

**MATHEMATICAL MODELLING OF TUBERCULOSIS
TRANSMISSION AND IMPACT OF ISONIAZID
PREVENTIVE THERAPY IN MALAYSIA**

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**THESIS SUBMITTED IN PARTIAL FULFILMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PUBLIC HEALTH**

**FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR**

2017

UNIVERSITI MALAYA

ORIGINAL LITERARY WORK DECLARATION

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Name of Degree: **Doctor of Public Health (DrPH)**

Title of Thesis (“this Work”): **Mathematical modelling of tuberculosis transmission and impact of Isoniazid Preventive Therapy in Malaysia**

Field of Study: **Medicine**

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ABSTRACT

Background: Tuberculosis remains one of the highest unresolved disease burden among re-emerging diseases in Malaysia for the last thirty years. The current treatment protocol guideline emphasizes treatment for only infectious tuberculosis patients. This study aimed to investigate tuberculosis transmission dynamics exclusive to the Malaysian environment and characteristics. This study applied the infectious disease modelling techniques to study the progression of latent tuberculosis infection and assess the likely impact of Isoniazid Preventive Therapy for latent tuberculosis high risk subpopulations in reducing tuberculosis incidence in Malaysia. **Methods:** This study explored the epidemiology of tuberculosis in Malaysia to develop a deterministic compartmental age-structured tuberculosis model which incorporated treatment for infectious as well as early preventive therapy for latent. The model assumed latently infected individuals develop infectious state of tuberculosis as a result of primary infection, endogenous reactivation and exogenous reinfection. This study assessed the likely impact of interventions in Malaysia by formulating and analysing the model under various scenarios. These included no intervention strategy then, extended to incorporate the Isoniazid Preventive Therapy only, treatment of infectious tuberculosis only and combination treatment of infectious tuberculosis and Isoniazid Preventive Therapy. The equilibrium of the model was determined, and stabilities were analysed. The model fitting and validation were performed. The national tuberculosis incidence was estimated and projected from 1990 till 2050. The effective reproduction numbers for the model were compared to assess the possible population benefits achieved by no intervention, treatment of infectious tuberculosis only, Isoniazid Preventive Therapy only and a combination treatment of infectious tuberculosis and Isoniazid Preventive Therapy for the latents. The model further determined the effectiveness of Isoniazid Preventive Therapy for early latent tuberculosis infection and quantified coverage of the

strategy to eliminate tuberculosis, when used in conjunction with treatment of infectious tuberculosis. The model then compared the selection of early latent tuberculosis infection versus late latent tuberculosis infection to effectively reduce the incidence of tuberculosis in Malaysia. **Results:** A transmission dynamic mathematical model of tuberculosis exclusive to Malaysian environment and characteristics was developed. The model projected a higher and increasing trend of national tuberculosis incidence till year 2030 at annual increment rates from 1% to 5.5%. Application of this model showed that combination treatment strategy of Isoniazid Preventive Therapy for early high risk latent tuberculosis sub-populations with current treatment for infectious tuberculosis is the most effective strategy for controlling tuberculosis epidemic in Malaysia. However, a minimal ten percent coverage of Isoniazid Preventive Therapy in population is required for effective reduction following eight to ten years of successful implementation with expected cumulative incidence reduction of 27.21% by 2050. **Conclusion:** Isoniazid Preventive Therapy may have substantial effect on controlling tuberculosis epidemic in Malaysia when used in conjunction with current treatment regime for infectious tuberculosis. However, a minimal ten percent coverage among the early latent tuberculosis infection sub-populations must be ensured to achieve effective reduction in incidence. This can be achieved by expansion of coverage to other high risk latent tuberculosis sub-populations such as healthcare workers, close contacts and in institutionalized settings, with comprehensive protocol and surveillance.

ABSTRAK

Latar Belakang: Penyakit tibi kekal sebagai salah satu beban penyakit tidak dapat diselesaikan yang tertinggi di kalangan penyakit ‘re-emerging’ di Malaysia sejak tiga puluh tahun yang lalu. Garis panduan protokol rawatan terkini hanya menekankan rawatan untuk pesakit tibi berjangkit. Kajian ini bertujuan untuk menyiasat transmisi dinamik tibi eksklusif kepada ciri-ciri persekitaran Malaysia. Kajian ini mengguna pakai teknik pemodelan penyakit berjangkit untuk mengkaji perkembangan jangkitan tibi terpendam dan menilai kesan yang mungkin terhadap “Isoniazid Preventive Therapy” untuk sub-populasi berisiko tinggi tibi terpendam dalam mengurangkan insiden penyakit tibi di Malaysia. **Kaedah:** Kajian ini meneroka epidemiologi penyakit tibi di Malaysia untuk membangunkan model khusus penyakit tibi yang berstruktur umur berketentuan yang menggabungkan rawatan untuk berjangkit serta terapi pencegahan awal untuk laten. Model ini menganggap bahawa individu laten dijangkiti disebabkan jangkitan tibi akibat jangkitan utama, pengaktifan semula dalaman dan jangkitan semula luaran. Kajian ini dinilai kesan kemungkinan penggunaan di Malaysia dengan merumuskan dan menganalisis model di bawah pelbagai senario. Ini termasuk ada strategi campuran untuk menggabungkan Isoniazid Preventive Therapy sahaja, rawatan tibi berjangkit sahaja dan rawatan kombinasi tibi berjangkit dan Isoniazid Preventive Therapy. Keseimbangan model telah ditentukan, dan stabiliti telah dianalisa. Pemasangan model dan pengesahan telah dilakukan. Insiden tibi kebangsaan dianggarkan dan diunjurkan dari 1990 hingga 2050. nombor pembiakan berkesan bagi model yang dibandingkan dengan menilai manfaat penduduk mungkin dicapai dengan tidak campur tangan, rawatan penyakit tibi berjangkit sahaja, Isoniazid Preventive Therapy sahaja dan rawatan kombinasi penyakit tibi berjangkit dan Isoniazid Preventive Therapy untuk terpendam. Model itu juga telah dipilih mengikut keberkesanan Isoniazid Preventive Therapy untuk jangkitan awal penyakit tibi terpendam dan kuantitinya

liputan daripada strategi untuk menghapuskan tibi apabila digunakan bersama dengan rawatan batuk kering berjangkit. Model ini kemudiannya dibandingkan antara pemilihan awal jangkitan penyakit tibi terpendam berbanding lewat jangkitan penyakit tibi terpendam untuk mengurangkan insiden penyakit tibi di Malaysia dengan berkesan.

Keputusan: Satu model matematik dinamik penyakit tibi eksklusif kepada persekitaran Malaysia telah dibangunkan. Model mengunjurkan trend yang lebih tinggi dan peningkatan insiden penyakit tibi negara sehingga tahun 2030 pada kadar kenaikan kes tahunan antara 1% hingga 5.5%. Penggunaan model ini menunjukkan bahawa strategi rawatan kombinasi Isoniazid Preventive Therapy untuk risiko awal tinggi penyakit tibi terpendam sub-populasi dengan rawatan semasa bagi penyakit tibi berjangkit adalah strategi yang paling berkesan untuk mengawal wabak penyakit tibi di Malaysia. Walau bagaimanapun, yang minimum liputan sepuluh peratus daripada Isoniazid Preventive Therapy penduduk diperlukan untuk pengurangan terkesan berikutan lapan hingga sepuluh tahun pelaksanaannya berjaya dengan pengurangan insiden terkumpul diharapkan daripada 27.21% pada tahun 2050. **Kesimpulan:** Isoniazid Preventive Therapy mungkin mempunyai kesan yang ketara kepada mengawal wabak penyakit tibi di Malaysia apabila digunakan bersama-sama dengan rejim rawatan semasa tibi berjangkit. Walau bagaimanapun, liputan sepuluh peratus di antara segelintir awal jangkitan penyakit tibi terpendam sub-populasi mesti memastikan untuk mencapai pengurangan berkesan dalam insiden. Ini boleh dicapai dengan perluasan liputan yang lain yang berisiko tinggi penyakit tibi terpendam sub-populasi seperti pekerja penjagaan kesihatan, kontak dan dalam tetapan institusi, dengan protokol komprehensif dan pengawasan untuk kawalselia.

ACKNOWLEDGEMENT

My deepest gratitude and appreciation to my supervisors, Associate Professor Dr Sanjay Rampal a/l Lekhraj Rampal and Professor Dr Awang Bulgiba Awang Mahmud whose guidance, commitment, stimulating discussions and suggestions with untiring encouragement that has inspired me all the time right from the conceptual phase till the writing of this thesis. They are my role models, inspire many new perspectives I never knew existed before in their own unique ways, and provide me with opportunities that will benefit me long after the completion of this thesis.

My expression of gratitude to my field supervisors, Professor Dr Nicolaas Jan De Nagelkerke from Institute of Public Health, United Arab Emirates University, Dr. Karina Razali from HART Consultancy and Mr Md. Omar Awang from Institute of Mathematical Sciences, Universiti Malaya and all panel of experts and supporting staff from the Malaysian Ministry of Health especially from the Director General of Health, the Department of Public Health and the Disease Control Division, who have supported and always been enthusiastic with the progress of this research outputs. I have furthermore to thank all my superiors, colleagues and administrative staff at Universiti Teknologi MARA for the support, sponsorship and training I received, who gave me all the possibilities to complete this thesis.

Finally, my heartfelt thanks to all lecturers, supporting staff and fellow students and friends at the SPM Department, Faculty of Medicine, University of Malaya for the untiring assistance and friendship, for going through the journey with me throughout the preparation and execution of this research.

Thank you.

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LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
BCG	Bacillus Calmette-Guérin
CDC	Centre for Disease Control
CDR	Case detection rate
CPG	Clinical Practice Guideline
DOTS	Directly Observed Therapy - Short Course
HIV	Human Immunodeficiency Virus
HUSM	'Hospital Universiti Sains Malaysia'
IPR	National Institute of Respiratory Medicine
IPT	Isoniazid Preventive Therapy
LTBI	Latent Tuberculosis Infection
MDG	Millennium Development Goals
MOHE	Ministry of Higher Education
NIH	National Institute of Health
NMRR	National Medical Research Register
NPHL	National Public Health Laboratory
NRIC	National Registration Identification Card
PLWHA	People Living with HIV/AIDS
PTB	Pulmonary tuberculosis
SPM	Social and Preventive Medicine
STD	Sexually Transmitted Diseases
TB	Tuberculosis
TBIS	Tuberculosis Information System
UN	United Nation
WHA	World Health Assembly
WHO	World Health Organization
WPR	Western Pacific Region

LIST OF APPENDICES

- Appendix A: Research ethics approval from University of Malaya
- Appendix B: Research ethics approval from National Medical Research Register (NMRR), Ministry of Health
- Appendix C: A sample of invitation letter for tuberculosis modelling meeting by Ministry of Health

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1.1 Overview of thesis and study project in brief

This thesis presents the research work on the infectious disease mathematical modelling of tuberculosis in Malaysia. The study consists of three main components that made up its objectives. Firstly, it used mathematical modelling techniques to develop a transmission dynamic deterministic compartmental model for tuberculosis that best fitted the Malaysian characteristics and environment. Secondly, the model developed was then used as a modelling tool to assess the potential impact of early preventive therapy to reduce tuberculosis incidence in Malaysia. Thirdly, the study findings were then used for formulating a policy recommendation that can be implemented and integrated in the current national tuberculosis control programme to effectively reduce tuberculosis incidence in Malaysia.

This study was conceptualized during the national collaborative meeting between University of Malaya, Ministry of Health, Malaysia and the World Health Organization of Western Pacific Region Office (WHO-WPRO) in August 2008. The meeting was organized by the Ministry of Health, Malaysia to discuss on possible new approaches to combat tuberculosis in Malaysia. Since the research project was discontinued by the Ministry of Health later, the possibility of applying the mathematical modelling technique to study the management of tuberculosis infection in Malaysia was then explored by the faculty. The research question that was raised, the objectives determined and the methods selected, and most importantly the contributions and implications of this research were feasible and sound. It fulfilled the urgent needs to

combat tuberculosis epidemic in Malaysia and work towards achieving the 6th Millennium Development Goals. That was the initiation point for the research work.

1.2 Problem statement and research gap

Despite being an avoidable and treatable disease with effective antimicrobial chemotherapy, the incidence of tuberculosis remains high in Malaysia for the last thirty years (Ministry of Health, 2016b). Tuberculosis is also as the highest as well as the leading cause of death from all infectious diseases in Malaysia (Ministry of Health, 2016a). More alarmingly, among the seven countries in the Western Pacific Region with intermediate tuberculosis burden, Malaysia has the highest incidence, prevalence and mortality associated with tuberculosis (Hiatt & Nishikiori, 2016; Region, 2008; WPRO, 2008). Why does the burden of tuberculosis infection remain high for that long in Malaysia?

Since the Millennium Development Goals (MDG) era, Malaysia failed to achieve the targets set to reverse the trend of tuberculosis epidemic (MDG 6) till now that Malaysia has persistent high incidence, prevalence and mortality associated with tuberculosis (Economic Planning Unit Prime Minister's Department Malaysia, 2006; United Nations & EPU, 2016). This is in spite of the tuberculosis national key indicators i.e. high cure rate of tuberculosis, the high DOTS (Directly Observed Therapy - Short Course) coverage, the high BCG (*Bacillus Calmette-Guérin*) vaccination coverage and very low multidrug resistance cases of tuberculosis reported by the national tuberculosis managers (Ministry of Health, 2016a). This triggers an urgent need for new approaches

to treat and prevent and curb the plateau trend, therefore effectively reducing the tuberculosis incidence in Malaysia.

One of the strategies yet to be explored by Malaysia is the additional treatment of tuberculosis chemoprophylaxis famously known as “Isoniazid Preventive Therapy (IPT)” for latent tuberculosis in conjunction with the current treatment protocol for infectious tuberculosis as per Malaysian Clinical Practice Guideline (CPG). Available evidence favouring success shows that this could be a promising answer for Malaysia (Smieja, Marchetti, Cook, & Smaill, 1999; Woldehanna S., 2004). But is this combination therapy of chemoprophylaxis and therapeutics more effective in reducing tuberculosis burden in Malaysia? Is it applicable in Malaysian setting?

To answer these questions, empirical evidence are required to prove if such strategy is a viable option in Malaysia. This research was designed to provide this empirical evidence if the tuberculosis incidence in Malaysia can be effectively reduced by deploying Isoniazid Preventive Therapy to treat the high risk latent tuberculosis sub-populations in conjunction with the current standard treatment regime for infectious tuberculosis in Malaysia. To address this, the research team used the dynamic mathematical modelling technique. The mathematical model developed was then used as a tool for policy makers and programme managers to assess its potential impact. The study findings were subsequently translated and formulated into public health policy recommendation to effectively reverse the tuberculosis epidemic trend in Malaysia.

1.3 Conceptual framework

This study project was designed to develop a mathematical model of tuberculosis transmission dynamic for Malaysia, as well as to assess the potential impact of a proposed chemoprophylactic intervention i.e. Isoniazid Preventive Therapy among latently infected high risk sub-populations in Malaysia. In this framework the Malaysian tuberculosis transmission dynamics at population level were reviewed, as well as the intervention strategies currently existed and that could be implemented to effectively disrupt the transmission cycle.

The conceptual framework of this study is illustrated in Figure 1.1. The transmission of tuberculosis takes place between an infectious tuberculosis patient and the susceptible healthy population i.e. the non-infected persons. All countries worldwide adhere to the intervention strategies at this point which mainly are early diagnosis and treatment with current tuberculosis treatment regime. However, owing to effective transmission, a proportion of susceptible population progresses into infected tuberculosis state following contact with infectious tuberculosis patients termed as latent tuberculosis (LTBI). Some of these latent tuberculosis patients carry higher risk than others and progress further into infectious state, also termed as disease state or cases. These latent tuberculosis populations are the potential source of infection to the susceptible healthy population.

The research focused on the argument that the strategies for disruption of tuberculosis transmission should not only be directed at infectious tuberculosis population but also included the high risk latent tuberculosis in the population as well. Only by adopting a combined strategy i.e. the strategy of disrupting the transmission at infectious state and

infected state (latent) of the disease, the controlling of tuberculosis can be achieved resulting in lower incidence in Malaysian setting.

Therefore, this research attempted to explore the role and possibility of deploying early preventive therapy for high risk latent tuberculosis into current tuberculosis management protocol also known as the Malaysian Clinical Practice Guideline for Tuberculosis Management to help curb this longstanding epidemic.

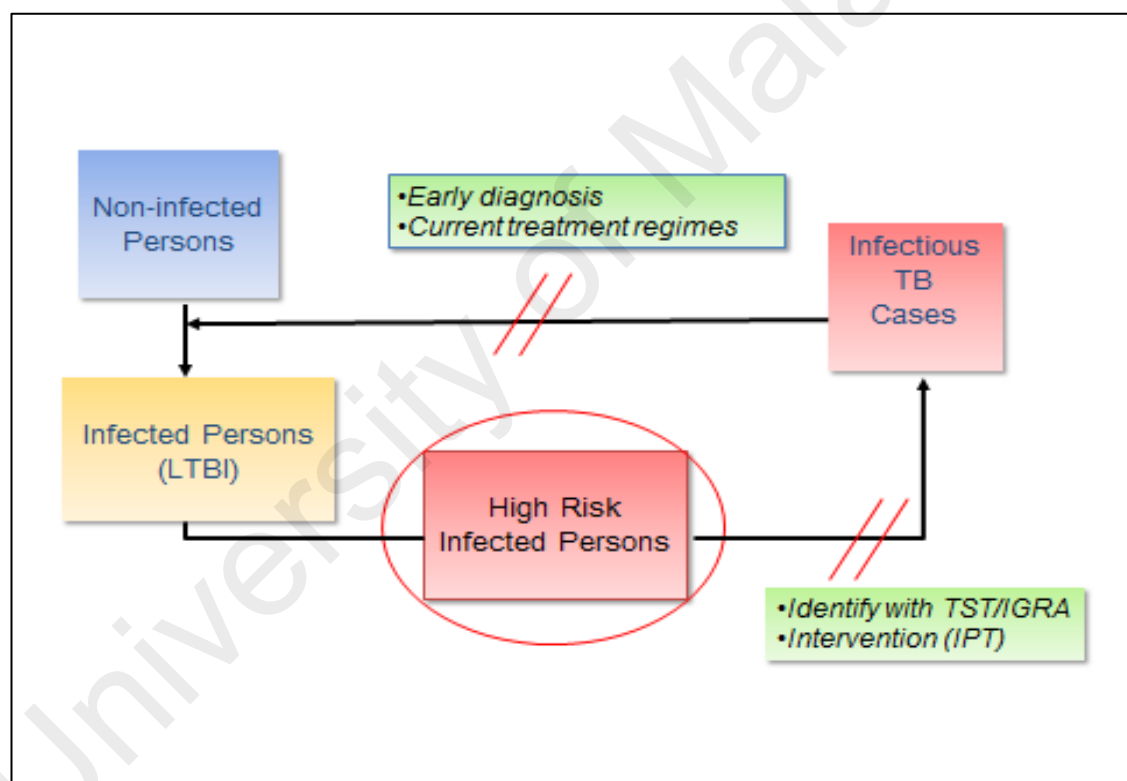


Figure 1.1: Tuberculosis transmission dynamic and intervention strategies (in green) available globally. The disruption of transmission or intervention strategies exist marked as “//” in red.

1.4 Research question and hypothesis

The research question addressed in this research was:

“Is the combination treatment of Isoniazid Preventive Therapy and therapeutics more effective in reducing tuberculosis burden in Malaysia?”

The research hypothesized that the combination treatment strategies of Isoniazid Preventive Therapy for latent tuberculosis and current treatment for infectious tuberculosis is more effective to reduce the tuberculosis incidence in Malaysia.

1.5 Objectives of study

1.5.1 General objective

To use mathematical modelling of tuberculosis epidemiology in Malaysia to develop a tuberculosis transmission dynamic mathematical model and assess the likely impact of early intervention among high risk latent subpopulations in reducing tuberculosis incidence.

1.5.2 Specific objectives

1. To develop a tuberculosis transmission dynamic mathematical model exclusive to Malaysian environment and characteristics

2. To apply mathematical modelling technique for potential impact assessment of various strategies (four scenarios i.e. no intervention, Isoniazid Preventive Therapy only, current strategy only and combination therapy of Isoniazid Preventive Therapy and current strategy) to reduce tuberculosis incidence in Malaysia
3. To formulate a policy recommendation on the potential intervention strategy to effectively reduce tuberculosis incidence in Malaysia

1.6 Structure of thesis

This thesis is divided into seven chapters.

Chapter 1 is the introductory chapter that summarised the work contributed by the research team and presented in this thesis. It also outlined the chapters included in this thesis. The background of this research and justifications for the research work were also explained. The research question and options for answering these questions were also included. Subsequently the objectives of the study were outlined.

Chapter 2 details the literature review of all aspects related to this research work. It is divided into three main sections. The first section summarised the situation of tuberculosis and its responses globally, regionally and at national level in Malaysia. Second section discussed the option of Isoniazid Preventive Therapy whereby all evidence-based articles that adopted the conventional epidemiological methods are appraised. Subsequently, the third section covers the theoretical aspects of mathematical modelling and appraisal of similar research work done using the infectious disease mathematical modelling approach.

Chapter 3 is the chapter on methodology that detailed the activities done to achieve the research objectives. Brief descriptions on options of methods used as well as problems encountered and solutions offered were also explained in this chapter.

Chapter 4 presents the comprehensive results according to the objectives. It started with description in great detail of the Malaysian tuberculosis model developed in this research. Later, it discussed the simulation work done to assess the impact of Isoniazid as early intervention into current scenario. Simulations on three other interventional strategies were also performed, compared and analysed. Further work demonstrating the effective coverage of the recommended strategy and justifications between groups within the latent groups were also performed.

Chapter 5 is the discussion chapter that highlighted the study findings and compared these findings to other similar work done in other settings or countries. The strength and limitations of study were also discussed in addition to the applicability of approach and techniques used in this research and the future works need to be done.

Chapter 6 presents the formulation of study findings as a policy recommendation to recommend Isoniazid Preventive Therapy in Malaysia. It discussed the option of continuing the current strategy versus the new strategy and how these will be manifested in the tuberculosis disease burden in Malaysia.

Chapter 7 is the concluding chapter that emphasized the study strength, limitation, thesis contribution and public health implications. It rounds up the thesis by providing a thesis conclusion statement.

1.7 Summary of Chapter 1

This thesis represents one of the few attempts to use the integrated field of infectious disease mathematical modelling within the field of preventive medicine to better manage the issue of infectious disease in public health and policy. It questioned if Isoniazid Preventive Therapy for latent tuberculosis infection is an effective measure that may substantially reduce the persistent high tuberculosis incidence in Malaysia. It hypothesized that Isoniazid Preventive Therapy is effective only as a combined strategy when used in conjunction with the current treatment for infectious tuberculosis. The following Chapter 2 covers all literature review related to this study.

CHAPTER 2: LITERATURE REVIEW

2.1 Tuberculosis epidemiology and control

2.1.1 Tuberculosis situation in Malaysia and Western Pacific Region

Ever since World Health Organization declared tuberculosis as a global emergency in 1993 (WHO, 1991), the status of the tuberculosis epidemic and progress in control of the disease was assessed by WHO annually since 1997 (WHO, 2000). Tuberculosis was placed by the World Health Organization and United Nation as one of the targets in the Millennium Development Goals 2015 (WHO, 2000); and prompted WHO to develop an internationally comprehensive, systematic and organized surveillance system control programmes for the tuberculosis epidemic (Dye, 1998; Dye, 2006; WHO WPRO, 2008). To date, the elimination of tuberculosis remains as one of the agenda in the new era of Sustainable Development Goals (SDGs) 2030 with an expanded programme of the End Tuberculosis Strategy 2035 (UN, 2015; WHO, 2014a).

As of 2013, the Western Pacific Region accounted for 23% of the global tuberculosis burden; mainly among the high burden countries i.e. China, Philippines and Viet Nam. Almost all countries including Malaysia (except Mongolia) reported a typical pattern with higher trend of new tuberculosis cases than previous years due to increased and improved national data rather than actual increase in the spread of the disease (Hiatt & Nishikiori, 2016). By 2015, significant progress has been made in prevention, diagnosis and treatment that the MDG target to halt and reverse tuberculosis incidence has been achieved globally. Tuberculosis incidence fell by an average 1.5% per year since 2000

globally with an estimated 43 million lives averted between year 2000 and 2014 (WHO, 2015a).

Similarly, as shown in Figure 2.1 below, Malaysia as an intermediate burden country in the Western Pacific Region observed the typical but sharp rise in trend of tuberculosis incidence from 2010 till the time of this study at an average rate between 1.10% to 6.06% per year. Even before that, between 1980 and 2010 the tuberculosis incidence trend had been persistently high and plateau with minimal fluctuation rate between - 3.32% to 4.86% per year (WPRO, 2008; Ministry of Health, 2016b). Nonetheless, among the intermediate burden countries i.e. Brunei Darussalam, Japan, Malaysia, the Republic of Korea, and Singapore - the incidence and mortality had been persistently highest in Malaysia for the last ten years as illustrated in Figure 2.2a and Figure 2.2b below. In addition, high foreign labour and higher mobilisation rates associated with robust economic growth due to the free trade and visa movement within neighbouring ASEAN countries since 2006 may have contributed to this sharp rise, whereby almost all ASEAN countries are categorised with high tuberculosis burden except Singapore and Brunei as shown in Table 2.1 (ASEAN, 2016).

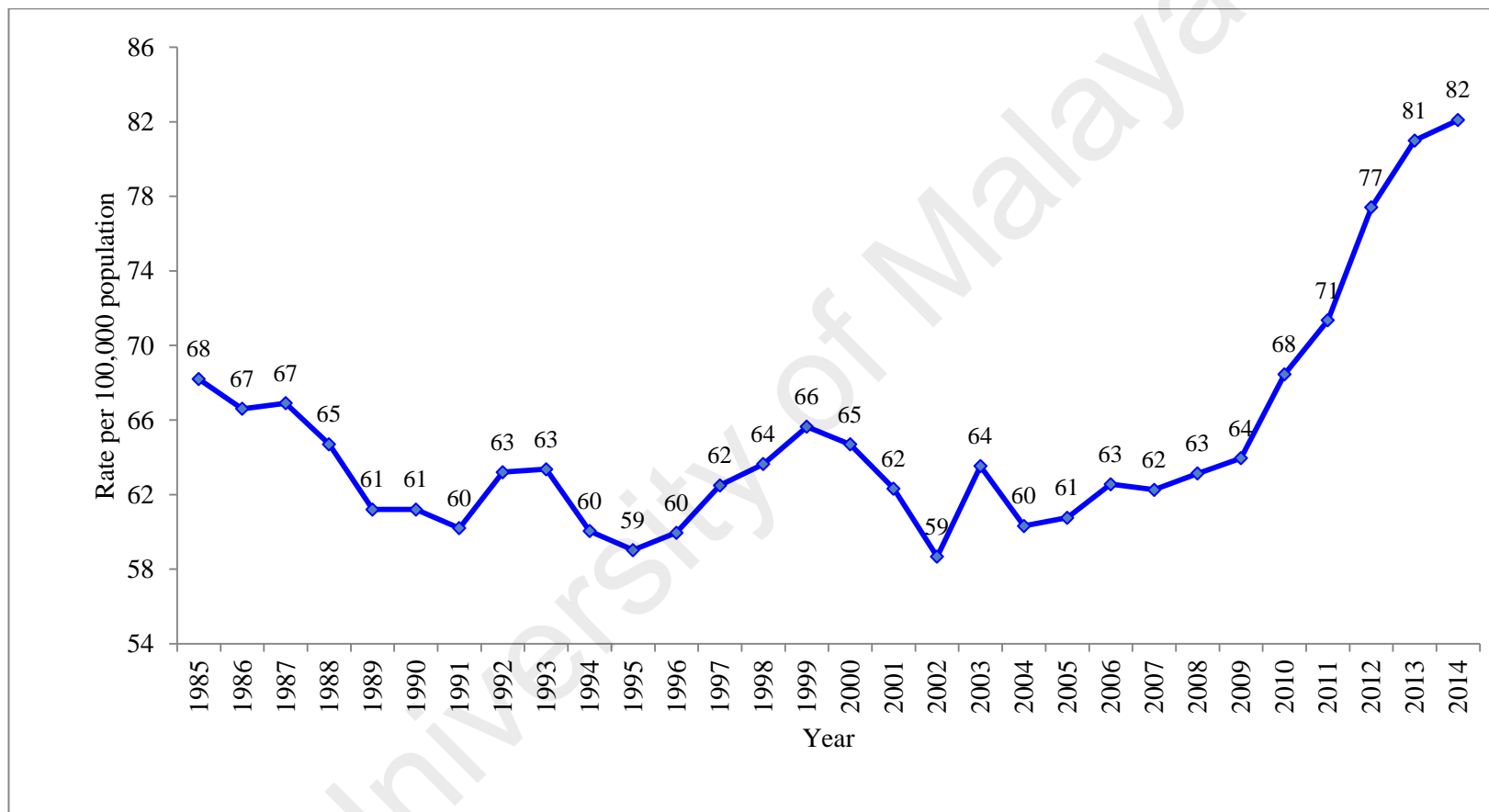


Figure 2.1: Notification rate (incidence estimates) of tuberculosis in Malaysia, 1985-2014
(WPRO, 2008; Ministry of Health, 2016b)

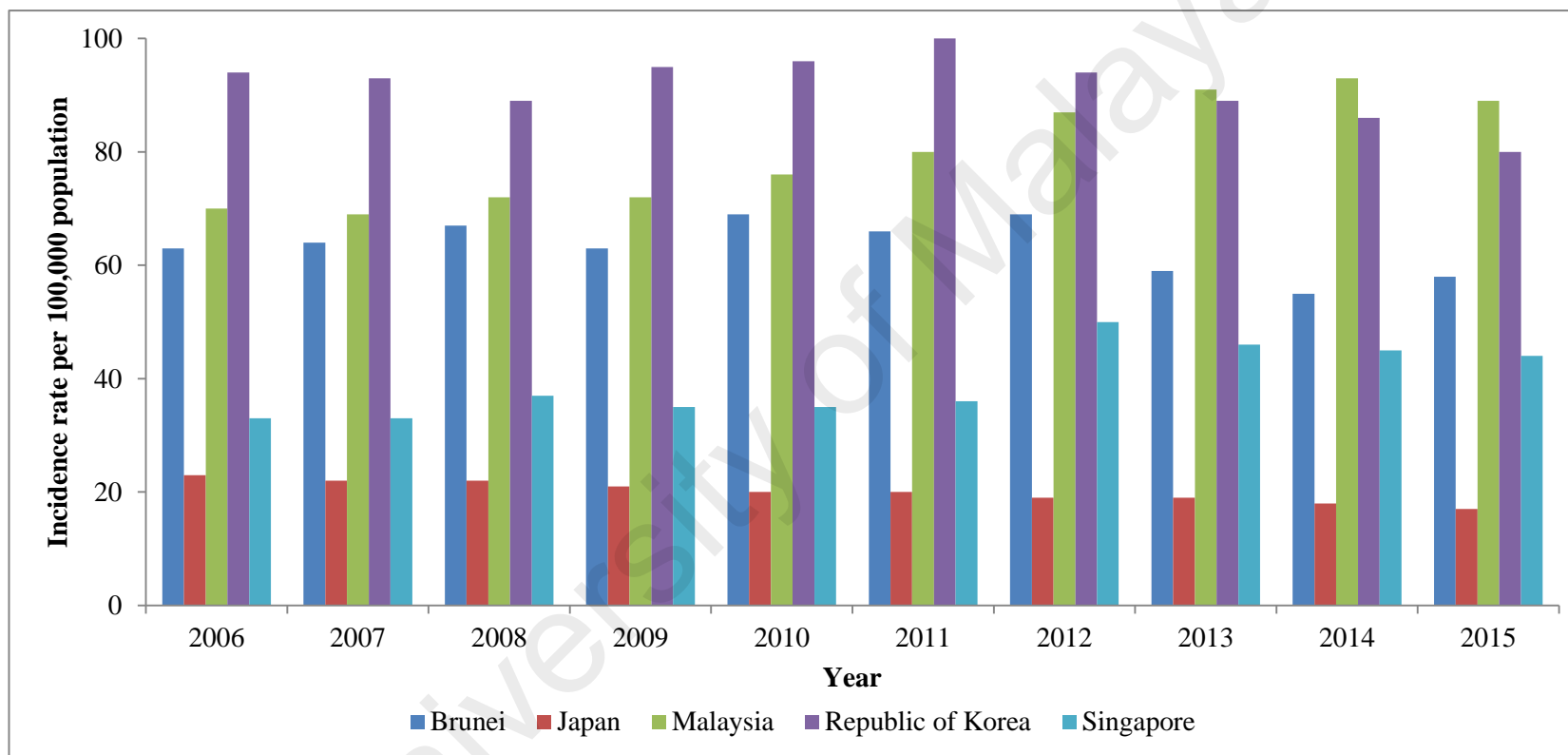


Figure 2.2a: Tuberculosis incidence trend in intermediate burden countries of the Western Pacific Region (WHO, 2016)

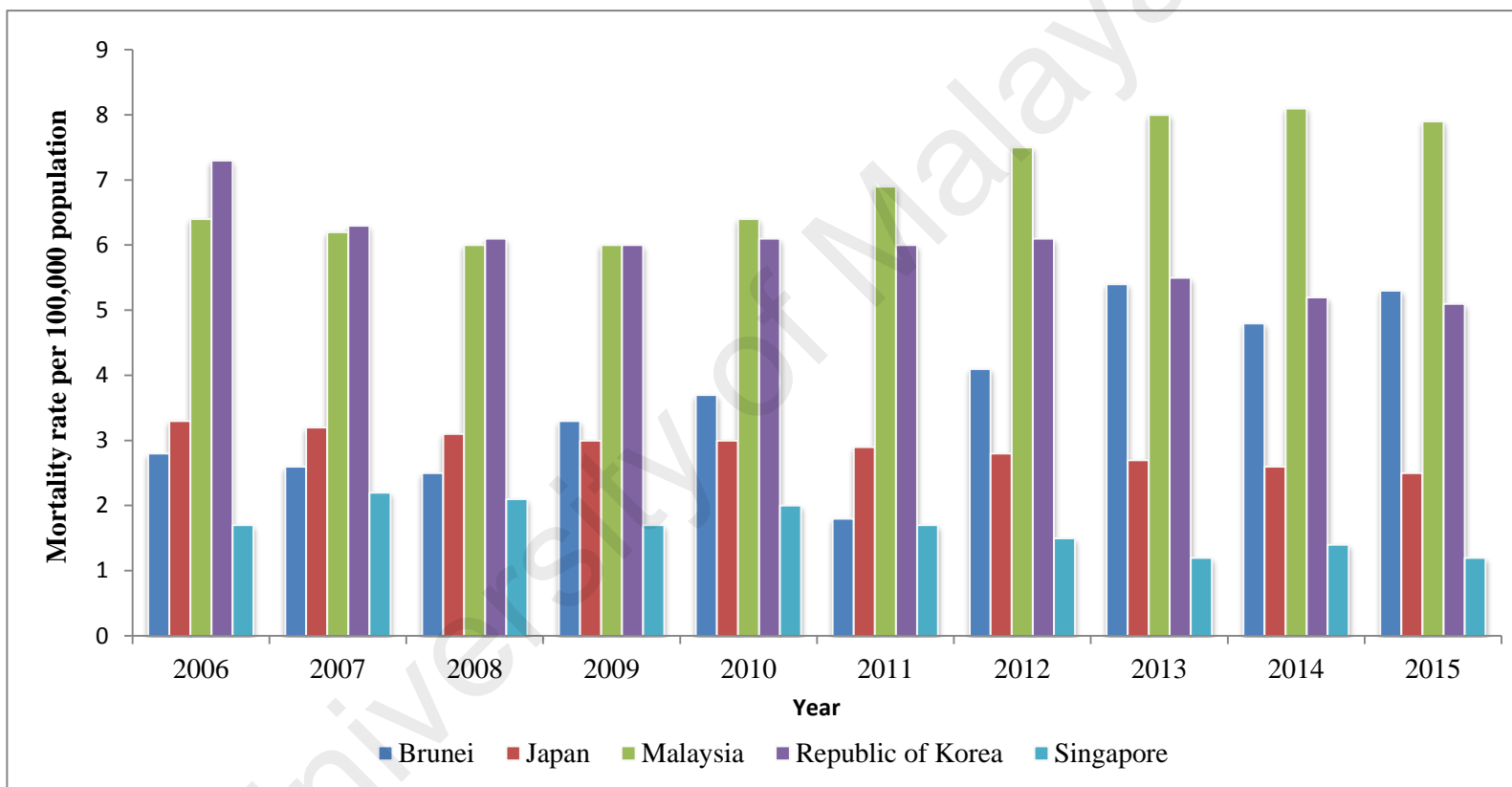


Figure 2.2b: Tuberculosis mortality trend in intermediate burden countries of the Western Pacific Region (WHO, 2016)

**Table 2.1: Estimated incidence & prevalence of tuberculosis in 2014 among Malaysian neighbours and ASEAN countries
(rates per 100,000 populations) (WHO, 2015a)**

Countries	Population (thousands)	Prevalence	Incidence
Thailand	67,726	236	171
Vietnam	92,423	198	140
Indonesia	254,455	647	399
India	1,295,292	195	167
Myanmar	53,437	457	369
Bangladesh	159,078	404	227
Philippines	99,139	417	288

Table 2.2: Top five communicable diseases in Malaysia in 2013 & 2014 (Ministry of Health, 2014; 2015a)

Disease	2014		2013	
	Incidence (per 100,000)	Mortality (per 100,000)	Incidence (per 100,000)	Mortality (per 100,000)
Dengue Fever	357.49	0.00	143.27	0.00
Dengue Haemorrhagic	3.66	0.71	2.60	0.31
Tuberculosis	82.1	5.33	78.28	5.37
Hand, Food & Mouth	104.07	0.00	78.52	0.00
Food Poisoning	58.65	0.01	47.79	0.04

Within the Malaysian context, among thirty notifiable communicable diseases in the country, tuberculosis remained in the top five with the highest incidence and the highest mortality for the last fifteen years, whereby an average of 66 new reported cases daily, as shown in Table 2.2.

