alcohol and injecting drug users (Nissapatorn, Kuppusamy, Rohela, Anuar, & Fong, 2004).

A review by Lonnroth et al., found that individuals from low socio-economic groups are at risk of being in proximity of a TB contact are more likely to live in crowded and poorly ventilated area (Lonnroth, Jaramillo, Williams, Dye, & Raviglione, 2009). Inmates have been known to have a history of contact in high TB prevalence environments from previous incarcerations, workplace or home. (Getahun et al., 2012; Moller et al., 2009). In the LTBI study in Kajang prison, it was found that frequent previous incarceration (AOR = 1.22 for each previous incarceration, $p = 0.01$) was significantly correlated with TST positivity (Al-Darraji et al., 2014). In another study in Pengkalan Chepa prison, it was also found that inmates having LTBI with history of previous incarceration were nearly five times more likely than those who had not been incarcerated before to significantly correlated of LTBI (AOR = 4.61, $p = 0.002$) (Margolis et al., 2013).

2.7.2 Inadequate Healthcare Services

In a country where national resources are limited, providing quality care and health services to inmates is often neglected or given low priority partially due to the stigmatization against criminals (World Health Organization, 2000). In many countries, there is insufficient health staff in the prison to deliver health services. The limited number of staff are often overwhelmed by the number of inmates entering concurrently, and during medical screening upon entry into the prison, only general screening are performed which in most of the cases do not include investigations or question about current or past history of TB (Dara et al., 2009; Moller et al., 2009). With inadequate health services in prison, infectious inmates will go untreated and spend weeks or months infecting other inmates before active TB is diagnosed. Despite the mandatory screening for HIV in Malaysia prison, screening for LTBI and active TB is non-existent with reliance on symptomatic patients presenting advanced TB disease (Al-Darraji, Abd Razak, Ng, Altice, & Kamarulzaman, 2013; Al-Darraji et al., 2014; Margolis et al., 2013). HIV prevalence among Malaysian inmates is estimated at 3 per cent (Al-Darraji et al., 2016). Antiretroviral therapy (ART) is not available in many Malaysian prisons, resulting in crowded cells full of immunosuppressed prisoners.

2.7.3 Prison Living Condition

The poor living condition in the prison such as severe overcrowding and the absence of adequate ventilation, exacerbate airborne disease, in particular TB (World Health Organization, 2000). Unfortunately, prison overcrowding is widespread throughout the world. In Brazil, overcrowding in prison has worsened with a growing disproportion between the increased number of inmates and available prison, of which from 2000 to 2010, there was an increase of 154 per cent of inmates compared to 107 per cent increase

of prison buildings (Santos, França, Sánchez, & Larouzé, 2012). In other high income countries, such as in the United Kingdom, nearly 60 per cent of the prisons in England and Wales were found to be overcrowded with some prisons operating at 150 per cent of its actual capacity (Berman & Dar, 2013). Malaysia is not an exception. The Kajang Prison, the largest prison Malaysia was built to accommodate a maximum 3,500 inmates but currently is operating at 119 per cent of its actual capacity (Al-Darraji et al., 2014).

According to the United Nations Office on Drugs and Crime (UNODC), in some countries, the level of overcrowding is very critical that inmates are forced to sleep in shifts, sleep on top of each other, share bed or tie themselves to window bars so that they sleep while standing (United Nations Office on Drugs and Crime, 2013). In a study of South African prisons, overcrowding at the level of 230 per cent from its actual capacity, poor ventilation and lack of access to outside yards, was found to be the main driver of TB transmission in these prisons (Johnstone-Robertson, Lawn, Welte, Bekker, & Wood, 2011). Overcrowding in prison is not only responsible in elevating the spread of respiratory disease, but it could adversely affect mental health among inmates, trigger violence and expose a dangerous environment to prison staff (International Centre for Prison Studies, 2004).

Figure 2.4: The condition of African prisons. Picture courtesy of Catherine Parker, a volunteer for the African Prisons Project (Source: http://www.the-platform.org.uk/2012/07/19/african-prisons-hope-for-the-future/)

The effects of pre-existing risk of incoming inmates, a combination of overcrowded prisons and inadequate ventilation, limited access to fresh air, the current presence of infectious TB in the prison and lack of provision for nutritious meals all contribute to the elevation of risk transmission of TB in the prison (Coninx et al., 2000; Dara et al., 2009; World Health Organization, 2000). In a prison where TB interventions are non-existent, delays in diagnosis result in increased risk of progression to active TB among non-infectious LTBI inmates due to the prolonged exposure to infectious TB or death as a result of advanced TB disease among active TB inmates (Baussano et al., 2010). Making things worse, inmates who are HIV infected are at greater risk of getting TB disease as evidence shows that HIV infected individuals have more than 20-fold increased risk of active TB than those without HIV infection (Pawlowski, Jansson, Sköld, Rottenberg, & Källenius, 2012).

2.8 The Impact of TB Transmission in Prison to General Population

With overcrowding and poor ventilation, prisons become a perfect place as a reservoir for TB bacteria. Infectious inmates could spread the disease to prison staff as they are in close contact with them daily. Prison staff may then spread the disease to their families and eventually cause ongoing spread to the community (Barbour et al., 2010). In a systematic review by Baussano et al., significant emergence of TB cases in the general population was attributable to TB exposure within prison. The median fraction of TB in general population attributable to the TB exposure in prison was 1 in 11 TB cases in high-income countries and 1 in 16 in low to middle income countries (Baussano et al., 2010). Another study by Stuckler et al., showed that there was a strong association between differences in incarceration rates among countries with incidence of TB. The study conducted for Eastern European and Central Asian countries found that for each percentage increase in incarceration rate, there is a 0.34 per cent increase in TB incidence

in the general population (Stuckler et al., 2008). A summary of incarceration rate and TB incidence rate in prison compared to the population is indicated in Table 2.1. TB incidence case is extremely high in prisons in low and middle income countries.

Table 2.1 : Incarceration rate, prison case notification rate compared to TB prevalence of selected countries (Source: Dara et al., 2009)

Country	Incarceration Rate (per 100,000)	Prison Case Notification Rate (per 100,000)	Country Prevalence Rate (per 100,000)
Prison notification rates found through passive findings			
Malaysia	132	Not available	131
France	98	41.3	8.6
Spain	147	2,283	18.2
Moldova	188	2,640	149
Thailand	398	1,226	208
Rwanda	492	3,363	79.3
Brazil	274	1,439 (Rio de Janeiro)	77
USA	716	156 (New York)	10.4
Prison prevalence found rates through active cases finding			
Malawi	76	5,142	144
Russian Federation	475	9,930	240

2.9 The Context of Tuberculosis Risk Before, During and After imprisonment

The risk of transmission of tuberculosis due to imprisonment could occur at any stage of the disease. The following diagram demonstrates the risk of transmission and its possible routes to the general population.

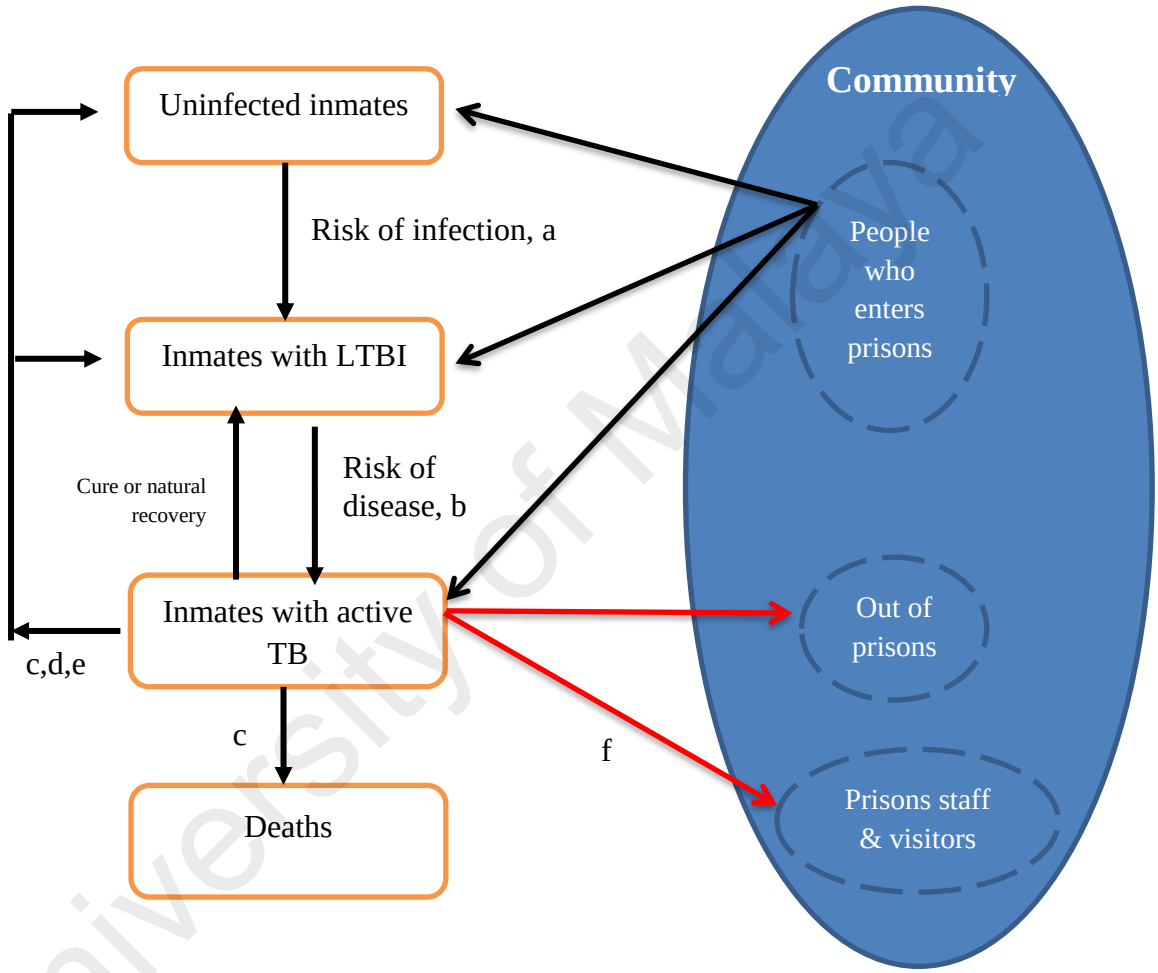


Figure 2.5 : Risk of TB transmission. Before, during and after imprisonment.

Notes:
a – prison conditions increase risk of TB transmission
b – socio-economic deprived background, co-existing morbidities (HIV, viral hepatitis), prison conditions (poor nutrition, poor hygine, overcrowding, poor ventilation, inadequate health services)
c – delayed in diagnosis and treatment
d – overcrowding, poor ventilation, poor hygiene
e – transfer between and within prisons
f – lack of coordination between prisons and inadequate health services

CHAPTER 3 : METHODOLOGY

3.1 Introduction

The section has been divided into nine sub-sections. The section begins with the design of the study to address the research questions. This is followed by a general description of the mathematical model, including a brief overview on deterministic and stochastic model and previous models of TB in closed setting. Next, the development of mathematical model applied in the study is explained thoroughly, starting from the formation of compartmental stages of the TB disease, incorporating treatment and environmental conditions of the prisons into the model, identification of variables required for the model simulation, translating the model system into differential equations to the validation of the model. Then, the identified variables such as the force of infection was clearly defined based on the available equations on transmission of airborne disease in closed setting. Following this, the section explained the process of data collection or more precisely, the defined variables required for the model simulation. The section ends with explanation of the three simulations of TB interventions and the uncertainty and sensitivity analysis.

