Factors Influencing the Prevalence of Multi-drug Resistant Tuberculosis in Thailand

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Master of International Health
14 September 2015 – 8 March 2017

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A thesis submitted in partial fulfillment of the requirement for the Degree of Master of International Health

by

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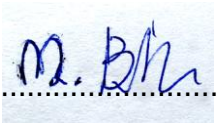
Signature:  ……

Master in International Health
14 September 2015 – 8 March 2017
KIT (Royal Tropical Institute)/ Vrije Universiteit Amsterdam
Amsterdam, The Netherlands

March 2017

Organised by:

KIT (Royal Tropical Institute) Health Unit
Amsterdam, The Netherlands

In co-operation with:

Vrije Universiteit Amsterdam/ Free University of Amsterdam (VU)
Amsterdam, The Netherlands

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Acknowledgements

I would first like to thank my thesis advisor; Dr. Lucie and back stopper; Dr. Maaike at KIT. Whenever I ran into a trouble spot or had a question about my research or writing. They consistently allowed this paper to be my own work, but steered me in the right the direction whenever she thought I needed it.

I would also like to thank the experts who were involved in the validation survey for this research project. Without their passionate participation and input, the validation survey could not have been successfully conducted.

Finally, I must express my very profound gratitude to my mom, my sister and to my friends for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

Author

Manussawinee Bhumiwat

Abstract

Thailand was ranking as one of the global highest MDR-TB burden worldwide for several years[4]. Although the NTP's performance has been improving continuously for treatment of TB patients, there is now increasingly concern on the emerging of MDR-TB cases. By the year 2015, there was an increase of estimated MDR/RR-TB cases among notified pulmonary TB cases while TB case notification rate of all forms in 2015 was decreased.

This thesis aimed to identify the potential factors which can affect MDR-TB prevalence and possible prevention strategies against MDR-TB in Thailand and explore experiences about MDR-TB prevention and control of other countries which can be applicable in Thailand's situation. This is a literature review with desk study, using the analytic framework to identify the potential factors associated with MDR-TB for find out the recommendations and interventions.

The major findings show many relationships among different kinds of factors. The potential factors for MDR-TB consist of the previous TB treatment history, socio-economic factors with especially mobility and many of health system related factors. Most of the previously-treated MDR-TB cases used to develop drug resistance from inappropriate treatment and poor treatment adherence. Moreover, there are poor access to get health services and resulting to delayed diagnosis and treatment.

The thesis concluded that primary prevention like TB Health promotion and preventive activities for MDR-TB is recommended to promote self-awareness and increase knowledge for good attitude for DOTS and TB care. Early case detection and strictly DOT are also highly suggested to prevent and decrease MDR-TB prevalence.

***Key words**: MDR TB, XDR TB, multi-drug resistant TB, epidemiology of tuberculosis, TB infection control, burden of MDR TB, TB prevention, DOT, drug resistant tuberculosis, MDR TB management, South East Asia, TB in Thailand, treatment adherence of TB*.

[Word count 10,524]

Abbreviation

AEC	ASEAN Economic Community
AFB	acid- fast bacilli
AIDS	acquired immunodeficiency syndrome
ART	anti-retro viral therapy
BCG	Bacille Calmette-Guerin
CDC	Centers for Disease Control and Prevention
DM	Diabetes Mellitus
DOT	Directly observed therapy
DOTS	Direct observed treatment, short course
DST	Drug Susceptibility Testing
DTC	District TB coordinator
FDC	Fixed dose combination
FLDs	First line drugs
H, INH	Isoniazid
HIV	human immunodeficiency virus
IC	infection control
IOM	International organization for migration
KIT	Royal Tropical Institute
LPA	Line probe assay
LTBI	latent tuberculosis infection
MDGs	millennium development goals
MDR-TB	multidrug resistant tuberculosis
MOPH	Ministry of Public Heath
NHCO	National Health Commission Office
NHSO	National Health Security Office
NTP	National tuberculosis control programme
PTB	pulmonary tuberculosis
PTC	provincial TB coordinator
R	Rifampicin
RTC	regional TB coordinator
SEA	South-east Asia
SLDs	second line drugs
SDG	Sustainable development goals
SMRU	Shoklo Malaria Resercg aasd
TB	Tuberculosis
UCS	Universal Coverage Scheme
WHO	World Health Organization
XDR-TB	extensively drug resistant tuberculosis

Introduction

Tuberculosis (TB) remains one of the major global health problems[1], especially in the low and middle-income countries and is included in the top ten cause of death worldwide[2]. Multidrug resistant tuberculosis (MDR-TB) has become a problem when isoniazid and rifampicin were introduced to TB treatment since 1970[3]. Later in 1990, fluoroquinolones has been used and then causing extensively drug resistant tuberculosis (XDR-TB)[3]. Thailand was ranking in top 22 of global high burden TB countries and 1 of 30 countries with highest MDR-TB burden worldwide for several years[4]. Addressing MDR-TB is a major challenge for both in terms of TB prevention and control. Although Ministry of Public Health (MOPH), Department of Disease Control (DDC) and Bureau of Tuberculosis (BTB) try to promote and develop strategies and policies, but there are many gaps to reach the standard of indicators.

As a medical doctor who was born and raised in Thailand, I have been working MOPH and DDC for several years. In most of my work, I have been involved with TB prevention and control programme in the lower northern region of Thailand, which consist of 5 provinces. One of them is Tak province that has its border connecting to Myanmar. This border area has a chronic problem of communicable disease control including tuberculosis, leading to high prevalence of MDR-TB cases in this region[5]. After working with TB supervision in the lower northern region for 4 years, I found it challenging to control the prevalence of MDR-TB patients. New MDR-TB cases report in this area has an increasing trend and compatible with the high default rate of TB treatment outcomes[5].

This study was inspired by the high burden of MDR-TB in Thailand that I want to find out what are factors. The results could be use as a key concept to identify gaps, development both domestic and international health policies, and recommendation for prevention and control of MDR-TB in Thailand.

CHAPTER 1: Background.

This chapter presents the country profile including demographic data, health situation, health finance and health system. The second and third topic will describe TB burden and national TB programme in Thailand which are related with thesis outline.

1.1 Country profile

Thailand is located in the centre of the Indochinese peninsular of South-East Asia with a total area of approximately 514,000 square kilometres[6] (see annex 1). Its north border connects with Myanmar and Laos whereas the south border situates to the Gulf of Thailand and Malaysia[6]. It is bordered to the east by Laos and Cambodia and to the west by the Andaman Sea and the southern of Myanmar[6]. The maritime boundaries are surrounded by Indonesia, Singapore and India on the Andaman sea to southwest and Vietnam by the Gulf of Thailand to southeast[6]. In 2015, there is a total population of around 68 million people with diversity of ethnicity, culture and nature among 4 geographic regions including northern, central, southern and north-eastern[7]. Approximately 10 million people live in the capital (Bangkok) and its vicinities[6]. Thai-speaking Buddhists are the major population around 94%[6].

Thailand is categorized as an upper-middle income country in 2011[8], with a gross national income 15,520 per capita (PPP, international $) in 2015[9]. The cities have grown faster than the countryside and poverty is still concerned and widespread in the rural northeast, far north and far south regions[6]. However, poverty in Thailand was significantly reduced from the past 25 years[6]. The poverty headcount ratio at national poverty lines has been progressively reduced from 42.3% in 2000 to 10.5% in 2014 (% of population)[10].

1.2 Demographic information

The structure of the population in Thailand has a large proportion of young people and a rapidly increasing trend of elderly people to be a third rank in Asia[6]. In the year 2014, around 17.6% were in age group of 0-14 years, 72.8% were in age group of 15-64 years and 9.5% were in age group over 65 years[11]. Male population was 49% and female population was 51%[11]. In 2010, 95.9% of populations were report to have Thai citizenship and the rest of 4.1% compose of 2% Burmese, 1.3% others and 0.9% unspecified groups[11]. Adult literacy rate is approximately 94% in 2015[12].

1.3 Health financing

Thai government through The Ministry of Public Health (MOPH) funds the majority of public health service activities. In 2014, the expenditure on health was calculated to be 23.2% of total government expenditure[7]. The private expenditure on health was 14.0% of total government expenditure in the same year[7].

1.4 Health situation

After starting investment in health infrastructure in particular primary health care, district and provincial referral hospitals in 1970s[13], life expectancy at birth has continuously increased to reach 71.9 years for male, 78 years for female and 74.9 years in both sexes in 2015[7]. The adult mortality rate also has decreased for both males and females, from nearly 240 per 1000 and 117 per 1000 in 2000 to be 205 per 1000 and 101 per 1000 in 2010, respectively[7]. There has been a decrease in neonatal and under-five mortality rates, estimated as 6.7 and 12.3 per 1000 live births in 2015, respectively[7].

Non-communicable diseases have been the major causes of death in Thailand since 1999[7]. The preventable causes such as ischemic heart disease, traffic injuries, diabetes and excessive use of alcohol are still the burden[7]. The trend of total disability-adjusted life years (DALY) loss from NCDs elevated from 58.5% in 1999 to 75% in 2009, while the trend of communicable disease declined from 27.7% to 12.5% in the same years[13].

1.5 Health system

Health care services are provided by primary health centres, public hospitals, private hospitals and practices including university hospitals. MOPH has adopted the Universal Coverage Scheme (UCS) since 2002[14]. Nowadays, over 90% of populations are covered by this public health schemes (see annex 2)[14]. This programme provides basic medical services to whole Thai population with free of charge prior to the introduction of the UCS[14]. The UCS health promotion and prevention budget covers only Thais citizens but not for non-Thais[14]. However, there has been some non-government organizations (NGOs) supporting health costs for non-Thai people[13].

Since 2001, many public health programmes have been intensely supported by the UCS budgets[13]. After the 2002 public-sector reform and the Decentralisation Act 1999, there has been decentralisation of some public health services from the MOPH to other public organizations[13]. After initiation of the UCS in 2002, the National Health Security Office (NHSO) which is responsible for the

UCS, has taken responsibility for the main financial source for personal health services, health promotion and prevention services instead of MOPH[13].

Shortage of doctors in public sector has been a chronic problem for many years, especially in the rural areas[15.] On the other hand, there has been an overflow of doctors in the private sector due to better incomes[15.]. In 2010, physician density was 0.393 per 1000 population while nursing and midwifery personnel density was 2.077 per 1000 population[16.].