Apart from that, tuberculosis cases in Malaysia are predominantly the pulmonary and infectious type (80-85%) rather than the extrapulmonary. Tuberculosis-HIV co-infection has been low; accounting for about 11-13% of all tuberculosis cases since the HIV nature in Malaysia is of concentrated type of epidemic. Multidrug resistant tuberculosis cases in Malaysia is also lower as compared to other countries in the region, accounting for 0.3-0.7% of all tuberculosis cases (Tuberculosis and Leprosy Unit Ministry of Health, 2008a; Ministry of Health, 2015b).

2.1.2 Tuberculosis surveillance in Malaysia

Uniform information management and reporting system is one of the key components in implementation of DOTS strategy (Directly Observed Treatment, Short Course). It was recommended by the World Health Organization when the worldwide tuberculosis epidemic was declared in 1990. In response, the Malaysian Health Management Integrated System for Tuberculosis (HMIS-TB) was established in 1993 and commenced since then. However, the registry remained in the chest clinics thus resulted in data incompleteness and inconsistencies. It was later in 2003, the Malaysian National TB Control Programme under the Department of Public Health developed a comprehensive National Tuberculosis Information System (TBIS) manually and adopted across the country. Through this reporting system, TB patients were registered and

monitored until completion of treatment (Tuberculosis and Leprosy Unit Ministry of Health, 2002).

The process of data collection and reporting of TB cases starts from clinic or treatment center to the District Health Office, state level Department of Health and then to the national level at Sector of TB/Leprosy, Disease Control Division. Since 2006, advances in computer technology allow transaction of the manual system to an online system to facilitate and expedite data collection and reporting called MyTB database. Through this system, data collected is easily updated, visualized and accessed in an efficient and portable manner at all state and national levels. In 2012, the online system was upgraded to MyTB version 2.1. MyTB version 2.1 is a comprehensive online data management system incorporating a line listing of individual cases with smooth data integrations from e-notification system to MyTB database. In MyTB version 2.1 the database was expanded to accommodate the detection and monitoring of cases and case holdings under DOTS programmatic monitoring (Jabatan Kesihatan Negeri Sabah Ministry of Health, 2014). These transformation of systems took approximately three years (year 2015) to achieve its completeness and full runway of system (Asmah Razali, 2016).

2.1.3 Tuberculosis intervention programmes in Malaysia

The first prevalence survey conducted in Peninsular Malaya in 1970 revealed an estimated tuberculosis burden of 250 per 100,000 and Malaysia has since acknowledged tuberculosis as one of the biggest threats till today as illustrated in Figure 2.3 (Ministry of Health Malaysia, 1970). The BCG vaccination programme was implemented nationwide since 1960 to combat tuberculosis meningitis which was predominant at that

time, although accessibility was a serious issue due to geographical limitations (Iyawoo, 2004; Norzila Mohamed Zainudin, 2011). Around the same time, anti-tuberculosis agents developed were made available in Malaysia; although sporadically and not without any serious issues on its side effects as well as lacking of surveillance. Only at the turn of 20th century, Malaysia established the systematic management and surveillance system to manage tuberculosis following early models of directly observed therapy – short course (DOTS) which was later expanded in line with development and recommendations by WHO (Dony, Ahmad, & Khen Tiong, 2004).

In view of the tuberculosis burden trends as discussed above, to date, Malaysia remained in the control phase of tuberculosis management aimed at reducing its incidence and mortality by identifying and treating the infectious cases to prevent further spread. Therefore, the measurement of DOTS implementation has so far focused on assessing progress in case detection and treatment success and the therapeutic regime of anti-tuberculosis drugs have been updated on regular basis to date.

Identifying and treating those infected but without clinical manifestation were given less emphasis. Till 1990s, only paediatric population among all high risk latent tuberculosis sub-populations were identified and treated with Isoniazid for early preventive therapy (Norzila Mohamed Zainudin, 2011). In June 2011, the HIV population were recognized as one of the high risk latent tuberculosis sub-populations hence included in the early preventive therapy programme (Ministry of Health Malaysia, 2011). To date, no other high risk latent tuberculosis sub-populations were formally included in the early preventive therapy programme; they were treated only on case to case basis (Ministry of Health Malaysia, 2012).

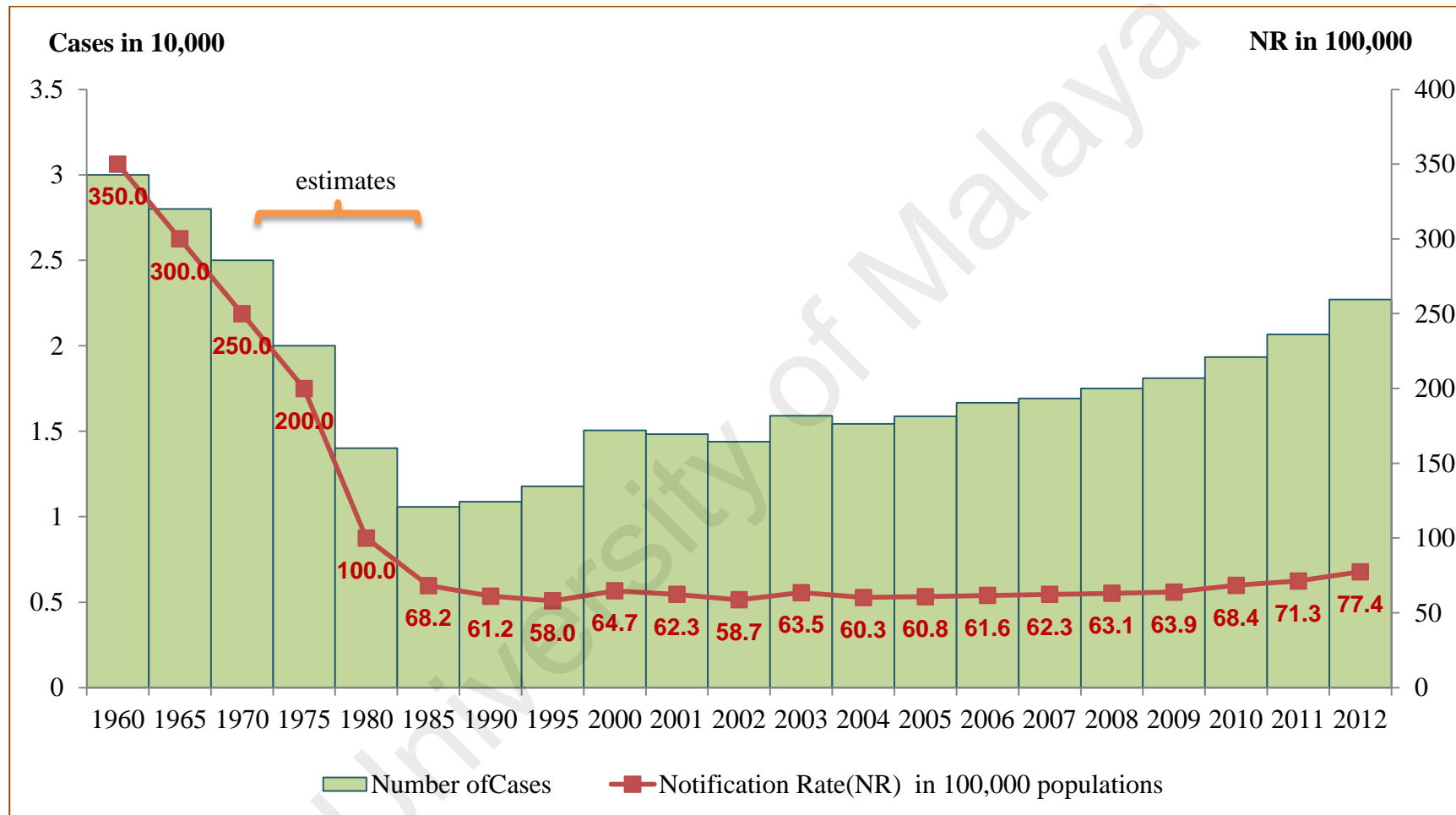


Figure 2.3: Trend of TB notification cases and rates in Malaysia, 1960-2012 (Ministry of Health, 2013)

2.1.4 Latent tuberculosis sub-populations and early preventive therapy

As recommended by the WHO, a combination treatment of chemoprophylaxis i.e. early preventive therapy for the latent cases and therapeutics for the infectious cases has evidently reduced tuberculosis burden in many industrialized countries such as United States of America, Netherland and Eastern Europe as well as India, Hong Kong, Philippines and Thailand (Grant, Charalambous, Fielding, & et al., 2005; Smieja, Marchetti, Cook, & Smaill, 1999; Woldehanna S., 2004). This preventive therapy substantially reduces the risk that tuberculosis infection will progress to disease. These groups who are at very high risk of developing tuberculosis disease once infected are called the latent tuberculosis infection population. They should be given high priority for preventive therapy, if they have positive skin test results, regardless of their age. These include: 1) persons known to have or suspected of having HIV infection, including persons who inject drugs and whose HIV status is unknown (induration of 5 mm or greater), 2) close contacts of a person with infectious tuberculosis (induration of 5 mm or greater), 3) persons who have chest radiograph findings suggestive of previous tuberculosis and who have received inadequate or no treatment (induration of 5 mm or greater), 4) persons who inject drugs and who are known to be HIV negative (10 mm or greater), 5) persons with certain medical conditions (induration of 10 mm or greater) and 6) persons whose tuberculin skin test reaction converted from negative to positive within the past 2 years (induration of 10 mm or greater increase if younger than 35 years of age; 15 mm or greater increase if 35 years of age or older) (CDC, 2008).

Other groups should be given priority for preventive therapy include: 1) persons who may have occupational exposure to tuberculosis (e.g. health care workers and staff of nursing homes, drug treatment centres, or correctional facilities) depending on the cut-

off point for defining a positive reaction 2) infected persons younger than 35 years of age in high-prevalence groups should be given priority for preventive therapy 3) close contacts in other situations such as in a high probability or prevalence of infection or the contact is immunosuppressed (WHO, 2015b).

2.1.5 Why Isoniazid Preventive Therapy?

2.1.5.1 Effectiveness, regime and duration of Isoniazid as preventive therapy

Isoniazid administered for six months has been used as the standard regimen to treat latent tuberculosis infection for more than forty years. Several regimens are also recommended, the variations change over time in view of newer evidence on adverse effects specifically idiosyncratic liver injury and hepatotoxicity. The latest WHO guideline based on consensus of a panel concluded that other alternative regimens such as 9-month Isoniazid and 3-month Rifapentine plus Isoniazid (exclusively for people living with HIV) as equivalent to the 6-month Isoniazid therapy in terms of efficacy and incidence of tuberculosis and hepatotoxicity (WHO, 2015b). The (at least) 6-month Isoniazid treatment regime remains the gold standard, although optimal benefits and protection was actually obtained at 9 months (Comstock G.W., 1999). It is because of the poor compliance following six months and above, there did not seem to be much difference between the two arms, and the U.S. Centre for Disease Control (CDC) concluded that six months would be more cost-effective.

2.1.5.2 Systematic review on Isoniazid as preventive therapy in non-HIV infected persons

The Cochrane systematic review in non-HIV infected persons comprised randomized control trials that estimated the effect of six and 12 month courses of Isoniazid as preventive therapy (Smieja, Marchetti, Cook, & Smaill, 2009). To date, the review had published its third issues in 2009 which remain unchanged since it was first published in 1999. It included eleven high quality trials that constituted a minimum of two year of follow up based on search coverage between year 1955 to 2003. Treatment with Isoniazid resulted in 0.40 risk ratio of developing tuberculosis (95%CI: 0.31, 0.52) over at least two years, consistent with trials conducted by the U.S. Public Health Service trials in 1970 with risk ratio [95%CI: 0.17; 0.41] (Ferebee, 1970). However, Cochrane systematic review in both HIV and non-HIV infected persons revealed no differences in efficacy in six or twelve months of Isoniazid (Smieja, Marchetti, Cook, & Smaill, 2009; Akolo, Adetifa, Shepperd, & Volmink, 2010). Overall hepatitis rate reported from this review was 0.46% with its rates at 3, 6, and 12 month regimen of Isoniazid were 0.25%, 0.36% and 0.52% respectively.

2.1.5.3 Concerns in Isoniazid Preventive Therapy

Apart from the treatment options for latent tuberculosis infection, two other main issues were raised among the stakeholders in Malaysia – the concerns about Isoniazid-induced hepatotoxicity and Isoniazid resistance. However, evidence showed that hepatotoxicity due to Isoniazid is very rare (<0.1%) and not associated with higher risk of hepatotoxicity (Grant, Charalambous, Fielding, & et al., 2005; Hoffman C.J., 2007;

Lawn S.D., 2007; Nolan C.M., 1999). Monitoring for clinical manifestation and liver function on regular basis and education on signs and symptoms of adverse effect and discontinuation to the patients are the main strategies discussed to minimize the occurrence of hepatotoxicity.

Apart from that, U.S. CDC are being highly selective whereby according the guideline, Isoniazid Preventive Therapy is not recommended for infected persons who are 35 years of age or older unless these persons are at high risk of developing tuberculosis disease (CDC, 2008). The concern on the Isoniazid resistance as well seems minimal since evidence shows despite no evidence about the threshold prevalence of isoniazid resistance at which Isoniazid Preventive Therapy risks exceeds benefits, Isoniazid Preventive Therapy remained effective even if it is relatively used in high prevalence area of Isoniazid resistance – e.g. 17% resistance in Haiti in 1990s (Chaisson R.E., 1996). Although multi-drug resistance cases towards tuberculosis in Malaysia is very low, we should still bear in mind, priority should be optimising tuberculosis treatment to ensure cure. However, the treatment is suboptimal hence failure to achieve the reversal trend of incidence as discussed earlier in many sections such as section 2.1.3. To date, Isoniazid Preventive Therapy implementation in Malaysia is only confined to paediatric and HIV population.

2.2 Mathematical modelling of tuberculosis transmission dynamics

2.2.1 Tuberculosis mathematical models

The application of mathematics to the study of infectious disease is thought to have been initiated by David Bernoulli in 1760 in his evaluation of effectiveness of the techniques of vaccination against smallpox (Anderson R.M., 1991). The first mathematical model of tuberculosis published by Waaler et al in 1962 and this technique have been used since then to evaluate the epidemic effect of treating active tuberculosis cases (Brewer T., 1996; Murray C.J., 1998; Saly M. Blower, 1995), vaccinating against tuberculosis (Carlos Castillo-Chavez & Zilan Feng, 1998) and providing therapy for cases of latent infection (Blower S., 1996; Christopher J. L. Murray, 1998).

Mathematical models used for spread of diseases are called dynamical models as they describe change taking place over time. They are generally either deterministic or stochastic. The former type of models is more suitable for a large population and for changes over relatively long periods of time. The latter type of models is more suitable for relatively smaller populations and relatively short periods of time. The rules governing the temporal change in the latter type are in probabilities and the conclusions are also in terms of probabilities. The former has, in contrast, deterministic rules and is not cast in a statistical framework (Kirit S Yajnik, 2003).

Most recent tuberculosis models used SEIR deterministic compartments exploring many aspects of tuberculosis using ordinary or partial differential equations or difference equations. The focus in the earlier works of the models for tuberculosis was to

incorporate the known epidemiology of tuberculosis to elucidate the role of various intervention processes (Waller H., 1962; Sally M. Blower, 1995; Blower S., 1996). The population is divided into several classes to differentiate between different stages of the development of tuberculosis infection as well as disease and the progress of intervention. As the disease evolved, they have become more complex to differentiate between treatment modes and age dependent processes (Lalande, Bourguignon, Maire, & Goutelle, 2016; Lemmer, Grobler, Moody, & Viljoen, 2014). Stochastic models with discrete-event simulations were also used to study individualistic or clustering effects of tuberculosis (Ozcaglar, Shabbeer, Vandenberg, Yener, & Bennett, 2012; Pertsev & Pichugin, 2010).

Any type of modelling method and the model assumptions showed simplicity of the models intended for use, or alternatively reflected the background knowledge of the modellers on depth of understanding of its natural history. It serves as important tool to assess the population-level effects of individual-level processes as well as for the policy makers and public health researchers to gain insight into the potential long-term consequences of programmatic decisions. Given the protracted course of tuberculosis epidemics (Sally M. Blower, 1995), the impact of policy decisions made today may not be observed for many decades in the future.

2.2.1.1 Age stratification in tuberculosis model

Age effects in tuberculosis are significant thus inevitable in any tuberculosis transmission dynamic modelling in order to reflect the reality (Martien W. Borgdorff, Nagelkerke, de Haas, & van Soolingen, 2001). The differences across age categories

are attributable to mainly the contact pattern. The contact pattern between individuals affects the force of infection hence risk of acquiring the infection termed as annual risk of tuberculosis infection (ARTI). This is due to the differences in exposure of infection as well as in susceptibility across age categories. For example children are more likely to contact other children and that between young and adult, the young individuals are more susceptible to infection than adult (Vynnycky, & White, 2010).

2.2.1.2 Gender stratification in tuberculosis model

Gender as a significant predictor in tuberculosis model may affect the disease progression and transmission dynamic (Martien W. Borgdorff, Nagelkerke, de Haas, & van Soolingen, 2001). Gender differences vary across countries and may be due to behavioural, social or biological reasons or even underreporting (Borgdorff, Nagelkerke, Dye, & Nunn, 2000). In general, men's disease rates exceed women's after the age of 15. (Holmes, Hausler & Nunn, 1998). In Malaysia, the gender ratio (male:female) among tuberculosis patients ranges between 2.1 to 2.3 for year period 2010-2014 (Jiloris F.D., 2014)

2.2.2 Epidemiologic basis in tuberculosis mathematical models

The epidemiologic basis of a tuberculosis mathematical model generally reflects the pathogenesis and natural history of the disease. It serves as the model frame that represents the closest-to-reality as possible. Common variation and details among most recent models differs according to the study interest and objectives and model

customization. For instance, models developed to assess the potential impact of early intervention in tuberculosis would elaborate the latency period of the history while models developed to assess the impact of multi drug resistance would elaborate the treatment and recovery period of the disease transmission. Customized models commonly contrive the model contexts based on specific populations such as high risk population, country-based population study etc.

In a high tuberculosis prevalence country like Malaysia, many susceptible individuals may acquire tuberculosis infection by direct inhalation or environmental exposure with either a known infectious case or undiagnosed cases. These individuals who have been infected but do not show any clinical manifestation of tuberculosis is said to be in the early infection state termed as Latent Tuberculosis Infection (LTBI) where the aetiologic agent, *Mycobacterium tuberculosis* is alive but in the dormant state without causing any bacteraemic activity. At this point, a small portion of these latent cases may progress into infectious state at an accelerated lifetime risk of 5-10% following the first five years of exposure (early latent), termed as primary tuberculosis.(E. Vynnycky, 1997) The majority remain latent longer (late latent), yet still at risk of developing infectious tuberculosis as a consequence of either via endogenous or exogenous route of infection. Any immunocompetent latent individual has about 5-10% lifetime risk of developing tuberculosis termed as reactivation via endogenous route. The risk of reactivation is much higher in immunocompromised individuals such as people living with HIV, end stage renal failure, cancer etc. In Malaysian setting, where human cross-border mobilization within neighbouring countries in South East Asia or Western Pacific with high tuberculosis prevalence is common, studies have also shown that exogenous route termed as reinfection also exists, whereby the individual contracted the disease following repeated exposures to infectious cases.

In infectious state, many models varied whether the majority manifested individuals may recover following anti-tuberculosis treatment only; while some may have also recovered naturally without receiving any form of treatment. The formers may then either: 1) recover and progress into recovery state or 2) relapse and revert into infectious state while those with natural recovery may either recover or return into latent infection. However, this is highly contextual depending upon factors such as the area hotspots, diagnostic tool and drug availability, initial patient default after diagnosis, treatment success rate etc. (Dye & Williams, 2010). The summary of transmission is as illustrated in Figure 2.4 below:

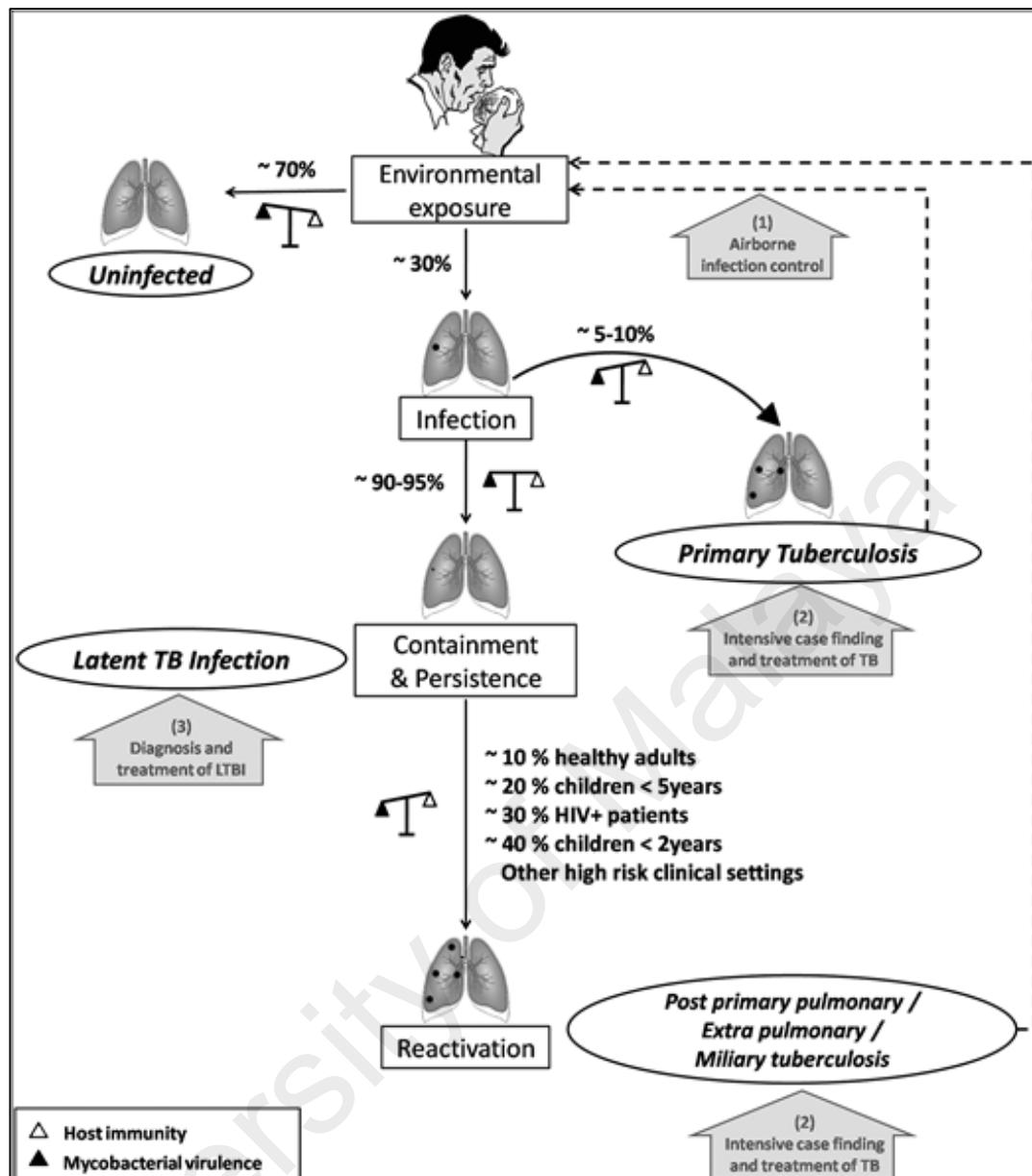


Figure 2.4: Transmission dynamic of tuberculosis infection

(Tuberculosishuman, 2016)

2.2.3 Tuberculosis mathematical models on Isoniazid Preventive Therapy

A number of studies on mathematical modelling of tuberculosis transmission dynamics in various contexts related to early preventive therapy are as shown in Table 2.3 below:

Table 2.3: Evidence table of mathematical modelling on Isoniazid Preventive Therapy for tuberculosis

Study/Year	Population	Modelling system	Reference model	Comments
1. Bhunu et al. /2008	Zimbabwe	Deterministic compartmental model	Blower et al., 1996	-Impact of IPT intervention. -Included exogenous reinfection pathway
2. Ziv et al. /2001	California	Deterministic compartmental model	Blower et al., 1996	-Extended model to quantify effectiveness of intervention -Comparing impact of intervention in early and late LTBI
3. Murray C., Salomon J. /1998	Nine states	Deterministic compartmental model	Murray C., Salomon J., 1998	-Epidemic effect of treating active tuberculosis -Very complex: includes treated and untreated cases, infected and uninfected cases
4. Porco T.C, Blower S.M. /1998	Simulation	Deterministic compartmental model	Blower et al., 1996	-Time-dependent uncertainty and sensitivity analysis. -Quantify the transmission parameters of tuberculosis epidemic in the absence of treatment
5. Feng Z, Huang W, Castillo-Chavez /2001	Simulation	Deterministic compartmental model	Castillo-Chavez C., Feng Z., 1997a	-Described the transmission dynamic. -Qualitative behaviour of different systems i.e. ODE versus DIE; determined by basic reproduction number.
6. Glaziou P., /2006	Western Pacific Region	Deterministic compartmental model	Murray C., Salomon J., 1998	Assessment of DOTS-plus programme in WHO-WPR for MDRTB
7. James M.T., /2014	Asia Pacific	Deterministic compartmental model	Multiple	-Assessment of MDRTB -Non age structured model -Assumed no further risk of infection after recovery

2.3 Applications of tuberculosis mathematical model

2.3.1 Tuberculosis mathematical models as tools for epidemic control

Knowing the way a disease behaves has become the holy grail of the modern epidemiology. Predicting it beforehand will be a head start to the policy makers in managing these diseases in a population. That has been the rationale behind all the research related to the investigating diseases, especially infectious diseases, in any Ministry of Health across the world. Conventional approach with prospective data collection has not been but time consuming, involved patients interventions as well as concomitant legal and ethical consequences. Application of mathematical modelling techniques has solved many of the problems associated with these conventional epidemiological approaches. (Garnett, Cousens, Hallett, Steketee, & Walker, 2011) It also helps to answer a research question from different perspectives. This is where the disease mathematical models are used as tools to assess the demography, disease burden, economic burden or impact assessment such as in compliance, treatment or other interventions.

For instance, the incidence of tuberculosis disease is impractical to measure directly at a national level, as this would require following up very large numbers of individuals and costly. Therefore, the vast majority of countries report tuberculosis notifications, which are collated by the World Health Organisation. While underdiagnosed and underreporting mean that these underestimate incidence, notification data do act as the closest proxy to provide very useful information for estimating tuberculosis incidence.

The Malaysian tuberculosis data is of no exception. It uses the notification data as the closest proxy to its incidence estimates, as illustrated in Figure 2.1. The notification data may approximate the incidence in the population when the gap or underrepresentation is the smallest possible. This notification data is highly sensitive to any operational change in the field, although that could mean for a higher case detection rates. Apart from that, both active and passive case detection programme need to exist and actively implemented in the population. However, in this case, the active case detection programme commenced recently from 2012 onward. Before 2012, the gap or underrepresentation was bigger since most data were collated via passive case detection only.

There are many different methods used to estimate the underrepresentation of cases. In this study, the underrepresentation was quantified via mathematical modelling technique during model optimisation and validation. The majority of tuberculosis the WHO incidence estimate is based on inflating the reported notification rate by an uncertain factor (the inverse of the case detection ratio, CDR) that represents knowledge about the shortfall (WHO, 2014b).

Information about the value of the CDR has historically relied on quantified expert opinion, but is increasingly based on capture-recapture modelling (WHO, 2012). WHO estimates of mortality due to tuberculosis are based on data from vital registration systems where they exist (adjusting for imperfect coverage and misclassification of deaths). Where the systems are not present data was based on uncertain knowledge of case fatality rates in notified and non-notified tuberculosis.

Tuberculosis is a disease with slow dynamics and consequently, tuberculosis epidemics must be studied and assessed over extremely long windows in time. Transmission takes place primarily within small clusters of acquaintances. Thus tuberculosis patterns are driven by processes which dynamics take place over distinct temporal, spatial and organizational scales.

For instance, tuberculosis in the US is in the declining phase of an epidemic that peaked around the middle of the nineteenth century. Full understanding of the actual course of tuberculosis dynamics in the US requires an appropriate description of historical epidemic patterns. Such description requires a sound modelling technique of epidemic processes that involves hundreds of millions of individuals over centuries. Simple standard compartmental models with some modifications turn out to be quite useful in the study of the long-term dynamics of tuberculosis, particularly when the age structure of a population is included. Naturally, the studies of all processes associated with transmission do not need to be incorporated in detail. The selection of a model is (or it should be) intimately connected to the question (Juan Pablo Aparicio & Carlos Castillo-Chavez, 2009).

Different models are used to study the long-term dynamics of tuberculosis globally. The list includes simple compartmental models with standard incidence, aggregated cluster models, and age structured models. All these models utilize demographic and epidemiological data as parameters while capturing the patterns of tuberculosis over long time horizons (Juan Pablo Aparicio & Carlos Castillo-Chavez, 2009).

In recent years, an increasing number of high-quality national prevalence surveys have been carried out in many countries.(WHO, 2014b, 2016) These provide direct

information on the tuberculosis prevalence in a country, and are much less affected by bias than notification or vital registration data. Gaining information on tuberculosis incidence from prevalence data requires a model of some kind that can describe the typical duration of prevalent tuberculosis cases. This is indeed the approach used by WHO to estimate tuberculosis prevalence from incidence in countries without prevalence surveys, and a reverse of this procedure is used in countries with direct prevalence data.

2.3.2 Assessment of tuberculosis intervention strategies

Mathematical models have played a key role in the formulation of tuberculosis control strategies and the establishment of interim goals for intervention programs (Blower S., 1996; Murphy BM, Singer BH, & Kirschner D., 2003; Song B, Castillo-Chavez C, & Aparicio JP, 2002; Zilan Feng & Carlos Castillo-Chavez, 1998). Most of these models are of the SEIR class in which the host population is categorized by infection status as susceptible, exposed (infected but not yet infectious), infectious and recovered. One of the principle attributes of these models is that the force of infection (the rate at which susceptible leave the susceptible class and move into an infected category, i.e., become infected) is a function of the number of infectious hosts in the population at any time t and is thus a nonlinear term. Other transitions, such as the recovery of infectious and death, are modelled as linear terms with constant coefficients.

However, the enormous public health burden inflicted by tuberculosis necessitates the use of mathematical modelling to gain insights into its transmission dynamics and to determine effective control strategies (Samuel Bowong & Jean Jules Tewa, 2009). It is

extremely challenging to have a full understanding of the complex dynamics in any infectious disease. However, mathematical modelling, mathematical analysis and numerical simulations have been providing a complementary tool to understand the disease dynamics better (Anderson R.M., 1991). Mathematical modelling in infectious diseases has played an important role to provide some insights on which counter measures would be more effective for reducing the negative impact of active-tuberculosis incidence (Sara K et al., 2014).

2.4 Policy recommendation of tuberculosis modelling findings

2.4.1 Formulation of a policy recommendation

Priority setting of health interventions in a country is generally dependent upon the local evidence translated and deliberated in the policy making process; apart from the usual environment of political-social processes and diverging interests. The local evidence-based policy healthcare in Malaysia is minimal. This is mainly either due to the fact that the evidence or information collective process is not exhaustive and comprehensive; or the fact that just the small fraction of researchers who actually forwarded their study findings to the relevant policymaking bodies. The evidence collective process is even more complex when the study methods used are researcher or operator dependent and too advance or too integrated to be understood as compared to the conventional observational study methods. Often, the evidence was misunderstood and justifiably disagreed about their relative importance. This includes that the healthcare policy is lacking in mathematical modelling work from academics, therefore good results were not known to policy makers, health manager or implementers

Policy recommendation is about translating modelling findings back to reality. It is a procedure that bridges the evidence gap between academics and policymakers and implementers. The policy recommendation need not be fully written. It is formulated by looking into feasibility or explore for any possibility of implementing this new findings to be integrated into existing control programme to achieve desired effects predicted from the modelling work. Such efforts are commendable by the policymakers that there are few government bodies in Malaysia that assist researchers in this work process such as the Institute for Health Behavioural Research under Ministry of Health (Sulaiman Che Rus, 2011).

2.4.2 Knowledge Translation (KT) and Get-Research-Into-Policy-and-Practice (GRIPP) concept

A huge number of scientist, doctors & public health practitioners go to work every day hoping that the work they do will make difference in the people health. They spend a life time trying to find the best way to prevent diseases like heart disease or infectious diseases such as tuberculosis and other public health problems. But sadly best scientific discoveries do not make into practice settings and those that do take a long time to get there. As a result of these evidence-practice and policy gaps, patients fail to benefit optimally from advances in healthcare and are exposed to unnecessary risks of iatrogenic harms, and healthcare systems are exposed to unnecessary expenditure resulting in significant opportunity costs (Grimshaw et al., 2012).

Application of the empirical research into decision making has always been an issue. Globally and at all levels of health care, health systems fail to use research evidence

optimally (Straus SE, Tetro J, & Graham I, 2009). This gap results in negative effects, such as a reduction in both quantity and quality of life (Davis D, Evans M, & Jadad A, 2003). This gap has also resulted in the inefficient use of limited health care resources (Graham I, 2006; Straus SE et al., 2009). Underutilization of evidence-based research is often described as a gap between “what is known” and “what is currently done” in practice settings (Davis, 2003). As political and societal pressures to use research evidence in decision making continue to rise, there is increased interest in the concept of knowledge translation. Knowledge translation (KT) and Get-Research-Into-Policy-and-Practice (GRIPP) are relatively new concepts for uptake of evidence that describe a relatively old problem i.e. the underutilization of evidence based research in systems of care. What more when recently the population and public health research has been shifting from describing factors that shape health to deliberation of the processes and outcomes of those evidence underpinning policy and programme interventions (Hobin Erin P, Hayward Sarah, Riley Barbara, Di Ruggiero Erica, & Birdsell Judy., 2012).

Knowledge translation is a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of population, provide more effective health services and products and strengthen the health care system. Knowledge translation is critical for bridging the gap between knowledge that has been generated through research and knowledge that is used to inform policy, practice, and programs with the goal of improving the health of local population and the global community, and reducing health inequities.

Translation of research evidence into policy and practice is challenging for disease prevention researchers (Giles-Corti, B. Sallis, & J. Sugiyama, 2015). A report of the World Health Organization suggests that “... toxic combination of bad policies,

economics, and politics is, in large measure, responsible for the fact that a majority of people in the world do not enjoy the good health that is biologically possible” (WHO, 2008). Factors such as availability and access to research/improved dissemination, clarity/relevance/reliability of research findings, timing/opportunity, policymaker research skills and costs are the most commonly reported barriers based on a systematic review of barriers to the use of evidence by policymakers around the world as tabulated in Table 2.4 below (Oliver, Innvar, Lorenc, Woodman, & Thomas, 2014). The similar study also reported the facilitators to overcome the barriers are availability and access to research/improved dissemination, collaboration, clarity/relevance/reliability of findings, relationship with policymaker and relationship with researchers.

Table 2.4. Most frequently reported barriers and facilitators of the use of evidence (Oliver et al., 2014)

Top 5 barriers to evidence use	Top 5 facilitators of evidence use
Availability and access to research/improved dissemination	Availability and access to research/improved dissemination
Clarity/relevance/reliability of research findings	Collaboration
Timing/opportunity	Clarity/relevance/reliability of findings
Policymaker research skills	Relationship with policymaker
Costs	Relationship with researchers

2.5 Summary of Chapter 2

The proposed Isoniazid Preventive Therapy may be an effective intervention to reduce the rising incidence. The use of mathematical modelling technique to provide this evidence is appropriate; what more when a customized Malaysian tuberculosis mathematical model is developed by studying the tuberculosis epidemiology within the Malaysian environment and characteristics. The model used as a tool to assess the likely impact of proposed interventions and determine the relevant details if such programme were implemented. It is also notable that several efforts were made to ensure the evidence produced is translated and recommended for policy adoption in clinical practice. The following Chapter 3 elaborates the study methods used in detail.

3.1 Research profile

3.1.1 Study population

This is a nationwide based study which involved all tuberculosis patients in Malaysia.

3.1.2 Ethics and confidentiality of data

The University of Malaya Medical Centre Ethical Committee (Reference number: 715.19) and National Medical Research Register (NMRR) under National Institute of Health (NIH), Ministry of Health of Malaysia (Reference number: NMRR-09-176-3739) approved this research. The confidentiality of data used was ensured during this study. Data was accessible to the research members during the time of study and all results were presented in an aggregated manner.