3.2 Research Design

TB is a disease with slow intrinsic dynamics (Blower et al., 1995). The slow progression of TB at the individual level leads to slow temporal dynamics and long-term outcomes of TB at the population level. The latent period and infectious period span long time intervals, in the order of years on average. Due to these characteristic, mathematical epidemiological models have been recommended and used to estimate prolonged results and future trends of TB (Aparicio & Castillo-Chavez, 2009; Ozcaglar et al., 2012; H. Waaler, Geser, & Andersen, 1962). Mathematical modelling has long been used as an important tool to explore epidemiological trends of TB (Brauer, 2009; H. Waaler et al.,

1962). Policy makers and public health researchers use mathematical models to gain insight into the potential long-term consequences of programmatic decisions (Colijn, Cohen, & Murray, 2007; Emilia Vynnycky & White, 2010; H. T. Waaler, 1970). For example, Dye and colleagues used mathematical model to assess the potential effect of DOTS strategy for each of the six WHO regions as it has yet to be evaluated worldwide since it was launched (Dye, Garnett, Sleeman, & Williams, 1998). The study showed that the potential effect of DOTS is greater with improved case finding instead of passive case detection.

3.3 General Epidemiological Model of Tuberculosis

Epidemiological models of TB were first introduced by Waaler et al. (H. Waaler et al., 1962; H. T. Waaler & Piot, 1969). The basic unit of an epidemiological TB model is an individual. Epidemiological models consist of compartments which represent the sets of individuals grouped by disease status. The links between compartments represent flow rates from one state disease to another state which allows the model to capture the feedback loops and non-linear dynamic of infectious disease epidemic. Common abbreviations for compartments used in population biology literature are S is susceptible, individuals not yet infected; E is exposed, latently infected but not infectious; I is infected and infectious and R is recovered by treatment, self-cure or quarantine. Various epidemiological models can be built using these compartments. Different compartments can be included or excluded and how they relate to each other based on the modelers's policy question of interest. For example a model focusing on drug-resistant TB must consider processes related to the acquisition and transmission of drug resistance and may therefore address TB-HIV co-infection. However, increased model complexity comes at substantial cost. Unnecessary complex model often lack transparency and interpretability is needed to inform decision making by policy makers (May, 2004). Therefore, the

simplest model that can adequately represent relevant processes is generally preferred. A typical TB model will include five compartments based on the TB disease status. They are non-infected, short-term latently infected, long term latently infected; active TB and recovered (Figure 3.1) and common parameters of the model are shown in Table 3.1.

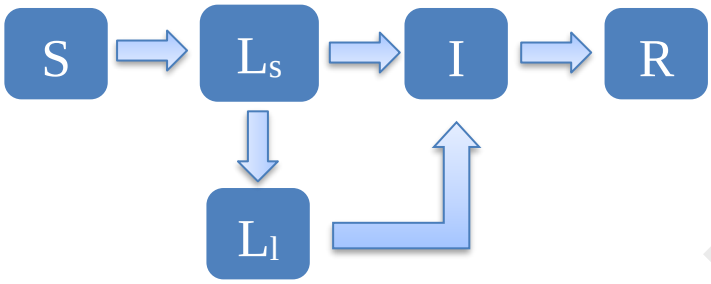


Figure 3.1: A Generic SEIR model. Arrow is indicating progression from one stage of disease to another. S-noninfected, Ls-latently infected (short term) L_l–latently infected (long-term) I-Active TB infection and R-recovered

Table 3.1: Common parameters of epidemiological model of tuberculosis

Transmission rate
Recruitment rate
Natural cure rate
Progression from latent TB to active TB
Latent TB treatment rate
Active TB treatment rate
Natural mortality rate
Mortality rate due to TB
Proportions of new infections that produce active TB cases

3.2.1 Deterministic versus Stochastic Model

Deterministic model attempts to describe and explain what happens on the average at the population scale. The model processes described by differential equations, with a unique input leading to unique output for well-defined linear models and with multiple outputs possible for non-linear models. These models categorize individuals into different subgroups. Further, the models specify the transition rates between the compartments such as susceptible may become exposed, exposed infectious and recovered.

Stochastic models rely on among-individual chance variation in risks of exposure, disease, and other factors. They are used when chance fluctuations or known heterogeneities are important as in small or isolated populations. Stochastic models have several advantages such as they allow follow-up of each individual in the population on a chance basis. Stochastic models, however, can be laborious to set up and need many simulations to yield useful predictions. Notwithstanding, incorporating chance variation into transmission processes provides a range of possible outcome-based probabilities (Bailey, 1975). These models can become mathematically very complex and do not lend themselves to an explanation of the dynamic.

There is a continuous debate concerning model mechanism of whether a stochastic model makes a better model over deterministic. However, most models of infectious disease processes used until now are deterministic because they require less data, are relatively easy to set up, and because the computer software are widely available and user-friendly (Emilia Vynnycky & White, 2010).

3.3 Previous Epidemiological Model of Tuberculosis in Closed Setting

Mathematical models of TB have been used to evaluate the impact of treating active TB cases and providing preventive therapy for latently infected cases (Basu, Maru, Poolman, & Galvani, 2009; Bhunu, Garira, Mukandavire, & Zimba, 2008; Blower, Small, & Hopewell, 1996; Bowong & Aziz Alaoui, 2013; Brewer et al., 1996; Brewer et al., 2001; Castillo-Chavez & Feng, 1997; Dye et al., 1998; Gabriela M Gomes et al., 2007; Johnstone-Robertson et al., 2011; Legrand, Sanchez, Le Pont, Camacho, & Larouze, 2008a; Mills, Cohen, & Colijn, 2011; C. J. Murray & Salomon, 1998; Mushayabasa & Bhunu, 2013; C. J. Silva & D. F. Torres, 2013; Ziv, Daley, & Blower, 2001). These models examined the impact of TB interventions strategy in a population and community level but very limited published studies examined the impact of TB control strategy in a

closed setting. Although studies by Legrand et al and Johnstone-Robertson et al were conducted in prison setting, both studies have some limitations. In the Legrand study, the transmission rate which is one of the most crucial parameter in infectious disease model, did not represent the actual TB transmission in a confined space as it was not directly measured from the contact with infectious individual in the confined setting. The transmission rate in confined setting determines the spread of TB which is calculated based on the environmental setting that enables close contact with infectious individuals (Ozcaglar et al., 2012). The study also did not consider the impact of preventive therapy and the structural changes on modelling the TB transmission in the overcrowded prison setting. The study by Johnstone-Robertson et al did not consider disease development and hence did not represent the full TB transmission dynamic as it was restricted only to acquisition of TB infection in the prison.

3.4 Development of Epidemiological Model Applied in the study

For this study, a deterministic population-based compartmental model of TB transmission was developed based on previously published model by Gabriela et al., and Silva et al., (Gabriela M Gomes et al., 2007; C. J. Silva & D. F. M. Torres, 2013). The development of the model is elaborated in the following steps.

3.4.1 Compartment – Stage of TB disease

To model the TB transmission in the prison, the population in a prison is firstly grouped into five compartments, reflecting the development of TB disease in five stages. They were susceptible (S), short-term latently infected (L1), long-term latently infected (L2), infectious (I) and recovered (R) compartments.

3.4.2 Transition of Population by Progression of Disease

The progression from one to another stage of disease is linked with arrow exiting from a compartment and entering to another compartment. After an exposure to TB bacteria, susceptible inmates progressed to latent infection stage. This is represented with a specific transition rate from susceptible to short term latently infected compartment. The transition rate also represents the most important parameter in the model which is the force of infection, βI. The force of infection determines the probability and rate at which one susceptible inmate becomes infected following close contact with an active infectious inmate. This parameter is explained in detail in section 3.6.

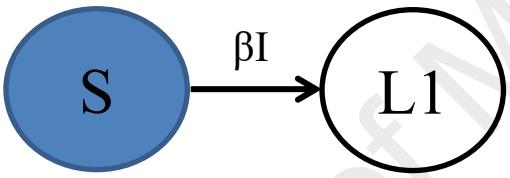


Figure 3.2: Development of TB model. Susceptible (S) inmate progressed to latent (L1) stage following exposure to infectious agent

The natural history of TB disease is still poorly understood (Dowdy, Dye, & Cohen, 2013). Therefore, the model structure and flow is based under some assumptions in accordance to widely acceptable natural history of TB disease. The model assumes that a patient infected with TB has a higher risk of developing active TB in the earlier stage of infection. After exposure to TB bacteria, only a proportion of five to ten per cent progressed rapidly to infectious stage with higher likelihood within the first two years (Chaisson, 2007; Ozcaglar et al., 2012). The rate of recently infected and rapid progression in the first two-year time is called primary progression rate, σ_1. The remaining proportion of 90 to 95 per cent progressed at slower rate to long term latent stage (Sutherland, Svandova, & Radhakrishna, 1982; E. Vynnycky & Fine, 2000). The proportion of individuals progressing to the different stage is represented as *p*. The

stabilization rate of recently infected person move to long term latent infection is represented by σ_2. The model assume that after infection, individuals in long term latent phase cannot acquire subsequent infection However, individuals at the long term latent infection would still have five to ten per cent lifetime risk to progress to active TB in due time (Hauck et al., 2009; P. Lin & J. Flynn, 2010). This transition is called reactivation rate and represented as ω. However, the natural history of TB disease is still poorly understood (Dowdy et al., 2013).

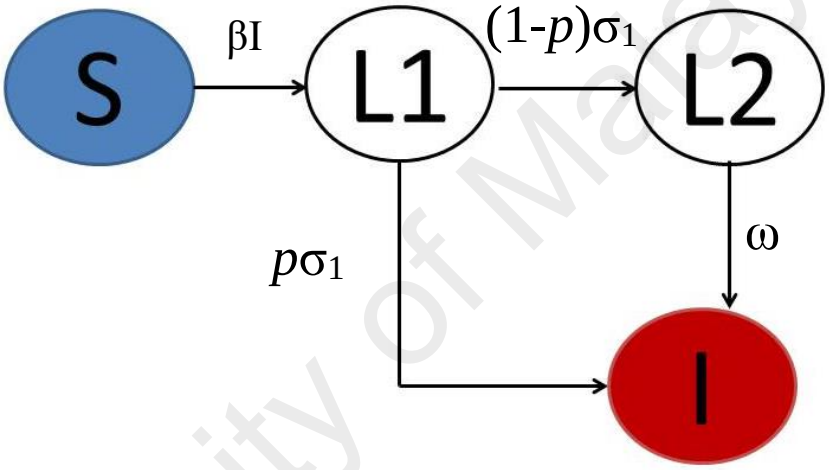


Figure 3.3: Development of TB model. Short term latently infected inmate, L1 progress to active TB, I. The remaining inmate develops to long term latent infection, L2 and progress to active TB, I.

In the absence of any TB interventions, delay in diagnosis and initiation of treatment result in mortality among inmates with active TB. This rate is represented as μ_I.