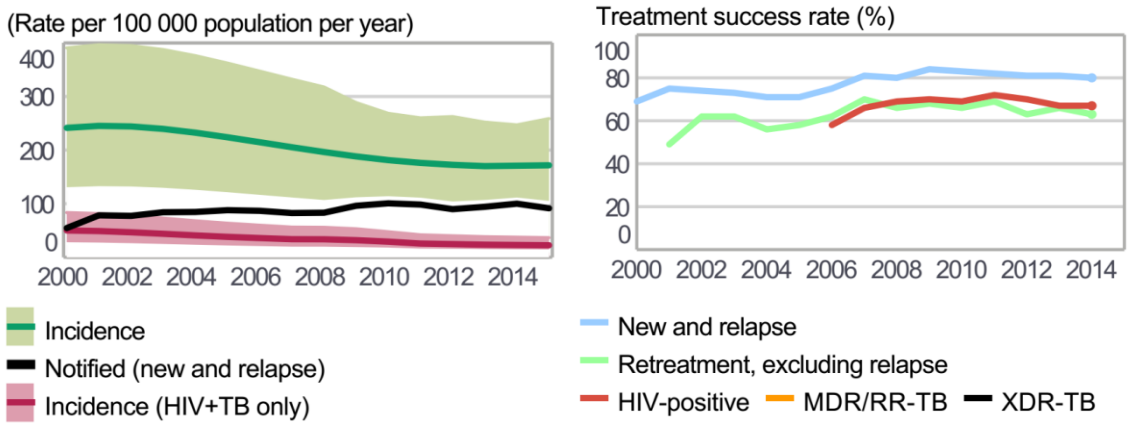
In the past, provision of public health services only was the responsibility of MOPH and its facilities[13]. However, after health reforming and evolutions since 1990s, these included the public-sector reform, the decentralisation of public administration, UCS, the establishment of the Thai Health Promotion Foundation and the National Health Commission Office (NHCO), and the local health funds initiative[13]. The organisation of public health services is demonstrated in annex 3.

1.6 TB burden in Thailand

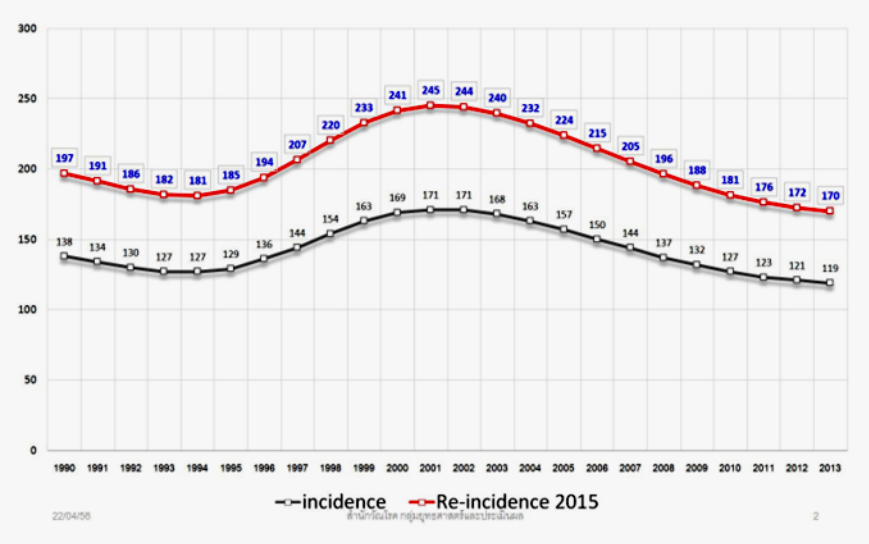
The latest report of WHO estimates that there were 10.4 million people infected with TB disease in 2015 worldwide and the largest number of new TB cases occurred in Asia with 61%[17]. Almost 90% of new TB cases occurred in 30 highest TB burden countries in 2015 and Thailand has been ranked as one of these countries for many years[17]. From the WHO report in 2015, the notification cases of all forms TB in Thailand was 66,179 and TB incidence of all forms was estimated 172 per 100,000 population[17]. TB mortality rate which excluded TB co-infected HIV in the same year was estimated 12 per 100,000 populations[17].

Although the MOPH try to promote and develop strategies and policies using National tuberculosis control programme (NTP), the TB problem is still difficult to control[18]. In Thailand, the success rate of TB treatment among new and relapse cases registered in 2014 was only 80 percents[1] which is lower than the standard of 90%[1]. The treatment success rates have been steadily lower than the standard of 90%[17] as shown in graph 1.1. The true burden of TB incidence has been higher than an estimate as seen with revised TB incidence in graph 1.2.

Graph 1.1: Incidence and treatment success rates of TB in Thailand (WHO: Thailand's TB profile, 2016)[17].



Graph 1.2: Comparison between estimated TB incidence and revised TB incidence (2015) in Thailand after national prevalence surveys. (Bureau of Tuberculosis of Thailand)



1.7 National tuberculosis control programme

The NTP has been established in Thailand under the supervision of Bureau of tuberculosis (BTB), Department of disease control (DDC)[18]. Thailand officially adopted directly observed treatment, short course (DOTS), the internationally recommended TB control strategy in 1996[18]. It was adapted to be Stop TB Partnership in 2006 with the collaboration from WHO to the MOPH. The Stop TB strategy has been funded from the Global Fund for AIDS, TB and Malaria and technical support from WHO, the MOPH, Centre for Disease Control and Prevention (CDC) collaboration and other health stakeholders[18]. Therefore, Thailand's NTP has been strengthened and more functioned after adopting this strategy[18].

WHO also supports MOPH with national TB prevalence survey and development of a five-year plan for programmatic management for MDR-TB[3.] Thai national TB programme has WHO's close collaboration to address the strategic priorities in TB programme and to reduce TB burden in the country[18].

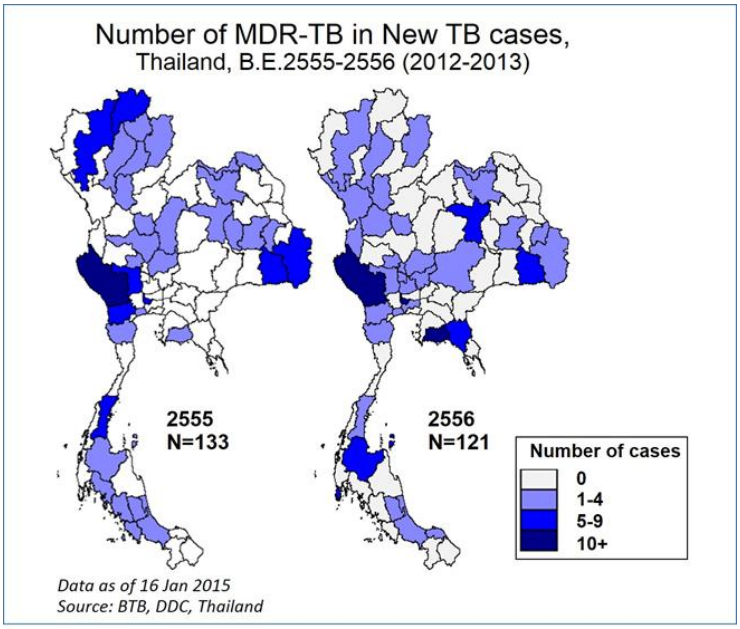
CHAPTER 2: Problem statement and methodology

This chapter describes the statement of problem, objectives and study questions. The justification of the study and methodology are also described including search strategy and inclusion criteria. The limitation of the study is present at the end of the chapter.

2.1 Problem statement

Thailand has many hotspots of MDR-TB cases, especially at the neighbouring borders as shown in figure 2.1, due to many ethnic groups, migrant populations and refugees living in this area[5]. A report in the fiscal year 2014 shows that estimate of MDR-TB burden of new cases and retreatment cases among notified pulmonary TB cases were 2.8 % and 31.1 %, respectively[5]. MDR-TB patients also receive treatment and directly observed therapy (DOT) by health care providers[5]. Most of patients who live in the refugee camps and displaced migrant population can receive DOT by local healthcare providers, but in many cases the patients lost follow-up or rejected treatment[5]. High MDR-TB burden in the border areas has been still one of the major concerns of TB problem[3].

Figure 2.1: Number and distribution of MDR-TB among registered new TB patients during 2012-2013 in Thailand.



Although the NTP's performance has been improving continuously for treatment of TB patients, there is now increasingly concern on the emerging of MDR-TB cases[3]. The precise magnitude of the problem is still unknown but BTB had arranged national anti-TB drug resistance surveillances for 4 times during period of 1997-2013[3]. The result shows

no significant change of drug resistance trend[3]. The estimate of MDR-TB burden among new cases and retreatment cases were around 2 % and 20 %, respectively[3].

Table 2.1 National Anti-TB Drug Resistance Surveillances of Thailand between 1997-2013.

Drug resistance	1st Surveillance (1997-1998)	2nd Surveillance (2001-2002)	3rd Surveillance (2006-2007)	4th Surveillance (2012-2013)
Drug resistance among new cases	**percentage**	**percentage**	**percentage**	**percentage**
- Any resistance	25.4	14.8	15.7	16.83
- Mono H resistance	NA	5.3	5.65	6.54
- Mono R resistance	NA	0.3	0.87	0.12
- Any H resistance	12.4	9.5	9.7	12.21
- Any R resistance	5.72	1.4	2.6	2.22
- MDR	2.01	0.93	1.65	2.03
Drug resistance among previously-treated cases	**percentage**	**percentage**	**percentage**	**percentage**
- Any resistance	NA	39	51.0	39.29
- Mono H resistance	NA	4.1	5.2	9.69
- Mono R resistance	NA	1.7	0.5	3.57
- Any H resistance	NA	30.8	44.3	29.59
- Any R resistance	NA	22.7	35.1	23.98
- MDR	NA	20.35	34.5	18.88

*NA = not available

Source: Guideline for programmatic management of drug-resistant tuberculosis in Thailand, 2015

However, by the year 2015, there was an increase of 13.6% estimated MDR or rifampicin resistant (RR) TB cases among notified pulmonary TB cases as compared with the same type of cases notified in 2014[17]. On the other hand, TB case notification rate of all forms in 2015 was decreased as compare to the year 2014, indicating growing-up of TB control problem[4,17]. Moreover, the prevalence of both newly-diagnosed and previously-treated MDR/RR-TB cases notified in 2015 were increased from 2.0% to 2.2 % and 19% to 24%, respectively[4,17]. Besides, treatment success rate for the re-treatment TB patients was also declined from 67% in 2014 to 63% in 2015[4,17]. Five laboratory confirmed XDR-TB cases were also reported in 2015 and all of them were started treatment in the same year[17]. The emergence of MDR-TB represents a sign of failure in TB control[3]. Most of MDR-TB patients suffered from adverse reaction from the second-line drugs (SLDs) for treatment of MDR-TB more than the first-line drugs (FLDs) using with drug-susceptible TB (DS-TB)[3]. Both MDR-TB and XDR-TB cause more anti-TB drug costs and decrease success rate of treatment outcome[3].

There are a few studies attempted to identify factors related with MDR-TB prevalence among people living in Thailand. Therefore, this

literature-review study would be considered to determine the factors associated with MDR-TB among adults with pulmonary TB in Thailand.

2.2 Justification/rationale

Mycobacterium tuberculosis can become drug-resistant strain during anti-TB treatment by selection pressure on a population of susceptible bacilli, resulting in spontaneous mutation[19]. Newly diagnosed MDR-TB patients are infected with a drug resistant strain and could develop primary resistance[20]. While acquired resistance is mostly found in the previously treated patients during anti-TB treatment after arising of resistance mutants[20]. However, drug resistant strains have a low virulence to be infected as compare with the drug susceptible strains[3].

The globally increase of MDR-TB prevalence among new cases and retreatment cases pulmonary TB notified (see annex 3) in the recent year[1] indicates ineffective TB prevention and control. Moreover, MDR-TB burden report is incomplete and does not reflect the real diagnosis as well as case detection coverage[21]. MDR-TB is difficult to cure because the treatment regimens are more complicated than that of DS-TB and also has higher drug costs[18]. MDR-TB patients particularly take longer period for treatment than DS-TB cases, and more adverse drug reaction would sufferred the patients[4]. Cure rate of MDR-TB cases is only 60-80 %, still lower than DS-TB cases (98-100 %)[4].