3.1.3 Study funding

This research was funded by the University of Malaya Post Graduate Research Fund (Reference number: PS386/2009B).

3.1.4 Work strategy

Four essential scopes of work were identified to ensure comprehensive coverage. These include: 1) comprehensive literature review, 2) engagement of all the stakeholders in the Malaysian health system, 3) engagement of study support system and network members and 4) acquisition of funds for training. Following Figure 3.1 illustrates the work strategy.

3.1.4.1 Comprehensiveness of literature review

Literature review of this research was exhaustive and extensive. It incorporated review in fields of mathematics as well as medicine. The review of mathematical modelling studies includes areas of pure mathematics, mathematical biology and its applications. The literature review for medicine includes conventional observational epidemiological and clinical trial studies related to research topic.

The literature review was carried out in three different dimensions: 1) literature search concerning the observational epidemiological and clinical studies on tuberculosis and IPT, 2) literature search on mathematical models of tuberculosis and 3) literature review on mathematical modelling of tuberculosis concerning Isoniazid Preventive Therapy. This comprehensive literature review is presented in Chapter 2.

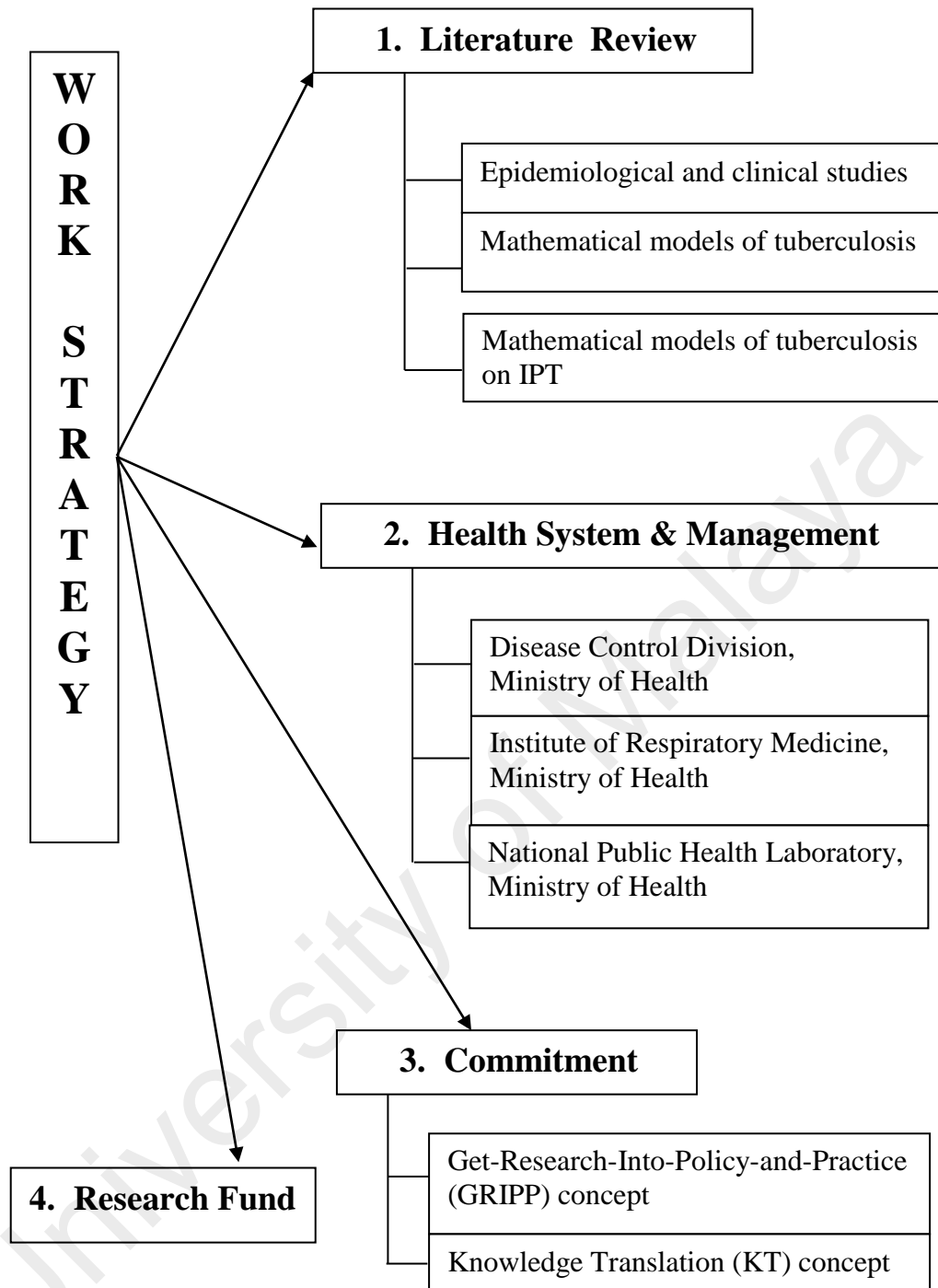


Figure 3.1: Work strategy for this study

3.1.4.2 Engagement of stakeholders of Malaysian health system

The research involves the entire population of Malaysia and used population parameters. Therefore it is imperative to engage all important aspects of tuberculosis data management at national level. This involved engaging all the stakeholders for understanding the processes involved in policy-making, data collection and analysis and evaluation of tuberculosis programmes and track the changes that has taken place over time. Three main stakeholders identified in Ministry of Health include; 1) Disease Control Division, 2) National Public Health Laboratory and 3) Institute of Respiratory Medicine.

3.1.4.3 Study support system, network members and consensus

This scope of work is the continuum of previous work scopes whereby the main stakeholders involved in the national tuberculosis management were kept actively engaged in this study at its conceptual phase, policy and implementation as well as evaluation phases. This was in accordance with the concept of “Get-Research-Into-Policy-and-Practice (GRIPP)” and “Knowledge Translation (KT)” advocated by the Ministry of Health Malaysia.

That approach was crucial for achieving consensus as means of synthesising evidence in situations where there is insufficient, conflicting even overload of information in the development process of the Malaysian tuberculosis transmission dynamic model in this study. A number of meetings and discussion were organized from time to time throughout the study period to ensure the continuous review of the work and achieving

the consensus (please refer to Appendix B for a sample of invitation letter for meetings conducted). Continuous engagement and commitment shown by these policymakers and the inputs provided were very beneficial to this research. This step ensured that is not only evidence-based, but also incorporated the inputs from local experts thus usable for future work in the national tuberculosis control programme and planning.

The stakeholders included experts and resource persons from the national tuberculosis management in Malaysia and were engaged in this research. The main resource persons involved in this study were:

1. Dr Jiloris F. Dony

Head, Sector of Tuberculosis/Leprosy, Disease Control Division, Ministry of Health

2. Dato' Dr Haji Abdul Razak Muttalif

Consultant Respiratory Physician, Head of Institute of Respiratory Medicine and National Advisor to Ministry of Health

3. Dr Suzana Mohd Hashim

Senior Principal Assistant Director, Sector of Tuberculosis/Leprosy, Disease Control Division, Ministry of Health

4. Dr Mohamed Paid Yusof

Head, Surveillance Section, Disease Control Division, Ministry of Health

5. Dr Fuad Hashim

Epidemiologist, Institute of Public Health, Ministry of Health

6. Dr Mariam bt Mohamad

Epidemiologist, National Public Health Laboratory, Ministry of Health

7. Dr Badrul Hisham Abd Samad

Epidemiologist, Johor State Health Department, Ministry of Health

8. Dr Mokhtar bin Pungut

Epidemiologist, Segamat District Health Department, Ministry of Health

9. Dr Mohd. Yusof bin Hashim

Epidemiologist, Seberang Prai District Health Department, Ministry of Health

10. Datuk Dr Hjh Aziah Ahmad Mahayiddin

Consultant Respiratory Physician, Institute of Respiratory Medicine,
Ministry of Health

11. Associate Professor Dr Pang Yong Kek

Consultant Respiratory Physician, University of Malaya

3.2 Development of model

This section elaborated the processes involved in the development of the model. This include: 1) development of model frame, 2) data collection and analysis of model parameters and 3) model optimization.

3.2.1 Model frame

The model frame was constructed before the model quantification. Two important steps performed for model frame construction were: 1) determination of the model structure and, 2) type of modelling method and system. This model was built upon previous work on tuberculosis models by Vynnycky et al. 1997, WPR-WHO Modelling 2006 and Blower et al. 1996.

3.2.2 Modelling structure

The model developed represented the updated pathophysiology of tuberculosis and customized to tuberculosis epidemiology in Malaysian setting. The latest and most comprehensive tuberculosis transmission dynamics and its population stages were included essential to address the research question. The time estimate used for the model structure were selected parallel to the time period that the individuals spent in each different stage of the disease. The format of model output was also designed to ensure that it could be compared to available data for testing and validating the model.

Figure 3.2 shows the various model structure and groups of compartments within these models. Among these model structures, the SEIR model was selected the most appropriate tuberculosis modelling structure that best fitted the research question and objectives. This model was further refined whereby the births, deaths and heterogeneity i.e. age and gender were incorporated in the model. SEIRS was not the model of choice since it contradicts the tuberculosis transmission dynamics. Persons who recovered from “R” compartment are only free from clinical manifestation; the pathogens still exit and remain dormant within the host (Hoff et. al, 2011). To date, there has no clear evidence that the host would be free from pathogen following recovery, hence violates progression to susceptible “S” compartment where persons are at risk but pathogen free.

The general SEIR model is a homogenous model as discussed in Chapter 2 on literature review. The customized Malaysian deterministic tuberculosis transmission dynamic model constructed in this study is the refined version than the existing homogenous model. The Malaysian model incorporated heterogeneity by stratification of age and gender according to its most up-to-date and comprehensive tuberculosis

pathophysiology which was consensually agreed upon by the stakeholders in the model development. The age in the Malaysian model was categorized in groups with 15 years interval based on annual risk of tuberculosis infection as discussed in Chapter 2 literature review. Later each age group was further stratified according to gender by using ratio male to female = 1.5:1 (Ministry of Health, 2007). The age categories used for model stratification and its annual rate of infection are shown in Table 3.1 and the diagrammatic refinement of model is shown in Figure 3.3.

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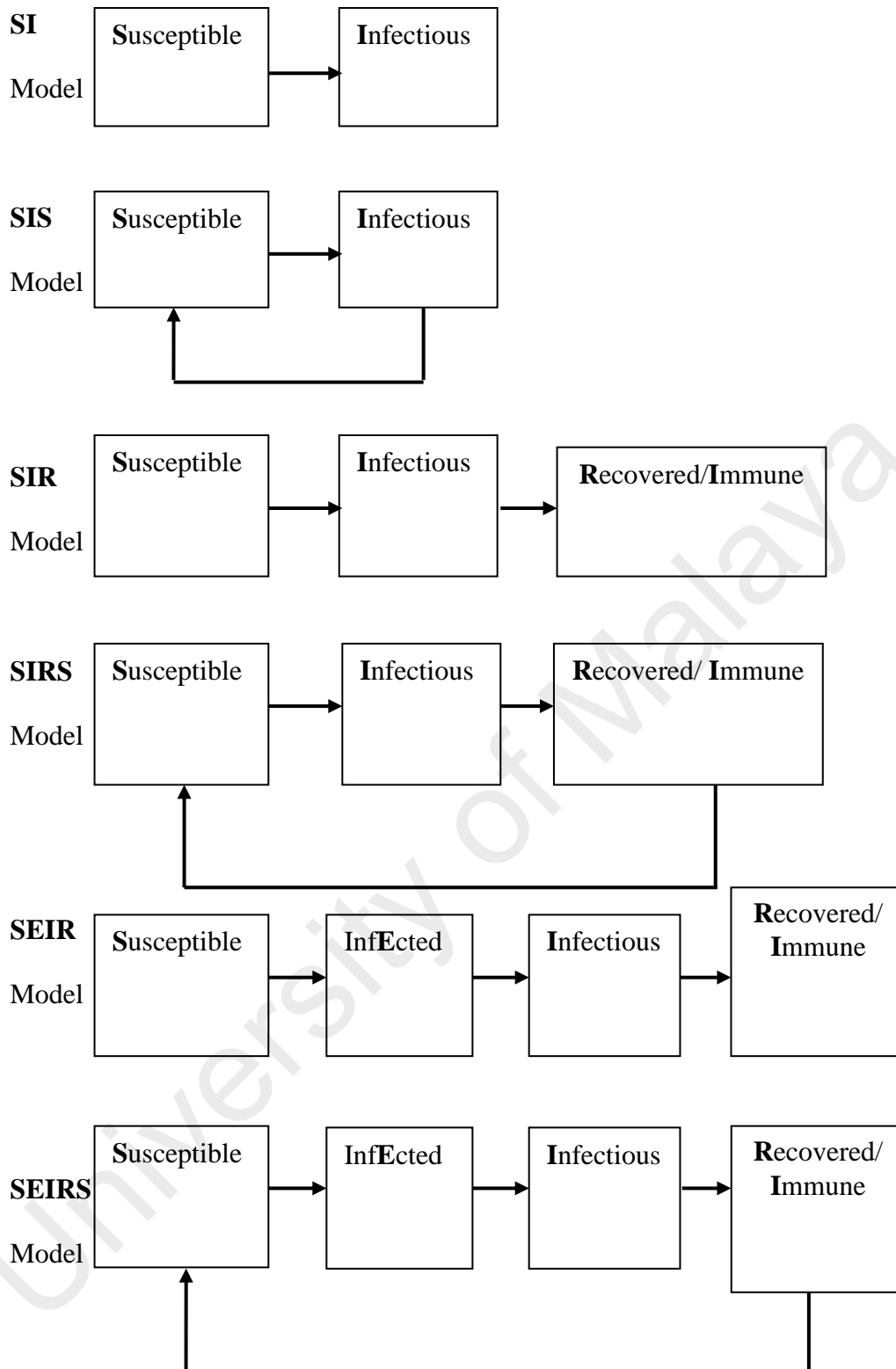


Figure 3.2: The various model structures in modelling infectious diseases (E. Vynnycky & R. White, 2010)

**Table 3.1: Categorization of age for tuberculosis model stratification
according to annual risk of infection**

No	Age Categories	Annual Risk of Tuberculosis Infection (ARTI) (Ministry of Health, 2009)
1	0 to 14 years	0.009
2	15 to 29 years	0.10
3	30 to 44 years	0.08
4	45 to 59 years	0.04
5	60 to 74 years	0.04
6	75 to 89 years	0.03
7	90 years and above	0.01

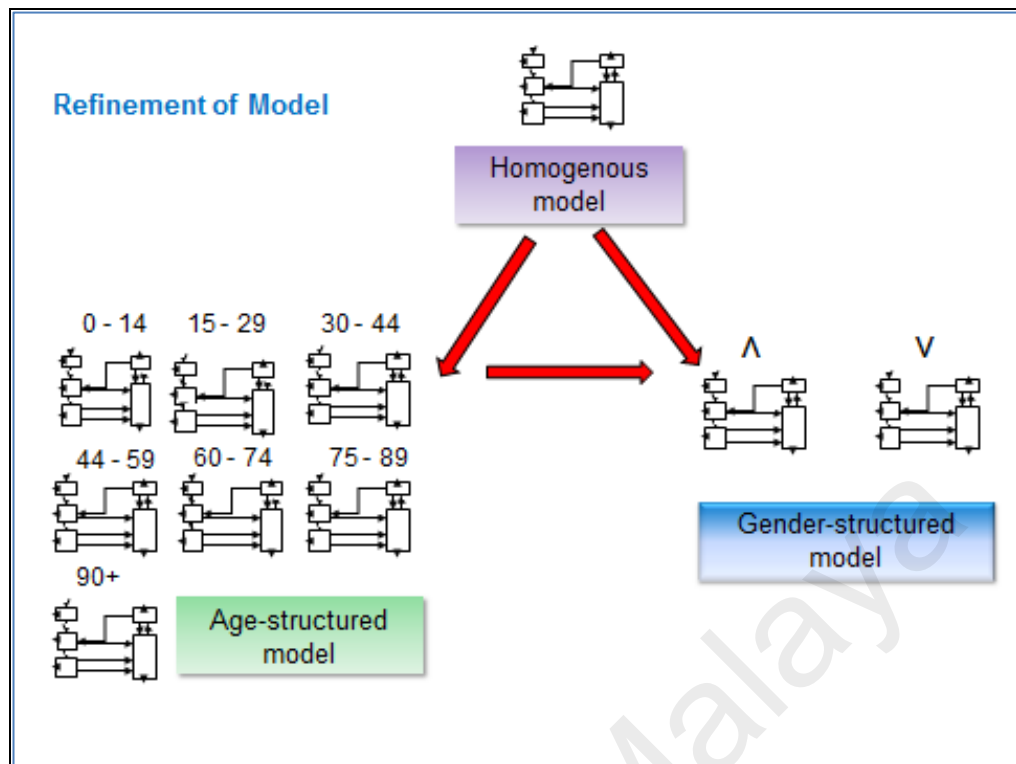


Figure 3.3: Refinement of SEIR tuberculosis model into age and gender structured deterministic tuberculosis transmission dynamic model for Malaysia

3.2.3 Modelling method

The development of disease model can be achieved by using two modelling methods, these include: 1) deterministic equations and 2) stochastic equations. These are based on difference equations with or without differential equations, or stochastic equations respectively. There is no distinctive difference between these methods. Some deterministic models also incorporate stochastic elements and nearly all stochastic models incorporate some deterministic elements.

The decision about the model structure and the modelling method is followed by the determination of the variables, terms and parameters to be used in the model. These are based on the existing definitions by the latest version of the Malaysian Clinical Practice Guideline on Tuberculosis Management as well as the definitions used by WHO. The assumptions of the models were also determined and applied to the model to address the research questions. The variables and parameters used in the models are (refer Appendix C for full definitions):

1. number of susceptible people, number of early latent tuberculosis infected people, number of late latent tuberculosis infected people, number of re-infected tuberculosis people, number of infectious tuberculosis case, number of recovered tuberculosis cases,
2. contact rate per case and basic reproduction numbers,
3. force of infection, rate of infection, rate at which people who have been infected or re-infected without developing the disease move into late latent group, rate of re-infection, rate of successful sputum conversion after initial treatment, relapse rate where sputum positive after completed treatment,

4. risk of developing infectious tuberculosis first primary episode, risk of developing infectious tuberculosis from re-activation (endogenous), risk of developing infectious tuberculosis from re-infection (exogenous),
5. birth rate, population growth rate, mortality rate due to infectious tuberculosis and mortality rate due to non-tuberculosis causes.

3.2.4 Data collection and analysis of model parameters

The model quantification followed the establishment of model frame. At this stage the rates and distributions of the flows between the model states were quantified. This section described the data collection, modelling software and modelling equation system and numerical analysis of choice for the analysis performed in this study.

All data extracted were analysed and outputs and other simulations were derived to address the research question and answer the study objectives. Data were presented in the forms of descriptive data and tabulations. Two main findings or outputs expected from this study were the proposed Malaysian tuberculosis mathematical model and the assessment of potential impact on the proposed Isoniazid Preventive Therapy to reduce the tuberculosis incidence.

3.2.5 Data source

Lack of reliable data has always been a major problem for the modelling research. Strategies were set to overcome this problem. The sources of data for this research were

an integration of both local data as well as external data. Steps were also taken to maintain the quality of data. With the progression of work, consistent communication among all stakeholders (as described in Chapter 2) was ensured to maintain the mutual consensus of the model as well as to sustain the networking and relationships with other research members who mainly are the national programme managers and policy makers.

In view of the development of national tuberculosis data management and reporting system, this study set to use data from year 1990 to 2010 as the most reliable range of data for model development and application i.e. data fitting in optimisation. The departure point was argued and selected for retrospective projection of case burden as only limited to year 1990 onward; and unlikely be extended to fifty or a hundred year earlier as described by Dye et al. and Blower (Dye, Garnett, Sleeman, & Williams, 1998; Sally M. Blower, 1995).

This is in view of several reasons - mainly the objectivity of trend assessment as well as the reality of Malaysian (or Malaya at that time) population at that point of time (say even at fifty years back from 1990 i.e. 1940). These include availability and reliability of data for model fitting, accessibility of anti-TB drugs, implementation of DOTS and political stability. The availability and reliability of data for model fitting is a huge question and unlikely to be accurate in view of war. There was no tuberculosis reporting existed till 1960 following the independence in 1950, that the National TB Control Programme was established. Nonetheless, the oldest data or report on tuberculosis was only available from 1970. Similarly, despite drug availability since 1940, it was only accessible in Malaya late 1950s. The DOTS or any other form of monitoring was only established and made available from 1990 onward. Apart from that, any available data before 1960 was only confined to either Peninsular Malaysia (or Malaya) or East

Malaysia before Malaysia was established, hence not comprehensively representing the Malaysian population. Data before year 1990 was sporadic while data from year 2011 onward was only collectively available from year 2015 due to the transformation of systems. Apart from that, from year 2012 onward a new active screening programme had also commenced in all health clinics nationwide that may be affect the modelling runway of epidemic.

These sets of epidemiological data range were retrieved from the national disease database, mainly the National Tuberculosis Information System under Sector of Tuberculosis/Leprosy and Sector of Surveillance, and the National Public Health Laboratory (NPHL) of Communicable Disease Control Division, Ministry of Health, Malaysia. The population census and demography data were extracted from the Department of Statistics of Malaysia. External data sources from International Union Against Tuberculosis & Lung Disease (IUATLD), World Health Organization and World Bank Databases were also used.

3.2.6 Modelling software

The modelling software used for this research was the modelling and analysis of dynamic system software of ModelMaker 4 (AP Benson, 2011) and Berkeley Madonna (Robert I. Macey & George F. Oster, 2001). Training for the fundamentals in mathematical modelling of infectious diseases was obtained from the certificate infectious disease modelling course by London School of Hygiene and Tropical Medicine in London from 6 to 17 July 2009.

3.2.7 Model equation system and numerical analysis

The research adopted the Ordinary Differential Equation (ODE) system as this was the most appropriate equation system in order to achieve the research objectives. The research used the Runge-Kutta at 4th Order (RK4) as its numerical iterative methods to best present the transmission dynamic changes of tuberculosis.

3.2.8 Model robustness and optimization

The model was optimized and validated using the model outputs against independent data sets. The processes included sensitivity analysis, scenario analysis and model fitting. At this stage, the model outputs were also exposed to critiques or peer-review from experts in this field.

3.2.8.1 Sensitivity and uncertainty analysis

In sensitivity analysis, the values of parameters were changed, one at a time, to assess its effect on model outputs. In uncertainty analysis, the ranges of parameter values were first specified, and then the output was generated a number of times, each time selecting random values from these ranges. Both provided a range in the predicted effectiveness of the various strategies. The one strategy that was always the most effective in all sensitive scenarios would be the choice. That has helped reporting the results with greater confidence.

3.2.8.2 Model fitting and optimization

The model was fitted against the national incidence data from year 1990 to 2014 and further optimized via Marquardt statistic test.

3.3 Impact assessment of intervention strategy

This section elaborated the work processes involved in the simulations of the tuberculosis transmission dynamic mathematical model constructed. It is an application of mathematical modelling technique where the model constructed was used as a tool to assess the potential impact of a proposed intervention i.e. Isoniazid Preventive Therapy for latent tuberculosis high risk sub-populations to effectively reduce tuberculosis burden in Malaysia. There were five simulations performed in this research in order to answer the research objectives.

3.3.1 Estimate and projection of tuberculosis burden in Malaysia 1990-2030

The model projected the estimates of tuberculosis cases in Malaysia from year 1990 to 2030 in year time unit. The observed data i.e. notification data was then compared to the projection in two scenarios: 1) between year 1990 to 2010; and 2) between year 1990 to 2014. This comparison is in accordance with the newly introduced nationwide active case detection programme called “intensified case finding” in year 2011 that has increased the number of cases detected and treated.

3.3.2 Effectiveness of Isoniazid Preventive Therapy

The model assessed the effectiveness of Isoniazid Preventive Therapy to reduce tuberculosis incidence in Malaysian under four intervention scenarios: 1) without treatment; 2) Isoniazid Preventive Therapy for latent tuberculosis only as treatment; 3) current treatment regime for infectious tuberculosis only; and 4) combined strategy of Isoniazid Preventive Therapy for latent tuberculosis and current treatment regime for infectious tuberculosis. These are simulations set according to secondary data available from year 1990 to 2010. The first two scenarios i.e. in the absence of treatment and Isoniazid Preventive Therapy for latent tuberculosis only as treatment are for simulation purposes only and treated as baselines.

All four scenarios were compared against number of tuberculosis cases and the tuberculosis effective reproductive numbers, R_{eff} . The effective reproductive number of tuberculosis was a relative ratio set between the current treatment for infectious tuberculosis only and the combined strategy of Isoniazid Preventive Therapy for latent tuberculosis and current treatment regime for infectious tuberculosis.

3.3.3 Quantification of Isoniazid Preventive Therapy optimal coverage in combined strategy

Once the most effective strategy to reduce tuberculosis incidence was determined, the model further quantified its effectiveness. Quantification was determined in terms of coverage, and how much Isoniazid Preventive Therapy would be needed (to cover) in the latent tuberculosis population in conjunction with the current treatment regime for

infectious tuberculosis to effectively reduce the incidence. Simulations projected the scenario in various percentages of coverage from 0% to 40% of latent tuberculosis population in conjunction with success treatment rates at lower and upper bound level i.e. 60% and 80% of current treatment regime for infectious tuberculosis.

3.3.4 Selection of high risk latent tuberculosis sub-populations for Isoniazid Preventive Therapy optimal coverage

It demonstrated the best selection of high risk latent tuberculosis sub-populations for Isoniazid Preventive Therapy at optimal coverage determined in section 3.3.3 mentioned above. This selection is defined in terms of the duration of first exposure to infectious tuberculosis i.e. between early or late latent group in accordance with the disease transmission dynamic 'at average' in the population. Early latent tuberculosis is defined as tuberculosis infection without clinical manifestation with exposure to infection within the first five years while late latent infection for five years of exposure and beyond, extending even till life end.

3.3.5 Overall impact of Isoniazid Preventive Therapy to curb tuberculosis epidemic in Malaysia

In this section, all evidences derived from this research were used to produce the overall potential impact of Isoniazid Preventive Therapy as an option to curb tuberculosis epidemic in Malaysia. Two scenarios were used to demonstrate it, these include: 1)

retrospectively from year 1990 till 2050 and 2) and prospectively from year 2015 till 2050.

In the retrospective simulation, it is assumed that the Isoniazid Preventive Therapy was introduced in the year 1990 in conjunction with current treatment for infectious tuberculosis as a combined strategy determined by the model. In the prospective simulation the Isoniazid Preventive Therapy was introduced in the year 2015 in conjunction with current treatment for infectious tuberculosis as a combined strategy predicted by the model. Subsequently, a comparative annual and cumulative rate reduction of tuberculosis in Malaysia with Isoniazid Preventive Therapy as combined strategy introduced at these two different points in time i.e. year 1990 and 2015 was then demonstrated.

3.4 Formulation of a policy recommendation

This section briefly described the methods involved to formulate the policy recommendation to affirm research team commitment to knowledge translation into policy and implementation. The study predicated its study evidence and conclusion. The objective of recommendation was formulated, followed by policy write-up and its application in the community. This section concluded with the documentation of the recommendation and suggestion of the further work for implementation. The results are presented separately in Chapter 6, the policy recommendation chapter.

3.5 Summary of Chapter 3

In general, this chapter elaborated the methods used in this study in order to answer the research question and achieve the research objectives. The layout is more clinically based. It elaborated all work process that had taken place and ensured all aspects were thoroughly explained. The research question and disease under study best fits the SEIR compartmental deterministic transmission dynamic mathematical modelling. The model was built upon the Ordinary Differential Equation (ODE) system and fourth order of iterative method, Runge-Kutta (RK4). Limitations and challenges of this study were generally highlighted with detailed discussion and solutions further elaborated in Chapter 5. Following this chapter is Chapter 4 which presented all results according to the objectives. The profile of this study model is summarised in Table 3.2 below:

Table 3.2: The summary of study profile

Study timeline:	July 2009 till November 2015
Study population:	Malaysian population
Population targeted for intervention:	Latent high risk sub-populations mainly those infected due to close contacts and those infected due to occupational exposure (healthcare workers)
Type of model:	SEIR compartmental deterministic transmission dynamic, age and gender-structured
Model system:	Ordinary Differential Equation (ODE) system, RK4
Modelling Software:	Model Maker 4 (main), Berkeley Madonna
Model built upon:	a) Vynnycky et al. 1997 b) Blower S. et al. 1996 c) WPR-WHO Model 2006
Main Data Sources:	i) Tuberculosis Information System, Ministry of Health ii) Department of Statistics, Malaysia iii) International Union Against Tuberculosis & Lung Disease (IUATLD) iv) WHO and World Bank Databases

4.1 The Malaysian tuberculosis transmission dynamic mathematical model

This section presents the tuberculosis model developed for Malaysia and its characteristics. The details of the model are presented in eight sub-sections, these include: 1) Introduction to the tuberculosis mathematical model, 2) Structure of the tuberculosis mathematical model, 3) Heterogeneity of the tuberculosis mathematical model (by age and gender), 4) Epidemiological basis and pathophysiology of the tuberculosis mathematical model, 5) Transmission dynamics of the tuberculosis mathematical model, 6) Parameters of the tuberculosis mathematical model, 7) Difference and Differential Equations of the tuberculosis mathematical model, and 8) Scope of the tuberculosis mathematical model.

4.1.1 Introduction to the tuberculosis mathematical model

The Malaysian tuberculosis model constructed in this research is a SEIR (Susceptible-Infected/Exposed-Infectious-Recovered) deterministic age-structured tuberculosis mathematical transmission dynamic model. The diagrammatic representation of this SEIR model is shown in Figure 4.1 below:

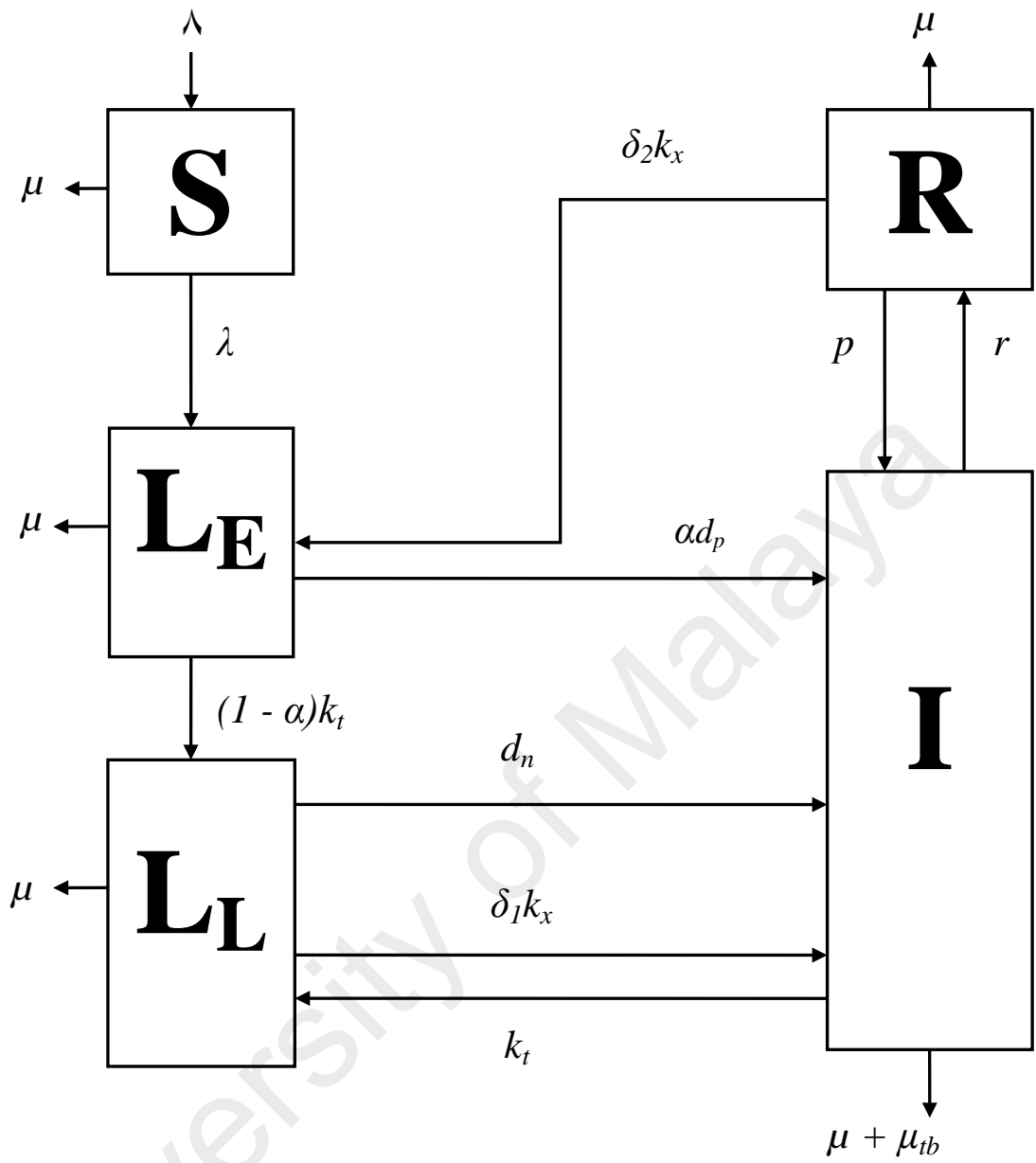


Figure 4.1: Diagrammatic representation of the SEIR deterministic tuberculosis transmission dynamic model for Malaysia

The expression of the SEIR model developed for Malaysia using the differential equations is shown in Figure 4.2.

$$\frac{dS(t)}{dt} = \Lambda(t)N - (\lambda(t) + \mu(t))S(t)$$

$$\frac{dLE(t)}{dt} = \beta I(t)S(t) + \delta_2 kx(t)R(t) - (\mu(t) + \alpha dp(t) + (1 - \alpha)kt(t))LE(t)$$

$$\frac{dLL(t)}{dt} = (1 - \alpha)kt(t)LE(t) - (\delta_1 kx(t) + \mu(t) + dn(t))LL(t)$$

$$\frac{dI(t)}{dt} = \alpha dp(t)LE(t) + (\delta_1 kx(t) + dn(t))LL(t) + p(t)R(t)$$

$$\frac{dR(t)}{dt} = r(t)I(t) - (p(t) + \mu(t) + \delta_2 kx(t))R(t)$$

Where:

S = Number of susceptible individuals at time t

Λ = Population growth at time t

N = Total number of population

λ = The acquisition rate of a susceptible individual becomes infected at time t

μ = Number of deaths from the susceptible population at time t

β = Probability that a specific infectious and susceptible individual comes into effective contact at time t

I = Number of infectious individual at time t

S = Number of susceptible individuals at time t

$\delta_2 kx$ = Proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection at time t

μ = Number of deaths from the susceptible population at time t

α = Proportion of early latent individual becomes infected via primary infection route

dp = Proportion of early latent becomes infectious at time t and $t + 1$ via primary infection route

LE = Number of Early Latent individual at time t

kt = Proportion of early latent individual who become late latent at time t

$\delta_1 kx$ = Proportion of late Latent individuals who become infected again via the first pathway of exogenous reinfection at time t

dn = Proportion of Late Latent individual who becomes infectious via endogenous route or reactivation at time t

LL = Number of Late Latent individual at time t

μ_t = Proportion of death due to infectious tuberculosis at time t

p = Proportion of recovered individuals who become infectious (relapse) at time t

R = Number of individuals who recovered at time t

r = Proportion of infectious individuals who recovered at time t

$\delta_2 kx$ = Proportion of recovered individuals who become infected again via second pathway of exogenous reinfection at time t

Figure 4.2: Differential equations of the SEIR deterministic tuberculosis transmission dynamic model for Malaysia

4.1.2 Scope of the tuberculosis mathematical model

This research designed the Malaysian tuberculosis transmission dynamic model as an age and gender structured deterministic compartmental model using the ordinary differential equation system. The model captures the entire Malaysian population. It incorporates primary tuberculosis infection, endogenous route (reactivation) and exogenous route (reinfection) of tuberculosis infection. The SEIR model incorporated the Malaysian demographic data from Malaysian Statistics Department. The data from the Malaysian Statistics Department included; Malaysian annual birth rate, Malaysian annual mortality rate, and annual Malaysian population growth rate. Immigration data was also included in accordance with the Prevention and Control of Infectious Disease Act 1988. The rate of BCG vaccination and immunization in Malaysian was also taken into account for constructing the SEIR model (Ministry of Health, 2015b).

4.1.3 Epidemiologic basis of tuberculosis used in the SEIR tuberculosis mathematical model

The study acknowledged that the complete pathophysiology and epidemiological triad of host, agent and environment for tuberculosis remain poorly understood. Despite this shortcoming the research ensured that the model developed during this research incorporate the most updated and comprehensive tuberculosis transmission dynamics. This required tremendous effort right from the design stage as discussed in Chapter 3.

The SEIR model framework for this research was built on a sound pathophysiology and epidemiological basis of tuberculosis transmission dynamics developed with the

consensus of main stakeholders of tuberculosis management in Malaysia. This consensual work done during the course of the research is described in detail in Section 3.1.4 in Chapter 3. The national consensus developed for the model construction included the natural history of tuberculosis in Malaysia, the management of tuberculosis in Malaysia and the Malaysian Ministry of Health (MOH) policy on tuberculosis.