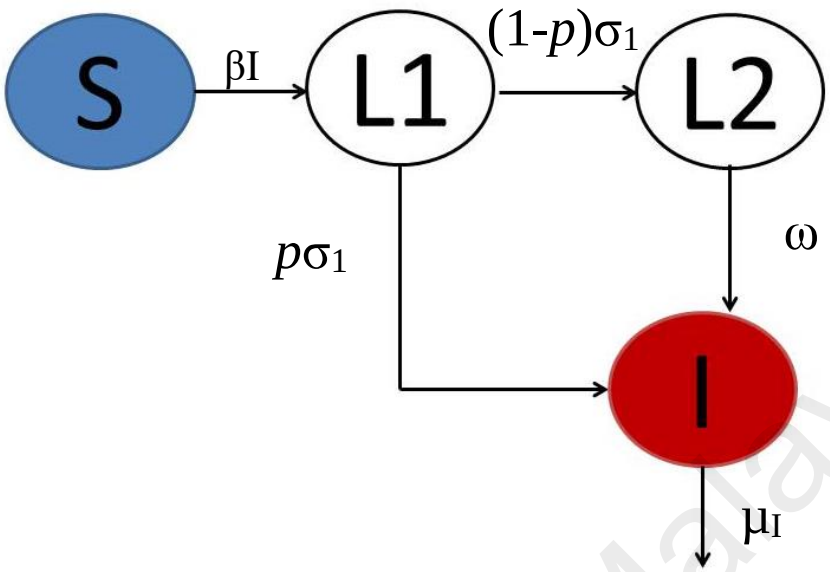


Figure 3.4: Development of TB model. μI represents death rate among inmates due to TB disease leaving the system.

3.4.3 Incorporating Treatment Interventions

To investigate the impact of TB interventions in the inmate population, we introduced two different TB interventions on the model. The first one was where we provided ATBT to infectious inmates and secondly, we provided IPT to those at the latent infection stage. Upon completion of successful treatment, inmates progress to recovery stage. It is also expected that certain percentage of inmates may recover naturally and some may experience treatment relapse. The recovery rate transition due to ATBT and IPT were represented as α and τ while the natural recovery and relapse rate is represented as α_n and r respectively.

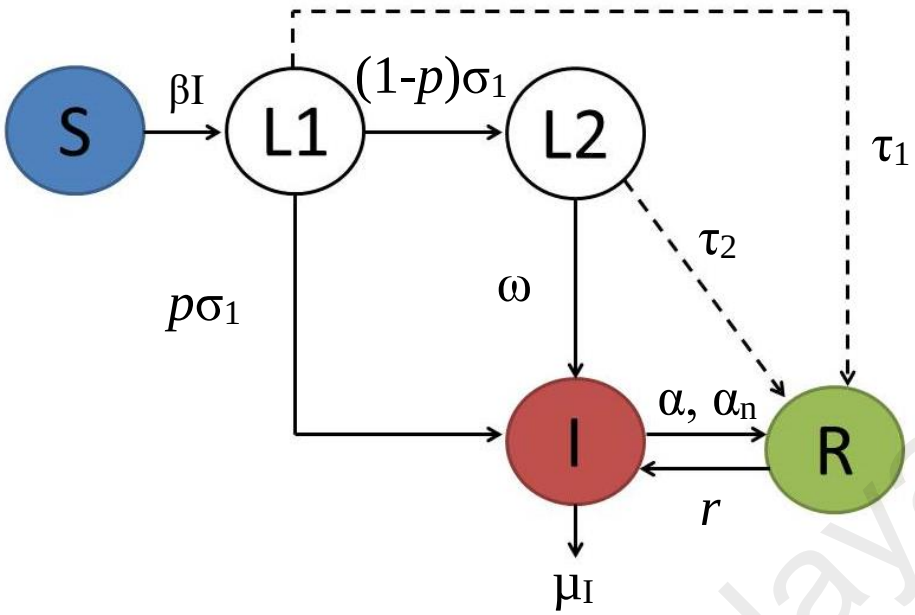


Figure 3.5: Development of TB model. Infectious inmates completed ATBT and latently infected inmates completed IPT leaving respective stage of disease to recovery stage.

3.4.4 Incorporating environmental prison conditions

The combination of poor environmental conditions such as overcrowding and poor ventilation accelerated the already high risk of transmission of TB in the prison. In a previous chapter, in countries with high disease prevalence where individuals work in closed settings, the risk of reinfection among recovered individuals in congregated setting is very high (E. Nardell & Churchyard, 2011). Thus, we incorporated the effect of reinfection in the model of which inmates who completed and recovered from TB disease, are still at risk of getting reinfected upon exposure to infectious inmates. However, the risk of reinfection is reduced as a result of acquired immunity from a previous infection (Dye et al., 1998; Sutherland et al., 1982; E. Vynnycky & Fine, 1997). The transition rate of reinfection among recovered inmates back to latently infection stage at reduced risk is represented as (1-f)βI.

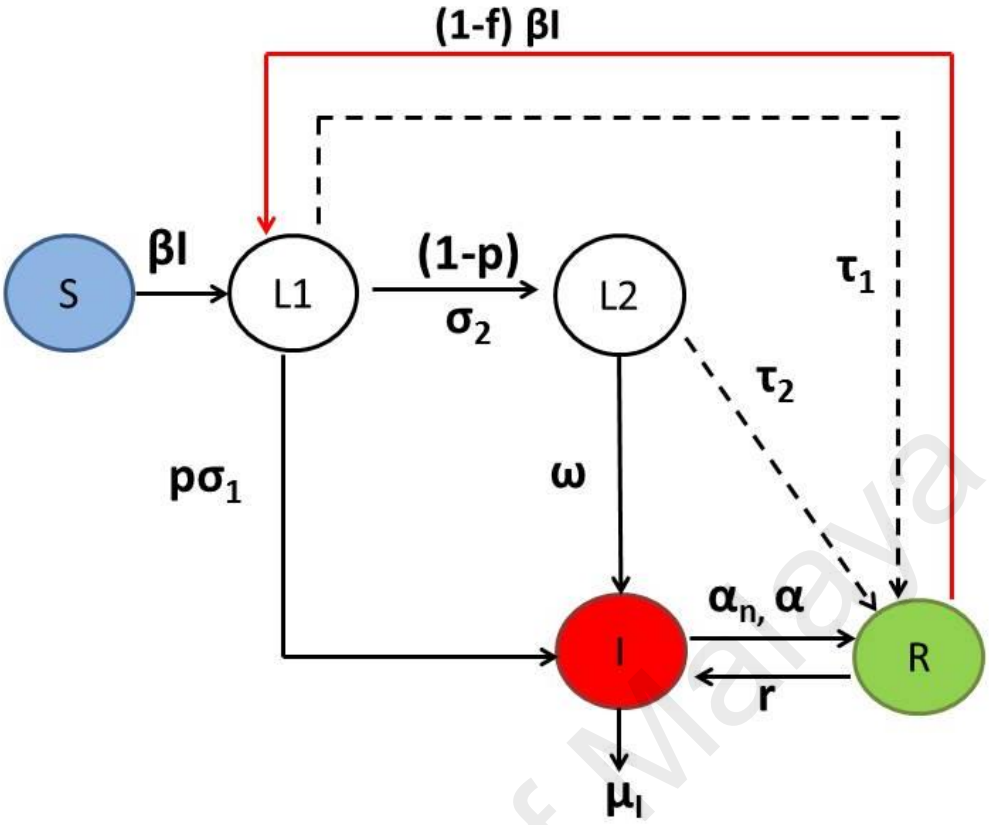


Figure 3.6: TB transmission model showing progression of disease from susceptible (S) to latent infection (L1,L2) then to active and infectious TB (I) and finally recovered (R).

3.4.5 Differential equations in projecting TB modeling

Differential equation describes the rate of change with a sufficiently small time step of a given quantity relative to a certain function. The mechanism of differential equations is perfect for modelling the dynamic transmission of TB. Each of the compartments in Figure 3.6 changed over time and allowed the inmate movement through exiting or loop back and non-linear behaviour is best described using differential equation. Although this can be set up easily in a spreadsheet, we may end up with a large spreadsheet and too burdensome for generating detailed long-term projections. In our study we have considered a 10-year period. Therefore it would only make sense to set up differential equations using programming language such as C, C++, Visual Basic, FORTRAN or to set up the model in a specialist modelling package. Several modelling package such as Berkeley Madonna, ModelMaker, Matlab, R, Maple and Stella are designed to

manipulate differential equations and estimate projections. The summary of specific variables is indicated in Table 3.2.

Table 3.2: Descriptions of variables and assigned symbols

Variables	**Descriptions**
B	Transmission rate (per person per year)
σ_1	Rate of short term progressor develop infectious TB (primary progression)
P	Proportion of fast progressor
σ_2	Rate of short term progressor move to long term progressor
Ω	Rate of long term progressor develop infectious TB (reactivation)
μ_I	TB death related
α, α_n	Rate of recovery under anti-tuberculosis treatment and self cure
τ_1, τ_2	Rate of recovery under preventive therapy for short/long term progressor
R	Relapse
F	Acquired immunity after primary infection after successful treatment
Ω	Entry rate
μ	Release or transfer rate

In this model, it is assumed that inmates are entering at the rate of Ω and exiting in every state (represented as μ), at constant rate due various reasons such as completion of serving time or transfer, of which arrows are not indicated for simplicity in Figure 3.6. This yields the following differential equations:

$$\frac{dS}{dt} = \Omega_S - \beta IS - \mu S \quad (1)$$

$$\frac{dL_1}{dt} = \Omega_{L1} + \beta IS + (1-f)\beta IR - p\sigma_1 L_1 - (1-p)\sigma_2 L_1 - \tau_1 L_1 - \mu L_1 \quad (2)$$

$$\frac{dI}{dt} = \Omega_I + p\sigma_1 L_1 + \omega L_2 + rR - (\alpha+\alpha_n)I - \mu I - \mu_I I \quad (3)$$

$$\frac{dL_2}{dt} = \Omega_{L2} + (1-p)\sigma_2 L_1 - \omega L_2 - \tau_2 L_2 - \mu L_2 \quad (4)$$

$$\frac{dR}{dt} = \Omega_R + (\alpha+\alpha_n)I + \tau_1 L_1 + \tau_2 L_2 - (1-f)\beta IR - rR - \mu R \quad (5)$$

Equation 3.1: System (1) - (5) represents the TB transmission dynamic model used in the study

In this study, R was chosen due to it simple programming language and yet effective in handling large data calculation. R is available as free software under the terms of the Free Software Foundation's GNU General Public License (Lab, 1996). However, before running the differential equation in the software, it is essential to conduct numerical analysis to validate the TB model equations (Bawa, Abdulrahman, Jimoh, & Adabara, 2013; van den Driessche & Watmough, 2002)

3.5 Model Analysis

3.5.1 Existence of Disease-Free Equilibrium State, E_f

At the state of disease-free equilibrium (DFE), we have absent infection, which the disease is leaving the population and everyone in the population is susceptible. Thus all differential equations will be equivalent to zero and the entire population will comprise of only susceptible populations.