2.3 Study questions:

1. What are potential factors contributing to the increase of MDR-TB cases?

2. What are the preventive strategies can be taken to decrease prevalence of MDR-TB in Thailand?

2.4 Aims and objectives

2.4.1. Aim

The aim of the study is to identify the potential factors which can affect being MDR-TB and possible prevention strategies against MDR-TB in Thailand.

2.4.2. Specific objectives

1) To describe potential factors associated with the increase of MDR-TB patients.

2) To review which are the most likely factors associated with MDR-TB patients.

3) Explore experiences about MDR-TB prevention and control of other countries which can be applicable in Thailand's situation.

4) Describe Thai current strategies to prevent and control MDR-TB and identify gaps.

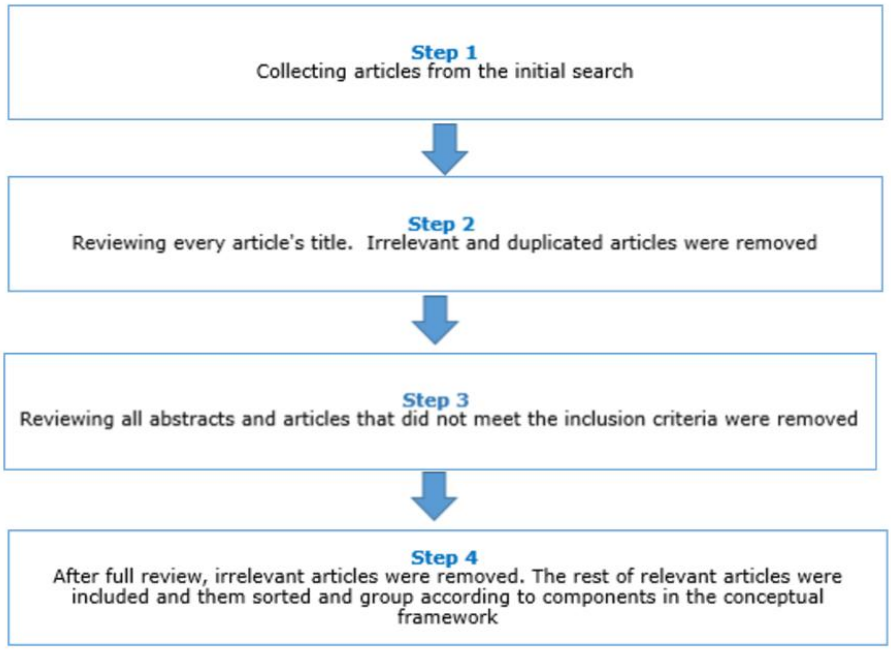
5) Give recommendations and/or intervention to minimize MDR-TB prevalence including prevent MDR-TB development and spreading in Thailand.

2.5 Methodology

A literature review and desk review study is depicted. Data is collected through reviewing the literature on TB and M/XDR-TB from different sources via internet and available data such as NTP reports and MOPH annual reports. Citation is used both in Thai and English. Internet sources using Pubmed, Cochran, Google scholar, KIT library and specific websites such as WHO, Stop TB partnership, SEA-TB and the Union are used. The conceptual framework is created using adaptation of the relevant articles and literatures to answer specific objectives number 1-3 and is used to complementary in the discussion chapter.

Key words: MDR TB, XDR TB, multi-drug resistant TB, epidemiology of tuberculosis, TB infection control, burden of MDR TB, TB prevention, DOT, drug resistant tuberculosis, MDR TB management, South East Asia, TB in Thailand, adherence in treatment of TB

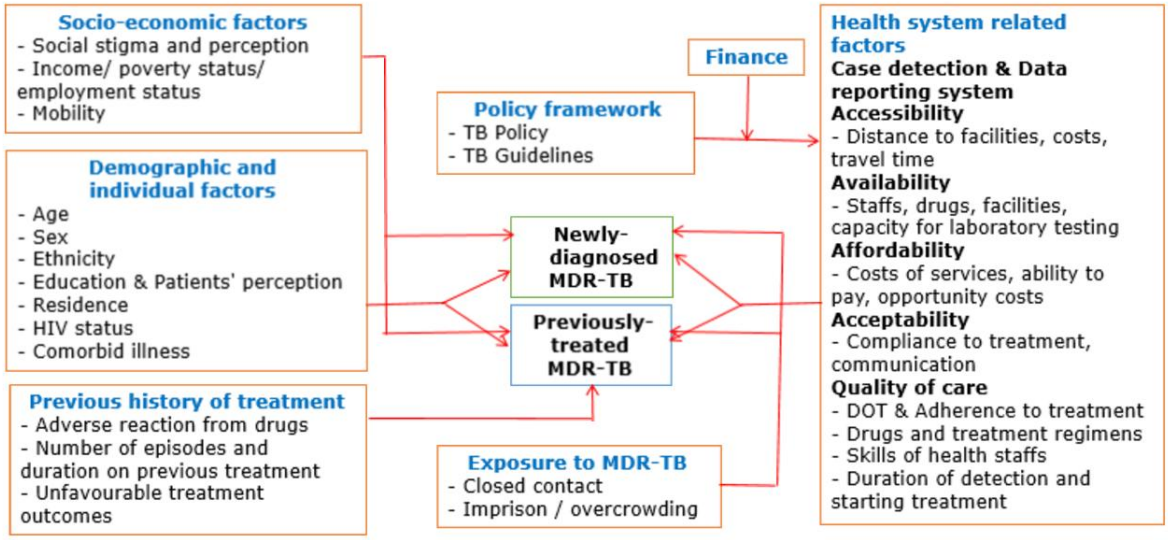
Figure 2.2 Flow diagram of literature review screening process.



2.6 Conceptual framework

This conceptual framework is developed after an extensive review of pertinent literatures on MDR-TB in developing countries[22-26]. The variables included in the framework are assumed to describe the reality experienced by most MDR-TB patients in Thailand. As could be seen in the figure, this study examined the problem of MDR-TB from five major groups namely the socio-economic factors, demographic and individual factors, previous history of TB treatment, exposure to MDR-TB and health system related factors which are related to policy framework and finance (see figure 2.4).

Figure 2.3: Conceptual framework of the study



2.7 Inclusion criteria

The literature search was limited at the last 10 years publishing. The search composes of the literature in English and Thai with full text available. Literature was not limited to only in Thailand or specific countries due to the nature and spreading of TB including the management of disease are quite similar in many countries. The priority of the literature was chosen by similarity of Thailand's situation.

2.8 Limitations of the study

This study is based on a literature review with limited literature search for the last 10 years. Primary data collection could provide more detail and analytic information but was not applicable due to time constraint, ethical clearance issue and funding support. Some scientific studies on MDR-TB in Thailand were not published or incomplete. Therefore, the international literature with the similar situation with Thailand's should be helpful to fulfil the next three chapters.

CHAPTER 3: Finding

This chapter described the factors which could associate with the prevalence of MDR-TB using the conceptual framework to analysis in different dimensions. There are some technical terms about tuberculosis that can be seen at key definitions part of the annex 4.

3.1 Policy framework

3.1.1 TB Guidelines

Thailand's National TB programme has always updated and implemented TB control guidelines from WHO since 1996, as DOTS strategy which was the internationally agreed strategy for TB control, and then modified to be the Stop TB Strategy in 2006[18]. Later in 2011, WHO has added focus points to be the Global Plan to Stop TB 2011-2015, in order to expedite and achieve TB strategic goals[18]. Latest in 2016, WHO has determined to use the End TB Strategy with the targets linked to Sustainable Development Goals (SDGs) [1,27]. The overall goal is to reduce TB incidence to less than 10 new cases per 100,000 populations by the year 2035 (see annex 5 for detail) [1].

3.1.2 MDR-TB policy and guidelines[3]

To early detect MDR-TB patients and to provide proper treatment to achieve successful treatment outcome are the main targets of MDR-TB control policy in Thailand[3]. According to MDR-TB surveillance survey in 2012 shows that there was 2.03% of MDR-TB among new TB patients, which was not higher than the global statistics[3]. So, MDR-TB policy is focusing on the vulnerable groups which consist of,

1) Previously treated patients who refer to groups of relapse, after failure of first treatment with FLDs or after failure of retreatment regimen with FLDs and after loss to follow-up

2) MDR-TB patients who are detected during or after treatment for 3 months

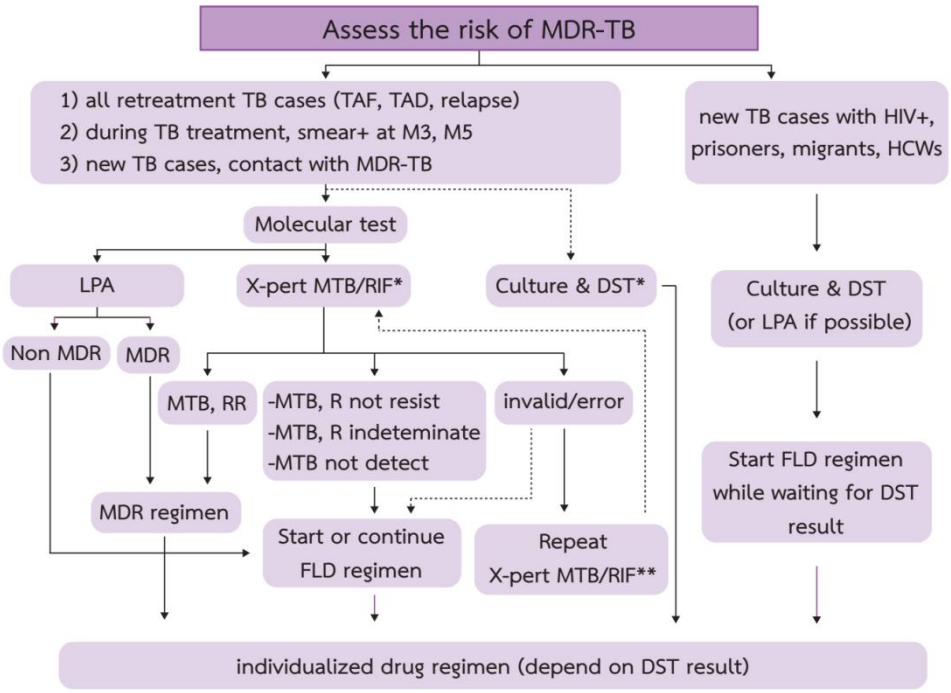
3) Patients with a history of exposure to MDR-TB patients or live in areas with a high prevalence of MDR-TB.

Current guideline for management of TB patients who are at risk for MDR-TB is demonstrated in figure 3.1.

These MDR-TB high-risk groups are recommended to receive drug sensitivity test (DST) prior to treatment[3]. Early diagnosis of MDR/RR-TB

can contribute to individually adjust the proper treatment regimens to suit each patient and promote strictly DOT until complete treatment[3]. Indicators and targets of MDR-TB control, viz. A) Previously treated TB patients have undergone sputum smear exam and DST for 90%. B) MDR-TB patients have received and have achieved treatment for 70%[3].

Figure: 3.1 Management of TB patients who are at risk for MDR-TB[3].