The natural history of tuberculosis in Malaysia incorporated the comprehensive pathophysiology which includes primary tuberculosis infection, exogenous re-infection (by exogenous route) and reactivation (endogenous route). The management of tuberculosis in Malaysia is based on the Clinical Practice Guideline for the Management and Control of Tuberculosis as well as the National Tuberculosis Information System; developed by Ministry of Health of Malaysia (Malaysia, 2002a; Ministry of Health Malaysia, 2012). The Malaysian Ministry of Health (MOH) policy on tuberculosis is adopted in line with the WHO guidelines and included the Five Elements of DOTS by WHO and the STOP-TB Strategy. Therefore, the definition of the terms and parameters used in this research were defined according to the standard terminology adopted by the Ministry of Health Malaysia. These include:

- **Pulmonary tuberculosis:** Tuberculosis cases of lung parenchymal involvement
- **Pulmonary tuberculosis smear positive:** Patient diagnosed with tuberculosis after 2 consecutive positive sputum smears or 1 positive sputum smear with positive radiological findings or 1 positive sputum smear with culture positive for *Mycobacterium tuberculosis*
- **Infectious tuberculosis:** Tuberculosis cases with positive sputum smear
- **Primary Infection:** result from initial infection of tubercle bacilli with a high chance of developing active tuberculosis within 5 years

- **Secondary infection:** individuals who progress to active tuberculosis for >5 years after infection as a result of prolonged and sustained close contacts with a primary case or endogenous reactivation and/ or exogenous re-infection
- **Latent Infection:** individuals who are neither clinically ill nor capable of transmitting tuberculosis but Mantoux positive
- **Exogenous Infection or Reinfection:** individuals in latent state but acquired infection from other individuals contracted with the disease
- **Endogenous Infection or Reactivation:** individuals in latent state who progress to active state due to intrinsic factor within himself
- **Drug resistance:** individuals who remain active with
 - either Isoniazid or Rifampicin (**for mono drug resistance tuberculosis**)
 - both Isoniazid and Rifampicin despite treatment commencement of at least 2 months (**for multi-drug resistance tuberculosis i.e. MDRTB**)
 - **or both Isoniazid and Rifampicin** as well as well as at least two of the six primary classes of second-line drugs, one being a fluoroquinolone and the other an injectable drug

(**for extremely drug resistance tuberculosis i.e. XDR-TB**)
- **Chronic tuberculosis case:** Tuberculosis cases whose sputum smear remained positive or turned positive after retreatment under the DOTS supervision
- **Recurrent or retreatment:** repeated tuberculosis cases or cases with interrupted treatment or failure of treatment who is undergoing the treatment regime
- **Recovery or Cure:** individuals whose sputum smear positive converted to negative at the end of treatment regime or at least 1 month before completion of treatment regime with at least 1 sputum smear negative of at least 1 month or more before the completion of treatment regime

- **Relapse:** individuals who have completed treatment regime and confirmed in cure state, yet noted remain in active state i.e. either by positive sputum smear or other laboratory findings or radiological findings or clinical findings
- **Tuberculosis Mortality:** Death where cases in midst of tuberculosis treatment regardless of the cause of death e.g. motor-vehicle accident, AIDS etc.

4.1.4 Structure and states of the tuberculosis mathematical model

The Malaysian tuberculosis model developed in this study was a SEIR compartmental deterministic model. This customized model was derived from the standard basic SEIR compartmental model as shown in Figure 4.3 below:

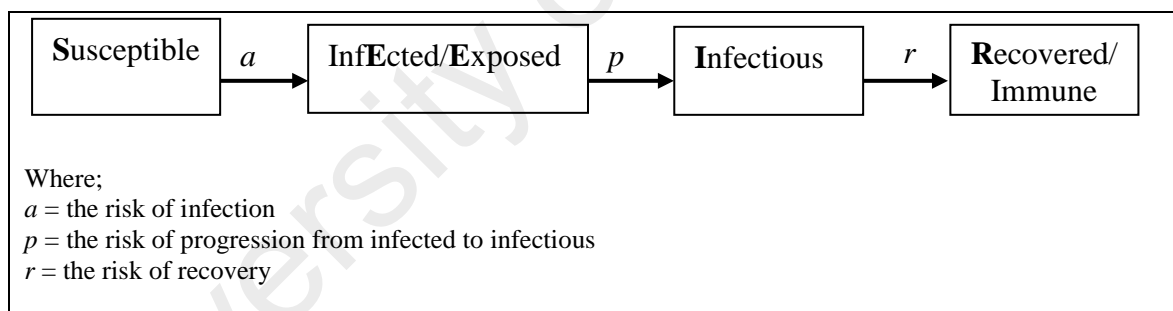


Figure 4.3: Standard basic SEIR compartmental model for tuberculosis

For the customized Malaysian model, the Infected/Exposed compartment of the standard basic SEIR model is expanded into early latent and late latent tuberculosis infection to address the research question. This is shown in Figure 4.4 below:

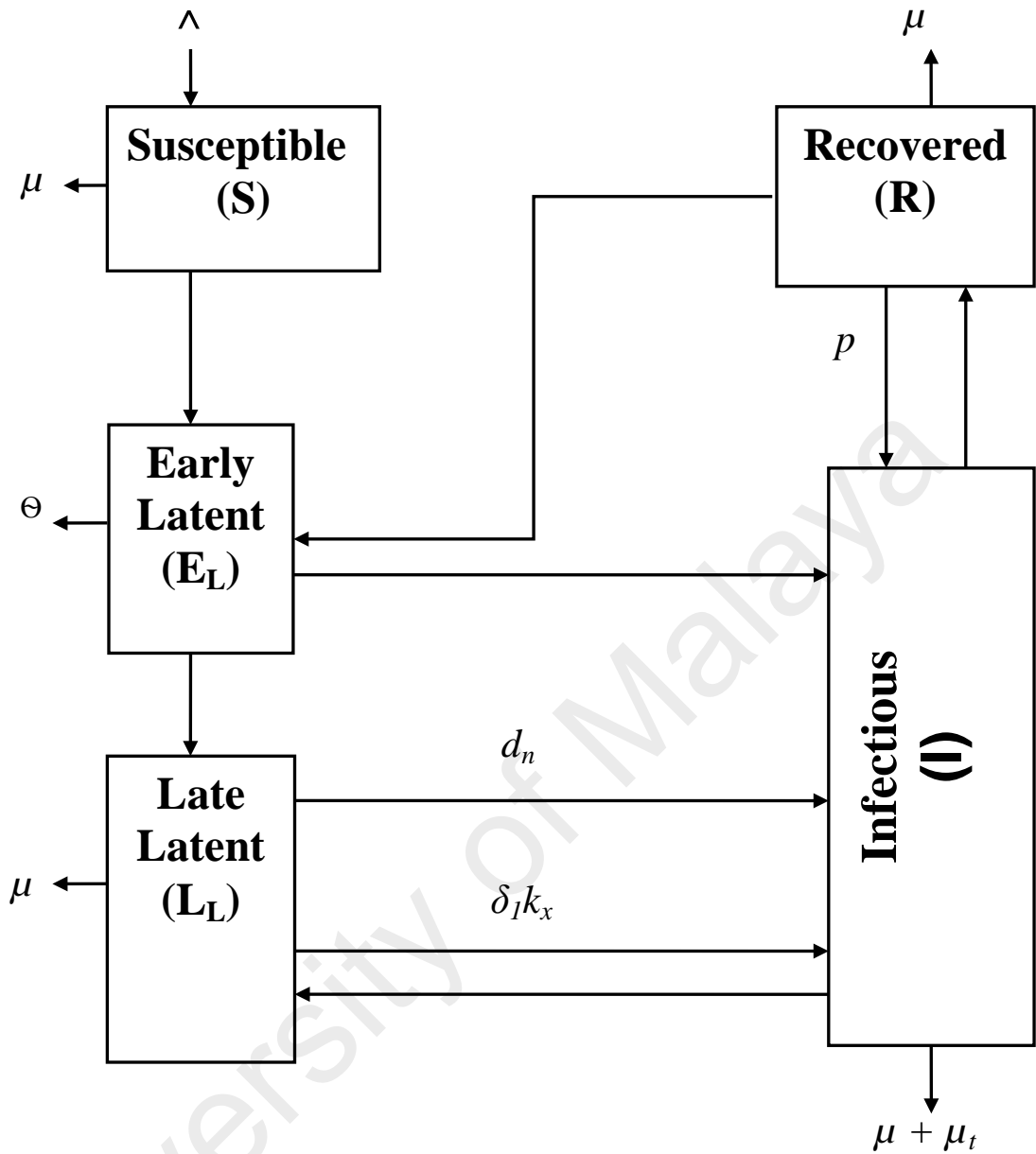


Figure 4.4: Expanded SEIR compartmental deterministic transmission dynamic tuberculosis model for Malaysia

The SEIR compartmental deterministic transmission dynamic tuberculosis model constructed for Malaysia captures the entire Malaysian population. The customized model shows the population disease transmission dynamics among various groups. There are 5 different population groups that explain the different disease states in the

entire Malaysian population. These are also termed as “state” and are shown in Figure 4.4.

The state variable “S” describes the number of susceptible individuals in the Malaysian population. At this stage these individuals are disease free, but still are at a risk of acquiring the tuberculosis infection.

The “L” state stands for ‘Latent’ that represents the Malaysian population who are infected with tuberculosis. this population group includes individual who are passively carrying the tuberculosis infection within the general population without population realizing it. This is because these “L” group do not have any clinical manifestation of tuberculosis infection, thus avoiding being captured in any formalized detection and intervention program. This “L” population group is enhanced further into 2 states expressed as “L_E” state and “L_L” state. The “L_E” state represents the ‘Early Latent’ tuberculosis infection. That means the members of this L_E group carry the infection without any clinical manifestation, during the first five (05) years from the time of first exposure. The “L_L” state represents the ‘Late Latent’ tuberculosis infection. That means the members of this L_L group carry the infection without any clinical manifestation, beyond the first five (05) years from the time of first exposure.

The “I” state represents the “Infectious” group in the Malaysian population. Infectious population consists of individuals who are infected with tuberculosis infection and manage to reach the disease state. They are captured using various formalized detection intervention programs in Malaysia due to their clinical manifestations that can range from mild to extensive signs and symptoms.

The “R” state represents the “Recovery” group in the Malaysian population. These include individuals who manifested tuberculosis infection and manage to recover completely with appropriate treatment. One of the assumptions in the model is that all individuals who progressed into state “R” received formalized tuberculosis treatment only. It was also consensually agreed that in Malaysian setting, individuals who recovered without formalized treatment were very highly unlikely, that it is negligible; given the persistent high rate of tuberculosis mortality as well as pathophysiological sound.

The summation of all these population states (S, L_E , L_L , I and R) equates the total Malaysian population given at any time t and is expressed as “N”. These states are summarized in Table 4.1 below:

Table 4.1: States of population used in the Malaysian tuberculosis transmission dynamic model

State	Descriptions	Assumptions
S	Number of susceptible individuals	
L_E	Number of early latent tuberculosis infected individuals	History of contacts within the first 5 years of exposure regardless of prior exposure status. Includes exogenous reinfection i.e. those reinfected following successful treatment (recurrent exposure)
L_L	Number of late latent tuberculosis infected individuals	History of contacts more than 5 years of exposure
I	Number of infectious tuberculosis cases	Equates annual incidence of tuberculosis at t time
R	Number of those recovered from tuberculosis following successful treatment	
*N	Total population	N equals to total Malaysian population i.e. aggregation of all other states at time ‘t’, $N(t) = S(t) + L_E(t) + L_L(t) + I(t) + R(t)$

*N is not one of the disease states, but the summation of all the other disease states

4.1.5 Heterogeneity of the tuberculosis mathematical model

The general SEIR model is a homogenous model. The customized Malaysian deterministic tuberculosis transmission dynamic model constructed in this research is the more refined version of the standard homogenous model. The Malaysian customized model incorporates heterogeneity by stratification of age and gender according to specific tuberculosis pathophysiology which has been consensually agreed upon by the main stakeholders of tuberculosis management in Malaysia during the development phase of the model. The age categories used in the customized Malaysian model were age groups with 15-year interval. Later each age group is further stratified according to male and female gender. The age categories used for model stratification are shown in Table 3.1. The illustration for refinement of customized model with gender stratification is shown in Figure 3.3.

4.1.6 Tuberculosis transmission dynamic for the Malaysian customized tuberculosis mathematical model

This section covered the transmission dynamic aspects of the customized Malaysian model developed in this study. Issues on the roles of BCG vaccination, illegal immigrants and HIV population were justified.

4.1.6.1 Transmission dynamic of the customized Malaysian tuberculosis mathematical model

This study designed the customized Malaysian tuberculosis transmission dynamic model as a deterministic compartmental model which incorporates primary infection, endogenous route (reactivation) and exogenous route (exogenous reinfection) of tuberculosis infection using the ordinary differential equation system.

At the beginning of the model designing process, the population is considered as “naïve” – population group that neither had infection nor exposure of tuberculosis prior to this. That will leave all the other five population groups (states) without any member. This is expressed as “N” state variable in the equation. Using the different population states, the total population size N at t time in Malaysia is expressed in Figure 4.5 below:

$$N(t) = S(t) + LE(t) + LL(t) + I(t) + R(t)$$

Figure 4.5: Total population size, N at t time in Malaysia

Susceptible individuals are recruited into the population at per capita rate, Λ . Applying frequency dependent mechanism (mass action), susceptible individuals acquire tuberculosis following exposure to an infectious individual at rate of infection, λ (as shown in Figure 4.6 below) and progress to the early latent stage.

$$\text{Recruitment rate, } \lambda = \frac{\beta c I}{N}$$

where;

λ is rate of infection

β is the probability of effective transmission that a susceptible individual becomes infected following exposure to an infectious individual

c as the per capita contact rate of the disease

N is the total population of Malaysia, and

I is population infected with tuberculosis and displaying the clinical manifestations

Figure 4.6: Recruitment rate of the Malaysian tuberculosis model

From this early latent stage (in which the exposure is less than 5 years), a proportion of the infected individuals α , develop the disease at a fast rate d_p (primary infection) while the rest progress to the late latent stage of infection at rate k_t .

Infected individuals at late latent stage moved into infectious stage via two mechanisms – via endogenous reactivation at rate d_n or exogenous reinfection following first exposure or recurrent exposure at rate $\delta_1 k_x$ and $\delta_2 k_x$ respectively, given that $k_x = a\lambda$ where a is the co-efficient of exogenous reinfection.

While many individuals at infectious stage moved to the recovery state of disease at a recovery rate of r , some may revert back to the late latent stage of infection at rate k_r , and become sign/symptom free. Some of these individuals in recovered state relapse back to infectious stage at rate p . Whereas those individuals not immune following effective treatment may be reinfected at recurrent rate $\delta_2 k_x$. The natural mortality rate at each stage is assumed to be $\mu > 0$ and the infectious stage has an additional mortality rate due to tuberculosis at rate μ_t .

4.1.6.2 BCG vaccination

This modelling study focused on the pulmonary tuberculosis as this is the main type of tuberculosis in Malaysia. The BCG vaccination is the preventive therapy of choice for tuberculosis meningitis; therefore it has no role in this modelling study (Moliva, Turner, & Torrelles, 2015; P. E. M. Fine, 1995; Tuberculosis Research Centre Chennai, 1999).

4.1.6.3 Immigrants in Malaysia

The immigrants were captured in this modelling research study via the mandatory notification system in accordance with the Infectious Disease Prevention and Control Act 1988. No active screening or prevalence survey conducted before. The total number of immigrants was estimated at one million as of year estimates in 1990 (Jiloris F.D., 2009; United Nation, 2013).

4.1.6.4 HIV population

HIV epidemic in Malaysia is the concentrated type of epidemic whereby the prevalence in general population is less than 1 in 100,000 populations. HIV patients with tuberculosis were captured in this modelling study during the HIV management intervals and recorded in the mandatory tuberculosis notification system in accordance with the Infectious Disease Prevention and Control Act 1988.

4.1.7 Parameters and equations of the tuberculosis mathematical model

This section presents the parameters used in the customized Malaysian tuberculosis mathematical model. The equations constructed for the model are presented as difference equations and differential equations.

4.1.7.1 Parameters used in the tuberculosis mathematical model

Once the population states were determined according to tuberculosis transmission dynamic, the parameters were identified and quantified before being used in the customized tuberculosis transmission dynamic model for Malaysia. This section stated the details of the parameters used.

The first parameter identified was the recruitment rate expressed as ' Λ '. It represented the annual birth rate of the Malaysian population. Immunization and BCG vaccination were taken into account but were not included in the customized Malaysian model because these factors did not provide protection against pulmonary tuberculosis.

The second parameter identified was α . It represented the proportion of early latent individuals who progressed into the state 'I', the infectious state, within the first five years to the tuberculosis exposure.

The third parameter identified was μ . It represented the mortality rate. There were two types of mortality rates used in this model. The first one was μ_t that represented the mortality rate due to infectious tuberculosis. It took into account the Malaysian national

tuberculosis notification rate and did not include those with successful treatment. The other was μ that represented mortality rates due to other causes. It was equal to the annual Malaysian crude death rate minus the μ_t .

The fourth parameter identified was λ . It represented the force of infection which assumed the frequency dependent mechanism or mass action with homogeneous mixing represented by the formula. This is shown in the Figure 4.7 below:

<p>Force of infection, $\lambda = \frac{\beta I c}{N}$</p>
<p>where; λ is rate of infection β is the probability of effective transmission that a susceptible individual becomes infected following exposure to an infectious individual and c as the per capita contact rate of the disease N is the total population of Malaysia, and I is population infected with tuberculosis and displaying the clinical manifestations</p>

Figure 4.7: Force of infection for tuberculosis model

The fifth parameter identified was k_t . It represented the rate of progression of individuals who have been infected but yet to develop the disease into late latent (L_L) group.

The sixth parameter identified was k_x . It represented the rate of exogenous reinfection which was defined as $k_x = a\lambda$ where a was the co-efficient of exogenous reinfection with similar infection and reinfection rate, $a = 1$

The seventh parameter identified was $\delta_I k_x$. It represented the rate of exogenous reinfection due to primary exposure where individuals at the state of late latent infection progressed into infectious state and δ_I was the coefficient of the first pathway of exogenous reinfection.

The eight parameter identified was $\delta_2 k_x$. It represented the rate of recurrent infection following successful treatment. This also represented the second route of exogenous reinfection but due to recurrent exposure. δ_2 was the coefficient of the second pathway of exogenous reinfection and based on pathophysiology and disease dynamic of tuberculosis in Malaysia, $\delta_1 = \delta_2$.

The ninth parameter identified was d_p . It was defined as the rate of developing infectious tuberculosis at state I, from early latent state. It represented the “Primary Infection”

The tenth parameter identified was d_n . It was defined as the rate of developing the infectious tuberculosis at state I, from late latent (LL) state. It represented the endogenous route of infectious acquisition, clinically termed as “Reactivation”

The eleventh parameter identified was r . It was defined as the rate of recovery. It was assumed that the rate of recovery represented the rate of progression following effective treatment of those with infectious tuberculosis. Individuals who recovered from the disease without effective treatment reverted to late latent state of disease at rate k_t were too small to be taken into consideration.

The twelfth parameter identified was p . It was defined as the rate of relapse where individuals in the recovery state became infectious for whatever reason, regardless of their bacteriological status.

The remaining thirteenth and fourteenth parameters were expressed as θ and π respectively. These represented the rate of progression of those individuals in the early

latent (L_E) and late latent (L_L) states respectively. These individuals did not progress into infectious state due to effective treatment of Isoniazid Preventive Therapy.

Table 4.2 below summarized the parameters identified for the model:

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Table 4.2: List of parameters used in the Malaysian tuberculosis model

Parameter	Descriptions & Assumptions	Value/Unit	Reference
Λ	Recruitment rate. Equates only birth rate Immunization, BCG vaccination and immigration excluded from the model given the seroprevalence data available and nature of the intervention recommended	0.03/year	Malaysian MOH, 2007
μ	Mortality rate due to other causes. The annual crude death rate minus μ_t	0.015/year	Malaysian MOH, 2007
μ_t	Mortality rate due to infectious tuberculosis. Takes into account the national tuberculosis death notification rate and does not include those with successful treatment	0.1/year	Malaysian MOH, 2008
λ	Force of infection, taking into account frequency dependent mechanism or mass action with homogenous mixing: $\lambda = \frac{\beta I c}{N}$	derivatives according to age and gender	
β	Probability of effective tuberculosis transmission	0.35	Dye et al., 1998
c	Per capita contact rate	10/year	
α	Probability of those who develop primary infection within 5 years of exposure	0.07	Dye et al., 1998
k_t	Rate of progression of those who have been infected yet to develop the disease into late latent group	0.2/year	Dye et al., 1998
k_x	Rate of exogenous reinfection. Exogenous reinfection rate k_x defined as $k_x = a\lambda$ where a is the co-efficient of exogenous reinfection and similar infection and reinfection rate, $a = 1$	derivatives according to age and gender	
$\delta_1 k_x$	Rate of exogenous reinfection where individuals at the state of late latent infection where δ_1 is the coefficient of the first pathway of exogenous reinfection and $\delta_1 k_x = \delta_2 k_x$	0.75/year	Styblo K., 1986; Comstock G.W., 1982; Verver S., 2005
$\delta_2 k_x$	Rate of recurrent infection of tuberculosis following successful treatment (recurrent exposure). where δ_2 is the coefficient of the second pathway of exogenous reinfection and $\delta_1 k_x = \delta_2 k_x$	0.75/year	Styblo K., 1986; Comstock G.W., 1982; Verver S., 2005

*The model table utilizes Table 3.1 for stratification of model according to age and gender

Table 4.2, continued

Parameter	Descriptions & Assumptions	Value/Unit	Reference
d_p	Rate of developing infectious tuberculosis from early latent state (primary infection)	0.25/year	Vynnycky & Fine, 1997
d_n	Rate of developing infectious tuberculosis from late latent group via reactivation (endogenous route)	0.00256/year	Vynnycky & Fine, 1998
r	Rate of effective treatment of those with infectious tuberculosis	0.8/year	Malaysian MOH, 2007
p	Rate of relapse for tuberculosis. Relapse back to infectious state regardless of bacteriological status	0.025/year	Malaysian MOH, 2007
gender	Gender stratification by ratio male to female = 1.5: 1	1.5	Malaysian MOH, 2007
θ	Rate of effective IPT for early latents. Individuals in the early latent (L_E) who do not progress into infectious state due to effective treatment of Isoniazid preventive therapy	0.03/year	Model output
π	Rate of effective IPT for late latents. Individuals in late latent (L_L) who do not progress into infectious state due to effective treatment of Isoniazid preventive therapy	0.007/year	Model output

*The model table utilizes Table 3.1 for stratification of model according to age and gender

4.1.7.2 Difference and Differential Equations of the customized Malaysian tuberculosis mathematical model

The Difference and Differential Equations for the customized Malaysian tuberculosis deterministic compartmental dynamic model were determined based on the tuberculosis transmission dynamic in Malaysia. These were stated in this sub-section.

Difference Equations of the model

The difference equations were required to measure the ‘progression’ i.e. movement of proportion of population from one state to another state according to the acquired state of disease dynamic. A total of five difference equations for the customized Malaysian model were described in details in this section. The difference equations derived for the customized tuberculosis deterministic compartmental model in Malaysia were summarized in the Figure 4.8 below:

DIFFERENCE EQUATIONS
$S_{t+1} = \lambda_t N + (1 - \lambda_t - \mu_t) S_t$
$LE_{t+1} = \beta I_t S_t + \delta_2 k x_t R_t + (1 - \mu_t - \alpha d p_t - k t_t + \alpha k t_t) LE_t$
$LL_{t+1} = (1 - \alpha) k t_t LE_t + (1 - \delta_1 k x_t - \mu_t - d n_t) LL_t$
$I_{t+1} = \alpha d p_t LE_t + \delta_1 k x_t LL_t + d n_t LL_t + p_t R_t + (1 - \mu_{tuberculosis_t} - \mu_t - r_t) I_t$
$R_{t+1} = r_t I_t + (1 - p_t - \mu_t - \delta_2 k x_t) R_t$

Figure 4.8: Difference equations for the customized SEIR deterministic tuberculosis transmission dynamic model for Malaysia

The first equation:

$$S_{t+1} = \lambda_t N + (1 - \lambda_t - \mu_t) S_t \text{ ----- Equation 4.1}$$

where;

S_t = Number of susceptible individuals at time t

λ_t = Population growth at time t

N = Total number of population

λ_t = The risk a susceptible individual becomes infected between time t and t+1

μ_t = Number of deaths from the susceptible population at time t

Figure 4.9: Difference equation of tuberculosis model for susceptible population as Equation 4.1

Equation 4.1 elaborated the relationship between the factors and risk involved for a susceptible individual becoming infected between time t and t+1. The factors involved were population growth, the size of population, the risk of a susceptible individual becoming infected between time t and t+1, and death from the susceptible population.

The second equation:

$$LE_{t+1} = \beta I_t S_t + \delta_2 k x_t R_t + (1 - \mu_t - \alpha dp_t - kt_t + akt_t) LE_t \text{ ----- Equation 4.2}$$

where;

LE_t = Number of Early Latent individual at time t

β = Probability that a specific infectious and susceptible individual come into effective contact between time t and t+1

I_t = Number of infectious individual at time t

$\delta_2 k x_t$ = Proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection between time t and t+1

R_t = Number of recovered individual at time t

μ_t = Number of death individual between time t and t+1

α = Proportion of early latent individual becomes infected via primary infection route

dp_t = Proportion of early latent becomes infectious between time t and t + 1 via primary infection route

kt_t = Proportion of early latent individual who become late latent between time t and t+1,

Figure 4.10: Difference equation of tuberculosis model for early latent population as Equation 4.2

Equation 4.2 elaborated the relationship between the factors and risk involved for an early latent becoming late latent between time t and t+1. The factors included: a) probability that a specific infectious and susceptible individual come into effective contact between time t and t+1, b) proportion of early latent becomes infectious between time t and t +1 via primary infection route, c) proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection between time t and t+1, d) number of recovered individual between time t and t+1, e) proportion of early latent individual becomes infected via primary infection route, f) number of early latent becomes infectious at time t via primary infection route, and g) proportion of early latent individual who become late latent between time t and t+1.

The third equation:

$$LL_{t+1} = (1 - \alpha)kt_tLE_t + (1 - \delta_I kx_t - \mu_t - dn_t)LL_t \text{ ----- Equation 4.3}$$

Where;

LL_t = Number of Late Latent individual at time t

α = Proportion of early latent individual becomes infected via primary infection route

kt_t = Proportion of early latent individual who become late latent between time t and t+1,

LE_t = Number of Early Latent individual at time t

$\delta_I kx_t$ = Proportion of late Latent individuals who become infected again via the first pathway of exogenous reinfection between time t and t+1

μ_t = Number of death individual between time t and t+1

dn_t = Proportion of Late Latent individual who becomes infectious via endogenous route or reactivation between time t and t+1

Figure 4.11: Difference equation of tuberculosis model for late latent population as Equation 4.3

Equation 4.3 elaborated the relationship between the factors and risk involved for a late latent individual between time t and t+1. The factors involved: a) number of Late Latent individual at time t, b) proportion of early latent individual becomes infected via primary infection route, c) proportion of early latent individual who become late latent between time t and t+1, d) number of early latent individual at time t, e) proportion of late latent individuals who become infected again via the first pathway of exogenous reinfection between time t and t+1, f) number of death individual between time t and t+1, g) proportion of late latent individual who becomes infectious via endogenous route or reactivation between time t and t+1

The fourth equation:

$$I_{t+1} = \alpha dp_t LE_t + \delta_1 kx_t LL_t + dn_t LL_t + p_t R_t + (1 - \mu_{tuberculosis_t} - \mu_t - r_t) I_t \text{ -----}$$

----- Equation 4.4

Where;

I_t = Number of infectious individual at time t

α = Proportion of early latent individual becomes infected via primary infection route

dp_t = Proportion of early latent becomes infectious between time t and t +1 via primary infection route

LE_t = Number of Early Latent individual at time t

$\delta_1 kx_t$ = Proportion of late Latent individuals who become infected again via the first pathway of exogenous reinfection between time t and t+1

dn_t = Proportion of Late Latent individual who becomes infectious via endogenous route or reactivation between time t and t+1

LL_t = Number of Late Latent individual at time t

p_t = Proportion of recovered individuals who become infectious (relapse) between time t and t+1

R_t = Number of individuals who recovered at time t

$\mu_{tuberculosis_t}$ = Proportion of death due to infectious tuberculosis between time t and t+1

μ_t = Proportion of death due to other causes between time t and t+1

r_t = Proportion of infectious individuals who recovered between time t and t+1

Figure 4.12: Difference equation of tuberculosis model for infectious population as Equation 4.4

Equation 4.4 elaborated the relationship between the factors and risk involved for an infectious individual between time t and t+1. The factors involved: a) number of infectious individual at time t, b) proportion of early latent individual becomes infected via primary infection route, c) proportion of early latent becomes infectious between time t and t +1 via primary infection route, d) number of early latent individual at time t, e) proportion of late latent individuals who become infected again via the first pathway of exogenous reinfection between time t and t+1, f) proportion of late latent individual who becomes infectious via endogenous route or reactivation between time t

and t+1, g) number of late latent individual at time t, h) proportion of recovered individuals who become infectious (relapse) between time t and t+1, i) number of recovered at time t, j) proportion of death due to infectious tuberculosis between time t and t+1, k) proportion of death due to other causes between time t and t+1, and l) proportion of infectious individuals who recovered between time t and t+1.

The fifth and last difference equation:

$$R_{t+1} = r_t I_t + (1 - p_t - \mu_t - \delta_2 k x_t) R_t \text{----- Equation 4.5}$$

Where;

R_t = Number of individuals who recovered at time t

r_t = Proportion of infectious individuals who recovered between time t and t+1

I_t = Number of infectious individuals at time t

p_t = Proportion of recovered individuals who become infectious (relapse) between time t and t+1

μ_t = Proportion of death due to other causes between time t and t+1

$\delta_2 k x_t$ = Proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection between time t and t+1

R_t = Number of recovered at time t

Figure 4.13: Difference equation of tuberculosis model for recovered population as Equation 4.5

Equation 4.5 elaborated the relationship between the factors and risk involved for a recovered individual between time t and t+1. The factors involved: a) number of individuals who recovered at time t, b) proportion of infectious individuals who recovered between time t and t+1, c) proportion of recovered individuals who become infectious (relapse) between time t and t+1, d) proportion of death due to other causes between time t and t+1, e) proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection between time t and t+1, and f) number of recovered at time t.

Differential Equations of the model

The model developed in this research was a deterministic model. In a deterministic model, the differential equations were pre-determined based on the disease dynamics and underlying pathophysiology. In this research, the research team ensured that not only the most updated pathophysiology but the stakeholders' inputs were also incorporated into the model.

The differential equations expressed the rate of change of different states of disease in the population dynamics. With the differential equation the research team have a dynamic model in hand because it incorporated *instantaneous change* to any changes of parameters in the model with relation to *time*. A total of five differential equations derived for the customized Malaysian model were expressed in detail in this section.

The differential equations derived for the customized tuberculosis deterministic compartmental model in Malaysia were summarized in the Figure 4.14:

DIFFERENTIAL EQUATIONS

$$\frac{dS(t)}{dt} = \Lambda(t)N - (\lambda(t) + \mu(t))S(t)$$

$$\frac{dLE(t)}{dt} = \beta I(t)S(t) + \delta_2 kx(t)R(t) - (\mu(t) + \alpha dp(t) + (1 - \alpha)kt(t))LE(t)$$

$$\frac{dLL(t)}{dt} = (1 - \alpha)kt(t)LE(t) - (\delta_1 kx(t) + \mu(t) + dn(t))LL(t)$$

$$\frac{dI(t)}{dt} = \alpha dp(t)LE(t) + (\delta_1 kx(t) + dn(t))LL(t) + p(t)R(t)$$

$$\frac{dR(t)}{dt} = r(t)I(t) - (p(t) + \mu(t) + \delta_2 kx(t))R(t)$$

Figure 4.14: Differential equations of the tuberculosis model

The first differential equation:

Rate of change of susceptible individuals;

$$\frac{dS(t)}{dt} = \lambda(t)N - (\lambda(t) + \mu(t))S(t) \text{----- Equation 4.6}$$

where;

$\frac{dS(t)}{dt}$ = Rate of change of susceptible individuals

$S(t)$ = Number of susceptible individuals at time t

$\lambda(t)$ = Population growth at time t

N = Total number of population; i.e.

$$N(t) = S(t) + LE(t) + LL(t) + I(t) + R(t)$$

$\lambda(t)$ = The acquisition rate of a susceptible individual becomes infected at time t

$\mu(t)$ = Number of deaths from the susceptible population at time t

Figure 4.15: Differential equation of tuberculosis model for susceptible population as Equation 4.6

Equation 4.6 showed the rate of change in the numbers of susceptible individuals over time. The equation was derived from disease dynamic as shown the Figure 4.16 below:

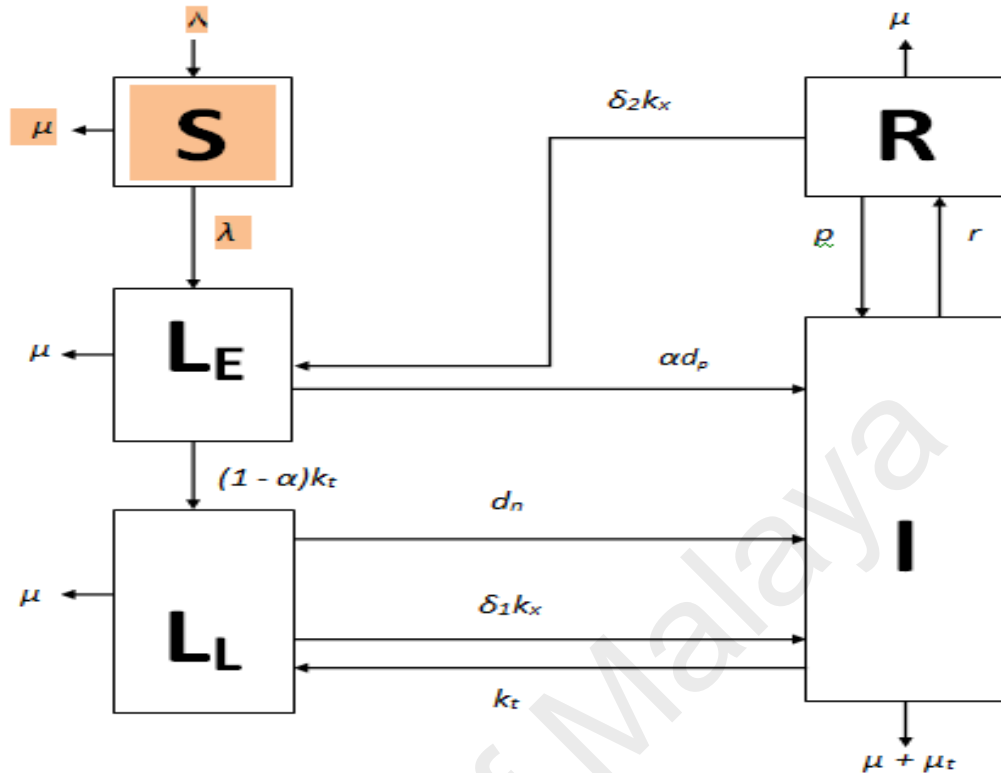


Figure 4.16: Highlighting the model parameters used in the building of the Equation 4.6

The factors involved in constructing the Equation 4.6: a) number of susceptible individuals at time t , b) population growth at time t , c) total number of population, d) acquisition rate of a susceptible individual becomes infected at time t , and e) number of deaths from the susceptible population at time t .