A disease-free equilibrium state of the model exist at the point

$$E_f = (S^*, L_1^*, I^*, L_2^*, R^*) = (\frac{\Omega}{\mu}^*, 0,0,0,0) \tag{6}$$

Proof: At equilibrium state, the rate of change of each variable is zero. Thus,

$$\frac{dS}{dt} = \frac{dL_1}{dt} = \frac{dI}{dt} = \frac{dL_2}{dt} = \frac{dR}{dt} = 0 \tag{7}$$

Let

$$(S, L_1, I, L_2, R) = (S^*, L_1^*, I^*, L_2^*, R^*) \tag{8}$$

at equilibrium state. Then from equations (1) – (5), (7) and (8) we have

$$\Omega - \beta I^* S^* - \mu S^* = 0 \tag{9}$$

$$\beta I^* S^* + (1-f)\beta I^* R^* - \rho\sigma_1 L_1^* - (1-p)\sigma_2 L_1^* - \tau_1 L_1^* - \mu L_1^* = 0 \tag{10}$$

$$\rho\sigma_1 L_1^* - \omega L_2^* + rR* - (\alpha + \alpha_n) I^* - \mu I^* - \mu_I I^* = 0 \tag{11}$$

$$(1-\rho)\sigma_2 L_1^* - \omega L_2^* + \tau_2 L_2^* - \mu L_2^* = 0 \tag{12}$$

$$(\alpha + \alpha_n) I^* + \tau_1 L_1^* + \tau_2 L_2^* - (1-f)\beta I^* R^* - rR^* - \mu R^* = 0 \tag{13}$$

And at any equilibrium point, the sum of population is equivalent to total population. Thus,

$$N^* = S^* + L_1^* + I^* + L_2^* + R^* \tag{14}$$

From equations (14), we have

$$N^* = \Omega - \beta I^* S^* - \mu S^* + \beta I^* S^* + (1-f)\beta I^* R^* - p\sigma_1 L_1^* - (1-p)\sigma_2 L_1^* - \tau_1 L_1^* - \mu L_1^* + p\sigma_1 L_1^* + \omega L_2^* + rR^* - (\alpha + \alpha_n) I^* - \mu I^* - \mu_I I^* + (1-p)\sigma_2 L_1^* - \omega L_2^* - \tau_2 L_2^* - \mu L_2^* + (\alpha + \alpha_n) I^* + \tau_1 L_1^* + \tau_2 L_2^* - (1-f)\beta I^* R^* - rR^* - \mu R^*$$

$$N^* = \Omega - \mu S^* - \mu L_1^* - \mu I^* - \mu_I I^* - \mu L_2^* - \mu R^*$$

$$N^* = \Omega - \mu(S^* + L_1^* + I^* + L_2^* + R^*) - \mu_I I^* \tag{15}$$

From equations (8), equation (15) become

$$N^* = \Omega - \mu N^* - \mu_I I^*$$

$$N^* = \frac{\Omega - \mu_I I^*}{1+\mu} \tag{16}$$

But at disease-free equilibrium, $I^* = 0$ and $N^* = S^*$. Therefore equations (16) become

$$S^* = \frac{\Omega}{1+\mu} \neq \frac{\Omega}{\mu} \tag{17}$$

Therefore, the model system (1) – (5) do not show a disease-free equilibrium but endemic equilibrium where infection persists in the population ($I \neq 0$).

3.5.2 Effective Basic Reproduction Number, R_0

One of the most important concerns about any infectious disease is its ability to invade a population. The basic reproduction number, R_0 is a measure of the potential for disease spread in a population (van den Driessche & Watmough, 2002). It represents the average number of secondary cases generated by an infected individual if introduced into a susceptible population with no immunity to the disease in the absence of interventions to control the infection. If $R_0 < 1$, then on average, an infected individual produces less than one newly infected individual over the course of his infection period. In this case, the infection may die out in the long run. Conversely, if $R_0 > 1$, each infected individual produces, on average more than one new infection, the infection will be able to spread in a population. A large value of R_0 may indicate the possibility of a major epidemic. Using the next generation operator technique described by Diekmann and colleagues (Diekmann & Heesterbeek, 2000) and subsequently analyzed by van den Driessche and coleagues (van den Driessche & Watmough, 2002), we obtained the basic reproduction number, R_0 of the model equations (1) - (5) which is the spectral radius of the next generation matrix, FV^{-1}.

We let $F_i(x)$ be the rate of appearance of new infections in compartment i, and let $V_i(x)$ represent the rate of infections leaving from one compartment to another. The corresponding Jacobian matrices for F_i and V_i are given, respectively, by

$$F = \begin{pmatrix} 0 \\ \beta IS + (1-f)\beta IR \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

And

$$V = \begin{pmatrix} -\Omega + \beta IS + \mu S \\ p\sigma_1 L_1 + (1-p)\sigma_2 L_1 + \tau_1 L_1 - \mu L_1 \\ -p\sigma_1 L_1 - \omega L_2 - rR + \alpha_1 I + \alpha_2 I + \mu I + \mu_I I \\ -(1-p)\sigma_2 L_1 + \omega L_2 + \tau_2 L_2 + \mu L_2 \\ -\alpha_1 I - \alpha_2 I - \tau_1 L_1 - \tau_2 L_2 + (1-f)\beta IR + rR + \mu R \end{pmatrix}$$

Jacobian matrices associated with F and V:

$$J_F = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ \beta I & 0 & \beta S + (1-f)\beta R & 0 & (1-f)\beta I \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J_V = \begin{bmatrix} \beta I + \mu & 0 & \beta S & 0 & 0 \\ 0 & p\sigma_1 + (1-p)\sigma_2 + \tau_1 + \mu & 0 & 0 & 0 \\ 0 & -p\sigma_1 & \alpha_1 + \alpha_2 + \mu + \mu_I & -\omega & -r \\ 0 & -(1-p)\sigma_2 & 0 & \omega + \tau_2 + \mu & 0 \\ 0 & -\tau_1 & -\alpha_1 - \alpha_2 c + (1-f)\beta R & -\tau_2 & (1-f)\beta I + r + \mu \end{bmatrix}$$

The basic reproduction number is obtained as the spectral radius of the matrix $J_F \times (J_V)^{-1}$ at the disease-free equilibrium.

The basic reproduction number R_0 for system (1) – (5) is given by

$$R_0 = \frac{\beta N}{\sigma_1 p + \sigma_2 (1-p) + \tau_1 + \mu} \qquad (18)$$

3.5.3 Public Health Implication of Numerical Analysis

The disease-free equilibrium state and effective basic reproduction number analysis method is used to validate the model equations. Both the analysis identified that the model has endemic equilibrium and that the disease persists in the population ($R_0 > 1$). This analysis is useful to inform the policy-makers that the model has been validated using numerical analysis and therefore increase feasibility of this model for public health applications.

3.6 Force of Infection, β

In a confined space, the transmission of airborne disease could be estimated based on three models; the Mass Action Model (MA), Riley-Murphy-Riley's Model (RMR) and Gammaitoni and Nucci's Model (GN) (Beggs, Noakes, Sleigh, Fletcher, & Siddiqi, 2003; Gammaitoni & Nucci, 1997; E. C. Riley, Murphy, & Riley, 1978).

3.6.1 Mass Action Model

The MA model defines that the number of infectious transmissions per infected case is a function of the number of susceptible individuals in the population (Equation 3.2). This model has been used to model the dynamics of measles outbreak (R. L. Riley, 1974), in which an increase in the number of infected individuals causes the number of susceptible individuals to decrease.

$$C = rIS$$

Equation 3.2: The Mass Action Model

Based on Equation 3.2, C is the number of new infection cases, S is the number of susceptible, I is the number of infected individuals and r is the effective contact rate.

3.6.2 Riley-Murphy-Riley's Model

The RMR model which is also known as Wells-Riley model, suggests that the number of new infectious cases were based on the probability of susceptible individual becoming infected by inhaling a quanta of infection. Their model is defined as the following equation

$$C = S(1 - e^{-\phi pt/Q})$$

Equation 3.3: The Wells-Riley model

Where ϕ is the average number of infectious doses generated per infector (quanta/min), p is the pulmonary ventilation rate (m^3/min), t is the duration exposure to infection (min), and Q is the room ventilation rate.

3.6.3 Gammaitoni and Nucci's Model

Similar to Wells-Riley Model, the GN model focuses on the probability of a susceptible individual becoming infected by inhaling a quanta of infection but it accounts for the change of quanta level over time. Therefore, the GN model is a further modification of Wells-riley model and it is defined as

$$C = S_0(1 - e^{f(p,I,\phi,V,N,n_0,t)})$$

Equation 3.4: The Gammaitoni and Nucci's model

Where S_0 is the number of susceptible at time t=0, V is the room volume (m^3), N is the ventilation rate (air changes/min) and n_0 is the initial quanta amount at time t=0.

Both the Wells-Riley and GN models focus on transmission of airborne disease in confined spaces with overcrowding and poor ventilation which enables close contact with infected person. However, these models are limited to describing the number of new infections for a fixed number of infectors, and not the full dynamics of an epidemic.

Noakes et al. addressed this limitation by incorporating the Wells-Riley model with classical Susceptible-Infected-Recovered (SIR) model that include an incubation period to stimulate the transmission dynamics of airborne infectious diseases in ventilated spaces (Noakes, Beggs, Sleigh, & Kerr, 2006). The exercise by Noakes et al. found that the β, which is the effective contact rate or transmission rate between infectors to susceptibles, can be quantified in terms of the room ventilation, environmental conditions and level of airborne infectious material in the space. This model quantified the airborne transmission rate in confined setting based on the effect of environmental factors such as the ventilation rate and occupancy of space. Therefore, the transmission rate in terms of ventilation rate and occupancy of space is defined as the following equation

$$\beta = \frac{\rho q}{VA}$$

Equation 3.5: Transmission rate using Wells-Riley equation

It is a product of the average pulmonary ventilation rate of the susceptibles, ρ, (m^3/h) and the quanta production rate per infector, q, (quanta/h), divide by the room volume per inmate, V, (m^3) and the ventilation rate in air changes per hour, A (ACH). This model has been used in estimating the effect of environmental control in nosocomial transmission of TB (Basu et al., 2007). Although the GN model is more comprehensive than the Wells-Riley model, it has yet to be incorporated and validated in epidemiological model.

3.7 Data Collection

The TB transmission model required input of the progression of the TB disease, epidemiological for inmates in prison and information on the building structure of the prison. The required information was obtained through an extensive review of published literature as well as data sources including government agencies such as Prison and Ministry of Health.

3.7.1 Progression to Active TB After Infection

The rate of TB progression applied in this study ideally should be reflected for the inmate population in Malaysia. However, as we have mentioned in the previous chapter, currently Malaysia do not have any specific TB interventions in the prison as outlined in in international guidelines described earlier. Thus, there is no retrospective data on TB in our prison setting that we could use for this study. The previous TB modeling study in prison in Brazil faced similar challenges that they had to rely on available published study in estimating the rates of disease progression (Legrand et al., 2008a). Therefore, we currently relied on available modelling studies from developed countries such as in Western Europe and United Kingdom that fit retrospective data of annual risk of TB infection at population-level, large population-based trials of interventions as well studies on TB molecular epidemiology (Barnes & Cave, 2003; Comstock, 2008; Dye et al., 1998; Godfrey-Faussett et al., 2000; Sutherland et al., 1982; E. Vynnycky & Fine, 1997). The studies by Borgdorff et al., and Vynnyck et al., suggested that after exposure, nearly 45 per cent would progress to active TB within a year of which the risk of progression declines over a period of five years. The study also found that the risk of progression is 10 per cent higher in adults as compared to children (Borgdorff et al., 2011; E. Vynnycky & Fine, 1997). It was unfortunate that currently there were no available studies that could provide us with more accurate data reflecting the risk of rapid progression in a present

high-burden setting. The findings of available studies among HIV infected people were also limited to small outbreak investigations before the availability of antiretroviral therapy (Golub et al., 2008; Holmes et al., 2006; Lawn, Myer, Edwards, Bekker, & Wood, 2009; Williams et al., 2010). Although they suggested that among people living with HIV, the progression to active TB is as high as 75 per cent and beyond, it is possible that the proportion is much lower among individuals on ART or with high CD4 counts. Other risk factors such as diabetes, nutritional status and smoking behavior affect progression to active TB but in modelling the transmission, it is a continuous debate among researcher of whether they should be considered as proportion of individuals progressing rapidly after exposure or as the rate of transition of progression (Cegielski & McMurray, 2004; Jeon & Murray, 2008; Lin, Ezzati, & Murray, 2007; M. Murray, Oxlade, & Lin, 2011). These determinants have important effects for the effectiveness of TB control interventions such as IPT and contact investigation strategy which depend on detecting TB infection before progression to active disease.