(Source Guidance for programmatic management of drug-resistance tuberculosis)

3.2 Financing

Thailand's financing for TB control has been supported from MOPH as a domestic fund, the Global Fund to fight AIDS, TB and Malaria which is a largest source of international donor funding, other NGOs and unfunded sources[1]. There were 31 million USD for national TB budget in 2016, slightly decreased from the last consecutive year but still higher than the last 2 year's budget[1]. The challenge of financing is the continuation of international funding which plays a vital role for many TB control projects, including active MDR-TB cases finding in the vulnerable groups, diagnostic tools for MDR/RR-TB, SLDs for M/XDR-TB, DOT and human resources for TB care, etc.[28].

3.3 Factor associated with the prevalence of MDR-TB

Several factors may lead to development and spreading of MDR-TB. I would like to explain these factors using the conceptual framework as demonstrated in the chapter 2.

3.3.1 Demographic and individual factors

3.3.1.1 Age

Several studies described that young age is likely to be associated with MDR-TB. Three case-control studies in Hong Kong, Bangladesh and Ethiopia stated that young age of less than 45 year-old was found to be significant factor for MDR-TB in both newly-diagnosed group and previously-treated group[24,25,29,30]. Another study in Bangkok concluded that age less than 65 years was a significant factor associated with MDR-TB[31].

Though there is no exact data about favourable age group for MDR-TB in Thailand[3]. Maokamnerd et al. described mean ages among two groups of Thai and non-Thai MDR-TB patients in border area to be 52.4 year-old and 36.8 year-old respectively[5]. While the analytic study in the high prevalence area of MDR-TB found that the mean age of newly-diagnosed MDR-TB patients was 47.9 year-old but was not a significant factor by statistics as compare to the mean age among new TB patients in the same setting[32].

3.3.1.2 Sex and gender

Akkasilp et al. had studied among MDR-TB patients in north-eastern region of Thailand and found that male sex was likely to be associated with MDR-TB[33], similar to the result of a case control study in China[34] while a population based study in Georgia stated that female sex was an independence factor for the presence of MDR-TB[35].

However, several case control studies from both in Thailand and other Asian countries show no relationship between sex and the prevalence of MDR-TB[22,30,31]. Besides, the recent meta-analysis study revealed that sex was not a significant factor for MDR-TB by meta-analysis of 23 related articles[36]. Seventeen articles show no relationship between sex and the presence of MDR-TB whereas the rest shows controversy result[36].

3.3.1.3 Ethnicity and immigrant status

Ethnicity may be linked to the other factors such as residence status, immigration or patient, family and social perception about MDR-TB including accessibility and affordability to access health services[5]. There are many non-Thai people crossing border from neighbouring countries to search for jobs in Thailand[5]. From the report in 2014, there were 3,091 non-Thai TB patients notified in Thailand[37]. Because of difference in MDR-TB burden among countries (as shown in table 3.1), patients from the higher prevalence areas can transmit infection to the lower prevalence one when they come across border[18].

There was a study in Tak province which has a border connected to Myanmar and has been reported as one of the high burden area of MDR-TB in Thailand[5]. There were 76.5% of MDR-TB patients in Tak province that were Burmese and did not have universal coverage for health like Thai people[5]. Moreover, non-Thai MDR-TB patients also have a higher rate of default treatment outcome than Thai MDR-TB patients in the same setting[5]. The result was similar to another two studies that being immigrant had higher rate of MDR-TB than non-MDR TB as compare to national TB/MDR-TB patients[38,39]. Immigrant has been noted as a major factor influencing the increase of MDR-TB due to lack of access to health service, poor working and living condition[25].

Table 3.1 Comparison of MDR-TB burden in 2013 among Thailand and neighbouring countries[40], NA = not available

MDR-TB among notified pulmonary TB cases	Myanmar Cases (%)	Cambodia Cases (%)	Laos Cases (%)	Thailand Cases (%)
New	5700 (5)	320 (1.4)	NA	1000 (2)
Re-treatment	3300 (27)	180 (11)	NA	880 (19)

3.3.1.4 Education and patient perception

Low level of education affects patient perception about disease. It may lead to poor knowledge of TB and causes less self-awareness for prevention[26,29,34]. Many articles demonstrated that low level of education was significantly related to the presence of MDR-TB and other socioeconomic determinants such as social perception, poverty and unemployment. Two studies found that education level of secondary school or lower was a significant factor to development of MDR-TB[29,34].

Another study claimed that poor knowledge of TB patient was a significant factor leading to become MDR-TB[26]. Poor access to TB health education before getting infection was potentially associated with treatment delay[41].

3.3.1.5 Residence status and region

In Thailand, most of high prevalence regions of MDR-TB have occurred at provinces connected to the neighbouring countries, especially Myanmar and Cambodia[3]. These places also have high rates of cross-border travelling or non-permanent residents[3]. Similar to a study result by in Hong Kong found that non-permanent residence was the independence predictor for MDR-TB among the re-treatment patients[25]. A study from Kazakhstan, Bangladesh and Nepal stated that urban residency, poor housing and homelessness were independently associated with MDR-TB[30,42,43] while meta-analysis study result in China documented that living in rural area was a significant predictor for MDR-TB[44].

3.3.1.6 HIV status

Since reports of MDR-TB spreading among immunocompromised patients were revealed, HIV has become an important risk factor for all forms of TB[45]. HIV co-infection is the major risk factor of being infected or reactivation of TB and increases spreading among patients with both primary and acquired TB infection[18]. A case-control study in Thailand found that the increase of MDR-TB was significantly associated with HIV co-infection[31]. But a study in Malaysia observed that patients with HIV co-infection were less likely to develop MDR-TB as compared with HIV sero-negative cases[38]. On contrary, several studies documented that HIV was not directly associated with MDR-TB[22,33,42,46].

Although the association between HIV-positivity and MDR-TB has been controversy about the statistical significance on the epidemiological studies, but DS-TB patients increase the vulnerability for resistance[45]. Because of adverse reaction between anti-TB and anti-HIV drugs lead to poor compliance and difficulty on treatment[45]. Many MDR-TB patients with HIV co-infection had poor treatment outcomes or rapidly died[45].

3.3.1.7 Immunity and co-morbid illness

Like DS-TB, patients who have been infected with MDR-TB are not present their symptoms until there is immunity disorder, as a host factor. When the people with low immunity from low prevalence places move to the higher prevalence areas, they can be easier infected[3]. However, history of receiving TB vaccination was not found to be associated with MDR-TB[31].

From a cohort study in high prevalence area of MDR-TB in Thailand, there were 47% of MDR-TB patients with Diabetes Mellitus (DM) as the highest proportion among MDR-TB cases with comorbid illness prior to TB diagnosis[32]. DM was a statistically significant factor for becoming MDR-TB both among newly-diagnosed TB group and previously-treated TB group that could explain from association between DM and compromised immune function might be leading to increased susceptibility to bacterial infections like MDR-TB[32]. Similar to a study result in Bangladesh that type 2 Diabetes was associated with MDR-TB as it caused impair immunity and might increase susceptibility to infect with MDR-TB strains[29]. For previously-treated TB patients, diabetes might affect treatment outcome leading to treatment failure[29]. Two studies in Georgia and China also found that diabetes was independently associated with an increase of primary MDR-TB and was associated with a longer sputum culture conversion time[47,48]. Otherwise, other comorbid illness was not found to be a significant predictor to MDR-TB from the reviewed literature.

3.3.2 Socio-economic factors

3.3.2.1 Social stigma and perception

A study in China found that social stigma was a risk factor for MDR-TB from developing of bad habits, such as patients refuse wearing face mask to avoid social discrimination of TB/MDR-TB[34]. Moreover, delayed access to health service might caused by patient perception about TB stigma[49]. There were 2 studies in Nepal documented that the negative perception towards TB/MDR-TB was common and could affect treatment adherence[43,50]. Not only patients' perception, stigma can also cause a fear of infection in the community[50]. Having MDR-TB was found to be associated with social stigma that as a consequence from interrupting and default treatment[43]. But some studies stated that socio-economic status was not a significant factor for MDR-TB[30].

3.3.2.2 Income, poverty and employment status

A study in Thailand showed that most of re-treatment patients had an occupational barrier for adherence of treatment and might develop MDR-TB[5]. TB patients in low socioeconomic communities are easy to be acquired MDR-TB because lack of good health services and MDR-TB transmission is still confined in these communities[34,44,51,52]. Another studies documented that patients with low income and/or long work hours increases risk for non-adherence of treatment[24,41,51]. There was an inverse association between TB and poverty that could also apply for MDR-TB[43]. Although several studies in China found that low income or poverty and unemployment status were associated with MDR-TB[34,52], but a study result in Bangladesh shows that the occupations related with services and business were more likely to associated with MDR-TB more than unemployed individuals[29].

3.3.2.3 Mobility

Since January 2016, Thailand has officially joined ASEAN Economic Community (AEC) with other countries in SEA. As a result, it has facilitated foreign workers from neighbouring countries to travel easier and has contributed to higher rate of mobility[5]. The border regions of countries with higher prevalence of MDR-TB seem to have the major effect of infection control[5]. As cross-bordered patients have frequent travelling and affect follow-up and monitoring by HCWs[5]. Basically, even some Thai TB patients who have frequent travel for work, they might have poor adherence for anti-TB treatment[53].

A study in Malaysia also showed the similar findings that MDR-TB was associated with being an immigrant from neighbouring countries[38]. Law et al. found that frequent travel was an independent predictor for MDR-TB[25]. The previously-treated MDR-TB patients were expected that frequent travel/social mobilisation activities might have facilitated non-adherence of anti-TB drugs and acquire drug resistance[29,38]. Even for the newly-diagnosed MDR-TB cases, there was a significantly higher proportion for patients with history of frequent travel[38].

3.3.3 Exposure to MDR-TB

3.3.3.1 Close contact

People who live or work with MDR-TB patients have high chance to be infected as a primary drug resistance such as family members or health care workers[3]. But it does not mean all TB patients who have a history of MDR-TB contact must be newly-diagnosed MDR-TB cases[3]. Contact persons might be infected with DS-TB strains before the index cases develop drug resistance[3].

Several studies found that there was a relationship between history of close contact with MDR-TB patients and subsequent MDR-TB cases in their study[24,44.] The association between MDR-TB strains and history of close contact with MDR-TB patients would be contributed to acquiring of primary drug resistant bacteria[24,30].

3.3.3.2 Imprison / overcrowding

People who live in the overcrowding places with MDR-TB patients, such as refugee camps, migrant villages or prisons are more likely to be infected with MDR-TB due to poor ventilation of places[18]. Hospitals are also needed special attention because most of them are always overcrowded, especially Out-Patient Department[18].

Jiraphongsa et al. studied and investigated a community with the outbreak of MDR-TB during January-June 2010[32]. There were 15 cases of newly-diagnosed MDR-TB detected at one of the high prevalence areas of MDR-TB in Thailand[32]. They found that the annual proportion of newly-diagnosed MDR-TB among new TB cases during 2007-2009 were 3.8%, 7.1% and 9.1%, respectively[32]. The prevalence was higher than that of national and worldwide statistics, indicating the outbreak[32]. Among these notified MDR-TB cases, 7.5% were prisoners[32]. A study from Kazakhstan in 2013 also stated that incarceration was independently associated with MDR-TB[42].