The second differential equation:

Rate of change of early latent state;

$$\frac{dLE(t)}{dt} = \beta I(t)S(t) + \delta 2kx(t)R(t) - (\mu(t) + \alpha dp(t) + (1 - \alpha)kt(t))LE(t)$$

--- Equation 4.7

where;

$$\frac{dLE(t)}{dt} = \text{Rate of change of early latent state individuals}$$

β = Probability that a specific infectious and susceptible individual come into effective contact at time t. It is derived from the equation;

$$\lambda = \frac{\beta cI}{N}$$

$I(t)$ = Number of infectious individual at time t

$S(t)$ = Number of susceptible individuals at time t

$\delta 2kx$ = Proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection at time t

$\mu(t)$ = Number of deaths from the susceptible population at time t

α = Proportion of early latent individual becomes infected via primary infection route

$dp(t)$ = Proportion of early latent becomes infectious at time t and t +1 via primary infection route

$LE(t)$ = Number of Early Latent individual at time t

Figure 4.17: Differential equation of tuberculosis model for early latent population as Equation 4.7

Equation 4.7 showed the rate of change in the numbers of early latent individuals over time. The equation was derived from disease dynamic as shown the Figure 4.18 below:

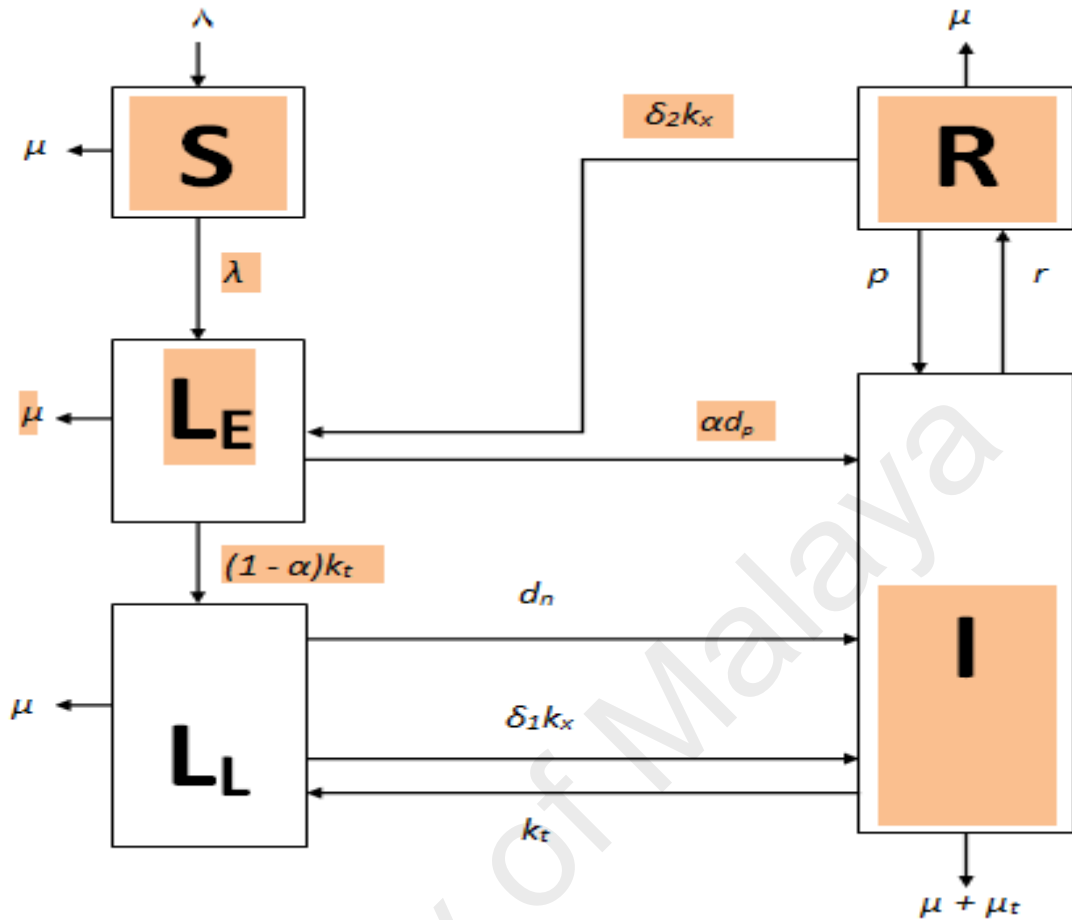


Figure 4.18: Highlighting the model parameters that are used in the building the Equation 4.7

The factors involved: a) probability that a specific infectious and susceptible individual come into effective contact at time t , b) number of infectious individual at time t , c) number of susceptible individuals at time t , d) proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection at time t , e) number of deaths from the susceptible population at time t , f) proportion of early latent individual becomes infected via primary infection route, g) proportion of early latent becomes infectious at time t and $t + 1$ via primary infection route, and h) number of early latent individual at time t .

The third differential equation:

Rate of change of late latent state;

$$\frac{dLL(t)}{dt} = (1 - \alpha)kt(t)LE(t) - (\delta_1 kx(t) + \mu(t) + dn(t))LL(t) \text{----- Equation 4.8}$$

where;

$\frac{dLL(t)}{dt}$ = Rate of change of late latent state individuals

α = Proportion of early latent individual becomes infected via primary infection route

$kt(t)$ = Proportion of early latent individual who become late latent at time t

$LE(t)$ = Number of Early Latent individual at time t

$\delta_1 kx(t)$ = Proportion of late Latent individuals who become infected again via the first pathway of exogenous reinfection at time t

$\mu(t)$ = Number of death individual at time t

$dn(t)$ = Proportion of Late Latent individual who becomes infectious via endogenous route or reactivation at time t

$LL(t)$ = Number of Late Latent individual at time t

Figure 4.19: Differential equation of tuberculosis model for late latent population as Equation 4.8

Equation 4.8 showed the rate of change in the numbers of late latent individuals over time. The equation was derived from disease dynamic as shown in Figure 4.20 below.

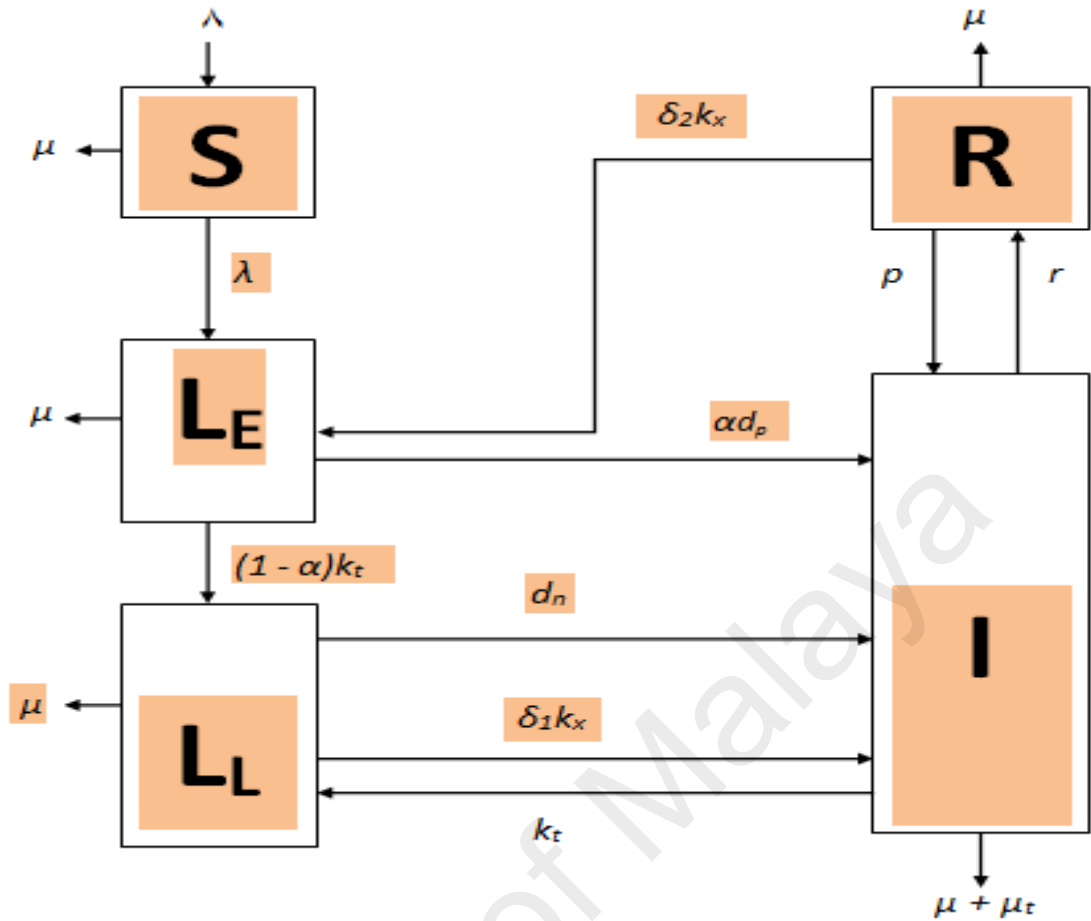


Figure 4.20: Highlighting the model parameters that are used in the building the Equation 4.8.

The factors involved: a) proportion of early latent individual becomes infected via primary infection route, b) proportion of early latent individual who become late latent at time t , c) number of early latent individual at time t , d) proportion of late latent individuals who become infected again via the first pathway of exogenous reinfection at time t , e) number of death individual at time t , f) proportion of late latent individual who becomes infectious via endogenous route or reactivation at time t , and g) Number of late latent individual at time t .

The fourth differential equation:

Rate of change of infectious state;

$$\frac{dI(t)}{dt} = \alpha dp(t)LE(t) + (\delta_1 kx(t) + dn(t))LL(t) + p(t)R(t) - (\mu tb(t) + \mu(t) + r(t))I(t)$$

----Equation 4.9

where;

$\frac{dI(t)}{dt}$ = Rate of change of infectious state individuals

α = Proportion of early latent individual becomes infected via primary infection route

$dp(t)$ = Proportion of early latent becomes infectious at time t via primary infection route

$LE(t)$ = Number of Early Latent individual at time t

$\delta_1 kx_t$ = Proportion of late Latent individuals who become infected again via the first pathway of exogenous reinfection at time t

$dn(t)$ = Proportion of Late Latent individual who becomes infectious via endogenous route or reactivation at time t

$\mu(t)$ = Number of dead individual at time t

$\mu tuberculosis_t$ = Proportion of death due to infectious tuberculosis at time t

$LL(t)$ = Number of Late Latent individual at time t

$p(t)$ = Proportion of recovered individuals who become infectious (relapse) at time t

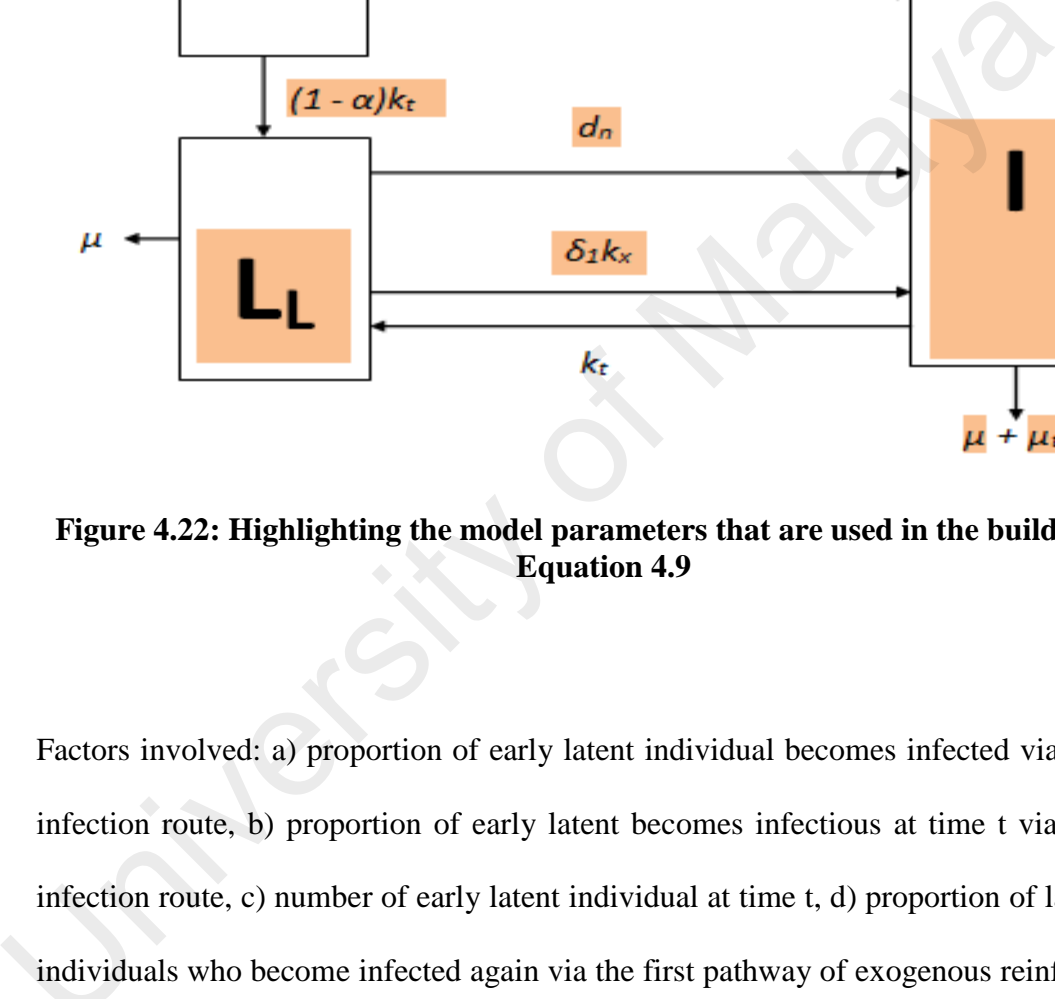
$R(t)$ = Number of individuals who recovered at time t

$r(t)$ = Proportion of infectious individuals who recovered at time t

$I(t)$ = Number of infectious individuals at time t

Figure 4.21: Differential equation of tuberculosis model for infectious population as Equation 4.9

Equation 4.9 showed the rate of change in the numbers of infectious individuals over time. The equation was derived from disease dynamic as shown in Figure 4.22 below.



individuals who become infected again via the first pathway of exogenous reinfection at time t , e) proportion of late latent individual who becomes infectious via endogenous route or reactivation at time t , f) number of dead individual at time t , g) proportion of death due to infectious tuberculosis at time t , h) number of late latent individual at time t , i) proportion of recovered individuals who become infectious (relapse) at time t , j) number of individuals who recovered at time t , k) proportion of infectious individuals who recovered at time t , and l) number of infectious individuals at time t .

The fifth differential equation:

Rate of change of susceptible individuals;

$$\frac{dR(t)}{dt} = r(t)I(t) - (p(t) + \mu(t) + \delta 2kx(t))R(t) \text{ ----- Equation 4.10}$$

where;

$$\frac{dLR(t)}{dt} = \text{Rate of change of susceptible individuals}$$

$r(t)$ = Proportion of infectious individuals who recovered at time t

$I(t)$ = Number of infectious individuals at time t

$\mu(t)$ = Proportion of death due to other causes at time t

$\delta 2kx(t)$ = Proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection at time t

$R(t)$ = Number of recovered at time t

Figure 4.23: Differential equation of tuberculosis model for recovered population as Equation 4.10

Equation 4.10 showed the rate of change in the numbers of recovered individuals over time. The equation was derived from disease dynamic as shown in Figure 4.24 below.

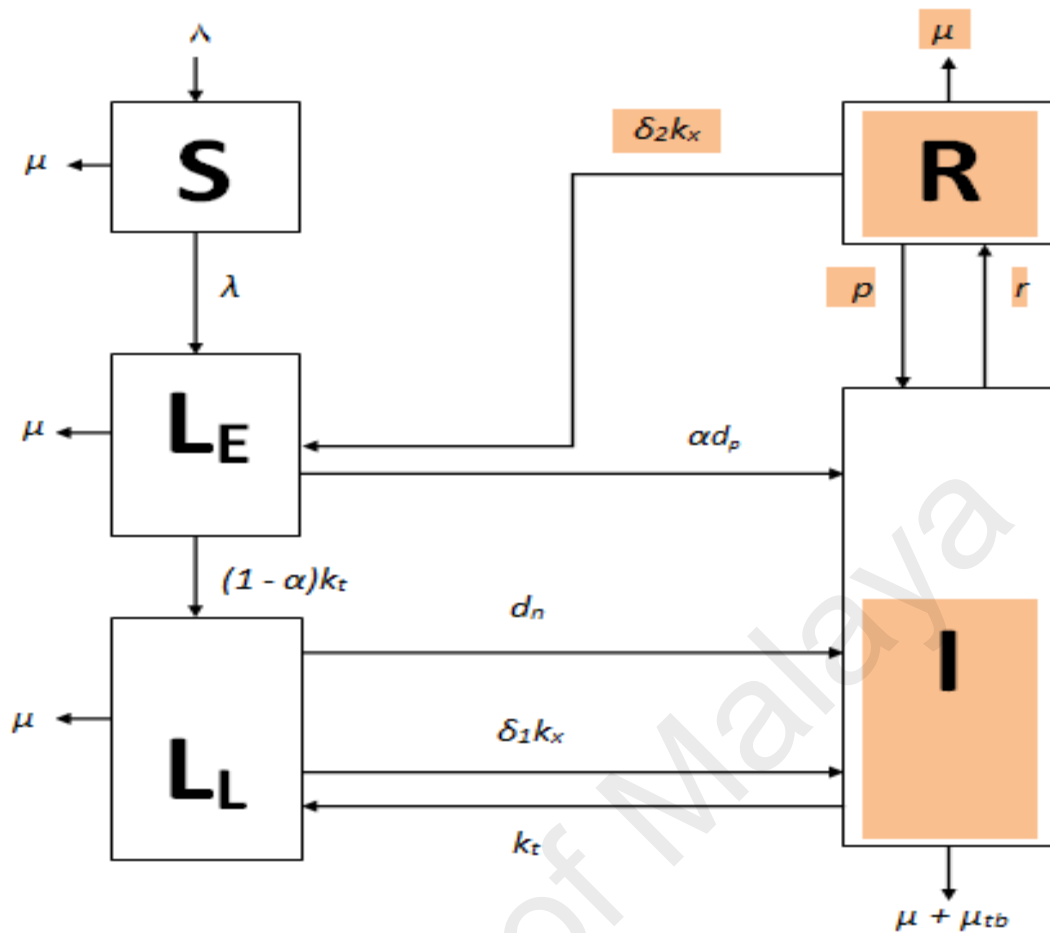


Figure 4.24: Highlighting the model parameters that are used in the building the Equation 4.10

Factors involved: a) proportion of infectious individuals who recovered at time t , b) number of infectious individuals at time t , c) proportion of death due to other causes at time t , d) proportion of recovered individuals who become infected again via the second pathway of exogenous reinfection at time t , and f) number of recovered at time t .

4.1.8 Model robustness, optimization and validation

4.1.8.1 Model robustness

Sensitivity and scenario analyses were performed on several selected parameters. These parameters included effective treatment rate, contact rate, relapse rate, exogenous re-infection rate and endogenous rate.

4.1.8.2 Model optimization and validation

Optimization and fitting of the model were performed against the observed number of tuberculosis cases in Malaysia from 1990 till 2010 in view of the reliability of data and event consistency as described in Chapter 3. The observed numbers of tuberculosis cases were extracted from the Malaysian Ministry of Health Tuberculosis Information System. The optimization and fitting work were illustrated in the following Figure 4.25. The predicted numbers were indicated as the continuous blue line (Inf_{total}) whereas the observed values of tuberculosis cases for the corresponding years were shown as the red dots (Case Notifications). The lower limit and upper limit projections of the optimized and best-fitted model were also shown as the pink dot-dash line (minimum) and the green dash line (maximum) respectively. The optimization statistics was derived using Marquardt method yield $r^2 = 0.9315$, $p < 0.0001$. The model was validated by using notification data from 1990 to 2014 and quantified the annual mean difference or underrepresentation was quantified at 13.49% (95%CI: 10.39;15.84) as illustrated in Figure 4.26. The optimized and best fitted model for predicting tuberculosis in Malaysia was presented as Figure 4.26 and showed a steady rise of incidence trend till 2030.

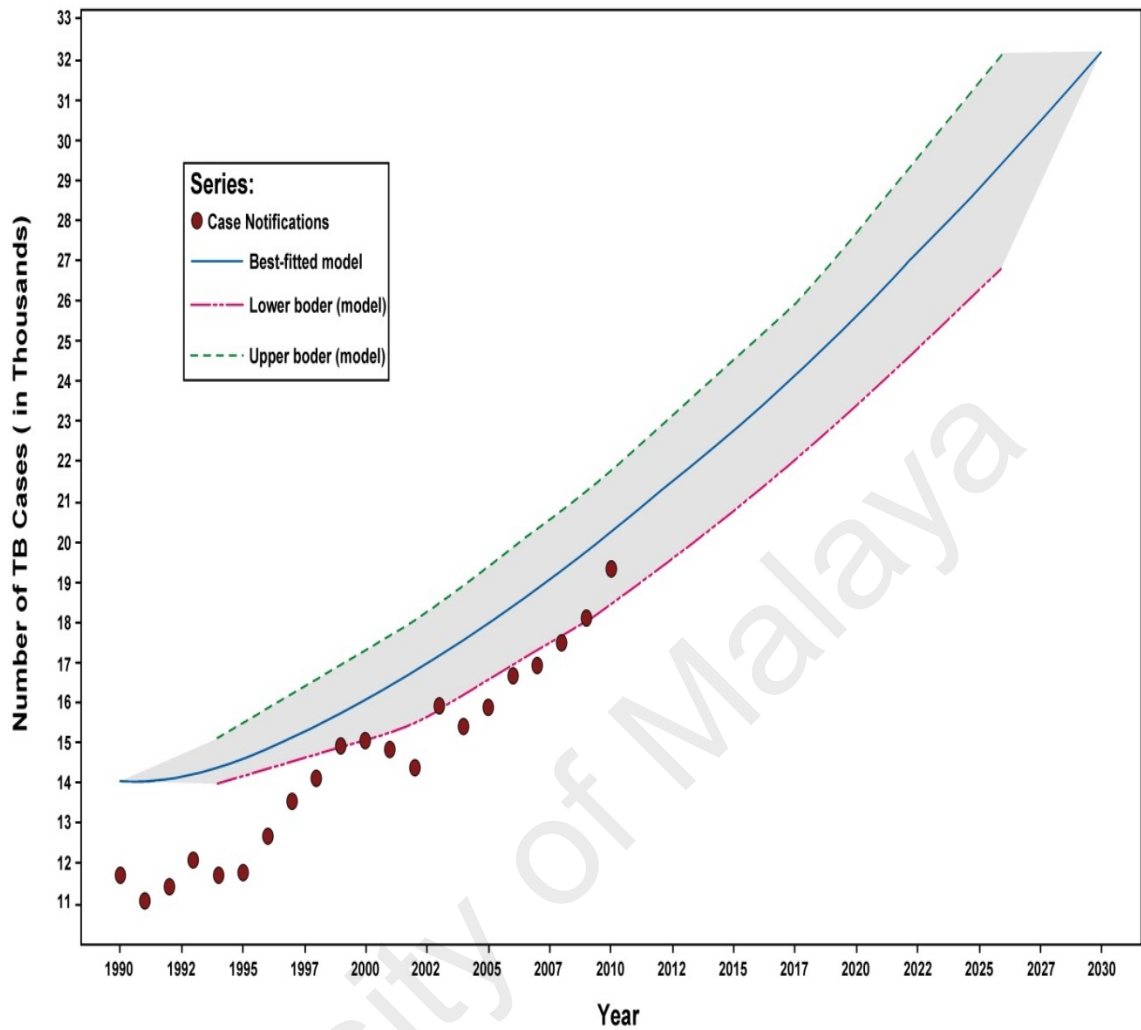


Figure 4.25: The optimization and best-fitting of the model showing the predicted tuberculosis incidence against the observed number of tuberculosis cases in Malaysia from 1990 till 2010 indicated as blue line (Best-fitted model) and red dots (Case Notifications) respectively. The lower and upper border projections of the model are also shown as pink dot-dash line and green dash line respectively.

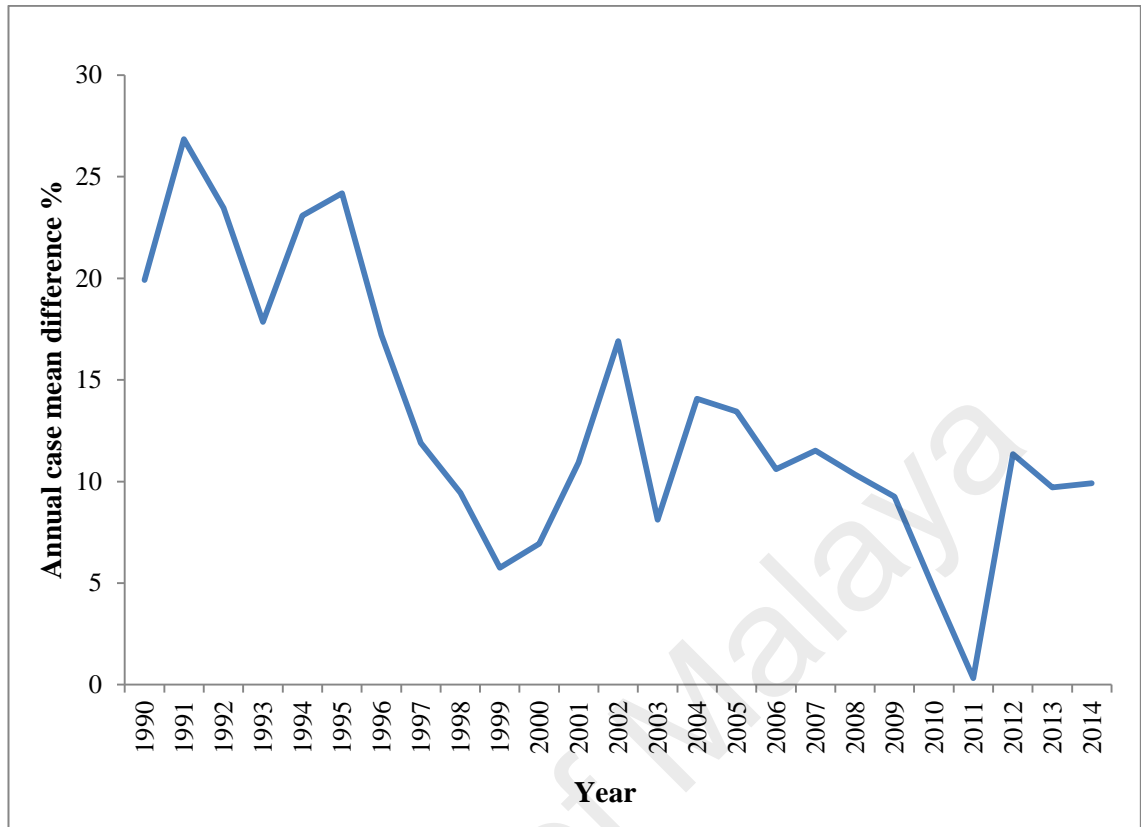


Figure 4.26: Distribution of tuberculosis case underrepresentation between 1990-2014 in Malaysia. The annual mean difference or underrepresentation was quantified at 13.49% (95%CI: 10.39;15.84).

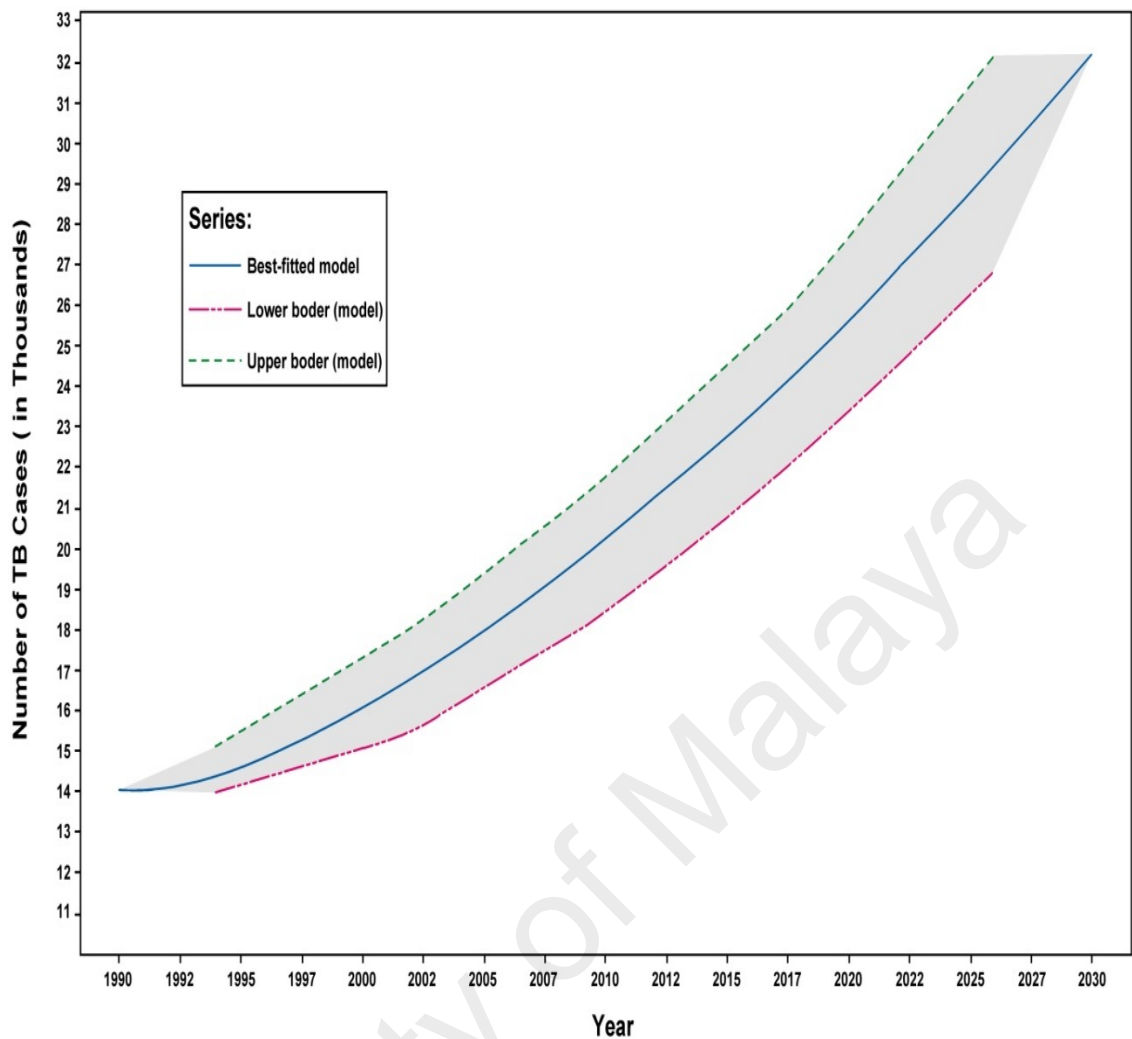


Figure 4.27: The optimized and best-fitted model for predicting tuberculosis incidence indicated as blue line shows a steady increase of cases in Malaysia till 2030. The lower and upper border projections of the model are also shown as pink dot-dash line and green dash line respectively.

4.2 Impact assessment on tuberculosis intervention strategies in Malaysia

This section presented the results of the use of the customized Malaysian tuberculosis transmission dynamic model presented in Section 4.1. It applied infectious disease mathematical modelling technique to assess the potential impact of a proposed intervention strategy to effectively reduce tuberculosis burden in Malaysia. The proposed intervention strategy of combination of current tuberculosis treatment for infectious tuberculosis cases and Isoniazid Preventive Therapy for high risk latent tuberculosis infection sub-populations is assessed in Malaysia using customized Malaysian tuberculosis transmission dynamic model developed in this study.

The results were presented in five sub-sections. The first sub-section presented the estimates and projections of current tuberculosis burden in Malaysia using the customized Malaysian tuberculosis transmission dynamic model. The second sub-section presented the results of combined intervention of current treatment strategy and Isoniazid Preventive Therapy (chemoprophylaxis) as an effective strategy for managing tuberculosis epidemic in Malaysia using the customized Malaysian tuberculosis transmission dynamic model. The third sub-section quantified how effective (in terms of coverage) Isoniazid Preventive Therapy that treated early latent infection cases needed to be to effectively reduce the incidence of tuberculosis in Malaysia using the customized Malaysian tuberculosis transmission dynamic model. The fourth sub-section presented selection of high risk latent tuberculosis sub-populations for optimal coverage by comparing early latent infection and late latent. The fifth sub-section presented the overall impact of combined intervention of current treatment strategy and Isoniazid Preventive Therapy (chemoprophylaxis) in relation to MDG targets and STOP TB

Strategy towards Tuberculosis Elimination 2050 using the customized Malaysian tuberculosis transmission dynamic model.

4.2.1 Estimates and projection of tuberculosis cases in Malaysia

This section presented the estimates of tuberculosis cases in Malaysia from 1990 till 2030 using the customized Malaysian tuberculosis transmission dynamic model. It is illustrated in Figure 4.28 below.

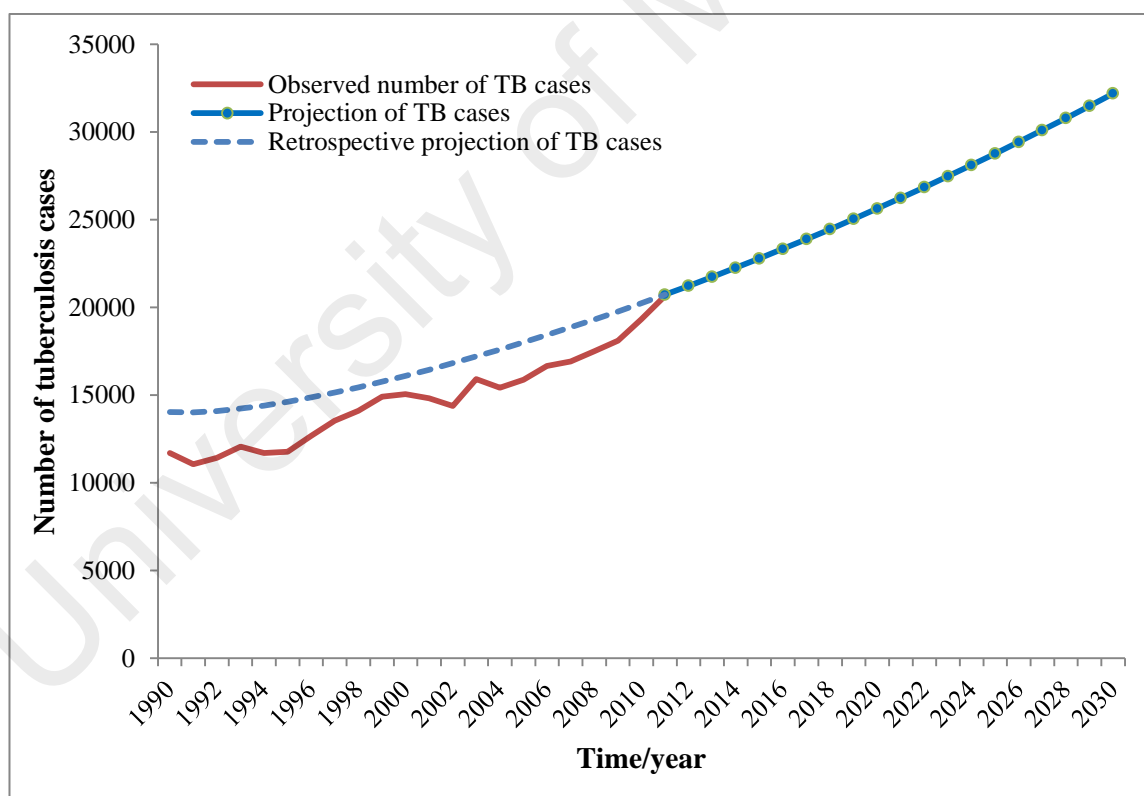


Figure 4.28: The observed and projections of tuberculosis cases in Malaysia from year 1990 to 2030

The graph shown in the above Figure 4.28 is a combination of two different graphs. Red line of the graph was derived from primary data i.e. the annual notification of tuberculosis cases in Malaysia and the blue line in the graph was a projection of tuberculosis incidence trend derived from the model simulation.. Between 1990 till 2011, tuberculosis notification cases in Malaysia showed a rising trend based on the observed primary data extracted from the Malaysian Ministry of Health Tuberculosis Information System. This was shown as the 'red line' in Figure 4.28.

Retrospective projection of the optimized and best-fitted model developed in this research showed similar trend, as shown by the 'dashed blue line' in Figure 4.28. Data from year 2012 and onwards was the prospective projected incidence trend and this was indicated as 'blue dotted line' in Figure 4.28. This trend was likely to continue to rise beyond this point up to 2030 based on the estimates and projections of tuberculosis cases derived from the validated Malaysian age-structured tuberculosis mathematical transmission dynamic model constructed during the research.

In general, the tuberculosis trend in Malaysia was expected to rise steadily from 1990 to 2030 based on the estimates and projections of the validated Malaysian tuberculosis model derived in this research. The persistent rise of incidence trend (shown by the blue line) was at increment rates ranged between 0.5% - 2.5% for both retrospective and prospective projections. Whereas the primary data trend i.e. tuberculosis notification cases (shown by the red line i.e. case notifications), fluctuated at annual difference rates between -5% and 10% between 1990 and 2011.

4.2.2 Effectiveness of Isoniazid Preventive Therapy in Malaysia

This section presents the results of the effectiveness of Isoniazid Preventive Therapy for reduction of tuberculosis incidence in Malaysia. It uses the validated Malaysian tuberculosis model developed in this study to demonstrate the results of the most effective strategy to reduce tuberculosis incidence in Malaysia. Four different strategies to effectively reduce tuberculosis incidence were compared. These include: 1) no intervention strategy (status quo), 2) current treatment strategy i.e. treatment of infectious cases only, 3) Isoniazid Preventive Therapy for latent tuberculosis cases only, and 4) combination strategy of current treatment for infectious tuberculosis cases and chemoprophylaxis (with Isoniazid) for high risk latent tuberculosis sub-populations. The results are demonstrated by: 1) the effectiveness by trends of number of tuberculosis cases over time, and 2) the effectiveness by effective reproductive number, R_{eff} .

4.2.2.1 Effectiveness of Preventive Therapy by tuberculosis trend of incidence over time

This sub-section provides the likely number of tuberculosis cases in Malaysia when there is no active management of tuberculosis based on the validated model developed in this thesis. The results are presented between years t_0 (1990) till t_{50} (2040), with t_0 population of 22,200,000 considered as 'Naive' Malaysian population. Malaysian annual birth rate, annual mortality rate, and annual population growth rate were also taken into account. Results are presented in four scenarios: a) trend of tuberculosis cases in Malaysia without any intervention, b) trend of tuberculosis cases in Malaysia with current strategy (treatment for infectious tuberculosis only), c) trend of tuberculosis

cases in Malaysia with alternative strategy (chemoprophylaxis) with Isoniazid Preventive Therapy only, and d) trend of tuberculosis cases in Malaysia with a combination of current treatment for infectious cases and the proposed Isoniazid Preventive Therapy for high risk latent tuberculosis sub-populations.