The estimates of rate of reactivation range from 0.03 to 0.01 per 100 person-years and have been said to have less influence on model projections (Ferebee, 1970; Horsburgh et al., 2010; E. Vynnycky & Fine, 1997). However, TB reactivation rates could be higher with immunosuppressed individuals. Among people living with HIV, the rate of reactivation has been quoted to be as high as 10 per cent per year although many empiric studies have estimated lower rates (Antonucci, Girardi, Raviglione, & Ippolito, 1995; Corbett et al., 2003). The mechanism of "immunity afforded by previous infection" against reinfection or prevention of rapid progression after reinfection is still poorly understood. The estimate of this parameter is currently based on population modelling studies that fit to large historical data in Netherland, England and Wales of which the value range from 41 to 65 per cent (Sutherland et al., 1982; E. Vynnycky & Fine, 1997).

Table 3.3**:** Probability of developing active TB after infection based on available published studies

Variables	Description	Values (per year)	Ranges	Sources	Study Description
P	Proportion of fast progressor	0.075	0.05 - 0.1	(E. Vynnycky & Fine, 1997)	Population modelling study for Wales and England in the early 1950's
σ_1	Rate of fast progressor develop infectious TB (Primary progression)	0.938	0.76 - 0.99	(Legrand, Sanchez, Le Pont, Camacho, & Larouze, 2008b)	Modelling study in a high risk prison in Brazil.
σ_2	Rate of fast progressor move to slow progressor	0.2		(Dowdy et al., 2013; E. Vynnycky & Fine, 1997)	Dowdy et al., interpolated data available from E. Vynnycky & Fine 1997 study.
W	Rate of slow progressor develop infectious TB (Reactivation),	0.00014	0.0001 - 0.0002	(Horsburgh et al., 2010)	Most recent study on TB reactivation rate, population based study among US in late 1990's.
F	Acquired immunity after primary infection after successful treatment	0.53	0.41-0.65	(Sutherland et al., 1982; E. Vynnycky & Fine, 1997)	Population based study among the dutch and the UK.

3.7.2 Epidemiological and Treatment data

The rate of recovery was estimated based on the completion of treatment regimen according to WHO guidelines (Ministry of Health, 2012; World Health Organization, 2011). The IPT regimen varied at 6, 12 and 36 months. The parameters on TB related death and relapse rate were estimated based on Malaysian population data available at MOH and WHO (Ministry of Health, 2012; World Health Organization, 2016) . The self-

cure parameter corresponds to a spontaneous transition from active TB to a non-infectious state without receiving treatment. Due to the unavailability of data in the Malaysian setting, the estimate was based on available published studies. A recent review prior to the chemotherapy era found that a 10-year case fatality rate of untreated cases of smear-positive TB and culture-positive smear-negative TB is estimated to be 70 and 20 per cent respectively (Tiemersma, van der Werf, Borgdorff, Williams, & Nagelkerke, 2011). These findings suggested that without treatment, there is considerable number of individuals with active TB who continue to live. However, the duration of infectiousness was estimated to be shorter in this study and may not be generalised to current modern TB epidemics.

Table 3.4: Epidemiological and treatment data from the Ministry of Health of Malaysia, WHO and available published data.

Variables	**Description**	**Values (per year)**	**Ranges**	**Sources**
τ_1, τ_2	Rate of recovery under preventive therapy for fast/slow progressor,	1/6 month	As per guidelines, 6 months	(Ministry of Health, 2012; World Health Organization, 2011)
A	Rate of recovery under anti-tuberculosis treatment	1/6 month	As per guidelines, 6 months	(Ministry of Health, 2012)
μ_I	TB death related	0.000052	0.000042-0.000058	(Ministry of Health, 2012)
R	Relapse	0.00553	0.00499 - 0.00602	(World Health Organization, 2016)
α_n	Self cure,	0.0935	0.02-0.167	(Dye et al., 1998; Tiemersma et al., 2011)

3.7.3 Prison Data

In this study, we used Kajang Prison data for the model simulation. Kajang prison is the largest prison in Malaysia with 11 separate prison units. TB infection control measures such as routine intensified TB screening and treatment is not currently implemented in the prison. The prison currently holds nearly 4,200 inmates where inmates are sentenced for various periods ranging from six months to lifetime imprisonment with an approximate annual turnover of inmates of one third. The prison is currently overcrowded with an occupancy rate of 20% more than its capacity and each prison's cell is occupied with an average of four inmates per cell. The current cell floor area is estimated to be 3.33 m2 per inmate, which is smaller than the WHO recommendation of 5.40 m2 floor area per inmate (World Health Organization, 2009). Measuring ventilation rate required a specific set of equipment and tools to measure the air changes to the room (Allard & Ghiaus, 2005). In low resource-setting, carbon dioxide have been used as a tracer gas to measure air exchange in a hospital ward (R. Menzies, Schwartzman, Loo, & Pasztor, 1995). However, this was not feasible to be conducted in this prison due to security concerns. International guidelines for prison recommend 1.38 – 3.58 ACH of ventilation rate (Dara et al., 2009). WHO recommends a minimum of 12 ACH for health settings and congregate settings where TB is prevalent (World Health Organization, 2009). Therefore, to represent the poor ventilation air in the prison, the air exchange was conservatively modelled at 2 ACH. The mean respiratory rate of adults was estimated to be 360 liters per hour corresponding to a normal adult respiratory minute volume of 6 litre per minute (Pinna, Maestri, La Rovere, Gobbi, & Fanfulla, 2006). A wide range of estimated values for the rate of production of infectious TB quanta has been reported. In a workplace outbreak due to an untreated smear-positive pulmonary case, the rate of production of infectious TB quanta was estimated at 12.7 infectious quanta per hour (E. A. Nardell, Keegan, Cheney, & Etkind, 1991). Over a 2-year period in a TB

ward, it was directly measured at 1.25 infectious quanta per hour (R. L. Riley, Wells, Mills, Nyka, & McLean, 1957). A study applying molecular strain characterization to track airborne TB transmission from HIV/TB-infected inpatients to guinea pigs demonstrated markedly variable infectiousness (Escombe et al., 2008). In order to be conservative, the rate of production of infectious TB quanta was modelled at a mean value of 1.25 to 12.7 infectious quantum per hour. There is no intensified routine TB detection at entry point and thereafter nor treatment for LTBI. The prevalence of infectious TB is 8%, obtained from a recent intensified TB case finding study in Kajang prison (Al-Darajji, personal communication, 15 April 2014). A summary of data collected from prison data and available published studies to inform parameters for Force of Infection, β is indicated in Table 3.5.

Table 3.5: Variable to inform parameter for Force of Infection, β based on prison's data and available published studies.

Variable	Description	Value	Reference
P	pulmonary ventilation rate of the susceptibles, (m^3/h)	6 liter/h	(Pinna et al., 2006)
Q	quanta production rate per infector, (quanta/h)	1.25 to 12.7 quanta/h	(E. A. Nardell et al., 1991; R. L. Riley et al., 1957)
V	the room volume per inmate, (m^3)	3.33m^2 for six inmates per cell 5.40 m^2 for four inmates per cell	(Al-Darajji, personal communication, 15 April 2014)
A	ventilation rate in air changes per hour, (ACH)	2 ACH, 12 ACH	(Dara et al., 2009; World Health Organization, 2009)
Pq/VA	Transmission rate (per person per year), β	0.075 (0.0135-0.1372)	Wells-Riley equation (Basu et al., 2007; Beggs et al., 2003; Gammaitoni & Nucci, 1997; Noakes et al., 2006; R. L. Riley, 1974)

3.8 Simulation of TB Intervention Strategy and Model Assumptions

In accordance with the research questions, the simulation of TB intervention in prison was executed according to three strategies. The first strategy was executed at the current environmental conditions in the prison as the baseline comparator. The second strategy was simulation with improved environmental conditions in the prison and the third one was prolonging preventive therapy strategy at current and improved environmental conditions in the prison. In this model, all strategies (including baseline), assumed that inmates are screened upon entry and TB diagnosis as per WHO recommended guidelines (Al-Darraji et al., 2013). For treatment strategy, the model assumed that all infectious inmates received the standard combination of anti-TB drugs treatment for six months while the latently infected inmates received isoniazid preventive therapy for six months unless stated in the third simulation of strategy. The details of simulation executed are as follows.

3.8.1 Initial Condition of the Model

The initial condition of the model is set based on the available data of Kajang Prison. Studies by Al-Darajji et al. found that the prevalence of active TB and latently infected among inmates in Kajang Prison is estimated to be 8 and 85 percent respectively. Therefore the Infectious and Latent compartment is set as 8 and 85 per cent respectively (Al-Darraji et al., 2013; Al-Darraji et al., 2014). Although, there is no TB intervention in the prison, considering there could be some incoming inmates who never get infected with TB or already recovered but very minimal, the Susceptible and Recovered compartment is set to be as low as 3 and 4 per cent respectively.

3.8.2 With Current Environmental Conditions of Prison

The first simulation adopted model parameters set to the values of the current environmental conditions of Kajang Prison (i.e., overcrowded cell occupancy and poor ventilation; see Table 3.6), with no interventions included. We termed this Strategy 1A which is also the baseline comparator. Then, we ran three simulations including TB interventions: (Strategy 2A) ATBT provided to all infectious inmates only; (Strategy 3A) IPT provided to all latently infected inmates only; and (Strategy 4A) both ATBT and IPT provided to all infectious and latently infected inmates, respectively.

3.8.3 Improved prison's condition

We repeated these simulations by changing the overcrowding factor (reducing the occupancy of the cell from six inmates (or 3.33m^2 floor area per inmate) to four inmates per cell (or 5.40m^2 floor area per inmate)) and improving the ventilation by increasing the air changes per hour to 12 ACH from 2 ACH. We termed these Strategies 1B through 4B (see Table 3.6).

3.8.4 Prolonging Treatment Regimen

We also repeated the simulation of the IPT intervention according to three different durations: 6 months (Strategy 3A-6; identical to Strategy 3A), 12 months (Strategy 3A-12) and 36 months (Strategy 3A-36) of IPT among the latently infected. Finally, we repeated the simulation of IPT for 36 months but additionally changing the overcrowding factor (reducing the occupancy of the cell from six inmates (or 3.33m^2 floor area per inmate) to four inmates per cell (or 5.40m^2 floor area per inmate)) and improving the ventilation by increasing the air changes per hour to 12 ACH from 2 ACH (Strategy 3A-36, see Table 3.6).