3.3.4 Previous history of anti-TB treatment

Previous anti-TB treatment history is widely accepted to be the strongest determinant for the increased prevalence of acquired MDR-TB. Therefore, I would not explain how many studies found its association with MDR-TB, but would like to describe how does the previous treatment history affects acquired drug resistant TB as followings.

3.3.4.1 Adverse reaction from drugs

Some DS-TB patients may suffer from adverse reaction of the first-line anti-TB treatment, resulting to a non-adherence DOT, eating only selected drugs or rejection of all anti-TB drugs[18]. This problem may be caused by inappropriate anti-TB drugs management by physicians or other health staffs such as using of non-standardised drug regimens, using mono-drug therapy, drugs overdosed or unawareness of patients with co-morbid illness that affected the bioavailability of the first-line anti-TB drugs[18]. Anti-TB drugs adverse reactions during their previous TB treatment were significantly associated with MDR-TB and could increase risk of developing MDR-TB[29,46]. Many studies in China also found that adverse reactions during TB treatment were independent predictors of MDR-TB[34,51,52]. Among the DS-TB patients who had adverse reaction, quitting the treatment is the main consequence and directly leads to the development of MDR-TB[52].

3.3.4.2 Number of episodes and duration on previous treatment

A study in Thailand found that patients with at least two episodes of prior pulmonary TB treatment had almost 40 times of risk for development of MDR-TB more than DS-TB patients who received treatment not more than 1 episode[22]. Similar to another studies in China showed that MDR-TB was significantly related to more than 3 prior episodes and long duration more than 8 months of anti-TB treatment[26,34,39,51]. The reasons of re-treatment episode(s) might be caused by impropriate first-line drugs treatment regimens or the outcomes of default and treatment failure[22,26,34,39,51]. Long period of treatment facilitates interruption and non-standard treatment regimens, resulted in poor-adherence and developing MDR-TB [39,51]. A previous study reported that MDR-TB patients had more than one episode or previous TB treatment due to non-responsive, incomplete previous treatment[29].

3.3.4.3 Unfavourable treatment outcomes

Although strictly DOT was administrated but after failure of retreatment regimen with FLDs still presents, the previously-treated DS-TB patients can develop a high possibility to become MDR-TB for more than 85%[3] while DS-TB patients with after failure of first treatment with FLDs can less develop MDR-TB for 50% or 10-90% depends on the

prevalence of MDR-TB among new TB patients in the regions, quality of DOT and extent of disease[3]. This is similar to study results by Chuchottaworn et al. and Jitmuang et al. that previously-treated TB patients with MDR-TB were found to have treatment failure or default in a higher proportion than other treatment outcomes[22,31].

Mahfuza et al. found that MDR-TB patients were more likely to have a history of incomplete TB treatment than non MDR-TB patients for four times[50]. Other study results also show that poor treatment outcome of prior treatments has strongly associated with the increase of MDR-TB [23,24,39,54].

3.3.5 Health system related factors

3.3.5.1 Case detection coverage and data reporting system

From the latest data in 2015, the estimated TB incidence of all forms was 117,000 but total TB case notified was 66,179[1], representing case detection rate only 56.5%. It can be implied that more than 50,000 cases of TB patients were not found, had no registration and no treatment. Moreover, the crisis of MDR-TB detection and treatment continues. In 2015, of the estimated 2,500 MDR/RR-TB cases among notified pulmonary TB cases, there were only 506 MDR/RR-TB cases and 5 XDR-TB cases enrolled for starting treatment[1]. It can reflect the problem of case detection coverage with high reporting gaps.

TB registration and data reporting system has been arranged by BTB via the same standard TB programme[18]. It has been used by all districts and provincial hospitals of MOPH. Every district TB coordinators are expected to send the reports to provincial TB coordinators and Regional TB coordinators every quarter via the same TB programme[18]. However, the recording and reporting systems on TB/MDR-TB still has had limitation. It could not reach or cover private hospitals and some public health facilities outside the MOPH[18]. Therefore, a current TB data and reports do not reflect the true TB situation in the country[18].

3.3.5.2 Accessibility

Access has been described as the opportunity for people to use health service with circumstance to allow them to use appropriate service[55]. In low and middle income countries (LMICs), geographical accessibility to health services is an important barrier to get essential

health care especially in rural and poor communities[34]. A study in China found that long distance of residence from health facilities, travelling difficulty to health facilities and travel time greater than 3 hours to reach health facilities were significant factors related to occurrence of MDR-TB[34]. In Thailand, the problem from geographical accessibility usually occurs in rural areas caused by long distance to health facilities, difficulty on transportation like residence on the hills or mountains, long travel time that affected works as well as socio-cultural beliefs in some ethnic groups[5,49]. Poor accessibility has been frequently presented at country borders areas with high proportion of non-Thai TB patients[56].

A study in Tak province, Thai-Burmese area among non-Thai patients demonstrated that legal status played a major role influencing accessibility to health care and eligibility to treatment for both these populations while refugees had fewer barriers than migrants[56]. Language of health services, availability of free or low cost services and psychosocial support were identified as important health system characteristics affected accessibility[53]. Otherwise, access to health education before diagnosis of TB can also help decreasing the prevalence of MDR-TB due to early TB detection and improved health seeking behaviour[53]. From a study in China, there were less than one-third of TB patients ever accessed to TB health education prior to diagnosis[41].

3.3.5.3 Availability

Staffs

Human resources play a vital role for successful of health care system[15]. There has been a chronic shortage of health staffs in the public sector of Thailand for many years[15]. The Global Fund and World Vision are the main NGOS who support finances for human resources especially in the high prevalence areas of TB/MDR-TB[28,57]. But the sustainability of budgets is unpredictable[57]. Otherwise, other NGOs such as World Vision and MSF also help hiring staffs for TB care for non-Thai TB patients[57].

Facilities

Currently, there are 1,026 first-line drug treatment centres as the basic health service units and 184 MDR-TB treatment centres in tertiary care units[28]. Both of them are available in public and private sectors with universal coverage system, which can provide TB care for patients

throughout the country[58]. There is at least one hospital per district for all 77 provinces in Thailand. Health posts or primary care units are also available in all sub-district levels[13].

Drugs

Shortage of drugs has been one of the most common reasons for the inadequacy of the initial anti-TB regimen, especially in resource poor settings[34]. For upper middle income country like Thailand, availability of drugs and supply chains is not a big concern for most of Thai patients who have universal coverage for health[13]. Even the foreigners, migrants and refugee who have been diagnosed as TB/MDR-TB can receive anti-TB drugs from public health facilities with support from the Global fund[28]. BOTB, NHSO and relevant organisations has taken responsibility to distribute anti-TB drugs to primary care units throughout the country, except for fourth-line drugs for XDR-TB that need to be imported from abroad[28].

Capacity of laboratory testing

Inadequate laboratory testing units make an indirect effect to the increase of MDR-TB cases due to the delay in diagnosis and prolong spreading of disease[41]. Thailand has improved laboratory testing capacity for several years since the introduction of NTP by WHO recommendation[18]. All district hospitals are capable to provide sputum smear for AFB as TB screening and follow-up[18]. The specimens of all suspected cases will be sent to tertiary care health units of public sector and university hospitals in central and regional parts for Mycobacterium culture and drug susceptible testing (DST) [18]. Number of available health units for laboratory testing is demonstrated in table 3.2.

However, some high prevalence areas of MDR-TB also have a high demand for DST laboratory testing and have to wait for at least 2-6 weeks for the results[3]. To resolve this problem, the molecular examination methods with high sensitivity and high specificity have been applied to decrease timing of interpretation[3]. Genotype MTBDR with line probe assay (LPA) technique can proof diagnosis of MDR-TB within 2 days while Gene Xpert MTB/RIF can detect RR-TB within 2 hours[3]. Because both methods are expensive, they are available in selected areas with funding support from the Global Fund[28].

Table 3.2: Capacity of laboratory testing in Thailand, 2013[18].

Type of laboratory testing	Number of available health units
Sputum smear for AFB	1,026
Mycobacterium cultures	74
DST for first-line drugs	33
DST for second-line drugs	4
Gene Xpert MTB/RIF or LPA	30

3.3.5.4 Affordability

Affordability refers to patient's ability to pay costs of services, and opportunity costs[55]. All patients who are Thai citizen and have national identification cards, can use universal coverage (UC) right to access public health services with free of charge for TB care[14]. But the latest data shows that TB treatment coverage among notified/estimated incidence was only 53% in 2015[1]. From the report in 2013, non-Thai TB patients at border region have been uninsured for 80-90%[56]. For majority of non-Thai patients who are migrant populations, different kinds of access to health facilities are provided to them depend on categories[56] as details (Table 3.3).

Table 3.3: Non-Thai populations categories at Thai-Burmese border of Tak province and health services supports in 2013[56].

Non-Thai categories	Health service rights and providers
Labour migrants **- Documented, informal sector** **- Documented, formal sector**	- Compulsory Migrant Health Insurance (CMHIS) which provides generally the same benefits as Thai UC system. - Social Security which provides broad health benefits than CMHIS.
- Undocumented labour and cross border migrants without insurance.	- Can access diagnostic care and first line TB treatment in MOPH facilities - Global Fund will pay for smear positive diagnosis and first line drugs for care by both MOPH and other providers (NGOs, SMRU, Mae Tao Clinic). - SMRU also provides diagnosis and second line drugs for MDR-TB patients. - DST cost for general hospital has been paid by TUC.
Displaced person shelters **- Temporary shelters** **- Resettlement persons**	- Diagnostic care and first line drugs are provided by INGOs - IOM provides full cares.

WHO TB supervision in Thailand 2013.

Limitation of funding supports from the global fund and other organisations is continuity of funding. As Thailand moves into the open

Asian Economic Community (AEC) which may affect the treatment of non-Thai TB patients[58].

3.3.5.5 Acceptability

Acceptability from a user perspective is one of the important dimensions to access health services[59]. If patients perceive ineffective services or feel discourage caused by health providers, it might decrease participant rate from patients[59]. Acceptability can affect monitoring of TB treatment as following.

Compliance to anti-TB treatment

Several studies have reported that poor compliance to treatment increased the chances to develop MDR-TB among non MDR-TB patients[24,31,34,52]. Poor compliance due to number of anti-TB drugs' pills has been usually found but can resolve by administration of fixed-dose combination drugs (FDCs)[18,52]. Jitmuang et al. found that there were almost two times of MDR-TB patients had poor compliance more than non MDR-TB patients[31]. Non-compliance is associated with unsuccessful treatment and development of MDR-TB[31]. Quitting the treatment was found to be significant factors for MDR-TB among TB patients with adverse reactions[52]. Some study result demonstrated that 50% of non MDR-TB patient did not complete their treatment because they felt better after starting treatment but later developing MDR-TB[29].

Communication

Advocacy communication and social mobilisation activities play an important role for acceptability of anti-TB treatment and observation, especially to avoid quitting drugs by the patients[29]. In some cases, DOT by health providers was refused by TB patients due to poor communication, social stigma from their neighbours[49].