Scenario 1: Tuberculosis trend in Malaysia without any intervention

Based on the Malaysian validated tuberculosis model developed in this research, it is projected that there is steady increase in the number of tuberculosis cases in Malaysia if there is no intervention from t_0 till t_{50} where t_0 is equated as 1990, and t_{50} is 2040. Figure 4.29 shows the projected output of the customized Malaysian tuberculosis model for the tuberculosis cases in Malaysia between t_0 till t_{50} (1990 - 2040). The graph shows the relationship between total numbers of tuberculosis cases in Malaysia over time. It shows that the total number of tuberculosis cases increase from 569,347 at t_0 (1990) to 15,159,700 cases at t_{50} (2040) as predicted by the validated customized Malaysian model.

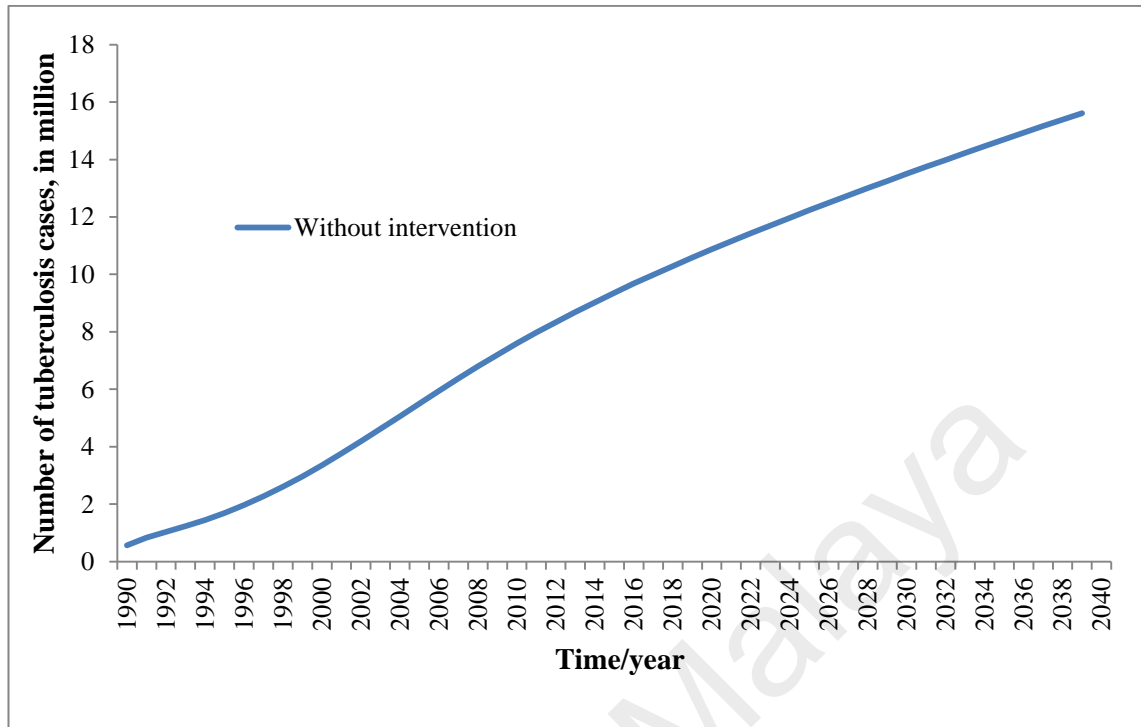


Figure 4.29: Scenario 1 simulation showing trend of number of tuberculosis cases in Malaysia without intervention projected by the model

Scenario 2: Tuberculosis trend in Malaysia with Isoniazid Preventive Therapy only

Scenario 2 is the projected output of the validated customized Malaysian tuberculosis model developed. Scenario 2 is the extension of the scenario 1. In this scenario we added Isoniazid Preventive Therapy only as a treatment option against no treatment option in Scenario 1.

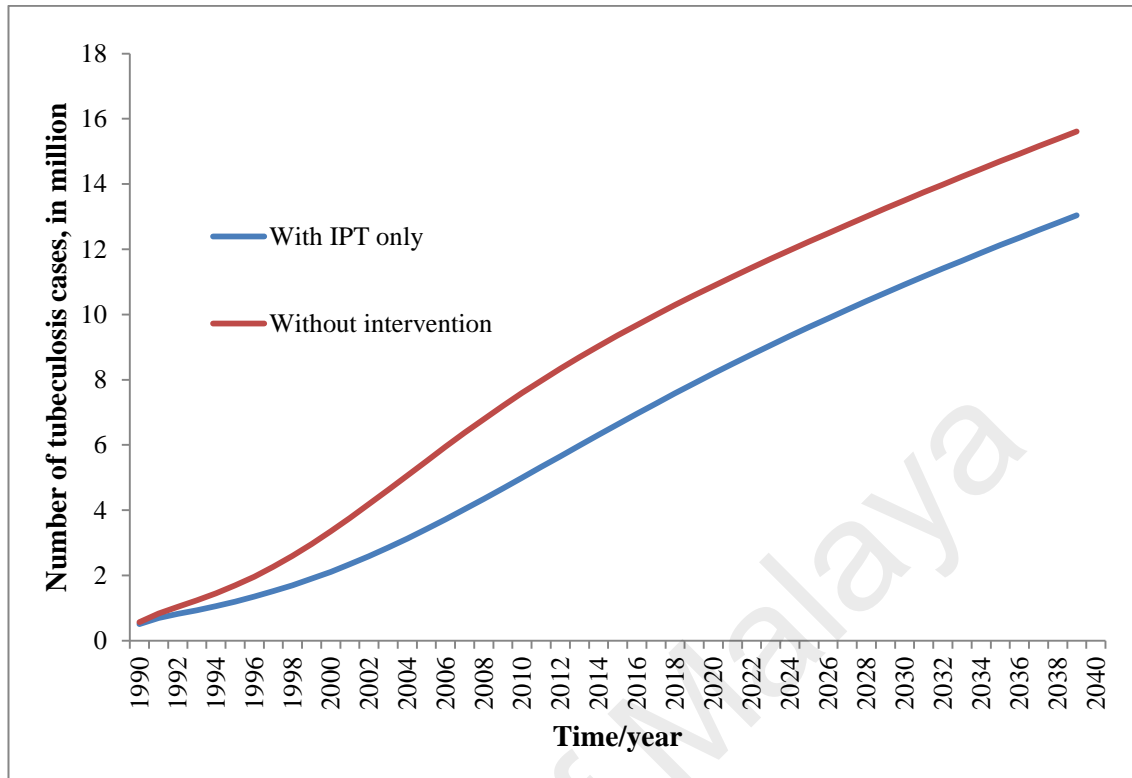


Figure 4.30: Scenario 2 simulation showing tuberculosis trend in Malaysia with two different strategies (without intervention versus Isoniazid Preventive Therapy only) of managing tuberculosis epidemic predicted by the model

The graph above in Figure 4.30 shows the relationship between total numbers of tuberculosis cases in Malaysia over time when Isoniazid Preventive Therapy is used as the only strategy to manage tuberculosis epidemic in Malaysia indicated by the blue line in graph. It shows the total number of tuberculosis cases increased from 0 at t_0 to 13,038,900 cases at t_{50} (from year 1990 - 2040). However putting Isoniazid Preventive Therapy as the only treatment option in the Scenario 2 still shows that there is an increasing trend in the tuberculosis cases in Malaysia, though less acute as compared to Scenario 1 (Figure 4.29).

Scenario 3: Tuberculosis trend in Malaysia with current strategy

Scenario 3 is the projected output of the validated model developed. Scenario 3 is the extension of Scenario 1 and Scenario 2. It incorporates the current strategy of treating the infectious tuberculosis cases only as shown in Figure 4.31.

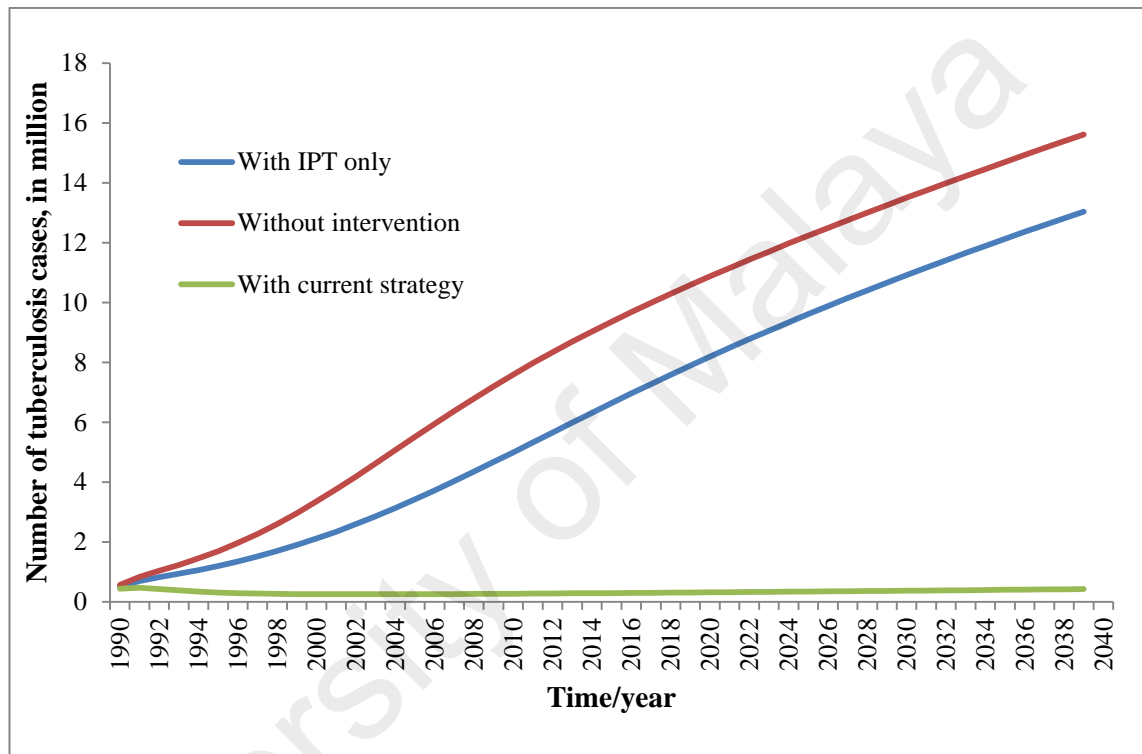


Figure 4.31: Scenario 3 simulation showing tuberculosis trend in Malaysia with three different strategies predicted by the model

Figure 4.31 graph above shows the relationship between total numbers of tuberculosis cases in Malaysia over time with current strategy of managing tuberculosis by treating the infectious tuberculosis cases only. It shows that as compared to the increasing trend of tuberculosis cases in Malaysia in scenario 1 and scenario 2, the number of tuberculosis cases with current strategy shows a flatter trend. This is in accordance with the current treatment regime based on Malaysian clinical practice guidelines on tuberculosis management. It shows the total number of tuberculosis cases increased

from 341,927 at t_0 to 363,409 cases at t_{50} (1990 - 2040). It shows a significant decrease in the tuberculosis cases when this strategy is implemented against no intervention and significantly more as compared to Isoniazid Preventive Therapy only strategy. Figure 4.31 shows the magnified figure of Scenario 3. Its trend is in line with the Malaysian tuberculosis trend via observed data of notified cases in Figure 2.3, however, shows significant underreporting as identified in Figure 4.26.

Scenario 4: Tuberculosis trend in Malaysia with combined strategy

Scenario 4 is the projected output of the validated customized Malaysian tuberculosis model developed. The scenario 4 is the extension of the scenario 1, scenario 2 and scenario 3. Scenario 4 incorporates the introduction of Isoniazid Preventive Therapy in conjunction with the current strategy of managing only the infectious tuberculosis cases. This combined strategy results in the marked decrease in the number of tuberculosis cases as compare to scenario 1, scenario 2 and scenario 3. This is illustrated in Figure 4.32a that shows marked decrease in the number of tuberculosis cases in Malaysia with this combination strategy for managing tuberculosis epidemic in Malaysia.

Figure 4.32a shows the potential comparative trends of tuberculosis cases over time in all four strategies i.e. treatment, Isoniazid Preventive Therapy only, current strategy only and combination of Isoniazid Preventive Therapy and current strategies. Figure 4.32b shows the comparative trends of tuberculosis cases over time in Malaysia when combination strategy for managing tuberculosis epidemic is implemented. The total number of tuberculosis cases increased from 95,900 at t_0 to 25,363 cases at t_{50} (1990 - 2040) with significant difference ($p < 0.05$). It shows that using the combination strategy

for managing tuberculosis epidemic significantly reduces the number of tuberculosis cases against the other three strategies. That makes the combination strategy for managing tuberculosis epidemic the best available option to manage tuberculosis epidemic in Malaysia.

Table 4.3 shows that with the Strategy 1, the annual rate difference of tuberculosis infection cases ranges from 1.47 – 47.01 % from year 1990 – 2040. With Strategy 2 i.e. Isoniazid Preventive Therapy only, the annual rate reduction of tuberculosis cases is significantly higher as compared to Strategy 1. The annual rate difference of tuberculosis cases with Strategy 2 ranges from 1.75 – 36.62 % from year 1990-2040 ($p < 0.001$). With Strategy 3, the annual rate difference of tuberculosis infection cases ranges from -11.34 – 1.60 % from year 1995 – 2040, which is a significant reduction as compared to Strategy 1 or Strategy 2 ($p < 0.001$). Lastly Strategy 4 i.e. the combination treatment of infectious tuberculosis and Isoniazid Preventive Therapy projected the maximum annual rate difference and significant rate reduction of tuberculosis cases as compared to all the other strategies. This is shown by consistent annual rate reduction ranges from -30.08 – -2.26 from year 1995-2040 ($p < 0.05$). The comparison among the four strategies clearly demonstrates that Strategy 4 i.e. the combination treatment of infectious tuberculosis and Isoniazid Preventive Therapy is the most viable and efficient strategy to manage tuberculosis epidemic in Malaysia.

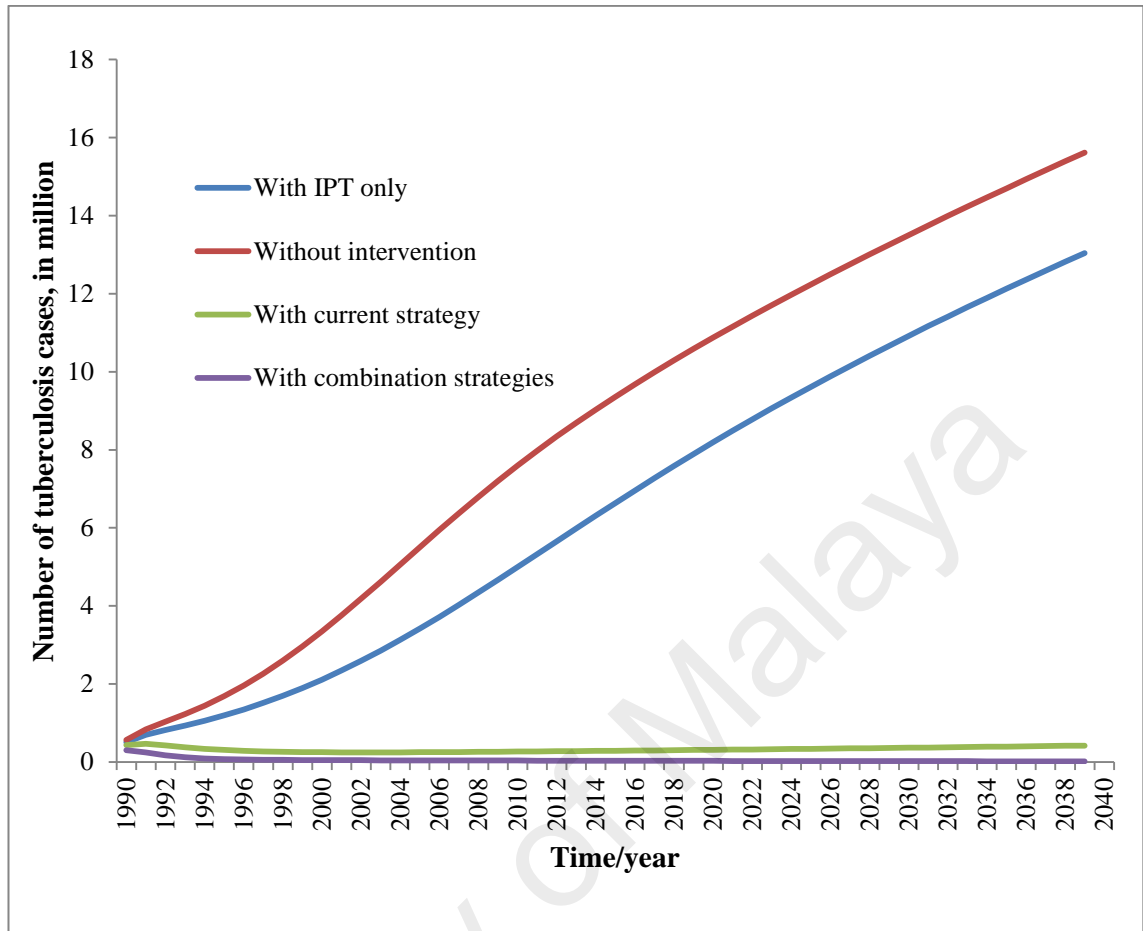


Figure 4.32a: Scenario 4 simulation showing comparative tuberculosis trend in Malaysia with four strategies for managing tuberculosis predicted by the model

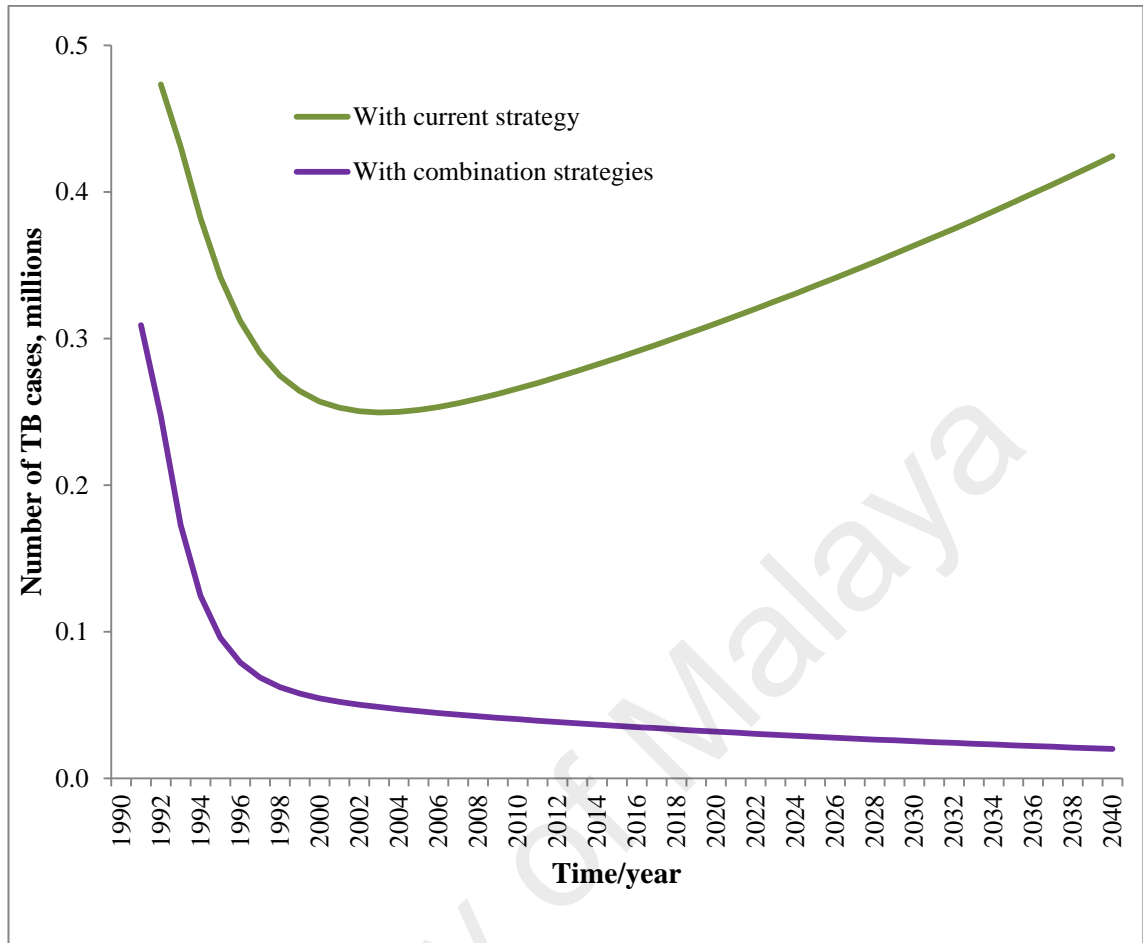


Figure 4.32b: Scenario 4 simulation showing comparing tuberculosis trend between current strategy and combination of Isoniazid Preventive Therapy and current strategy for managing tuberculosis predicted by the model

Table 4.3: Summary of four scenarios with different treatment strategies according to projected number of tuberculosis cases from 1990 and 1995 to 2030 and the range of annual rate difference

Scenario	Treatment strategy	Projected number of tuberculosis cases from 1990 to 2030	Projected number of tuberculosis cases from 1995 to 2030	Range of annual rate difference of tuberculosis cases (incidence, %)	<i>p</i> value
1	No treatment	569,347 to 15,159,700	-	16.8 – 1.86	-
2	IPT only	510,809 to 13,038,900	-	12.97 – 2.37	<0.001 [^]
3	Treatment of infectious tuberculosis only	-	341,927 to 363,409	-6.97 – 1.57	<0.001 [~]
4	Combination treatment of infectious tuberculosis and IPT	-	95,900 to 25,363	-12.95 – -2.27	<0.05 [*]

[^]Scenario 1&2, [~] Scenario 2&3, ^{*}Scenario 3&4 respectively. [^]Scenario 3 & 4 marked the rate difference at year 1995 onward. [~]Annual rate difference denotes estimation of case underrepresentation.

4.2.2.2 Effectiveness of Isoniazid Preventive Therapy by effective reproductive numbers in similar scenarios by trend

Reproductive number R_{eff} , expresses the effective average secondary number of infectious tuberculosis cases following effective transmission by a primary infectious case. The R_{eff} of the four alternative strategies of managing tuberculosis in Malaysia are compared. These strategies include: a) without any intervention, b) with current strategy (treatment for infectious tuberculosis only), c) with alternative strategy (chemoprophylaxis) with IPT only, and d) with a combination of current strategy and chemoprophylaxis strategy with IPT. Figure 4.33 shows the relationship of Reproductive number R_{eff} , for the four different strategies over time.

The trend of the basic reproduction numbers R_{eff} , for the four alternative strategies of managing tuberculosis in Malaysia shows that the strategies of no intervention and IPT only shows an upward trend, that is project to cross $R_{\text{eff}} > 1$ at from t_{72} and t_{96} onward respectively. Figure 4.32 also show that the trend of current and combined strategies shows a flatter trend as compared to other two strategies where the $R_{\text{eff}} < 1$ for extended period of time. In addition to that the R_{eff} with the combined strategy is the smallest as compared. It demonstrates the combination of current strategy and chemoprophylaxis strategy with IPT is the best available strategy to effectively manage tuberculosis epidemic in Malaysia.

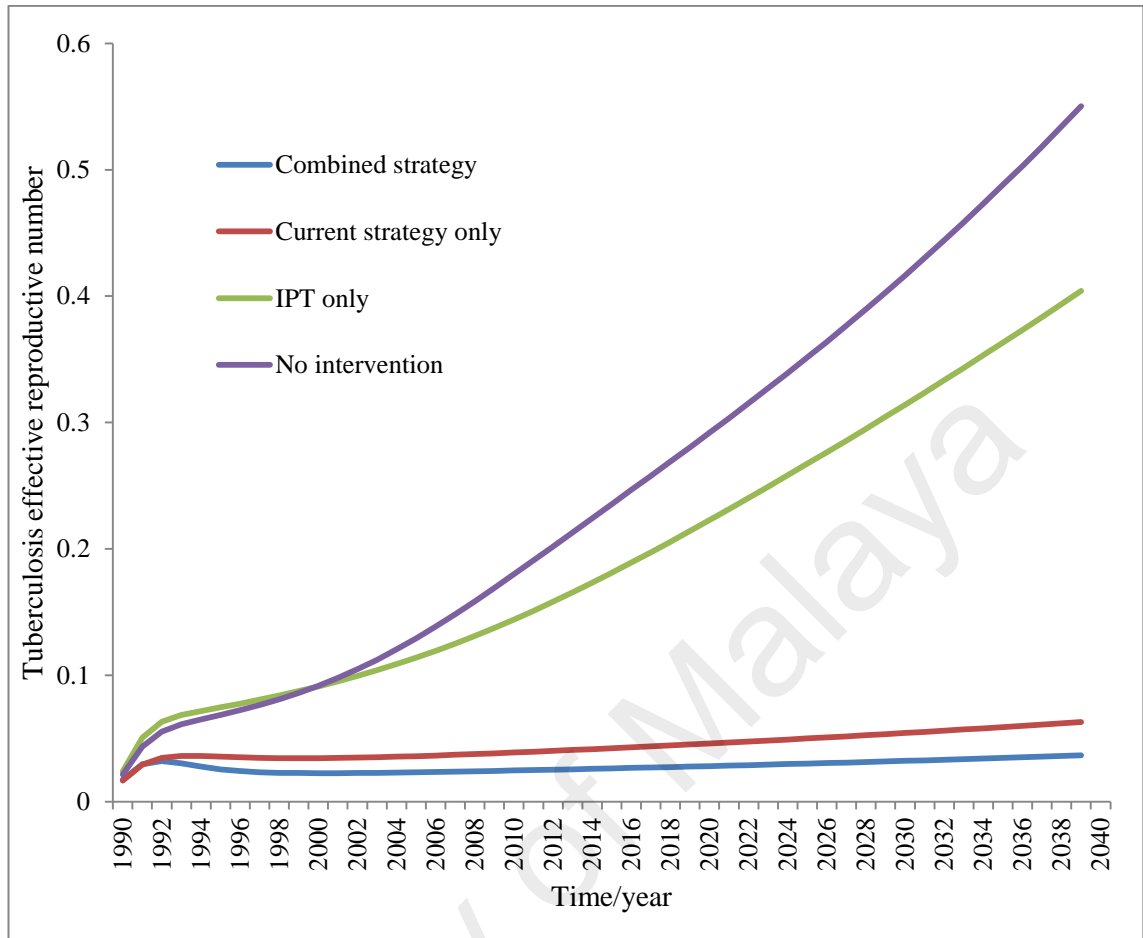


Figure 4.33: Effective reproductive number, R_{eff} for four alternative strategies for managing tuberculosis epidemic in Malaysia

4.2.3 Quantification of effectiveness of Isoniazid Preventive Therapy in terms of coverage as combined strategy

The results in section 4.2.3 demonstrate that the combination of current strategy and chemoprophylaxis strategy with IPT is the best available strategy to effectively manage tuberculosis epidemic in Malaysia. This is shown by the reduction in the total number of tuberculosis cases as well with very flat R_{eff} . The success of this strategy depends upon the optimal coverage of the population of IPT for the high risk latent tuberculosis sub-populations. This is a prerequisite to start observing effective reduction in the number of tuberculosis cases in Malaysia.

This section shows the results for the optimal coverage of IPT needed to be achieved in order to effectively reduce the tuberculosis incidence as shown in Figure 4.34a and Figure 4.34b below.

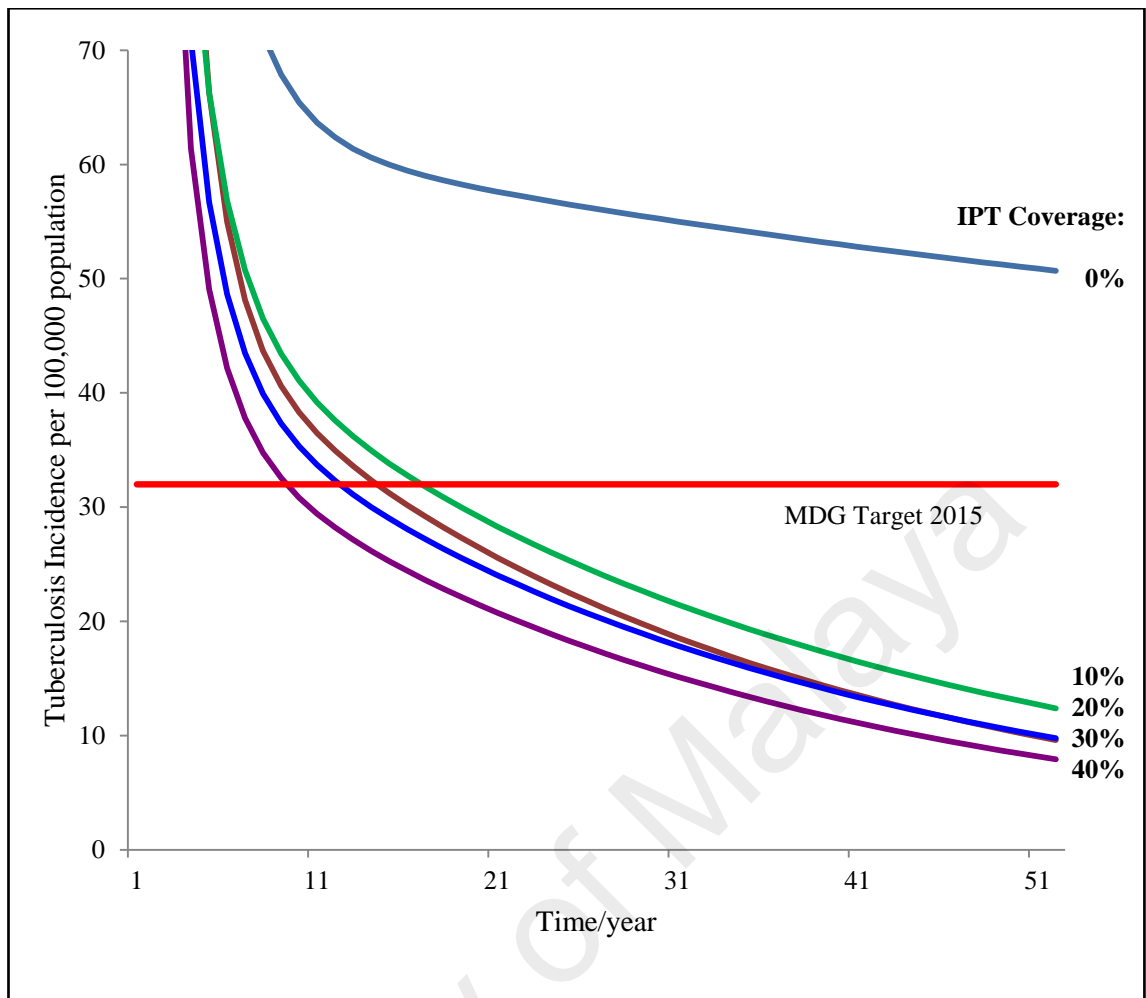


Figure 4.34a: Impact of Isoniazid Preventive Therapy at various levels of coverage on tuberculosis incidence given success current treatment coverage of infectious tuberculosis at 60%

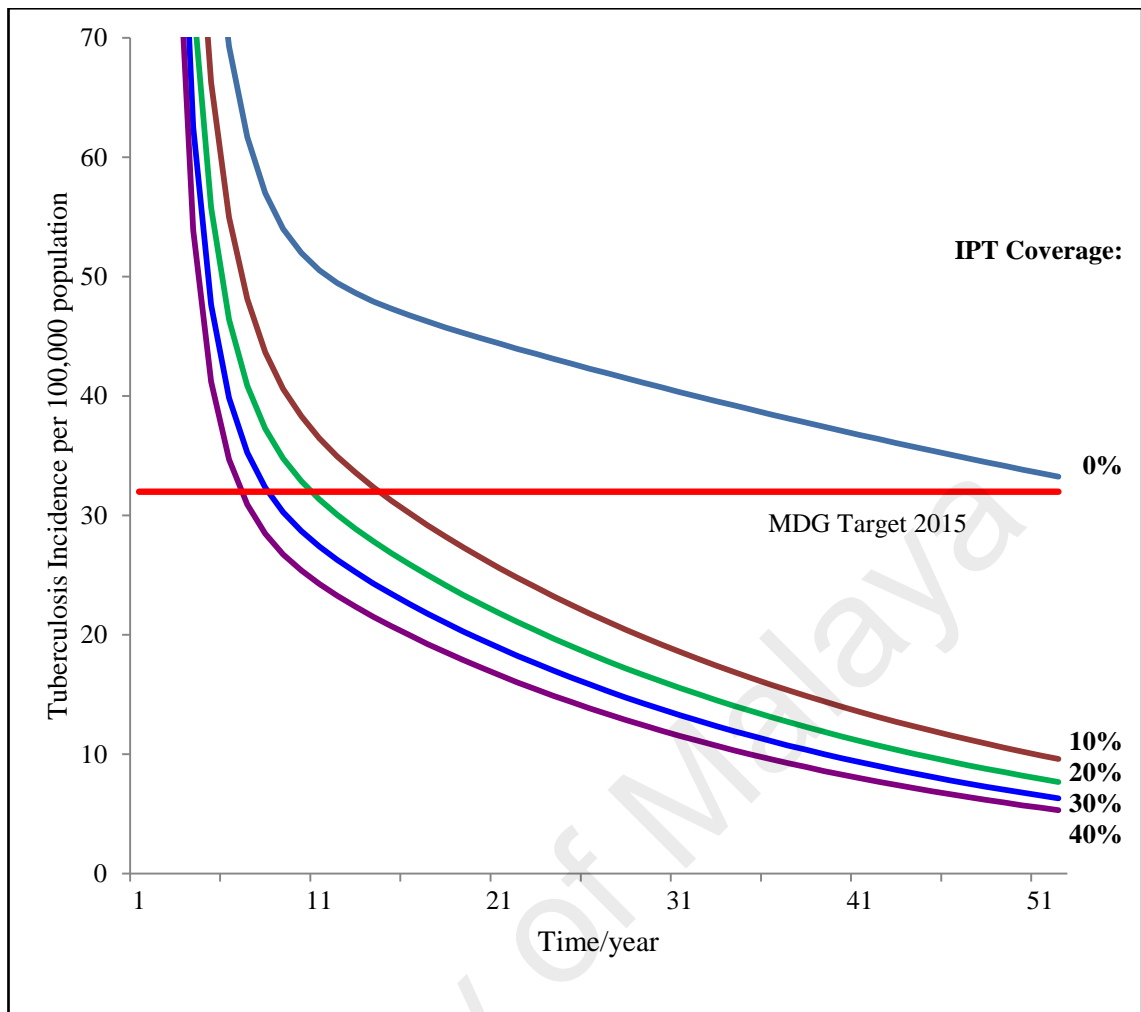


Figure 4.34b: Impact of Isoniazid Preventive Therapy at various levels of coverage on tuberculosis prevalence given success current treatment coverage of infectious tuberculosis at 80%

Above Figure 4.33 showed further impact on reduction of tuberculosis incidence by varying coverage of IPT for high risk LTBI against time. Two scenarios of current treatment coverage for infectious tuberculosis at 60% and 80% are shown in Figure 4.34a and Figure 4.34b respectively. These percentages represent lower and upper limits of Malaysian success current treatment coverage of infectious tuberculosis, averaging between 70% - 75% per year. Figure 4.34a and Figure 4.34b show that ten percent coverage of IPT is minimally required to effectively reduce tuberculosis incidence.

4.2.4 Selection of high risk latent tuberculosis sub-populations for Isoniazid Preventive Therapy optimal coverage

The results in section 4.2.3 demonstrate that the combination of current strategy and Isoniazid Preventive Therapy is the best available strategy to effectively manage tuberculosis epidemic in Malaysia. The results in section 4.2.3 quantify the optimal IPT with the combination strategy needed to achieve the effective reduction of tuberculosis incidence in Malaysia. The optimal coverage of IPT with combination strategy needed for effective management of tuberculosis epidemic was calculated to be 10 % of LTBI. This section demonstrates further, the projected selection of the optimal coverage of high risk latent tuberculosis population for effective implementation of combined strategy. According to the disease dynamic, the latent tuberculosis populations are divided into: a) early LTBI and b) late LTBI. Therefore the Late latent tuberculosis and the Early latent tuberculosis population are the two selections.