Table 3.6: Simulation of TB intervention strategies

Strategy	No IPT + No ATBT (Baseline)	ATBT	IPT-6	IPT + ATBT	IPT-12	IPT-36
A) Overcrowding and poor ventilation (Current environmental condition is six inmates per cell and 2 ACH)	Strategy 1A	Strategy 2A	Strategy 3A	Strategy 4A	Strategy 3A-12	Strategy 3A-36
B) Reducing occupancy rate from six to four inmates per cell and improved ventilation from 2 ACH to 12 ACH	Strategy 1B	Strategy 2B	Strategy 3B	Strategy 4B	n/a	Strategy 3B-36

3.9 Uncertainty and sensitivity analyses

We performed uncertainty and sensitivity analyses using Latin Hypercube Sampling (LHS) and partial rank correlation coefficient (PRCC) to identify the contribution of uncertainties around the parameters on the active TB prevalence and to rank these parameters according to their characterized relationship on the active TB prevalence. The LHS has been known as the efficient tool for assessing variability and robustness of transmission model results (McKay, Beckman, & Conover, 1979). Based on the specified range of parameter values provided in Table 3.1, we repeated 1,000 random combinations of parameter values of which the values for each parameter were assumed uniformly distributed between their lower and upper bounds. In LHS procedure, the parameter values within the specified range are divided equally, randomly sampled one at a time

and have the same probability of being selected for each run without replacement and therefore fewer total numbers of simulations is required. We generated the analysis for all strategies under the current environmental factors and after the environmental factors were changed. Using PRCC method, we then quantified the impact variation of each parameter and ranked the parameters according to their correlation on the predicted active TB prevalence after 10 years.

3.9.1 Translating ODE to R programming language

The model differential equations are translated into the R programming language and available in the appendix.

CHAPTER 4 : RESULT

4.1 Introduction

Results of the impact of the three TB intervention strategies are presented in this chapter. Then, results were used to explore the contribution of uncertainty in the parameters and the relationship characteristics of the parameters to the prevalence of active TB. The high prevalence of TB among inmates in a highly endemic and overcrowded prison led to primary questions of whether introducing TB interventions in this setting would reduce the incidence of TB among inmates. Secondly, would changing the current conditions by improving the air ventilation and reducing the overcrowding in the prison affect the effectiveness of TB interventions implemented in the prison? Thirdly, given the evidence of increased IPT effectiveness in similar setting elsewhere, would prolong IPT beyond the minimum duration improve the effectiveness of TB interventions?

4.2 With Current Environmental Conditions of Prison

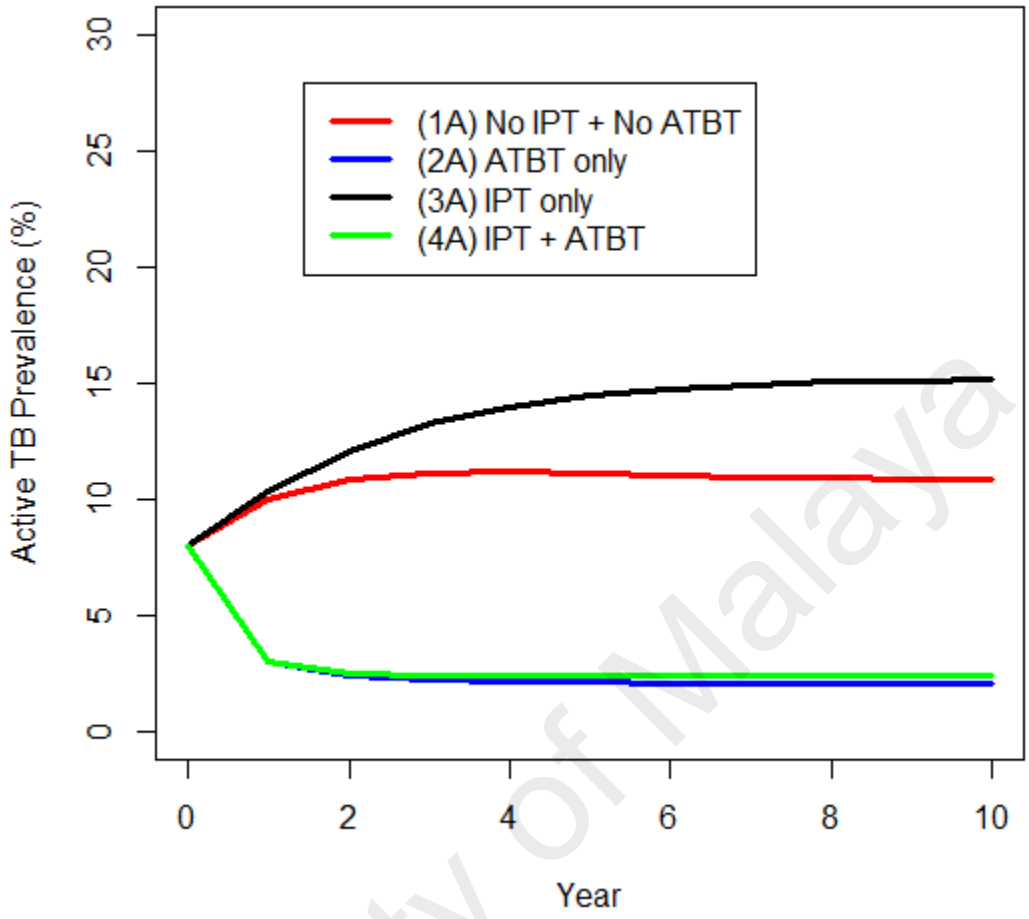


Figure 4.1: Estimated prevalence of active TB in baseline strategy (Strategy 1A) against three different TB control strategies (Strategy 2A, 3A and 4A) based on the current environmental condition in prison, which is poor ventilation at 2 ACH and overcrowded space with six inmates per cell.

Based on the current environmental conditions in the prison, if neither IPT nor ATBT is implemented (Strategy 1A), the model estimated that, after two years, the prevalence of active TB would increase to 11% (9.373 – 11.718) and remain at this level for the next eight years (See Figure 4.1). Implementation of both ATBT and IPT (Strategy 4A) would result in a similar trend as the simulation of implementing ATBT only (Strategy 2A). The model estimated that after ten years, these strategies would reduce the prevalence of active TB significantly to below 3%. The ATBT intervention resulted in the lowest prevalence of active TB (2.024%) compared to the combined intervention

(2.363%). The effect appears to be mostly from the implementation of ATBT, as the difference in prevalence of active TB between the combined intervention and ATBT only intervention was not large (Figure 4.1). Conversely, implementing only IPT (Strategy 3A) in the prison would increase the prevalence of active TB to as high as 15% over the next 10 years.

4.3 Impact of Improved Environmental Conditions of Prison

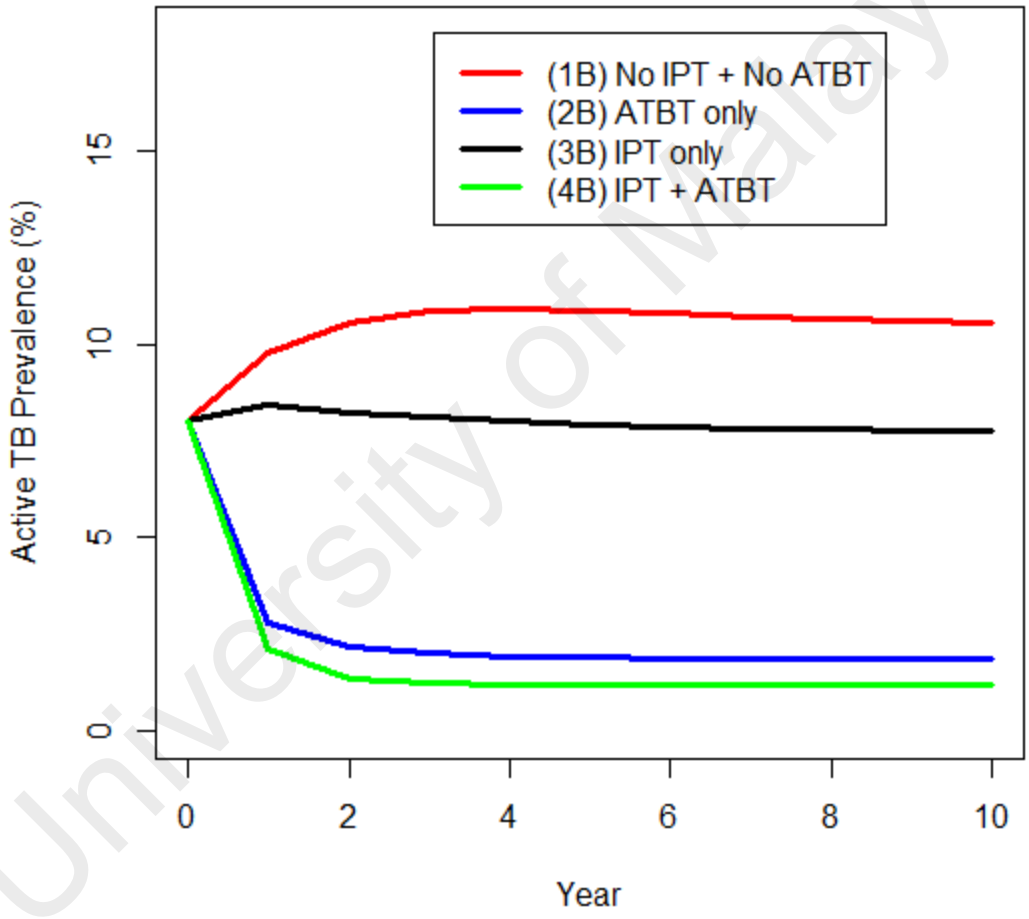


Figure 4.2: Estimated prevalence of active TB in TB in baseline strategy (Strategy 1B) against three different TB control strategies (Strategy 2B, 3B and 4B) after changing the air ventilation rate from 2 to 12 ACH and reducing the occupancy rate from six to four inmates per cell.

By improving the air ventilation rate from 2 ACH to 12 ACH and reducing the occupancy rate from six to four inmates per cell, in the absence of any TB control measure (Strategy 1B), the strategy showed a similar curve with the previous simulation but with

prevalence of active TB slightly dropped to 10.8% (8.694% -12.645%) and stabilized at 10.5% (6.998% – 10.716%) after ten years (Figure 4.2). Similar to the previous simulation, the combined (Strategy 4B) and ATBT only (Strategy 2B) interventions showed a similar trend in reducing the prevalence of active TB (See Figure 4.2). However, the combined strategy resulted in lower prevalence of active TB (1.183%) as compared to ATBT only (1.826%) when the environmental parameters were changed. Changing the environmental parameters resulted in only a minor reduction to the already low prevalence of active TB when these strategies were implemented. Our model also showed that implementing IPT and changing the environmental parameters (Strategy 3B) would overall result in a lower active TB prevalence as opposed to previous simulation (Strategy 3A) and when no interventions were implemented (Strategy 1B). This strategy would gradually reduce the prevalence of active TB to 7.8 (5.153% - 10.539%) and projected to be in the same level after ten years.