3.3.5.6 Quality of care

Directly Observed Therapy (DOT) and adherence to treatment

Many studies noted that poor quality of DOT and poor adherence of treatment was one of the strongest significant factors for the prevalence of MDR-TB and linked to other determinants[24,31,34,41,44,46]. Since WHO standard for TB treatment success rate has been elevated to 90%[4], but

treatment success rate among new and relapse TB case in Thailand was only 81%[17] in 2015 and never reached the standard. It can reflect ineffective DOT and poor treatment adherence and has affected TB control in Thailand[3]. In 2007, a study in Thailand reported that only 24% of TB patients received DOT by HCWs while 59% of them used family DOT, and 18% of patients had self-administered therapy[60]. The result also represented the highest percentage of treatment success rate among patients that received DOT from HCWs for 93%, better than family DOT(89%) and no DOT(69%)[60]. As a result, treatments which are not directly observed by HCWs should be associated with poor treatment outcomes and finally develop MDR-TB[41,46]. It can be explained by HCWs are the most reliable among types of the observers[60].

MDR-TB was found to have higher rate among patients who had poor or non-adherence of treatment during intensive and continuous phases[34,46]. Non-adherence to treatment can be linked to other determinants such comorbid illness, alcoholism, drug addiction poverty, and long work hours[34,41].

Drugs and treatment regimens

Quality of drugs, bioavailability tests, administrative control and distribution are important for efficacy of treatment[43]. If patients receive anti-TB drugs which have poor quality due to placebo or poor storage control from light, temperature and humidity, bacteria can not be killed and can develop drug resistance[34].

MDR-TB can occur from initiation of an inadequate first-line drugs regimen, using anti-TB drugs in different way from prescription, wrong doses, wrong period for taking the drugs that could be due to misunderstood communication between health care providers and patients[34,41]. Prior pulmonary TB management with an irregular (non-category I) regimen and retreatment TB cases with the category II regimen are the most important influencing factor of MDR-TB[22,26,34,46] .

Skills of health staffs

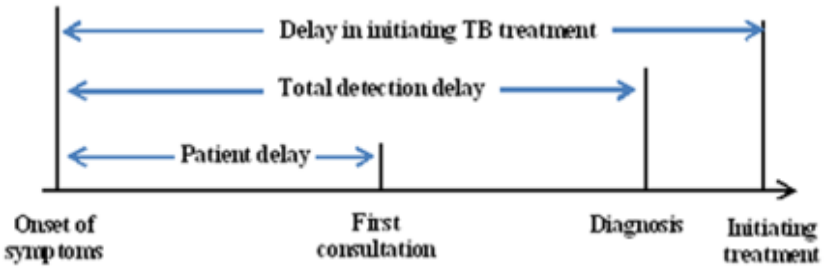
Tuberculosis has complexity on diagnosis, treatment and follow-up. Thus, professionals, knowledge and skills must be provided to health staffs both new and current groups for a standard of TB care[18]. Lack of professionals on treatment and TB care or using non-standard methods

can lead to development of MDR-TB[44]. A study in China found that TB patients who came to consult at non-TB health facilities more than 3 times before seeking care at drug stores, was a significant factor for both detection delay and delay in starting treatment that could develop MDR-TB[41].

Duration of diagnosis and starting treatment

There are 3 types of delay among TB patients which are related to each others as explained in figure 3.2[41]. Patient's awareness of TB from passive TB detection can be measured by patient delay, while efficiency of TB case notification can be observed from total detection delay, and barriers in access of treatment can be represented by delay in initiation of treatment[41].

Figure 3.2: Definitions and relations between the different types of delay among tuberculosis patients[41].



Source:doi.org/10.1371/journal.pone.0088330

A study result showed that a half of TB patients faced with longer all three types of delay which can be associated with development of MDR-TB[41]. A study in Thailand found that duration of illness more than 60 days before starting treatment was a significant factor for developing MDR-TB, similar to a study result in China[22,26]. A qualitative study also showed that poor TB education and socioeconomic factors caused patient delay[41]. Moreover, seeking care and receiving treatment from non-TB health facilities such as pharmacies or traditional medicines was a major reason for detection delay[41].

Chapter 4: Discussion

For this chapter, I will discuss how the findings from previous chapters have relationship with each others and will analyse and interpret using the conceptual framework. This will lead to discussion about potential factors on MDR-TB prevalence and TB strategies with MOPH, to address recommendations made in the next chapter.

4.1 Demographic, individual and socio-economic factors

- **Age and Sex**

From the literature review, DS-TB patients with young age not over than 45 years and male sex were more likely to develop MDR-TB in several studies in different settings. According to Thailand's TB data in 2015, male sex was predominant among both all forms TB and MDR-TB cases notified while male to female ratio among notified TB patients is 2.25[1]. Thus, sex may not be the independent factor for MDR-TB because the proportion of male and female TB patients is obviously different before developing drug resistance.

On contrary, the major proportion of patients who were first diagnosed with DS-TB, was an elderly group of age 65 years and over[18]. In Thai culture, men with working age usually take a main responsibility to work and earn family income. As a result, many TB patients who work outside also have a higher possibility of poor treatment adherence, difficulty for DOT by HCWs and poor treatment outcomes than female TB patients who usually work at home. Age factor can be linked to socio-economic factors because most of DS-TB/ MDR-TB patients have poverty or low socio-economic status. So, it cannot conclude that age is the independence factor for MDR-TB as well.

- **Ethnicity and immigrant status**

Few studies found that ethnicity was associated with MDR-TB prevalence[5,18,37-39] but it was not proofed to be an independence factor. It can be linked with other demographic and socio-economic factors. A previous study in Thailand's border shows a difference in age groups among Thai and non-Thai MDR-TB patients, as non-Thai MDR-TB patients had a lower mean age compared with Thai group[5]. This can be explained as many of non-TB patients are migrant workers who are in working age group.

Immigrant status is remarked as the vulnerable group being infected with MDR-TB in Thailand that screening test is needed. Most of immigrants have travelled from their own countries for residing, searching for jobs or health care seeking in Thailand. It can be explained that they have mobility, which is a potential factor associated with transmission of disease. Moreover, mobility, communication, education and socio-cultural belief are the important barriers to reach successful of treatment outcomes among these patients.

- **Residence status and regions**

Non-permanent residence or homelessness was found to be independence factor for occurrence of MDR-TB for several literatures because it can lead to non-adherence of treatment, loss follow-up and finally developing drug-resistance among previously-treated patients. Moreover, MDR-TB patients with non-permanent residents can spread disease to every place they visit, making more complicated infection control. Residency in the high burden regions of MDR-TB can affect its prevalence, depends on crowded places and exposure periods from the previous studies' results.

- **Education and patient's perception**

Low level of education was found to be strongly related to socioeconomic determinants, as described from the literature review. Many studies also found that patient's perception affected health seeking behaviour, treatment delay and knowledge to prevent themselves from the infection. Although education and patient's perception are not the independent factor but they are significant factors for development of MDR-TB.

- **Immunity and co-morbid illness**

From the literature review, patients with low immunity of MDR-TB can be easier infected when they travel to higher prevalence areas of MDR-TB. So, host immunity can be related to other factors, such as mobility and residence. Patients with immunecompromised conditions such as DM or HIV/AIDS are also prone to be infected with TB or MDR-TB both from reactivation of latent infection, primary infection or recurrent disease. DM was found to be a significant factor for developing MDR-TB both among newly-diagnosed and previously-treated TB groups in several studies. But the association between HIV co-infection and MDR-TB are still controversy from the literature review. However, patients with TB-HIV co-infection also have high chance to develop MDR-TB from adverse reaction

among drugs, leading to treatment interruption and drug-resistance. As a result, based on national-TB guidelines, patients with co-morbid illness such as HIV/AIDS, DM or other immunocompromised conditions can be considered as the vulnerable group for developing MDR-TB which is recommended to confirm laboratory diagnosis[18].

4.2 Socio-economic factors

- **Social stigma and perception**

Although the association with MDR-TB from the literature review is controversy, social stigma and social perception are strongly related to delayed diagnosis of new TB patients and poor treatment adherence among previously-treated TB cases. From my experience, some TB patients don't want their neighbours to know about illness, as it is social stigma. So, they do not cooperated with DOT by HCWs or choose their family DOT instead. It can lead to treatment interruption and development of MDR-TB as indirect effect.

- **Income/poverty/employment status**

As many studies from Thailand and other countries stated that majority of TB cases had low-socioeconomic status and could be linked to other determinants. From my opinion, TB patients who work outside are likely to facilitate poor adherence of treatment due to occupational barriers and later develop MDR-TB. Poverty status and low income also contribute to vulnerability for MDR-TB exposure due to living conditions and poor access to health services.

- **Mobility**

Many literatures found that mobility or frequent travel was the significant factor or independent predictor for MDR-TB. In Thailand's situation, mobility can affect both the prevalence of newly-diagnosed and previously-treated MDR-TB patients, especially in neighbouring border areas. As mentioned above, mobility also has a strong relationship with residence status, regions and ethnicity. Moreover, it can be linked to the exposure between 2 places with different MDR-TB prevalence, including treatment continuation. From my experience, there were non-Thai TB patients who received partial treatment in Thailand before coming back their country, then discontinued treatment and developed MDR-TB.

4.3 Exposure to MDR-TB

- **Closed contact, overcrowding living condition and history of imprison**

Many articles confirmed that closed contact and overcrowding living condition have been the potential factors associated with MDR-TB, especially for newly-diagnosed MDR-TB cases. Most of them came from family members or colleagues who were involving with the index MDR-TB cases. Similarly, new TB patients who are living or used to live in crowded areas such as prisons, hospitals or migrant/refugee villages, also have high possibility to be infected with MDR-TB. According to MDR-TB guidelines in Thailand, these aforementioned special populations are listed in the vulnerable group who need laboratory tests for diagnosis of MDR-TB.

4.4 Previous treatment history of TB

- **Adverse reaction from drugs**

Many studies found that adverse reactions from anti-TB drugs were significantly associated with MDR-TB among previously-treated TB patients. Treatment interruption or poor compliance to treatment can consequently occur and can develop drug-resistance. Some studies stated that adverse reactions are the independence predictors of MDR-TB. This factor can be linked to the quality cares of health system related factors, such as compliance to treatment, drugs regimens, DOT and skill of HCWs. Besides, the individual factor like co-morbid illness is prone to develop adverse drug reaction due to altered bioavailability of drugs. From my supervision experience, several MDR-TB patients used to have adverse reaction from the first treatment, resulting in discontinuation of the therapy.

- **Number of episodes and duration on previous treatment**

Some studies demonstrated that at least two episodes of treatment and long period over than 8 months of first treatment were significantly related to development of MDR-TB. It can imply to previously-treated TB patients with poor treatment outcome of default or treatment failure. Long period of first treatment with category I regimen more than 6-8 months also indicates sputum conversion problem (remained positive

sputum AFB) due to poor-adherence of treatment, or being primary drug resistance.

- **Unfavourable treatment outcomes**

As indicated in many literatures, there has been a strong relationship between MDR-TB and unfavourable treatment outcomes among previously-treated non MDR-TB patients. Both defaulter and treatment after failure are the treatment outcomes which have higher possibility to develop MDR-TB than the relapse result or during first anti-TB treatment. This factor is directly influenced by health system related factors, as quality of DOT, drug regimens and skill of health staffs.

The previous treatment history of TB is highly accepted to be the strongest determinant for the increase in prevalence of MDR-TB among cases with acquired infection. Hence, previously-treat TB patients have been arranged as the first priority of MDR-TB vulnerable group for further investigation regarding to national MDR-TB guidelines.