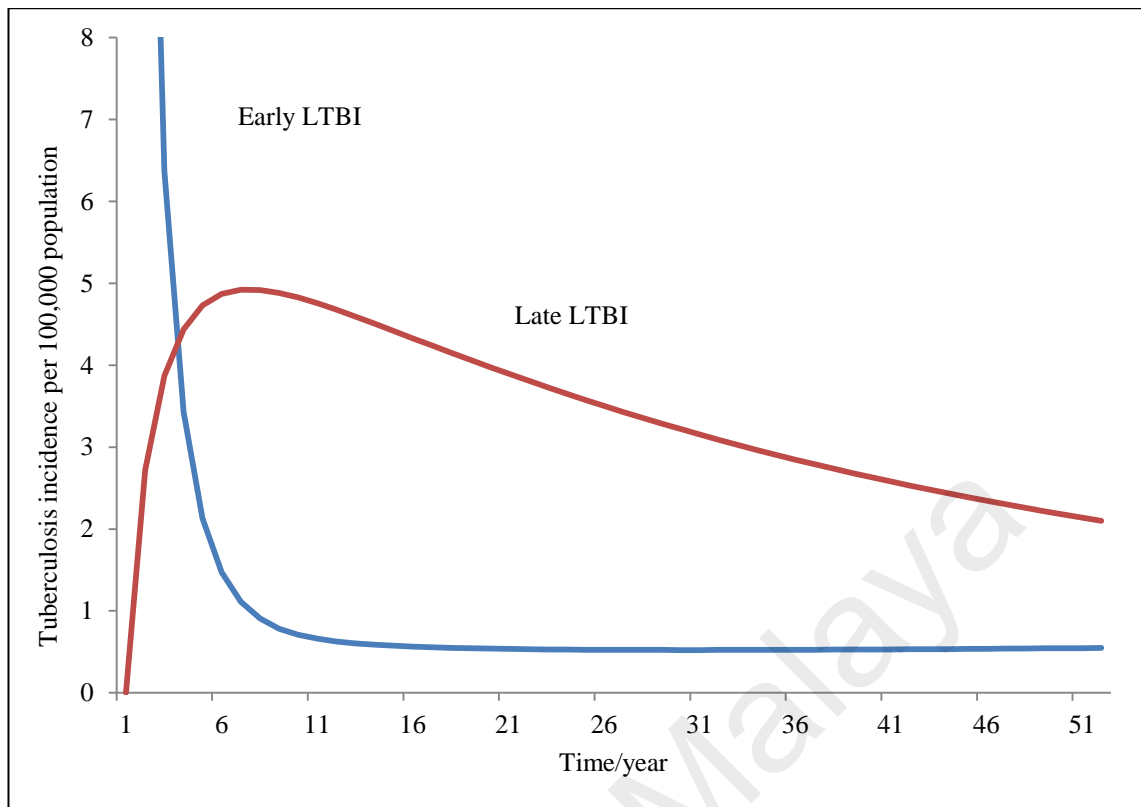


Figure 4.35: Likely impact of treating early latent cases versus impact of treating late latent cases in the combined strategy for managing tuberculosis epidemic in Malaysia, as predicted by the validated model [p=0.021]

Figure 4.35 showed the likely impact of treating early LTBI versus impact of treating late LTBI in the combined strategy for managing tuberculosis epidemic in Malaysia, as predicted by the validated model. The model projected significant difference that the incidence of tuberculosis trend that treated early LTBI has the early and continuous reduction as compared to late LTBI that showed initial increasing trend in the first seven years before the actual reduction of incidence were predicted in both early and late cases at different rates, [$p=0.021$]. Treating early LTBI is a more effective control measure as compared to late LTBI as projected by the validated model.

4.2.5 Overall impact of Isoniazid Preventive Therapy to curb tuberculosis epidemic in Malaysia

This section presents the overall impact of IPT as early preventive therapy for tuberculosis prevention in Malaysia. Results are presented for introduction of IPT at two different points in time. The first introduction was proposed in 1990 and alternatively the second introduction is modelled for year 2015 onwards.

4.2.5.1 Estimates and projections of tuberculosis incidence in Malaysia from 1990 till 2050 (retrospective simulation of Isoniazid Preventive Therapy introduction in the year 1990 as a combined strategy as predicted by the model)

This section presents the customized Malaysian Tuberculosis model simulation of the likely impact of tuberculosis incidence in Malaysia if IPT were introduced in the year 1990. Figure 4.36 below shows the likely impact of tuberculosis incidence in Malaysia

with the strategy of treating infectious tuberculosis cases only in comparison with combined treatment strategy with IPT.

The projection of current treatment strategy shows minimal reduction in tuberculosis incidence over time between 1990 and 1995; followed by a steady upward trend from year 1995 onwards. This is consistent with pattern expressed in the global tuberculosis emergency declared by WHO in 1995. On the contrary, the combined strategy with Isoniazid Preventive Therapy for latent tuberculosis shows marked reduction of tuberculosis incidence. This is consistent with higher cumulative rate reduction shown in Table 4.4 below; an estimated cumulative reduction of 49.29% with annual rate reduction ranged between 0.35-4.8% in 60 years (from 1990 – 2050), as shown Figure 4.36 below.

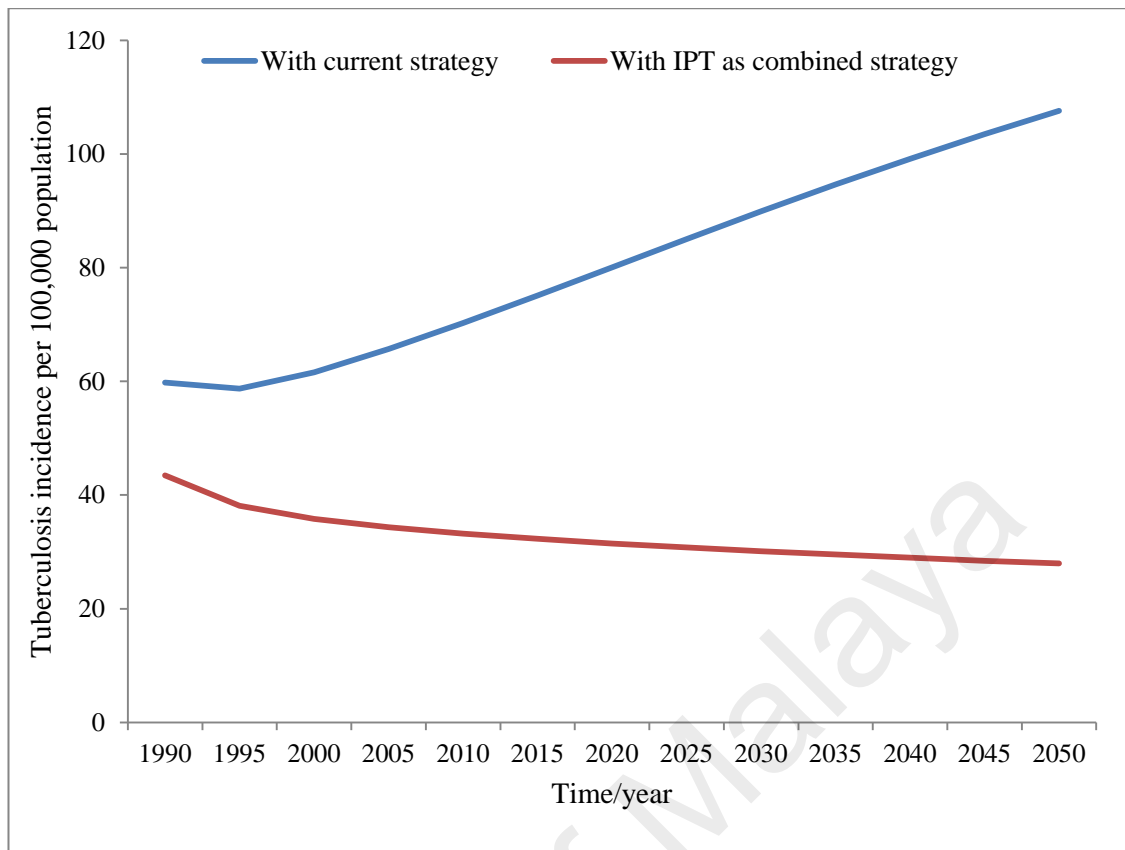


Figure 4.36: Estimates and projections of tuberculosis incidence in Malaysia with current strategy and Isoniazid Preventive Therapy as combined strategy from 1990 till 2050 following retrospective introduction of Isoniazid Preventive Therapy in 1990

Table 4.4: Estimates and projections of tuberculosis incidence in Malaysia from 1990 to 2050

Year	Tuberculosis incidence estimates with current strategy per 100,000 Malaysian population (A)	Projected tuberculosis incidence with IPT as combined strategy per 100,000 Malaysian population (B)	Annual rate reduction in percentage (C)	Cumulative rate reduction in percentage (D)
1990	59.819	43.482	4.797	4.797
1995	58.705	38.100	1.811	18.200
2000	61.585	35.783	1.021	24.515
2005	65.687	34.321	0.747	28.703
2010	70.293	33.208	0.616	32.012
2015	75.142	32.284	0.537	34.841
2020	80.091	31.483	0.484	37.359
2025	85.040	30.770	0.445	39.655
2030	89.912	30.123	0.415	41.786
2035	94.646	29.526	0.393	43.791
2040	99.193	28.969	0.375	45.699
2045	103.520	28.445	0.360	47.527
2050	107.601	27.948	0.3493	49.293

Note: $C = [(A-B)/A]*100\%$, $D_n = D_{n-5} + C_{n-4} + C_{n-3} + C_{n-2} + C_{n-1} + C_n$

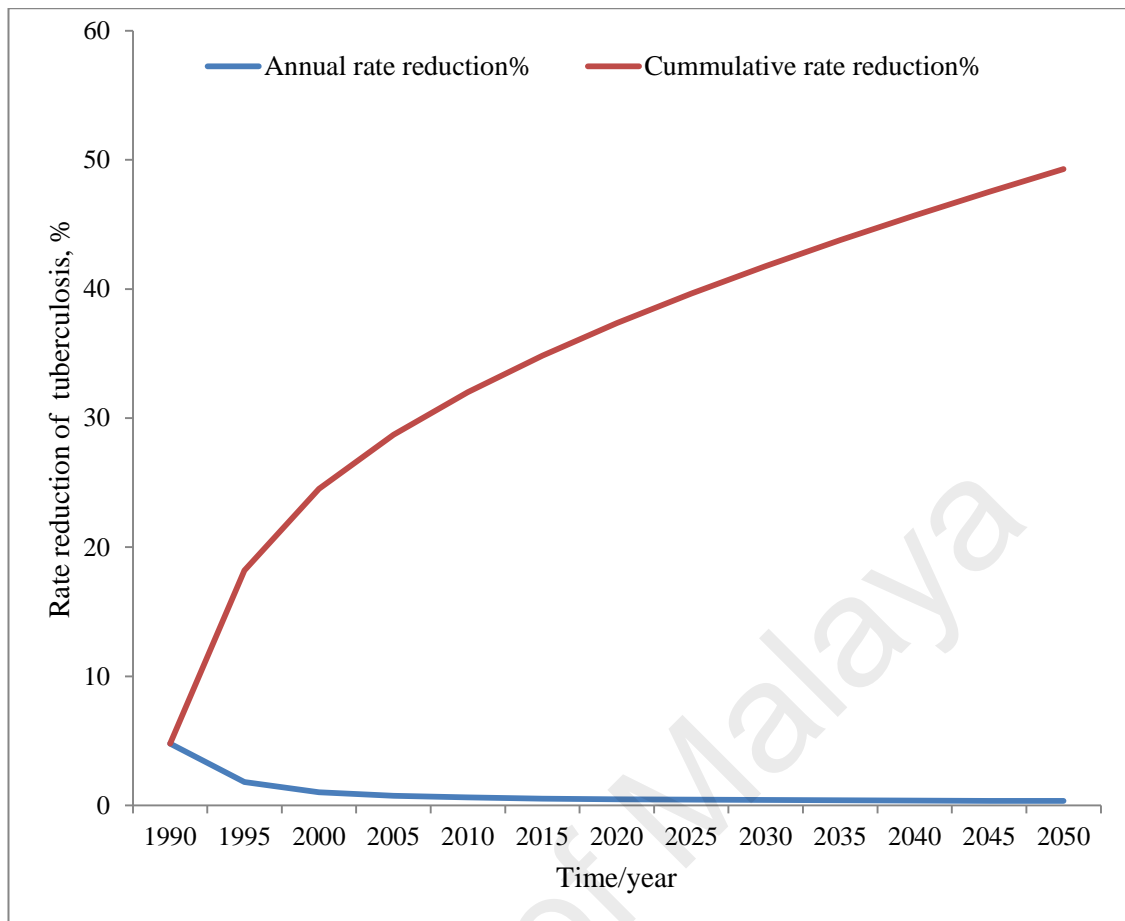


Figure 4.37: Cumulative and annual rate reduction of estimates and projections of tuberculosis incidence in Malaysia from 1990 – 2050 (between current strategy and combined strategy)

4.2.5.2 Estimates and projections of tuberculosis incidence in Malaysia from 2015 till 2050 (prospective simulation of IPT introduction in the year 2015 as a combined strategy predicted by the model)

This section presents the customized Malaysian Tuberculosis model simulation of the likely impact of tuberculosis incidence in Malaysia if IPT were introduced in the year 2015. Figure 4.38 below show the likely impact of tuberculosis incidence in Malaysia with the strategy of treating infectious tuberculosis cases only in comparison with combined treatment strategy with IPT.

The projection of current treatment strategy shows minimal reduction in tuberculosis incidence over time between 2015 till 2020; followed by a steady upward trend from year 2020 onwards.

On the contrary, the combined strategy with Isoniazid Preventive Therapy for latent tuberculosis shows marked reduction of tuberculosis incidence. This is consistent with higher cumulative rate reduction shown in Table 4.5 below; an estimated cumulative reduction of 27.21% with annual rate reduction ranged between 0.08-5.1% in 35 years (from 2015 – 2050), as shown in Figure 4.39 below.

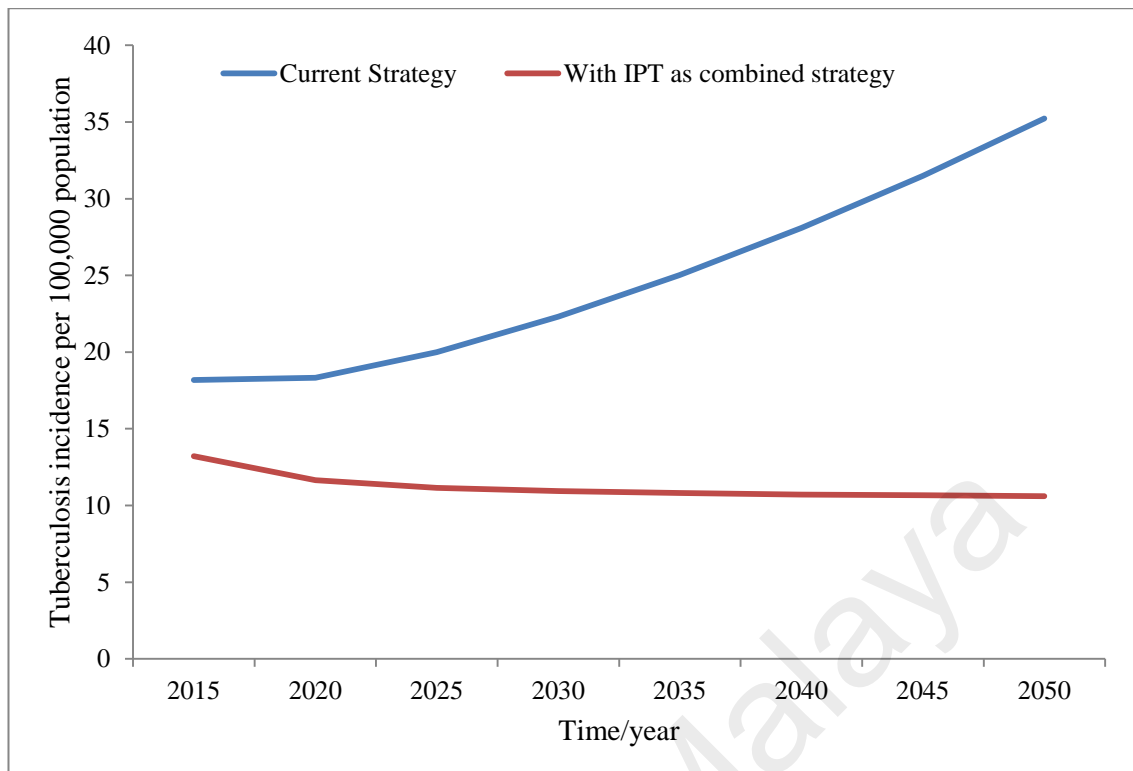


Figure 4.38: Estimates and projections of tuberculosis incidence in Malaysia with current strategy and Isoniazid Preventive Therapy as combined strategy from 2015 till 2050 following prospective Isoniazid Preventive Therapy introduction in 2015

Table 4.5: Estimates and projections of tuberculosis incidence increment in Malaysia from 2015 till 2050

Year	Tuberculosis incremental incidence estimates with current strategy per 100,000 Malaysian population (A)	Projected tuberculosis incremental incidence with IPT as combined strategy per 100,000 Malaysian population (B)	Annual rate reduction in percentage (C)	Cumulative rate reduction in percentage (D)
2015	18.189	13.216	5.060	5.060
2020	18.328	11.649	1.516	17.858
2025	20.005	11.155	0.594	22.209
2030	22.306	10.934	0.312	24.217
2035	25.017	10.806	0.198	25.401
2040	28.087	10.720	0.138	26.199
2045	31.498	10.658	0.102	26.776
2050	35.239	10.612	0.079	27.212

Note: $C = [(A-B)/A] * 100\%$, $D_n = D_{n-5} + C_{n-4} + C_{n-3} + C_{n-2} + C_{n-1} + C_n$

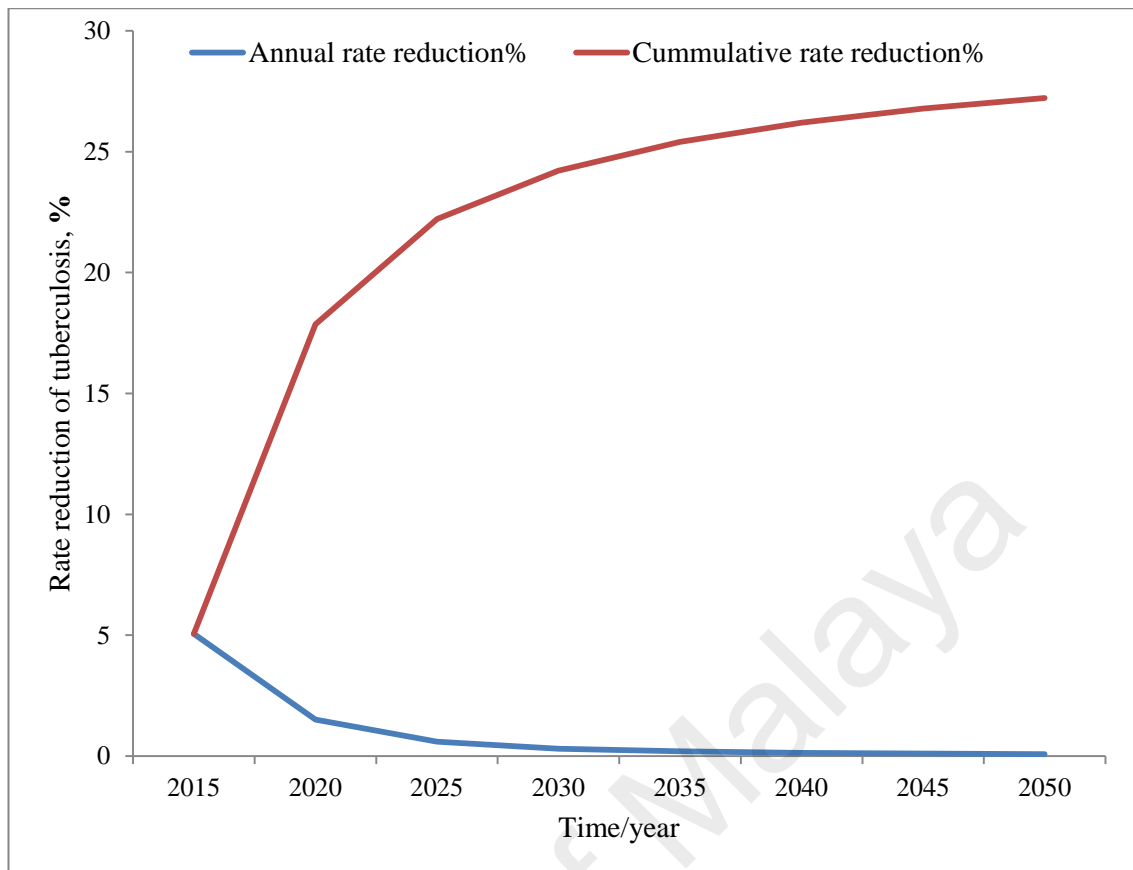


Figure 4.39: Cumulative and annual rate reduction of estimates and projections of tuberculosis incidence in Malaysia from 2015 – 2050 (between current strategy and combined strategy)

4.2.5.3 Comparative annual rate reduction of tuberculosis in Malaysia with IPT as combined strategy introduced at two different points in time i.e. 1990 and 2015

Both curves shown in Figure 4.40 appeared similar where the red curve seemed like as a right shift of the blue curve. On the contrary, both curves are different and independent with unique positions on the timeline. The rate of change of each curve is also different; which is expressed by the different slopes of curves on the timeline. This implies that the IPT intervention along the two curves will be unique depending upon the characteristics of the curves at that point in time. The magnification of the above curves at the point of intersection is shown below in Figure 4.41.

At a first glance, it appears that the intervention carried out at year 2015 yield better result as compared to intervention started at year 1990 as shown by the lower position of red curve. On the contrary, this graph shows an annual rate reduction of tuberculosis cases on y-axis. The lower position of the red line (from intersection at 2025-2030 midpoint) does not signify a better result because the blue line at the same point in time would have yield a better annual rate reduction of tuberculosis cases.

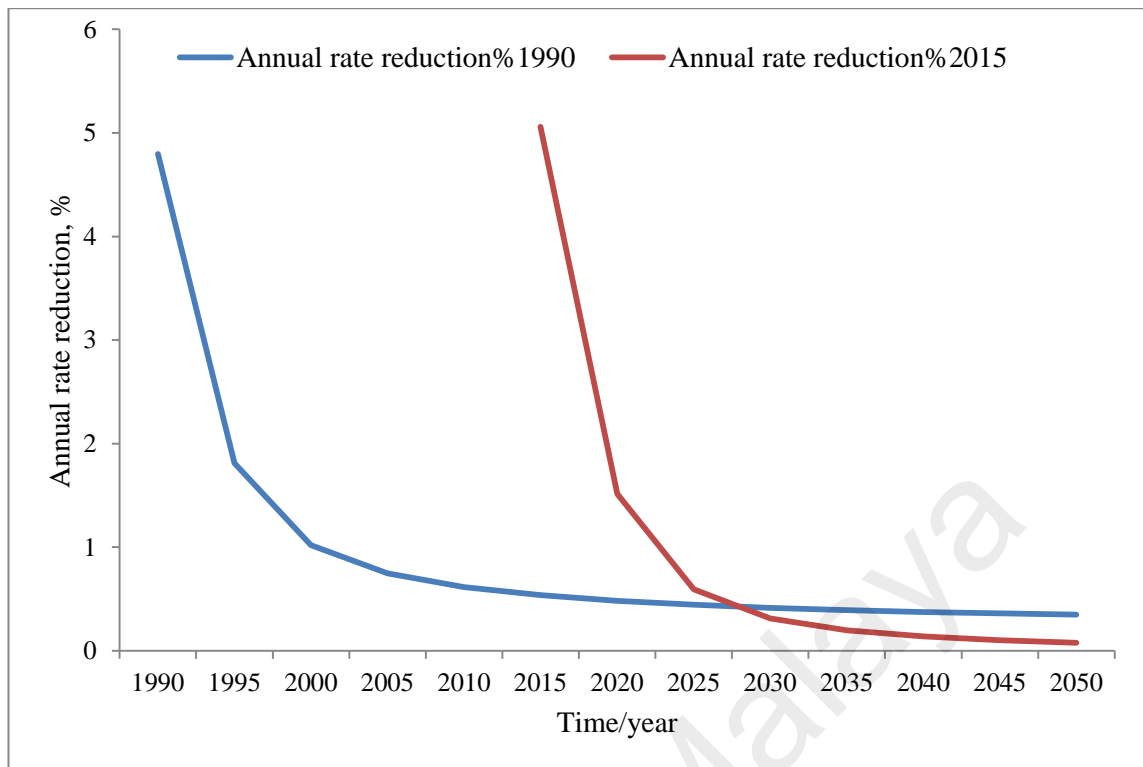


Figure 4.40: Annual rate reduction of tuberculosis incidence in Malaysia for Isoniazid Preventive Therapy combined strategy between year 1990-2050 and 2015-2050

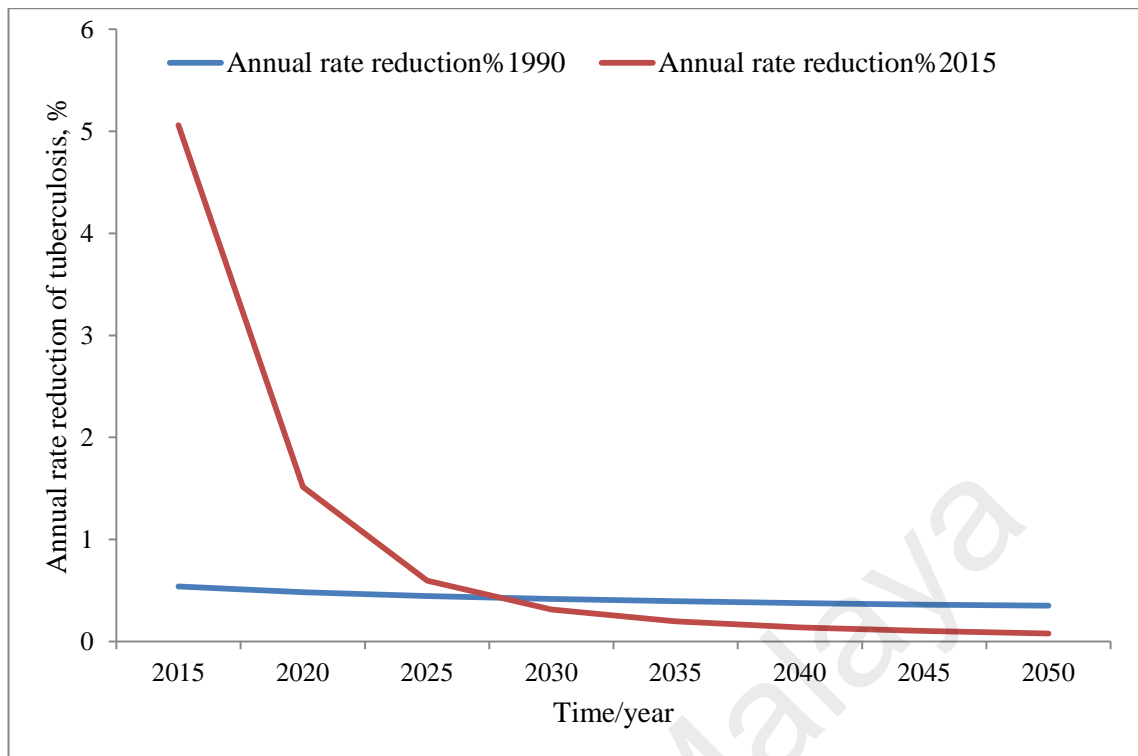


Figure 4.41: Annual rate reduction of estimates and projections of tuberculosis incidence in Malaysia for Isoniazid Preventive Therapy combined strategy between year 1990-2050 and 2015-2050 with enhanced intersection

4.3 Formulation of policy recommendation

The results of this section are presented separately in Chapter 6 as the policy recommendation chapter.

4.4 Summary of Chapter 4

A Malaysian tuberculosis model was developed as an age and gender structured deterministic compartmental transmission dynamic mathematical model using the ordinary differential equation system. Application of this validated model projects a steady rising trend of tuberculosis incidence in Malaysia. However, the proposed intervention of combined strategy with current treatment for infectious tuberculosis and IPT for high risk latent tuberculosis sub-populations shows effective reversal of increasing tuberculosis trend. Various simulations of coverage of high risk latent tuberculosis populations revealed a minimum of 10% coverage of IPT is mandatory among the early latent tuberculosis sub-populations to show substantial reduction in tuberculosis trend.

5.1 Research question and study findings

Elimination of tuberculosis in industrialized nations hinges not only on diagnosis and treatment of infectious cases but also include managing latent tuberculosis infection cases in order to prevent the disease spread (Barnes P., 2004). This is because the risk of progression of tuberculosis infection to disease i.e. the life-time risk in immunocompetent adults is about 10% and it is highest in first five years after infection (about 5%) (Ferebee, 1970). The risk also increases in certain medical conditions in immunosuppressed state such as HIV, cancer and haemodialysis patients (Reider H.L., 1989).

In the MDG era, Malaysia failed to achieve the targets set for combating the tuberculosis to halt and reverse the trend of tuberculosis despite performing very well towards achieving other MDGs (Economic Planning Unit Prime Minister's Department Malaysia, 2006). The incidence, prevalence and mortality of tuberculosis have been persistently high in Malaysia for the last thirty years; although Malaysia tuberculosis burden is in the intermediate category in the Western Pacific Region.

On the contrary, the national tuberculosis key indicators showed good performance in the management of tuberculosis despite the alarming and persistent rise in the incidence trend of the disease. This triggered an urgent need for a new approach in the treatment and prevention of tuberculosis to effectively reduce the incidence. The current tuberculosis control programmes mainly focuses on efforts to find and treat infectious

cases. Therefore, further steps to prevent spread and progression into infectious or disease state should be explored and exploited.

One area in tuberculosis management yet to be adopted by Malaysia is by focusing at the earlier state in tuberculosis transmission dynamics before it reaches the infectious state, which concerns the high risk latent tuberculosis sub-populations. In this latent group, the high risk latent cases are detected and treated with an additional treatment of early intervention or chemoprophylaxis termed as Isoniazid Preventive Therapy (Clinical Practice Guideline) (Malaysia, 2000, 2002a, 2002b, 2006b). Available evidence favouring success showed that this could be a promising answer for Malaysia (C.P. Bhunu, 2008; Elad Ziv, 2001; P., 2004; Sally Blower, 1996). But before the Malaysian Ministry of Health can be convinced to develop strategies in that regard, the empirical evidence is required that such strategy is a viable option in Malaysia.

Therefore, this study developed a Malaysian tuberculosis model as an age and gender structured deterministic compartmental transmission dynamic mathematical model. It uses the ordinary differential equation system and embodies primary infection, endogenous route (reactivation) and exogenous route (reinfection) of tuberculosis infection. The model captures the entire Malaysian population and incorporates the Malaysian data between 1990-2010 such as tuberculosis national data, demographic data, annual birth rate, annual mortality rate, annual population growth rate etc. This model was optimised and validated against the Malaysian tuberculosis notification data of that same period.

The model was then used as a tool to assess the potential impact of early interventions that effectively reduces tuberculosis incidence in Malaysia. The model projected that the

rising trend of tuberculosis cases in Malaysia is likely to continue to rise beyond this point till 2050. The combined strategy of current treatment for infectious tuberculosis and IPT for high risk latent tuberculosis sub-populations effectively reduces the incidence substantially and yields the smallest number of secondary tuberculosis cases. This strategy has demonstrated to be the best available option to effectively manage tuberculosis epidemic in Malaysia.

However, it was also demonstrated that 10% coverage of IPT is minimally required among the early latent tuberculosis sub-populations to effectively reduce tuberculosis incidence in Malaysia. The results showed an estimated cumulative reduction of 27.21% tuberculosis cases by 2050 following eight to ten years of implementation from 2015 if Isoniazid Preventive Therapy for early latent tuberculosis infection sub-populations is implemented in Malaysia in conjunction with the current treatment regime for infectious tuberculosis cases.

5.2 Development of the Malaysian tuberculosis transmission dynamic mathematical model

The infectious disease modelling technique used in this study answered similar research question at different level and perspectives. It provides a different outlook – in terms of prediction and insight. The language of mathematics is used to translate the disease behaviour and movement between stages of disease at various scales and provide solutions to any problem related to those disease behaviours – in terms of predictions or understanding.

5.2.1 The model type, system and analysis method

The deterministic transmission dynamic tuberculosis compartmental model developed in this study is the best choice of modelling method as compared to stochastic models in view of the research questions posed. Deterministic models answer at population level at average how the disease dynamic likely behaves given the environment and characteristics for example in Malaysian setting. In contrast, when an infectious disease has just invaded, when control measures are successfully applied or when the population size is small, stochastically which is concerned with the element of randomness or chance in the nature of disease dynamics is of the most important choice of method to find the solution. This model also uses ordinary differential equation system with fourth order integration numerical analysis i.e. the Runge-Kutta 4 (RK4) as the best and most accurate iterative method used in temporal discretization for approximation of numerical solution.

5.2.2 The SEIR deterministic compartmental model system

This model employed the SEIR deterministic compartmental system to best capture all states of disease transmission dynamic according to pathophysiology of tuberculosis as illustrated as Figure 4.1 in Chapter 4 of this thesis. It incorporated the entire Malaysian population as well as the immigration data both legal and illegal based on case notification and case holding of those patients. Other intervention modalities such as BCG vaccination were also taken into account in the development of model.

5.2.3 Other tuberculosis mathematical models and its applications

Academicians have been trying to model the tuberculosis epidemic in various part of the world. The earlier efforts were neither comprehensive nor robust due to limited computational power of machine and software. With recent advancement in technology and subsequent increase in computational power in the last ten years, the use and applications of mathematical modelling technique in the field infectious diseases has been revived.

One of the earliest mathematical models for tuberculosis was presented by Waaler et. al in 1962. Following that, several other authors published numerical studies on tuberculosis focusing on cost-effectiveness of different treatment strategies. At that time, the models were primarily focusing on finding the best treatment options rather than concentrating on predicting the behaviours of tuberculosis epidemic along a timeline. The primary reason may have been limited understanding of tuberculosis disease dynamics and limitation related to computational power and technology. Because of this reason, very little work related to tuberculosis model published before mid-1990s.

In 1995, Blower et. al published the first SEIR model to explain the tuberculosis transmission dynamics (Blower S., 1996). This is followed by a large number of work published on applications of mathematical modelling of tuberculosis. The models developed can be divided into three different structures. These include: a) ordinary differential equation models (SEIR type models), b) age-structured and delayed models and c) spatial structured models.

5.3 Application of Malaysian tuberculosis transmission dynamic mathematical model to assess impact of intervention strategies

Following development of the Malaysian tuberculosis transmission dynamic model, this study used the model as a tool to estimate the disease burden and to assess the likely impact of interventions on reducing incidence in Malaysia. Tuberculosis burden between 1990 and 2050 were estimated and projected, and the likely impact of interventions was studied under four (4) scenarios. These include: no intervention strategy, treatment of infectious tuberculosis only, chemoprophylaxis of IPT only and combination treatment of infectious tuberculosis and IPT.

5.3.1 Estimates and projection of tuberculosis burden in Malaysia 1990-2030

Based on estimates and projections of number of cases illustrated in Figure 4.28 in Chapter 4, the trend in tuberculosis burden is expected to rise steadily from 1990 to 2030. The persistent rise of trend is at an annual increment rate range from 0.5% - 2.5% for both retrospective and prospective projections comparable to the observed values i.e. case notifications at an annual difference rate range from -5% and 10% between 1990 and 2011.

5.3.2 Effectiveness of Isoniazid Preventive Therapy

The Malaysian tuberculosis epidemiology behaviour was assessed according to four scenario analyses. These were: 1) when there is no treatment strategy 2) when Isoniazid

Preventive Therapy is the only treatment strategy 3) when treatment of infectious tuberculosis is the only treatment strategy and 4) when combined treatment of infectious and preventive therapy is the main strategy.

The result discussed the model projection for the four strategies mentioned above. Scenario 2 showed significant reduction of tuberculosis cases in comparison with Scenario 1, however, steady rise in trend of new cases remained high amounting annually up to 2040 ($p < 0.001$). Scenario 3 showed significant reduction of cases as well as trend compared to Scenario 2 from 1990 to 2040 ($p < 0.001$). Scenario 3 & Scenario 4 showed not only that the total number of tuberculosis cases were significantly reduced in Scenario 4 but also with significant reduction of trend from 1990 to 2040 thus indicated as the most effective strategy to reduce tuberculosis incidence in Malaysia. All outputs of four treatment strategies were summarised in Figure 4.32.

In Strategy 1, the annual rate difference of tuberculosis infection cases range from 1.47 – 47.01 % from year 1990 – 2040. With Strategy 2 i.e. Isoniazid Preventive Therapy only, the annual rate reduction of tuberculosis cases was significantly higher as compared to Strategy 1. The annual rate difference of tuberculosis cases with Strategy 2 ranges from 1.75 – 36.62 % from year 1999-2040 ($p < 0.001$). However, Scenario 1 and Scenario 2 (Strategy 1 & 2 included) did not reflect the reality, thus were simulated and treated as baselines only.

With Strategy 3, the annual rate difference of tuberculosis infection cases ranges from - 11.34 – 1.60 % from year 1990 – 2040, which is a significant reduction as compared to Strategy 1 or Strategy 2 ($p < 0.001$). Lastly Strategy 4 i.e. the combination treatment of infectious tuberculosis and Isoniazid Preventive Therapy projected the maximum annual

rate difference and significant rate reduction of tuberculosis cases as compared to all the other strategies. This is shown by consistent annual rate reduction ranges from -30.08 – -2.26 from year 1990-2040 ($p < 0.05$).

The comparison among the four strategies clearly demonstrated that Strategy 4 i.e. the combination treatment of infectious tuberculosis and Isoniazid Preventive Therapy is the most viable and efficient strategy to manage tuberculosis epidemic in Malaysia.