4.4 Impact of prolonging the duration of treatment with IPT for longer than 6 months

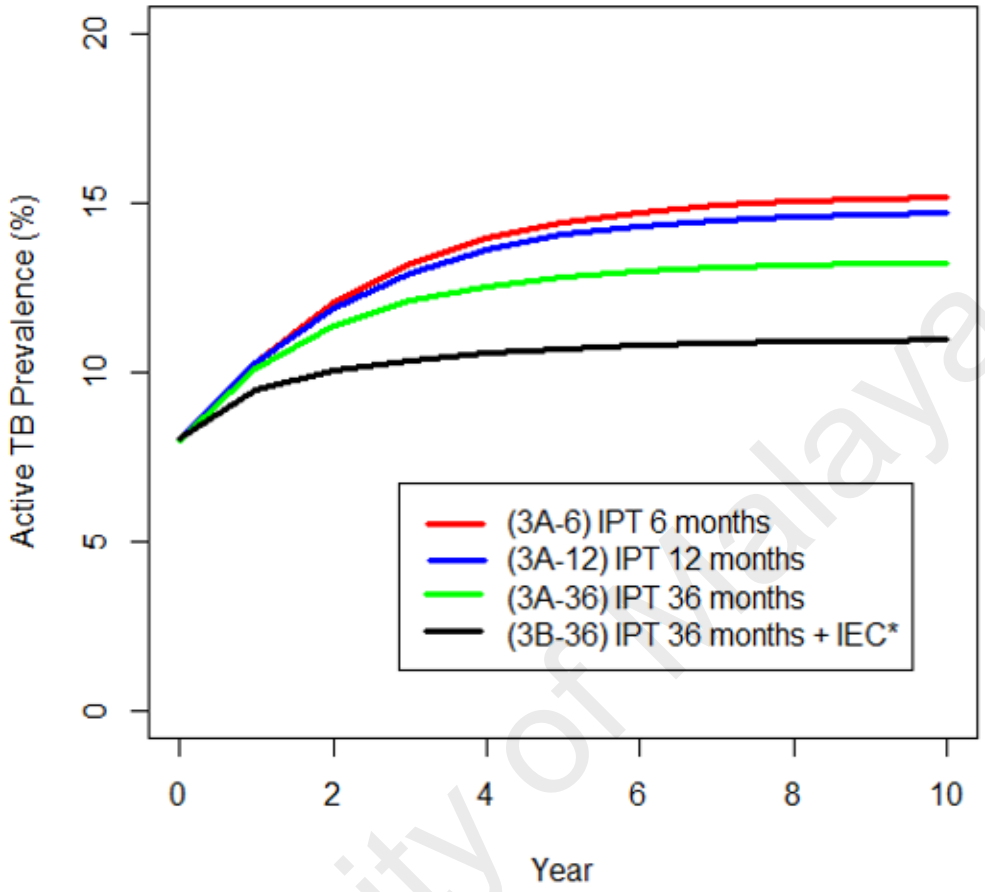


Figure 4.3: Estimated prevalence of active TB in four different IPT strategies in prison. The simulation for (3A-6) to (3A-36) is executed without changing the current environmental conditions in the prison. The simulation for (3B-36) is executed for IPT of 36 months at improved environmental condition (IEC) by changing the ventilation rate from 2 ACH to 12 ACH and reducing occupancy rate from six to four inmates per cell

Our model estimated that there would be little impact on prevalence of active TB when IPT is implemented for 6 or 12 months (Strategy 3A-6 to 3A-12 in Figure 4.3). Our model also estimated that prolonging the duration of IPT for 12 and 36 months would increase the prevalence of active TB to 14.7% and 13.2% respectively, a similar trend was observed when implementing IPT for 6 months (Strategy 3A-6 to 3A-36 in Figure 4.3). However, implementing IPT for 36 months would result in a slightly lower prevalence of active TB as opposed to IPT for 6 or 12 months. After changing the air ventilation rate from 2 ACH to 12 ACH and reducing the occupancy rate from six to four inmates per

cell, implementing IPT for 36 months (Strategy 3B-36) would reduce the prevalence of active TB to 11% but this would remain at the same level for the next ten years. However, when compared to no interventions strategy (Strategy 1A), the prevalence of active TB is still slightly higher.

Table 4.1: Active TB Prevalence under different TB intervention strategies after 10 years

Strategy	No IPT + No ATBT (Baseline)	ATBT	IPT-6	IPT + ATBT	IPT-12	IPT-36
A) Overcrowding and poor ventilation (Current environmental condition is six inmates per cell and 2 ACH)	10.807 (8.694 12.465)	2.024 (1.749 - 2.105)	15.165 (10.641 - 17.694)	2.363 (1.417 - 2.744)	14.717 (11.334 – 16.856)	13.238 (10.410 – 15.304)
B) Reducing occupancy rate from six to four inmates per cell and improved ventilation from 2 ACH to 12 ACH	10.555 (6.998 - 10.716)	1.826 (1.604 - 1.907)	7.748 (5.153 - 10.539)	1.183 (1.078 - 1.262)	n/a	10.961 (7.689 - 13.283)

4.5 Uncertainty and sensitivity analyses

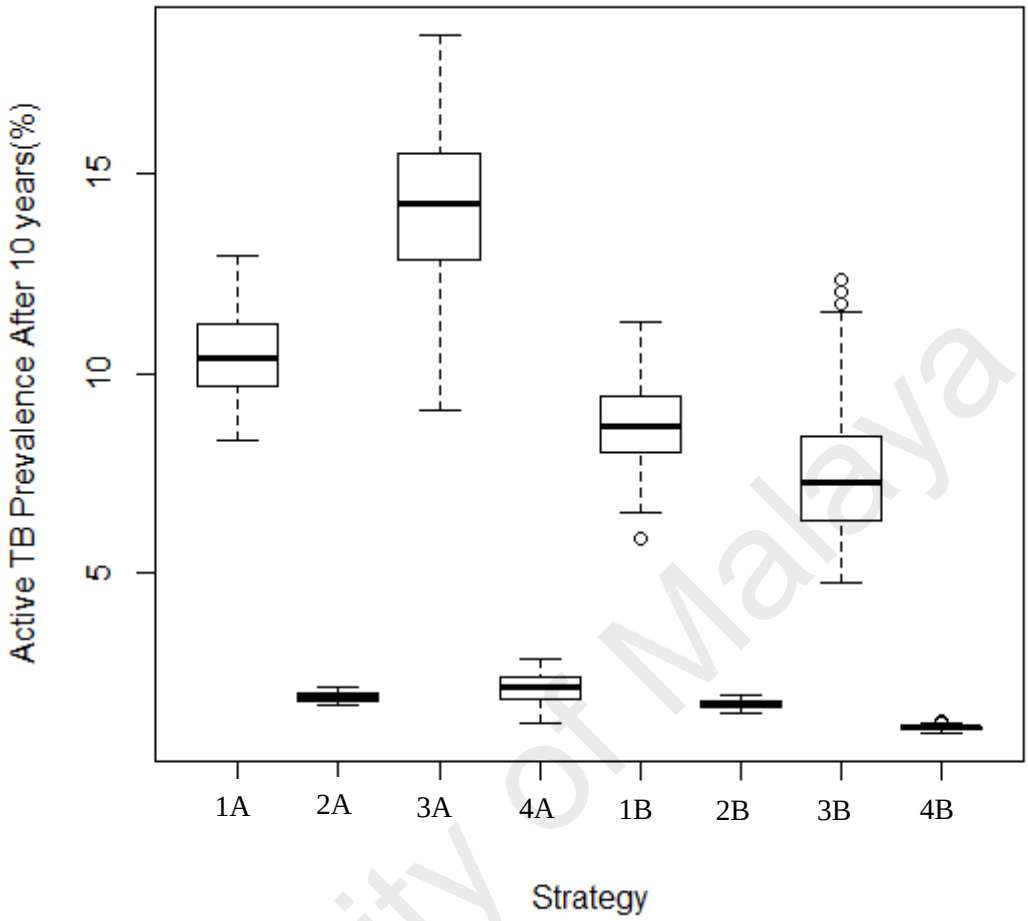


Figure 4.4: Results of the uncertainty analysis. Boxplots of the average prevalence after 10 years (%). For each set of parameters of the sample generated by the Latin Hypercube Sampling method and each strategy, we performed 1000 runs of the model and computed the average prevalence after 10 years. Each boxplot represents the median the first and third quartiles (Q1 and Q3), the mean and the maximum and minimum values which are in the range [Q121.5 IQR, Q3+1.5 IQR] with IQR equal to the inter-quartile range (Q3-Q1)

The boxplots in Figure 4.4 represent the possible outcomes based on the range of parameter values provided in Table 4.2. With LHS method, for 95 per cent of the input parameters sets, the probability distribution of active TB prevalence could be lower for combined strategies or ATBT alone but higher for IPT strategy. The boxplots also suggest that the contribution of uncertainty for IPT strategy could be larger. The sensitivity analysis showed that for all the simulated strategies except for combined strategy in current environmental condition, the primary progression rate was observed to have a

positive correlation on the predicted prevalence but negatively correlated with natural recovery rate (See Table 4.2). This suggests that at current environmental condition, overestimating or underestimating these parameters would greatly influence the outcome of all strategies except for combination strategy. On the other hand, in the improved environmental condition, it was found that the positive correlation on the predicted prevalence was observed for transmission rate for ATBT strategy but negatively correlated with partial immunity for combined strategy. The reinfection transmission parameter had a positive correlation on the predicted prevalence for all strategies except for baseline strategy. Overestimating reinfection parameter would underestimate the efficacy of the simulated strategy.

Table 4.2: Partial rank correlation coefficient (PRCC) between each parameter and the average predicted prevalence after 10 years, for the current scenario and TB control strategies.

	With Current Environmental Conditions in Prison				**Improved Environmental Conditions in Prison**			
Parameters	(1A) No IPT + No ATBT	(2A) ATBT only	(3A) IPT only	(4A) ATBT + IPT	(1B) No IPT + No ATBT	(2B) ATBT only	(3B) IPT only	(4B) ATBT + IPT
TB Transmission	0.034	0.452	0.014	0.065	0.001	**0.938***	0.259	0.628
Primary progression	**0.985***	**0.996***	**0.853***	0.799	**0.976***	**0.997***	**0.812***	**0.963***
Reactivation	-0.035	0.059	-0.076	0.011	0.046	0.080	0.044	0.004
Partial Immunity	0.025	-0.348	-0.366	-0.616	-0.287	-0.764	-0.798	**-0.840***
Reinfection	0.180	**0.871***	**0.853***	**0.959***	0.752	**0.966***	**0.975***	**0.981***
Untreated TB death	0.015	0.060	0.037	0.000	-0.011	0.027	0.047	0.000
Self-cure	**-0.997***	**-0.971***	**-0.948***	-0.437	**-0.982***	**-0.986***	**-0.970***	**-0.957***

* p-value < 0.003

CHAPTER 5 : DISCUSSION

5.1 Introduction

This section discussed the result of simulation presented in the previous chapter.

5.2 Effectiveness of ATBT intervention under various strategies

To our knowledge, this is the first modelling study that simulates the impact of treatment intervention strategies and environmental factors in a closed setting with high TB burden. The greatest impact in reducing the active TB prevalence was achieved through provision of anti-tuberculosis treatment to infectious inmates in combination with preventive therapy for latently infected inmates over a ten year period, while reducing overcrowding and improving air ventilation rates (Strategy 4B). Providing ATBT treatment for those infected with active TB (Strategy 2A) alone even in the absence of structural changes such as reduction of overcrowding and improvement of poor ventilation significantly reduced the prevalence of active TB over a ten year period. A combined treatment strategy of treating both active and latent TB was effective in reducing the prevalence of active TB even in the absence of improvements to the level of overcrowding and to ventilation. Importantly, implementing preventive treatment alone without addressing environmental factors (Strategy 3A) was predicted to actually increase the burden of TB in prison.