4.5 Health system related factors

- **Case detection coverage & data reporting system**

Like most of LMICs, case detection coverage has always been a big gap to represent the exact TB prevalence and incidence in Thailand[1]. With TB case detection rate of 56.5% in the recent year, there were only approximately 20% of estimated MDR/RR-TB cases among notified pulmonary TB cases enrolled for starting treatment[1]. While almost 2,000 suspected MDR/RR-TB cases were not detected and had no treatment, they could spread infection to communities, died, or developed more aggressive resistant strains. This problem can be linked to other health system related factors, such as accessibility, availability and affordability to access health services, causing delayed case detection. Moreover, demographic and socio-economic factors such as ethnicity, residence status, mobility, socio-cultural beliefs and communication can contribute to be MDR-TB case detection barriers.

TB data reporting system has been continuously improved for completeness and accuracy. But the coverage and accessibility gaps are still present, causing underestimated TB/ MDR-TB prevalence reports.

- **Accessibility**

Geographical accessibility seems to be the most influencing factor to access health services in Thailand as well as other LMICs mentioned in the literature review. Distance to health facilities, long travel time and difficulty on transportation are strongly associated with poor access to health services. It also affected by other determinants, compose of low income people in the rural areas or border regions, non Thai ethnicity with diversity of socio-cultural beliefs.

- **Availability**

From the literatures, availability of staffs, health facilities, drugs and laboratory testing can affect MDR-TB case detection and efficacy of TB treatment. A chronic shortage of human resources in the public sector has been caused by high workloads and unsatisfied salaries or other incomes. Thus, many of health staffs especially doctors choose to work in private sector which provides higher incomes instead. From my experience, HCWs who responsible for TB clinics have changed or switched their jobs frequently, due to higher workloads as compare to other non-communicable diseases care. Some of them have to take responsibility for TB, HIV and infection control in one person, especially in rural health facilities. Although the Global Fund has supported finances for human resources, but the sustainability of budgets is unpredictable.

Availability of health facilities in Thailand is not in a crisis, as its distribution to sub-district levels. But there are problems in some PCUs or hospitals with the quality of infection control, ventilation and separate rooms for TB/MDR-TB patients. For availability of drugs and laboratory testing are still not much concerned in Thailand.

- **Affordability**

Affordability is the influencing factor to reach health services, especially among patients with poverty. TB patients who are Thai can use UC rights to afford TB care. For non-Thai TB patients, the financial support for TB care is different depends on non-Thai populations categories. But some of them may not understand their rights and access to health services, lead to delay in diagnosis and treatment. According to TB treatment coverage of 53% as reported in 2015, it could be caused by low case detection rate in the same year[1].

- **Acceptability**

Several studies explained a strong relationship between poor compliance to anti-TB treatment and development of MDR-TB among previously-treated TB patients. If the number of separate FLDs tablets is the cause, changing to FDCs drugs can increase compliance to treatment. But if this problem is caused by drugs' adverse reaction, it needs to be managed carefully by physicians. So, communication between HCWs and TB patients is very important to avoid quitting treatment of the patients themselves.

- **Quality of care**

DOT & adherence to treatment

Quality of DOT and treatment adherence has been noted by many studies as one of the strongest significant factors for the prevalence of MDR-TB both among new and retreatment TB cases. Other determinants such as adverse reaction from drugs, social stigma, working outside residence, mobility, comorbid illness, alcoholism and drug addiction are closely related with DOT and treatment adherence.

TB treatment success rates in Thailand have never been reached WHO's standard, representing a big gap of poor quality of DOT. Moreover, the proportion of non-HCWs DOT which has less reliability than HCWs DOT, is about three-quarter of the total DOT. Causes of low proportion of HCWs DOT can be due to high workloads of HCWs, lack of compensation for home visit and patient's factors as previously mentioned.

Drugs and treatment regimens

From TB supervision experience, some hospitals has drug storage rooms with humidity and/or temperature higher than the standard, causing poor quality of drugs. It can affect treatment efficacy and contribute to be drug resistance. Category II regimen for MDR-TB treatment has been applied in several TB cases before disclosure of DST results. Although TB treatment guidelines are available at every hospitals, some doctors still order the irregular regimens, causing drug side effects to the patients. Inadequate or irregular treatment regimens are noted to be one of the most important influencing factors of MDR-TB.

Skills of health staffs

Well-trained health professionals are needed to improve quality of TB care. From my experience as TB supervisor, there has been young doctors who just graduated and other new-coming health care providers who have no experience for TB care. They have a chance to misdiagnose TB/MDR-TB, give wrong treatment regimens, poor quality of DOT, or misinterpret of sputum examination. These can lead to development of MDR-TB.

Duration of diagnosis and starting treatment

The previous studies found that delay in diagnosis and starting treatment was a significant factor for developing MDR-TB. It can be linked to education, socioeconomic factors and seeking care from non-TB health facilities that are correlated with TB situation in Thailand.

Chapter 5: Conclusions and recommendations

5.1 Conclusions

Although previous treatment history of TB has been reported as the most influencing factor for development of MDR-TB among previously-treated TB cases, but other determinants are also the potential factors contributing to increase MDR-TB cases. Unless demographic-individual factors, exposure and socio-economic determinants, many of health system related factors are strongly associated with MDR-TB prevalence both direct and indirect ways. Hence, medical teams and other health staffs play the important roles for TB care to reduce MDR-TB burden.

Poor quality of DOT and treatment adherence, impropriated treatment regimens, mobility, and barriers to access TB care among cross border migrant populations are also remarked as potential factors for MDR-TB that need improvement. MDR-TB cases detection coverage has been a big gap to find almost half of estimated MDR-TB cases as well as incomplete and non coverage of data reports, resulting delay in diagnosis and treatment, and prolonged spreading period. According to End TB Strategies with the main goal to decrease TB estimated incidence by the year 2035, high case detection rates and high success rates are required.

5.2 Recommendations

1) TB Health promotion and preventive activities for MDR-TB

Health education is the primary prevention that plays an important role for diseases prevention and control, but it is often neglected. With a limited budget, the investment for primary prevention can provide the worth results. If people have a good understanding about TB and MDR-TB can recognize the importance of self-protection from infection, and proper health seeking behaviour, they can help eliminating the spreading and development of MDR-TB. DS-TB patients who are well-educated about illness and have a good attitude for DOTS and TB care also have high chance to cure from disease without MDR-TB development. Hence, it is important for HCWs to provide health education about TB/MDR-TB to people in communities, both Thai and non-Thai populations. Knowledge also should be provided before starting treatment among TB patients. For MOPH, DDC and involved stakeholders, the new releases about TB/MDR-TB awareness and prevention should be promoted and addressed frequently via social medias and networks.

2) Early case detection of MDR-TB among contacts and vulnerable groups

The NTP guidelines for assessment of MDR-TB in the vulnerable groups of retreatment TB cases, TB in migrants populations, TB patients with co-morbid illness and MDR-TB contacts as the first priority has been properly arranged. But barrier to access these vulnerable groups is the problem for the coverage of case detection even if available health facilities and diagnostic tools. So, advocacy communication and social mobilisation between HCWs and communities for active case finding are important to increase case detection rate and decrease spreading period of MDR-TB.

3) High quality of DOT and effective treatment with patient-centred care

Because TB has individual complexity on treatment, so TB care should be based on patient centre. The screening of co-morbid illness and risky behaviour should be done for all TB patients prior to treatment to avoid adverse reaction of drugs. The adequate, standardise anti-TB regimens must be chosen properly and individually for effective treatment outcomes. Strictly DOT by HCWs for a whole period of treatment is highly recommended for good treatment adherence and cured treatment outcome, especially TB patients with high risk for MDR-TB. Well-trained community volunteers can be helpful as treatment observers to decrease workload from the responsible HCWs and less family DOT as possible.

4) Infection control

Infection control in health facilities should be standardising with the proper implementation to protect HCWs safe from infection and prevent TB/MDR-TB in the future. Administrative measures, engineering controls for ventilation in separate rooms and respiratory protection using particulate respirators are the three main standard activities that should be done in every health facilities. For infection control of MDR-TB in the outbreak/ high prevalence area or prisons, the measures are similar with that of health facilities but prompt separation of suspected patients and low immune persons is highly suggested.

5) Political commitment with international collaboration for TB prevention and control policies and funding

Since the opening of AEC for a year, there has been increasing trend of mobility from the neighbouring countries to Thailand. The screening for active TB should be considered among these cross-border people to decrease incidence of new TB/MDR-TB cases. Follow-up and further investigations for suspected TB/MDR-TB cases should be done systematically with definite guidelines. The international collaboration for TB prevention and control funding and policies should be promoted among ASEAN countries with ministry of health and ministry of foreign affairs.

6) Social protection and poverty alleviation for TB patients

Socio-economic factors are still a concern for prevention of MDR-TB. Lower socioeconomic people should have more opportunity in MDR-TB prevention and control efforts. In addition to TB care, social assistance and protection, including supportive allowance to low-socioeconomic TB patients who have to quit jobs for treatment are suggested to make a successful treatment and reduce the chance to develop MDR-TB.

7) Increase quality and capacity of human resources

For new doctors in district hospitals, TB care knowledge and training for management of TB patients with co-morbidities, is very important before start working. The other health professionals also should have mentors as consultants on works. On the job training, conference meetings, supervision, refresher courses, learning from best practices and scholarships for education are the activities that should increase quality and capacity of human resources.

8) Engagement of communities, public and private care providers

Engagement with communities and NGOs networks should be promoted to help active case finding of TB/MDR-TB cases, identify and give prompt treatment. Strengthen cooperation and coordination with public and private sectors outside MOPH are highly recommended to create a partnership network connection for standardise TB/MDR-TB cares, good referral system, and increased coverage of TB data.

9) Completeness and prompt data records with monitoring and evaluation

In addition to public-private sectors coordination, TB data records and registration can be completed by the effective TB recording and reporting system. Intense, regular supervision with monitoring and evaluation are noted to improve and evaluate TB/MDR-TB situation.

10) Intensified research and innovation

Research topics that meets the needs both national and local levels should be promoted, such as screening methods for MDR-TB in prisons, efficacy of using video observed therapy via smart phone instead of DOT as new innovation etc. Systematically innovative operation of TB should be promoted as well.