5.3.3 Quantification of Isoniazid Preventive Therapy coverage in combined treatment strategy to effectively reduce tuberculosis incidence

Figure 4.34 in Chapter 4 showed the likely impact on reduction of tuberculosis incidence by varying coverage of IPT for high risk LTBI against time. What it explains is that there exist two scenarios for current treatment coverage for infectious tuberculosis, these are; at 60% and 80% treatment coverage. These are shown in Figure 4.34a and Figure 4.34b respectively. These percentages represent lower and upper limits of Malaysian current treatment coverage of infectious tuberculosis, averaging between 70% - 75% per year.

In the model developed, instead of taking the average treatment coverage of 70 – 75 % we took into consideration a much wider range from 60 – 80 % of current treatment coverage. The reason for this wider range was make sure that we include the worst and the best possible scenario for the current tuberculosis treatment coverage.

With this wider coverage range (60 – 80 % of treatment current treatment coverage), the model demonstrate that the minimal 10% coverage of IPT is required to effectively reduce tuberculosis incidence. With this strategy the reduction rates varied from 1% to 5% annually in both (60–80 %), following eight to ten years of implementation. Marked increases in impact are predicted when the treatment coverage is $\geq 20\%$ and is attained between two to five years at rates of 17.6% - 38.5% per year.

With current strategy, treatment for infectious tuberculosis cases only, the MDG 6 targets on tuberculosis incidence (32 per 100,000 populations) which is supposed to be achieved by year 2015 but in reality can only be realized after 55 years with 80% and can never achieved if the treatment coverage is 60% only.

This can be is drastically reduced to 14 - 17 years if we utilize the combination strategy of current treatment for infectious tuberculosis and IPT for high risk LTBI. This can be achieved with coverage of only 10% of IPT. The time to achieve reduction in incidence can further be reduced by IPT coverage of 20% and more. Time taken to achieve these targets is reduced to 7 - 11 years (at reduction rate of 80% and more) and 9 - 15 years for 60% and 80% treatment coverage respectively.

The optimal coverage required to effectively reduce the tuberculosis incidence if IPT at least cover 10% of the total population used in combination treatment for infectious tuberculosis and IPT for high risk LTBI.

5.3.4 Selection of high risk latent tuberculosis sub-populations for Isoniazid Preventive Therapy optimal coverage

Now a new question arises - which latent tuberculosis (Early Latent or Late latent) patients should be given included to effectively achieve the reduction in the tuberculosis incidence. The model provides answer to this question and is explained in Figure 4.35. It shows that the proportion of early LTBI treated has the early and continuous reduction in tuberculosis cases as compared to late LTBI that shows an initial increase before the actual reduction is observed. Treating early LTBI is a more effective tuberculosis epidemic control measure as compared to late LTBI.

5.3.5 Overall impact of Isoniazid as early preventive therapy for tuberculosis prevention in Malaysia

The components of successful strategy for reduction in the tuberculosis incidence include: 1) combination treatment strategies of treatment of infectious tuberculosis cases and treatment of latent infected cases, 2) 80% of the current treatment coverage for infectious tuberculosis cases, 3) at least 10% IPT coverage for high risk LTBI population and 4) treatment of IPT among early LTBI group rather than late LTBI, 5) The effective reduction rates range from 1 – 5 % cases whereby 6) the reduction trend significantly reduces after 8 – 10 years of implementation IPT combined strategy.

Given the scenario findings, if Malaysia had implemented this strategy back in the year 1990, the cumulative rate reduction of 50% tuberculosis cases (and subsequent achievement of MDG 6) can be realized by the year 2050. Unfortunately that was not

the case. Projection showed that if Malaysia decided to implement this strategy in the 2015, it can only cumulatively reduce up to 27.21 % of tuberculosis incidence by the year 2050. That still falls short of achieving neither MDG 6 nor complete elimination of tuberculosis by 2050.

5.4 Summary of Chapter 5

Modelling approach is an alternative option to effectively study the reduction in the tuberculosis burden in Malaysia. The application of the age-structured tuberculosis transmission dynamic mathematical developed for Malaysia shows that IPT for high risk early LTBI is an effective strategy when used in combination with current treatment of infectious tuberculosis. This combined approach can be optimized by ensuring a minimal IPT coverage of 10% of population with an expected cumulative rate reduction of about 27.21% by 2050 following eight to ten years of implementation from 2015.

6.1 Study findings

The study findings are significant and important for Malaysia to effectively reduce the burden of tuberculosis. A Malaysian tuberculosis model was developed as an age and gender structured deterministic compartmental transmission dynamic mathematical model using the ordinary differential equation system.

Application of this validated model projected a steady rising trend of tuberculosis incidence in Malaysia. However, the proposed intervention of combined strategy with current treatment for infectious tuberculosis and Isoniazid Preventive Therapy for high risk latent tuberculosis sub-populations showed effective reversal of increasing tuberculosis trend.

The application of this tuberculosis transmission dynamic mathematical developed for Malaysia also showed that Isoniazid Preventive Therapy for high risk early latent tuberculosis sub-populations is an effective strategy as compared to the late latents; when used in combination with current treatment of infectious tuberculosis patients.

Various simulations of coverage of high risk latent tuberculosis populations revealed a minimum of 10% coverage of Isoniazid Preventive Therapy is mandatory among early latent tuberculosis sub-populations to show substantial reduction in tuberculosis trend. Further simulation showed that this optimized combined approach with a minimal IPT

coverage of 10% of population will result in a cumulative rate reduction of about 27.21% by 2050 following eight to ten years of implementation from 2015.

6.2 Study commitment to Knowledge Translation and Get-Research-Into-Policy-and-Practice concepts

While research is considered as a domain of the academia, the implementation of research findings and development of the strategies for policy amendments is perceived only for the policy makers i.e. career bureaucrats, the ones who usually make all the decisions. In most of countries, even developed countries, these two major players do not look eye to eye. Suffice to say that there exists an invisible wall between the two players hence disconnect between the academic research and its implementation at the policy level.

Many attempts have been made to bridge this gap. The Malaysian Ministry of Health acknowledged this problem and has been advocating the practice of Knowledge Transfer (KT) and Get Research into Policy and Practice (GRIPP) in the Malaysian healthcare environment. The research team has considered this issue from an early stage in research rather than as an “end of project” add-on (Andrew Barnett, Christina Wille, Anna Khakee, & Williams, 2010). The team ensured that the research question was modelled around the ground issues so the results of the research can be used and translated as the empirical evidences for developing the policies in managing the ground realities of tuberculosis epidemic in Malaysia.

6.3 Commitment of policymakers and academics throughout study process

There have been strong advocacy in this relatively new field of infectious disease mathematical modelling to directly involve all relevant stakeholders in tuberculosis management in many developed country settings and this study. However, it is not without tremendous effort that this study managed to maintain the network while the study progressed. The study findings were directly communicated to the stakeholders as a local national evidence to assist in decision making process and policy development especially during urgent national disaster management such as disease epidemic, pandemic or bioterrorism, given the advantage that the evidence could be provided in a relatively shorter time (as compared to conventional studies which requires primary data collection), yet at the same time remained reliable, valid and comparable.

The age and gender structured deterministic transmission dynamic model of tuberculosis developed in this study is a consensual model based on inputs from not only respiratory physicians, tuberculosis state/district epidemiologists, microbiologists and primary care physicians but also included inputs from policy makers from main stakeholders in Ministry of Health nationwide. The model developed was then presented at various national and international congresses for peer-review and validation. All valuable inputs were taken into account to refine the model developed. This was a time-consuming with extensive development and review process that resulted in establishing a consensual model for managing tuberculosis burden based on mathematical modelling technique.

Never before in Malaysia, has such an extensive exercise ever been undertaken for investigating and managing the local tuberculosis epidemic using mathematical

modelling technique. The results presented at different congresses have shown that the model outputs have been consistent with the disease dynamics and therefore have the potential to bring along positive changes in managing tuberculosis epidemic in Malaysia.

6.4 Study support system, network members and consensus

Work coordination was uniquely strategized in an organized systematic manner in two sections as illustrated below in Figure 6.1. First, the main research team engaged all stakeholders involved in tuberculosis management in Malaysia. They include the policymakers, public health personnel, clinicians and domain experts from academic institutions and Ministry of Health as research supporting members who continued to engage as the study progressed till its completion. Following that, an in-depth pathophysiology of tuberculosis in Malaysia was consensually determined among all research members who subsequently formed the foundation to develop a customized tuberculosis transmission dynamic model exclusive for the Malaysian environment and characteristics. The model was then validated and optimized using the observed/actual Malaysian data, and used to assess the likely impact of IPT as a proposed early intervention (chemoprophylaxis) strategy in addition to current therapeutic regime to reduce tuberculosis incidence in Malaysia.

The impact assessment started off by demonstrating estimates and projections of tuberculosis burden in Malaysia till 2050 given current treatment management. Following that, the most effective strategy that reduces the incidence was determined – without treatment versus IPT only versus current treatment only versus combination of

IPT and current treatment. That most effective strategy assessment was detailed further by: 1) quantifying the coverage of latent tuberculosis as target population needs to be in order to effectively reduce the incidence, given current treatment 2) demonstrating target high risk latent tuberculosis population between early latent and late latent for effective reduction in incidence 3) demonstrating overall tuberculosis behaviour till 2050 and quantifying the total reduction of incidence achieved given 1) and 2) assessment details demonstrated above in two scenarios – if the strategy were implemented in 1990 (retrospective) versus if the strategy were implemented in 2015 (prospective).

There have been strong advocacy in this relatively new field of infectious disease modelling to directly involve all relevant stakeholders in tuberculosis management in few developed country settings. This is because the study findings are directly communicated to the stakeholders for providing local national evidence in decision making process and policy development especially during urgent national disaster management such as disease epidemic or pandemic or bioterrorism where the evidence can be provided in a relatively shorter time (as compared to conventional studies which requires primary data collection), yet remained reliable, valid and comparable.

In view of that, this thesis demonstrates similar commitment and advocacy as one of its study objectives as written in Chapter 6 of this thesis. This thesis adopts similar local concepts by Ministry of Health Malaysia for that matter - Get Research Into Policy and Practice (GRIPP) and Knowledge Translation (KT). These concepts are standardized pathways for forwarding all local research findings for implementation and policy framework development.

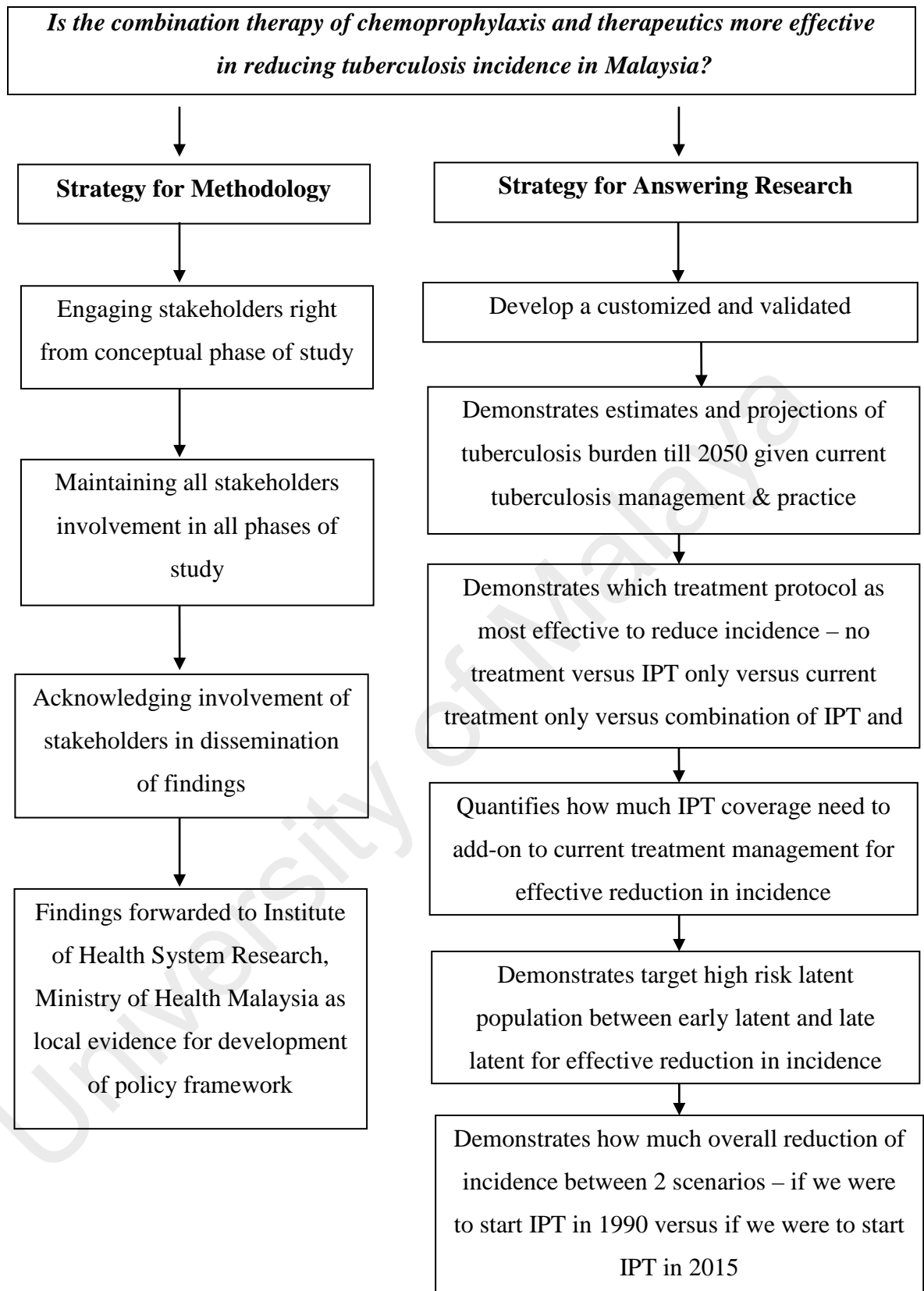


Figure 6.1: Diagrammatic presentation on coordination of strategies on methods and answering research question by using mathematical modelling techniques and its applications

6.5 Policy recommendation

This policy recommendation section includes objective, policy write-up and evidence and policy application in the community.

6.5.1 Objective of recommendation

This study formulates a clear national policy direction via recommendation that Isoniazid Preventive Therapy for high risk early latent tuberculosis sub-populations is an effective intervention strategy to effectively reduce the Malaysian tuberculosis incidence when used in conjunction with current treatment for infectious tuberculosis.

6.5.2 Policy evidence and application in the community

This study was set to explore how the use of mathematical modelling can help manage the tuberculosis epidemic effectively in Malaysia. We developed the customized age and gender structured tuberculosis transmission dynamic mathematical model for Malaysian population. It is a consensual model encompasses the tuberculosis disease dynamics and the local inputs from major stakeholders and policymakers. This chapter briefly translates the research work and its finding into policy recommendations and implementation with reference to current practices and realities in managing tuberculosis epidemic in Malaysia.

The main finding of this research is to provide evidence if Isoniazid Preventive Therapy for the LTBI is an effective measure to effectively reduce tuberculosis incidence. The first question rose whether it is effective to introduce the Isoniazid Preventive Therapy for the target population, and if it is effective how much of the target population should be covered with this Isoniazid Preventive Therapy coverage. The study demonstrates that Isoniazid Preventive Therapy is an effective and viable option that successful Isoniazid Preventive Therapy introduction is at least 10% of the target population can achieve the policy objective when used in combination with the current treatment protocol for infectious tuberculosis.

Nonetheless, identifying the 10% of the target population for Isoniazid Preventive Therapy implementation poses potential challenge. This can be achieved either by local disease dynamics pathway or according to the WHO guidelines on selection of high risk LTBI sub-population. The study provides the guide to effectively identify the 10% of the target population so as to maximize the benefits of the IPT introduction. According to study results, this 10 % target population should include that high risk EARLY latent sub-population as oppose to late latent.

The early LTBI sub-population includes healthcare workers and contact population. Management of IPT for healthcare workers can be implemented by integrating and extending their current pre-employment health screening programme to ensure the catchment following first five years exposure at the start of their job in any healthcare settings. For contact population, management of IPT can be achieved by adopting “intensified active case detection” following the notification of an index infectious case. This can be ensured by adhering to the recommended WHO guidelines in tracing at least ten contact persons per an index active tuberculosis case identified.

Other high risk early LTBI can be effectively managed by establishing a disease registry for immuno-compromised cases and institutionalized such as paediatric tuberculosis population, tuberculosis with diabetes, HIV population, tuberculosis with neoplasm, and tuberculosis with chronic disease etc. With current policy, Malaysia has started IPT in the paediatric population since 1980's, and HIV population since June 2011. But that effort has not been enough; that there has never been any reduction of cases for the last thirty years. The modelling quantified that the coverage of minimum 10 % of the target population needs to be identified. That may be the reason why the current practice fails to produce identifiable reduction in the tuberculosis incidence in Malaysia.

With this 10 % coverage of the early LTBI, tuberculosis incidence in Malaysia can be reduced to 17.86 % by 2020, following implementation of IPT in 2015. This can be reduced further to a cumulative reduction of 27.21 % by 2050.

The IPT introduction for the target population can follow different regimen from 6 months to 12 months (6 months, 9 months and 12 months). According to feasibility studies, WHO recommends that IPT should be administered at least for 6 months, and 6 months is preferred due to compliance related issues.

This reduction in tuberculosis incidence is substantial and convincing, so why was the community-based trial not done before? The study concluded that the resistance to the IPT implementation revolved around two major concerns: 1) Isoniazid induced hepatotoxicity, and 2) concerns about the possible drug tolerance and resistance. However, in both cases the drug induced hepatotoxicity and drug tolerance and resistance cases were reported to be < 0.01 %. Furthermore, this could be managed by introducing a comprehensive active surveillance model framework that encompasses all

aspects right from the detection point i.e. screening and diagnosis and throughout the treatment protocols and adverse events for the IPT recipients. Before IPT can be administered, the target population of early LTBI should be effectively identified to ensure the success of the programme. That requires an efficient screening programme in place. An efficient screening programme requires identification of the proper screening method, cost of the screening programme, and capacity development human resource to effectively manage the programme. However, this fall beyond the scope of the current research and requires further studies by other research teams. Besides that, other important aspects such as economic evaluation should also be conducted to justify the resource allocation for IPT programme.

6.6 Return on Investment (ROI)

The work of this thesis focused on the tuberculosis disease burden arguments rather than its economics. Therefore, further study that evaluates the economic implication of the proposed combined treatment strategy is highly recommended. It is understudied - there is only one empirical study conducted in Malaysia that estimated the treatment cost of tuberculosis patients by Elamin et al and published in 2008. (Elamin, Ibrahim, Sulaiman, & Muttalif, 2008) The study was done in the state of Penang, and stated that the cost of treating the illness of tuberculosis per patient was US\$916.4 in 2004 (equivalent to MYR 3,271.54 (calculated with an exchange rate of 1 USD = MYR 3.57, 25 April, 2015)). That estimation included all the cost of treatment for tuberculosis i.e. the direct medical and non-medical costs as well as indirect costs. These include the cost for anti-tuberculosis drugs and supplies, the costs for X-ray examinations, the costs for laboratory tests, the costs for healthcare staff time, the costs for hospitalisation, and

overhead costs. The indirect costs include transportation and meals and the costs for time away from work.

The ROI study recommended include a comprehensive cost-effectiveness analysis that shall project the economic implication or evidence of Isoniazid Preventive Therapy as an effective added value to the current treatment strategy that confines to treatment of infectious tuberculosis. Apart from that, an updated and current costing analysis for tuberculosis treatment in Malaysia is also beneficial to complement the the economic implication of treatment.

6.7 Implementation of Isoniazid Preventive Therapy in other countries

The screening and treatment of latent tuberculosis infection in people living with HIV and child contacts of pulmonary tuberculosis cases less than 5 years old existed in Malaysia since 2006 and 1990s respectively. In 2015, following a systematic evidence synthesis exercise, WHO has strongly recommended the existed programmes and that the coverage should be extended to close contacts of pulmonary tuberculosis cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis conditional in high and middle income countries with an estimated tuberculosis incidence less than 100 per 100,000 population. Other risk groups such as prisoners, health-care workers, immigrants from high TB burden countries, homeless persons and illicit drug users should be considered (WHO, 2015b).

To date, despite developed countries with low burden of tuberculosis implementing the IPT screening and treatment, the screening and treatment of latent tuberculosis infection in people living with HIV and child contacts remain with low uptake globally mainly by resource constraint countries. Even fewer countries have expanded the programme to include non-HIV population such as the close contacts and healthcare workers in neighbouring countries like Japan, South Korea, Singapore and Thailand. Some studies had identified that unclear national policy, fear of Isoniazid resistance and poor adherence and lack of commitment of health managers to scale up the program as the main barriers in IPT implementation in both HIV and non-HIV population (Moolphate et al., 2013; Teklay, Teklu, Legesse, Tedla, & Klinkenberg, 2016)

6.8 Further work for implementation

A comprehensive management system for monitoring and surveillance is highly recommended once it is implemented in the community. Several targeted programmes in line with implementation of Isoniazid Preventive Therapy in the high risk early latent tuberculosis sub-populations should be included such as TB-Diabetes, TB-Migrants, TB-elderly, TB-prison etc. These programmes should include impact assessment, selection of screening methods for early latent, surveillance for Isoniazid induced hepatotoxicity and monitoring programmes for Isoniazid resistance.

6.9 Summary of Chapter 6

This chapter provides the policy recommendation following new evidence to be translated into practice. It recommends Isoniazid Preventive Therapy as a viable option to effectively reduce the Malaysian tuberculosis incidence when used in conjunction with current treatment protocol for infectious tuberculosis. However, an optimal coverage of 10% of the early latent tuberculosis sub-populations is required for significant reduction of incidence. Based on current tuberculosis control programmes in Malaysia, this study recommends the early latent coverage to be extended to two contacts populations i.e. those who are exposed in close proximity to the infectious tuberculosis or close contacts and those who are exposed due to occupational hazard i.e. the healthcare workers. Coverage of healthcare workers and close contacts demonstrates the effective reversal of incidence trend for Isoniazid Preventive Therapy combined therapy once implemented in the community.

7.1 Strength of the research

The age and gender structured deterministic compartmental model of tuberculosis dynamics model developed during this study is a consensus model based on inputs from not only respiratory physician, tuberculosis state epidemiologists, microbiologists and primary care physicians but also included inputs from policy makers from main stakeholders in Ministry of Health. The model developed was then presented at various national and international congresses for peer-review and validation. All valuable inputs were taken into account to refine the model developed. This was a time-consuming and extensive development and review process that resulted in establishing a consensual model for managing tuberculosis burden based on mathematical modelling technique. Never before in Malaysia, has such an extensive exercise ever been undertaken for investigating and managing the local tuberculosis epidemic using mathematical modelling technique. The results presented at different congresses have shown that the model outputs have been consistent with the disease dynamics and therefore have the potential to bring along positive changes in managing tuberculosis burden in Malaysia.

Being a mathematical modelling study, it does not interfere with the clinical management of patients ensuring that there is no physical harm brought to the patient during the research period.(Brauer, 2009) Yet, the model is based on sound pathophysiology of tuberculosis ensuring that all aspects of tuberculosis dynamics are taken into account while developing the model. Therefore the projections of the model

represent the entire pathophysiology of tuberculosis and projects results comparable with the results of community based trial methodology.

The model projected that a minimum of 10% of total population should receive the proposed intervention to bring along the substantial reversal of tuberculosis burden in Malaysia. Quantifying the output in terms of the extent of coverage of target population and identifying that target population ensure that objective results are achieved with identifiable variants. That ensures that the implementation can be adjusted according to the variants targeted to achieved and obtained. This is the advantage of using age and gender structured deterministic compartmental model of tuberculosis dynamics as an efficient way of managing resources for reducing the tuberculosis burden in Malaysia.

Conventional methodology of managing tuberculosis burden usually employs and explores whether incorporating IPT will help to reduce the longstanding high tuberculosis burden. Most of the time the research stops at this point without identifying the target population, optimal coverage of target population and pinpointing the time (of tuberculosis transmission dynamics) to be targeted. We understand in conventional methodology of community based trial is usually associated with apprehension regarding “more harm than benefit” to the target population. Alternative way by using this mathematical modelling method may overcome the above mentioned shortcoming and quantify the target population, coverage of target population and the intended time of intervention without causing any harm to the population.

7.2 Limitations of the research

This field is an applied and integrated field of epidemiology, infectious disease, mathematics and bioinformatics. Although it was thought to have been initiated by David Bernoulli in late 19th century, it is a relatively new field locally. Therefore, such expertise and modalities for frequent discussion and training was very limited. There was also no previous study on mathematical modelling of tuberculosis done in Malaysia. This is the first study to be conducted in the field of infectious disease mathematical modelling in Malaysia. Appraisal on the model was in comparison to the neighbouring countries such as Hong Kong. The national data on tuberculosis although centralised under TBIS system, may not be comprehensive and complete, representing the population in Malaysia.

When the primary data is not available, the secondary which may or may not be representative of the settings need to be borrowed from neighbouring countries (Dowdy, Dye, & Cohen, 2013). This scenario could be further improved by ensuring and prompting more local researchers to collect the data in the field either picked up in the service or by conducting operational/implementation research to achieve those parameters with local values. In addition, the local expertise in the mathematical modelling in the infectious disease modelling is very limited. That may have been the reason that there is no comprehensive disease specific data available to carry out such research.

7.3 Contribution of thesis

The study has provided the evidence that IPT is a significant and effective measure to reduce the long standing tuberculosis incidence in Malaysia. This knowledge discovery has marked advancement in the tuberculosis care and management in Malaysia and that the focus needs to be expanded beyond the scope of detecting and treating the infectious cases only. It is also imperative to diagnose and treat at the earlier state of tuberculosis infection even without clinical manifestation especially in the high risk latent tuberculosis sub-populations. This study also emphasized that despite the existing IPT programme for tuberculosis prevention in paediatric and HIV populations in Malaysia, the coverage is still inadequate for effective reversal trend of incidence. This is because HIV epidemic in Malaysia is the concentrated type of epidemic and low incidence in paediatric population (less than 5 years old).

Apart from that, this study is one of the few in Malaysia that demonstrated and made use of mathematical modelling techniques in infectious disease and provided new knowledge or evidence from different disease perspectives. There are only a small number of physicians involved in research that goes beyond the field of their interest in Malaysia. That may be the reason for the lacking of evidence in the field of infectious disease mathematical modelling on disease behavioural predictions and disease outbreaks in Malaysia. This research opted the long standing chronic disease of priority in Malaysia i.e. tuberculosis by studying the Malaysian tuberculosis epidemiology. It used the model developed as a tool to assess the potential impact of early intervention to effectively reduce the incidence. This has introduced a new dynamics in the field of infectious disease epidemiology and work on mathematical disease modelling in Malaysia. It is hoped that this approach may become a popular alternative for

exploratory research to be conducted in the field of public health that offers different perspectives to study the disease for the epidemiologist, public health specialist, clinicians and health management staff in the Malaysian healthcare system.

This research is the first empirical research in Malaysia that attempt to manage tuberculosis epidemic with an early diagnosis and interventions of tuberculosis infection. Instead of the current treatment that advocates management of infectious tuberculosis population only, the current research focuses on the latent tuberculosis infection sub-populations. The adoption of the new proposed strategy will result in reducing the tuberculosis disease burden more effectively.

This research utilized the concepts developed in the emerging fields of infectious disease epidemiology and mathematical epidemiology. These fields complement the conventional epidemiologic methods to answer the research questions raised by policymakers and programme managers in Malaysia.

This research advocates a more systematic and organized academic syllabus for a new high-paced, dynamic and integrated field of infectious disease mathematical modelling in postgraduate public health training programme in Malaysian academic institutions.

7.4 Public health implication

This research recommends the adoption of Isoniazid Preventive Therapy as an additional treatment to the current treatment regime of tuberculosis management protocol into policy to effectively reverse the disease burden of tuberculosis as per the

Clinical Practice Guidelines of Ministry of Health Malaysia and World Health Organization (WHO). Mathematical modelling techniques give us the liberty to assess the impact of an intervention without disturbing the current clinical management of the patients, thus reducing the possibility of any harm to the patients. By identifying the target population evidence derived from this study can help clinicians to objectively focus on early latent tuberculosis cases in the population for IPT programme. It will also assist the surveillance and DOTS of target population. This early detection programme provides the advantage of prioritizing the management of the early latent tuberculosis cases, and thus avoiding the progression into infectious phase of the disease for such patients.

This research also propagates the idea of earlier diagnosis and treatment of tuberculosis patients i.e. targeting high risk latent tuberculosis subpopulations to effectively reduce the Malaysian tuberculosis incidence; and subsequently reverses the Malaysian burden of tuberculosis.

7.5 Further work following this study

The customized Malaysian tuberculosis transmission dynamic mathematical model developed in this study provides a simple homogeneous mathematical and logical foundation of system engineering and software. The model can be further used as a basis for system specification, system development by refinement and system implementation for software development. Further work in the field of software engineering and computer science on language programming is highly recommended in order to fully utilize the model developed as an end-user application for epidemiologists

and programme managers to efficiently improve the Malaysian tuberculosis surveillance system.

At the same time, this model can be further improved hence more representative if the secondary data used was substituted with the local primary data. That prompts the need for local empirical data collection. But before this data can be collected, researchers should identify the types and scopes of such data collection exercise to be conducted, to ensure data can be effectively used for improving the quality and robustness of the model. Future research is highly recommended to properly address if influence of assumptions on completeness of data be assessed by sensitivity analyses.

Further empirical evidences in the Malaysian environment is also needed with regard to the most appropriate screening programme to be in place once this programme is implemented. These include screening methods and validity testing, surveillance and reporting system, treatment strategies, human resource and capacity development, and economic evaluation. This will ensure adequate resources allocated and justified and made accessible in the community.

The study has also identified the need of a scale-up intervention in a general population to reduce the burden. Further work should be advocated for co-morbidity-specific mathematical modelling studies for high risk LTBI sub-populations. These include specific studies on TB-diabetes, TB-cancer, and TB-CKD etc. that investigate the detailed impact of interventions for specific and targeted management of the proposed intervention.

The policy paper produced in this thesis has also been customized to the local formulation and format of an evidence paper for policy adoption by Ministry of Health. Further effort for study findings dissemination and implementation would be planned such as in the forms of presentation, round table discussion and publication among all stakeholders, programme managers and researchers.

7.6 Thesis conclusion statement

This study highlights that the Malaysian tuberculosis incidence likely continues to rise till year 2050. The Malaysian age-structured tuberculosis transmission dynamic model developed in this study demonstrates that deploying early intervention strategy that diagnose and treat early high risk latent tuberculosis infection called Isoniazid Preventive Therapy is an effective measure to reduce the incidence when used in conjunction with current treatment for infectious tuberculosis. Further analyses predict that diagnosing and treating early high risk latent tuberculosis infection at ten percent minimal coverage of Isoniazid Preventive Therapy significantly reduces the incidence 27.2% cumulatively by 2050 following eight to ten years of implementation from 2015. This study formulates the policy recommendation that Isoniazid Preventive Therapy coverage should be expanded to other high risk latent sub-populations such as healthcare workers and close contacts in addition to the current existing coverage confined to paediatric and HIV populations only. It should be deployed as a scale-up and additional intervention strategy of the national tuberculosis management and adopted as part of the Malaysian Clinical Practice Guidelines for Tuberculosis.

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LIST OF PUBLICATIONS AND RELATED ACTIVITIES

Publications, paper presentations and related activities arising from the work presented in this thesis are summarised as follows:

Government related activities:

- 1) “Mesyuarat Infectious Disease Modelling” (Meeting on Infectious Disease Modelling), National Public Health Laboratory, Ministry of Health, Sungai Buloh, Malaysia, 9 December 2015 (*Invited Speaker*)
- 2) “Latihan Penambahbaikan Kualiti Pengurusan Data Program Kawalan Penyakit Tibi” (Data Quality Management Training for Tuberculosis Control Programme), Disease Control Division, Ministry of Health, Putrajaya, Malaysia, organized by Sector TB/Leprosy, Disease Control Division, Ministry of Health, Malaysia, 18 – 22 November 2013 (*Invited Speaker*)
- 3) HIV Surveillance Technical Meeting of the Malaysian HIV Epidemic 2009, Putrajaya, Malaysia, organized by Malaysian Ministry of Health and World Health Organisation, 22 – 26 June 2009 (*Rapporteur - Professional/Academic Attachment*)
- 4) National Consensus Workshop on Estimation and Projection of the Malaysian HIV Epidemic 2009, Putrajaya, Malaysia, organized by Malaysian Ministry of Health and World Health Organisation, 26 – 29 May 2009 (*Rapporteur - Professional/Academic Attachment*)

- 5) UPM Mathematical Modelling Workshop, Serdang, Malaysia, organised by Institute of Mathematical Research, Universiti Putra Malaysia (UPM), Malaysia, 17 – 19 November 2009 (*Facilitator - Professional/Academic Attachment*)
- 6) IMR Mathematical Modelling Workshop, Kuala Lumpur, Malaysia, organised by Institute for Medical Research (IMR), Ministry of Health, Malaysia, 26 – 27 October 2009 (*Facilitator - Professional/Academic Attachment*)

Journals and Proceedings:

- 1) Ismail N, Awang M Bulgiba, Sanjay Rampal, Nicolaas JD Nagelkerke, Jiloris F Dony, Omar Awang. Quantifying Tuberculosis Burden and Underrepresentation in Malaysia, 1990-2014. International Journal of Infectious Diseases 45(1):349
- 2) Ismail N, Bulgiba AM, Nagelkerke NJD, Awang O, Jiloris FD, Suzana MH. Quantifying impact of Isoniazid for tuberculosis prevention in Malaysia: An-age structured model. Proceeding of 16th International Congress on Infectious Diseases, Cape Town, South Africa, 2-5 April 2014
- 3) Ismail N, Bulgiba AM, Nagelkerke NJD, Awang O, Jiloris FD, Suzana MH. Assessing impact of Isoniazid as early preventive therapy for non-HIV population in Malaysia: An-age structured model. International Journal of Infectious Diseases, Volume 16 (Supplement 1), 2012: 47.015

Presentations at Conference:

- 1) Ismail N, Awang M Bulgiba, Sanjay Rampal, Nicolaas JD Nagelkerke, Jiloris F Dony, Omar Awang. Quantifying Tuberculosis Burden and Underrepresentation in Malaysia, 1990-2014. 17th International Congress on Infectious Diseases 2016 (ICID 2016), Hyderabad, India, 2 – 5 March 2016
- 2) Ismail N, Bulgiba AM, Nagelkerke N.J.D, Awang O, Jiloris F.D., Suzana M.H. Quantifying impact of Isoniazid for tuberculosis prevention in Malaysia: An-age structured model. 16th International Congress on Infectious Diseases, Cape Town, South Africa, 2-5 April 2014
- 3) Ismail N, Bulgiba AM, Nicolaas JD Nagelkerke, Omar Awang, Jiloris F Dony, Suzana M Hashim. Assessing impact on tuberculosis interventions in Malaysia: A mathematical modelling application for outbreak and control. The Malaysian Thoracic Society Annual Scientific Meeting 2011: p49. Kuala Lumpur, Malaysia. 22 – 24 July 2011, Malaysian Thoracic Society
- 4) Ismail N, Bulgiba AM, Nagelkerke NJD, Awang O, Jiloris FD, Suzana MH. An age-structured mathematical tuberculosis transmission model as tool for outbreak modelling and control in Malaysia. The 43rd Asia Pacific Academic Consortium for Public Health (APACPH) Conference: p237-8. Seoul, Korea. 20-22 October 2011, Asia Pacific Academic Consortium for Public Health (APACPH)

Awards:

- 1) 17th International Congress on Infectious Diseases 2016 (ICID 2016), Hyderabad, India, organized by International Society for Infectious Diseases (ISID), 2 – 5 March 2016 (*Poster presenter and ICID 2016 Congress Best Poster Award Finalist*)
- 2) 20th Congress of the Asian Pacific Society of Respiriology 2015, Kuala Lumpur, Malaysia, organized by Asian Pacific Society of Respiriology (APSR), 3-6 December 2015 (*Oral presenter and APSR Travel Award Recipient*)
- 3) 15th International Congress on Infectious Diseases 2012 (ICID 2012), Bangkok, Thailand, organized by International Society for Infectious Diseases (ISID), 13 – 16 June 2012 (*Poster presenter and ICID 2012 Congress Scholarship Recipient*)
- 4) The Malaysian Thoracic Society Annual Scientific Meeting 2011, Shang-ri La Hotel, Kuala Lumpur, Malaysia, organized by Malaysian Thoracic Society and Lung Foundation of Malaysia, 22 – 24 July 2011 (*Oral Presenter and Best Oral Presenter Award Recipient 2011(2nd prize) & 2011 MTS Travel Award Recipient*)
- 5) The 4th Regional Conference on Occupational Health (RCOH) 2011, Seri Pacific Hotel, Kuala Lumpur, Malaysia, organised by The Society of Occupational & Environmental Medicine, Malaysian Medical Association (MMA) and PERKESO, 23 – 25 June 2011 (*Poster Presenter & Best Poster Award Recipient*)

Workshop:

- 1) A Practical Short Course on Infectious Disease Modelling, Julius Centre University of Malaya, Kuala Lumpur, Malaysia, organised by Julius Centre University of Malaya in collaboration with Harvard School of Public Health and School of Public Health, University of Hong Kong, 21-23 July 2014 (*Invited Speaker*)
- 2) Workshop on Infectious Disease Modelling and Its Applications 2010, Kuala Lumpur, Malaysia, organised by Julius Centre University of Malaya, Kuala Lumpur, Malaysia, 22-25 March 2010 (*Workshop Coordinator*)