Mathematical models of TB have been used to evaluate the epidemic impact in a high prevalence setting by treating active TB (Dye et al., 1998), preventive therapy (Cohen, Lipsitch, Walensky, & Murray, 2006; Mills et al., 2011; Mushayabasa & Bhunu, 2013; Ziv et al., 2001) and for both interventions (Basu et al., 2007; Bhunu et al., 2008; Blower et al., 1996; Bowong & Aziz Alaoui, 2013; Kasaie, Andrews, Kelton, & Dowdy, 2014; C. J. Silva & D. F. M. Torres, 2013). However, the majority of these studies were conducted at population or community level. Mathematical models of TB in closed setting have been very limited. Legrand et al. modelled the impact of administrative

interventions on TB control in closed settings, but they did not consider the IPT impact or environmental interventions (Legrand et al., 2008b). Another study of closed setting by Johnstone-Robertson-et al. have considered in their modelling the impact of overcrowding and poor ventilation on TB transmission but the analysis was limited to acquisition of infection and not development of the disease (Johnstone-Robertson et al., 2011). A study by Basu et al., modelled various effects of infection control including administrative, environmental and personal infection for nosocomial transmission of extensively drug resistant (XDR) TB (Basu et al., 2007). The study found that a combination of nosocomial infection control measures such as mask use with shortening hospitalization time as well as improved ventilation and providing rapid drug resistance test, HIV treatment and facility for isolation of TB cases could prevent nearly half of XDR cases.

5.3 Effectiveness of IPT intervention under various strategy

In our model, IPT reduces subsequent risk of progression and reactivation to infectious compartment by removing latently infected inmates to the recovered compartment. However, this protection diminishes over time following completion of IPT (Johnson et al., 2001; Quigley et al., 2001). If the infectious inmates are not treated, inmates who have completed the IPT regimen are at risk of reinfection. In overcrowded and poorly ventilated prison conditions this can facilitate on-going reinfection and transmission which will result in a high number of recovered inmates becoming re-infected. This also explained why the prevalence of active TB is high when IPT is implemented alone (Strategy 1B) than with neither ATBT nor IPT interventions are in place (Strategy 1A). In Strategy 1A, the number of inmates who recovered is very minimal as the majority of them are in long term latently infected compartment, allowing very minimum inmates at risk of reinfection. However, implementing only IPT (Strategy 1B) would result in a high

number of inmates who completed IPT, again at the risk of reinfection. Thus, the active TB prevalence was even higher when implementing IPT as opposed to no TB interventions at all being implemented. Our findings can be viewed as radical in comparison to previous IPT modelling studies. We did not set out to refute the effectiveness of IPT, but rather to highlight that in certain settings - namely a highly TB endemic and overcrowded prison – our model suggests IPT alone is less effective due to high rates of reinfection.

These findings are consistent with a recent study among South African gold miners which found that treatment of LTBI had no significant effect on community TB control despite the mass use of isoniazid in that population (Churchyard et al., 2014). Another study among South African gold miners also found that reinfection is a predominant mechanism for recurrence of TB after successful treatment, particularly among those who are immunosuppressed (Charalambous et al., 2008). In a high-TB incidence area of Cape Town, a study found that the incidence rate of TB attributable to reinfection after successful treatment was four times higher than new infection of TB (Verver et al., 2005). This is supported by epidemiological models that suggest that in a high burden TB setting, the majority of new cases of TB are due to reinfections rather than to reactivation (Cohen & Murray, 2005; Viljoen, Pienaar, & Viljoen, 2012). Therefore, in a high burden setting, IPT effectiveness is compromised but it may not be in medium or lower burden setting. A recent study among immunosuppressed individuals found that IPT is significantly effective in reducing risk of TB transmission in a medium-burden setting, contrasting result with the gold miners study (Golub et al., 2015).

Our projection where IPT was prescribed for longer than six months showed that the prevalence of active TB will remain high even after ten years of implementation. In high-prevalence settings, reinfection compromises the long-term benefit of IPT regardless of its efficacy (E. Nardell & Churchyard, 2011). However, when overcrowding was reduced

from 6 to 4 inmates per cell and air ventilation is improved from 2 to 12 ACH, the reinfection rate was reduced and our model suggests that IPT showed improved effectiveness by decreasing the active TB prevalence gradually over time (Strategy 3B).

In the setting of overcrowding and poor ventilation where the burden of disease is high, our model suggests the most effective intervention to reduce the prevalence of active TB over a ten-year period is providing ATBT. The second most effective intervention was the combined treatment strategy. The ATBT eliminate any risk of TB infectivity in the prison by treating every infectious inmate in the prison. Therefore, regardless of the environmental condition in the prison, our model suggests implementing ATBT intervention has the greatest impact in controlling TB transmission. Reducing TB transmission by active case finding and prompt institution of ATBT is therefore an urgent priority not only for the individuals infected but in ensuring that onward transmission is reduced in a high-burden confined setting.

5.4 Limitation of Study

Our model has been useful in projecting the burden of disease based on different interventions that can be employed however it has several limitations. We used a dynamic transmission model in projecting the impact of TB control strategies over time which assumed homogenous mixing, active TB screening upon entry to prison, all inmates received treatment based on TB status (infectious and latently infected) and 100 per cent compliance to treatment. Thus, our results are interpreted based on the underlying model assumptions. The airborne transmission model used in the model was based on the even distribution of infectious particles in a room and does not account for how the probability of infection is modified by complexities such as the distance between individual patients. Our study depended on data from a single prison in Malaysia and thus may not be fully representative nationwide. Nevertheless, the Kajang prison setting which is overcrowded

and poorly ventilated is a common setting for a prison, and therefore this model may be applicable to other prisons in Malaysia with similar structural challenges where tuberculosis transmission is prevalent.

Our study looked at TB control measures based on treatment of active and latent infection strategies, we did not simulate the effect of delays in initiating treatment, screening and diagnostic for TB (Legrand et al., 2008b). Given the low prevalence of drug-resistance reported to date in the country (<1%), we did not take into consideration the effect of drug-resistance and drug-sensitive strains in the model (Ministry of Health, 2012). We also did not take into account the adverse events related to IPT in the model based on published systematic review which found that isoniazid-induced hepatotoxicity among high risk groups were insignificant (Bliven & Podewils, 2009). In comparison to the many prisons worldwide, the HIV seroprevalence in our study population is relatively low (3%) (Al-Darraji et al., 2014; Chaves et al., 1997). Therefore we did not consider the effect of HIV infection on TB.

The parameter estimates for natural progression of TB disease used to inform the model relied on available published studies from other countries due to the lack of local parameter estimates. The available published studies were mainly modelling studies from developed countries such as Western Europe and United Kingdom. This may have underestimated the result of the modelling because the parameter estimates from these studies may be lower to inform our model that focus on higher risk population. Due to the unavailability of data in Kajang prison, we were unable to validate our simulation against multiple real data. Due to the lack of available time series data which we can use to validate the model simulation, this focus of this study is not on quantitative (absolute) prevalence levels, but rather on making comparisons of the prevalence across the various interventions and the no intervention scenario. However, our findings were consistent with previous studies (empirical and mathematical) done in a high-burden setting

(Charalambous et al., 2008; Churchyard et al., 2014; Cohen & Murray, 2005; Verver et al., 2005; Viljoen et al., 2012; E. Vynnycky & Fine, 1997). Thus, our findings should be viewed as a starting point for further research, rather than as mathematical proof of any particular idea discussed here. Although these limitations suggest the need for further investigations, our current projections highlighted the need for immediate action in addressing TB transmission in our local prisons. The burden of TB in prison is critical and without any interventions, will continue to remain very high and contribute to the general population TB burden.

CHAPTER 6 : CONCLUSION

6.1 Introduction

In this final chapter, key findings from the research have been summarized and implication of study for recommendations in prison setting. The chapter ends with suggestions for future research.

6.2 Summary of key findings

Our model has investigated the impact of treatment and environmental control strategies that have been previously outlined in WHO and other guidelines. The epidemiological model has demonstrated that ATBT is the most effective intervention in mitigating TB transmission in a highly endemic and overcrowded prison. However, our results are interpreted based on our model assumptions that if active intensified case approach is implemented and every active TB case received and completed treatment in the prison. Our model found that mitigating TB with only IPT intervention in a highly endemic and overcrowded prison is less effective due to reinfection from untreated infectious TB compared to those who completed preventive therapy, irrespective of the duration of therapy. However, in the absence of treatment for infectious TB, our model suggests improving the environmental conditions such as reducing overcrowding and improved air ventilation in the prison would reduce the reinfection effect and therefore increase the effectiveness of IPT in controlling TB transmission in the prison.

6.3 Implications of study

The study has important implication for TB control in prison settings. We demonstrated that important steps could be taken to significantly reduce the burden of TB in prisons by the provision of anti-TB treatment and ensuring adherence. This should be feasible given that these individuals are confined within the prison, which reduces the

probability of non-adherence. Nevertheless, many prisons – particularly in low and middle income settings lack medical services, which means that inmates have poor access to even basic medical care. Our simulation results suggest that policymakers should improve access to medical care in prisons to ensure adequate treatment for those infected with TB. They should also improve the environmental conditions within these closed settings. Such measures will not only lead to better health for the inmates, but may also play an important role in controlling the burden of TB within prisons and, ultimately, the general population

6.4 Recommendations for future studies and research

The present study only considered the impact of treatment and environmental control strategies. Future studies could compare other screening and diagnostic strategies such as X-Ray and GeneXpert to explore its impact in reducing TB transmission in highly overcrowded prisons. Future studies could also consider a model with disaggregation of inmate population by HIV status to investigate the impact of ART treatment combined with ATBT and preventive therapy in particular among HIV infected but non-infectious TB.

Finally, much focus of the current study is transmission of the disease in closed setting. However, as previous literature have suggested, TB cases occurring in close setting is attributing to the increase in TB cases at the population level. Therefore, future research efforts should focus on exploring risk factors contributing to transmission of TB among post release inmates to the population and the effective interventions to mitigate further transmission of TB.

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LIST OF PUBLICATIONS AND PRESENTATIONS

Publication

1. Naning, H., Al-Darraji H., McDonald, S., Ismail, N.A., Kamarulzaman, A. (2015). Modeling the impact of different TB control interventions on the prevalence of TB in an overcrowded prison. Submitted to PLOS ONE for publication

Presentation

1. Naning, H., Al-Darraji H., Ismail, N.A., Kamarulzaman, A. (2014). Safety of Isoniazid Preventive Therapy Among People Co-infected with Hepatitis C – A Systematic Review. Poster presentation at the National Tuberculosis and Lung Diseases 2014 Conference, Kuala Lumpur Malaysia. [P14]

2. Naning, H., Al-Darraji H., Ismail, N.A., Kamarulzaman, A. (2015). Modeling the Impact of Tuberculosis Control in High-Burden Prison Setting. Poster presentation at the International Harm Reduction 2015 Conference, Kuala Lumpur, Malaysia. [67]