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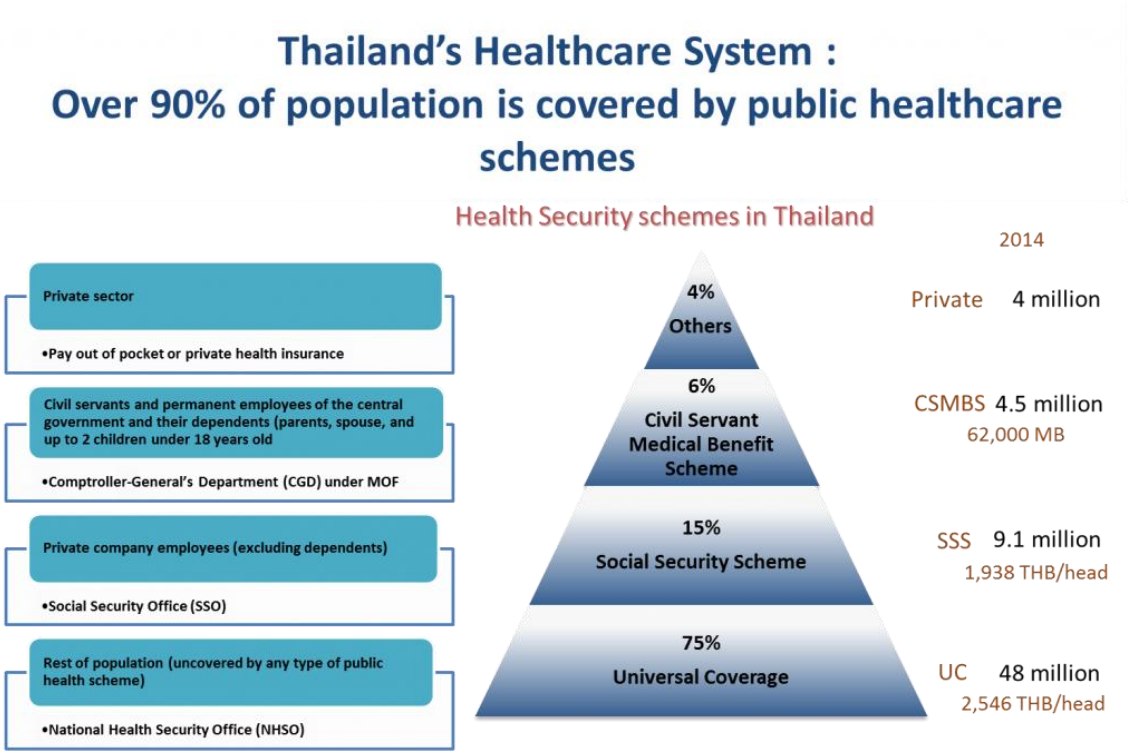
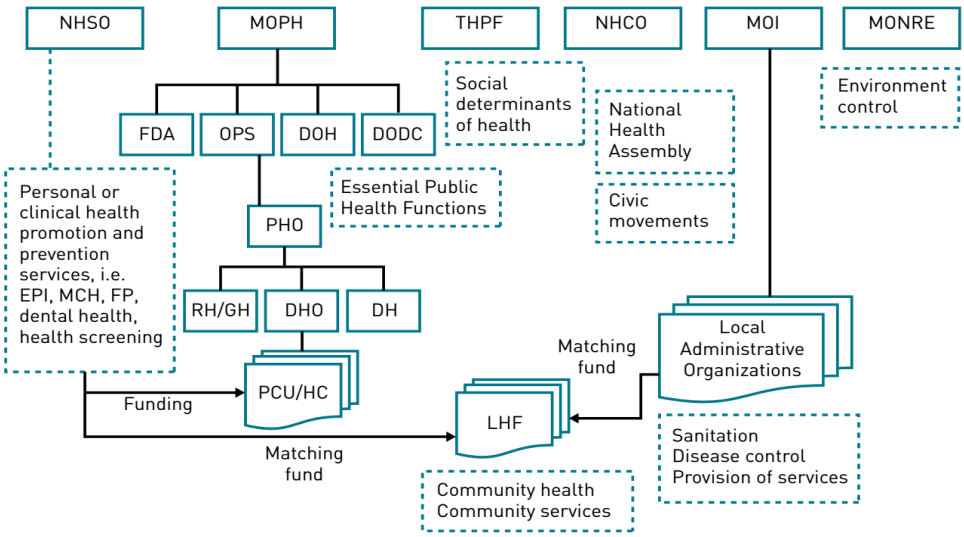
Annexes

Annex I: Map of Thailand

Annex 2: Thailand's health system[14]

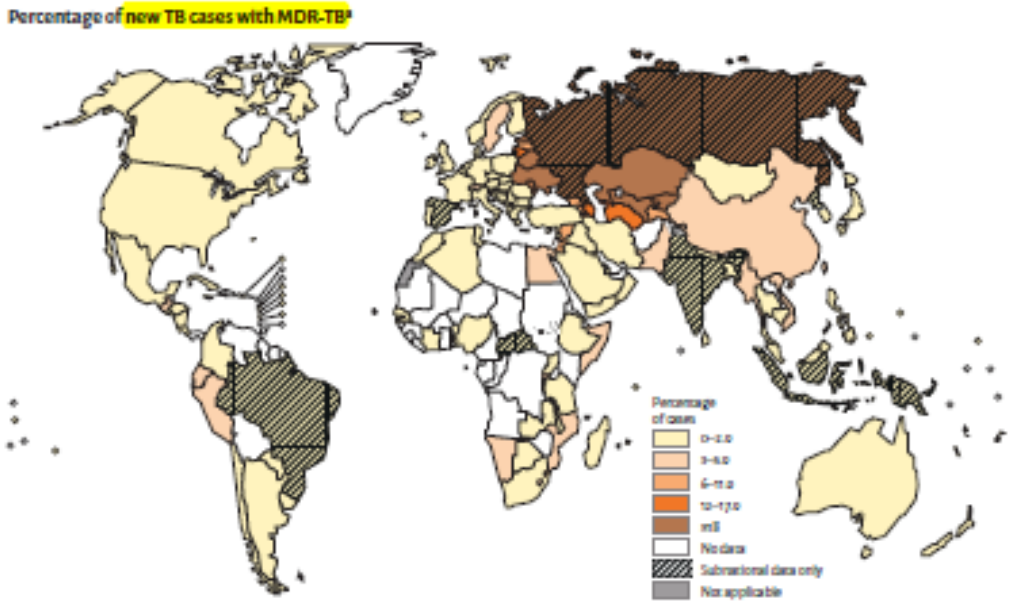


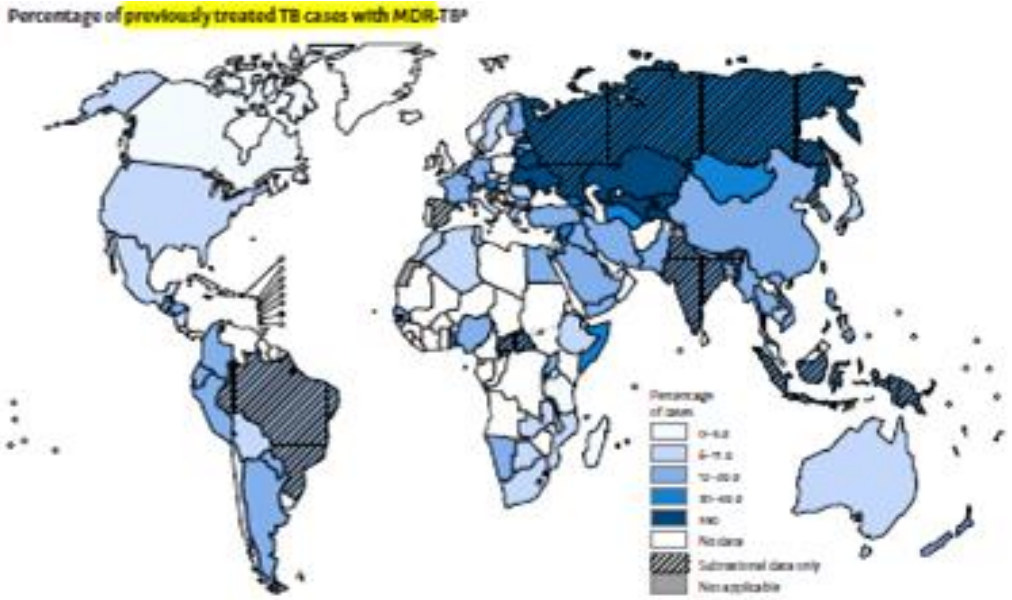
Organisation of public health services in Thailand[13]



NHSO: National Health Security Office; MOPH: Ministry of Public Health; THPF: Thai Health Promotion Foundation; NHCO: National Health Commission Office; MOI: Ministry of Interior; MONRE: Ministry of Natural Resources and Environment; FDA: Food and Drug Administration;OPS: Office of Permanent Secretary; DOH: Department of Health; DODC: Department of Disease Control;PHO: Provincial Health Office; DHO: District Health Office; RH/GH:Regional or General hospitals; DH: District hospital; PCU = primary health-care unit; HC: health centre; LHF: Local Health Fund; EPI: Expanded Programme for Immunization; MCH: maternal and child health; FP: family planning.
Source: Synthesis by the Author

Annex 3: Percentage of new and previously-treated cases with MDR-TB worldwide in 2014.





(source: Global TB 2015)

Annex 4: Definitions of key concepts

Keywords	Definition
TB	*M. tuberculosis* infection of all types that have been confirmed by clinical, AFB microscopy, culture (DST) and/or radiology.
Drug susceptible TB (DS-TB)	All forms of TB cases which are sensitive to first line TB drugs.
Mono-resistant TB	Resistance to one first-line anti-TB drug only.
Poly-resistant TB	Resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin
Multi-drug resistant TB (MDR-TB)	Resistance to at least isoniazid and rifampicin without resistance to any other second-line drugs-line drugs.
Extensive drug resistant TB (XDR-TB)	MDR-TB plus resistance to a fluoroquinolone and at least one second-line injectable agent: amikacin, kanamycin and/or capreomycin.
Rifampicin resistant TB (RR-TB)	Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR.
Primary drug resistant TB	Patients infected with *M. tuberculosis* that is resistant to anti-TB drugs from the outset, prior to anti-TB treatment.
Acquired drug resistant TB	Patients infected with *M. tuberculosis* that Develop drug resistant strains during anti-TB treatment process.
Newly-diagnosed MDR-TB cases	Drug resistance found in new TB patients who have never been treated with anti-TB drugs or who were treated briefly (for a period of less than 1 month).
Previously-treated MDR-TB cases	Drug resistance found in patients who have been treated with anti-TB drugs for 1 month or more
Non-adherence	Patient who missed more than 20% of the prescribed doses during the intensive phase of the treatment period as recommended by WHO that can be confirmed from TB register of the patients.
Cured	TB patient who has a sputum smear becomes negative at, or one month prior to the completion of treatment (at the 5th month)
Treatment completed	TB patient who has completed the treatment course and smear results are not available at or one month prior to the completion of treatment
Relapse	TB patient who was declared cured or treatment completed by a physician, but who reports back to the health service and is now found to be sputum smear positive.
Defaulter	TB patient who has been on treatment for at least 4 weeks and whose treatment was interrupted for more than 8 consecutive weeks.

Keywords	Definition
Treatment failure	A patient remains or becomes again smear-positive at 5 months or later during treatment

(Caminero 2013 and WHO2014)

Annex 5: The End TB Strategy[1].

VISION	A WORLD FREE OF TB — zero deaths, disease and suffering due to TB			
GOAL	END THE GLOBAL TB EPIDEMIC			
INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030[a]	END TB 2035
Percentage reduction in the absolute number of TB deaths (*compared with 2015 baseline*)	35%	75%	90%	95%
Percentage reduction in the TB incidence rate (*compared with 2015 baseline*)	20%	50%	80%	90% (approximately 10 per 100 000 population)
Percentage of TB-affected households experiencing catastrophic costs due to TB (*level in 2015 unknown*)	0%	0%	0%	0%

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. **INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION**
   - A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
   - B. Treatment of all people with TB including drug-resistant TB, and patient support
   - C. Collaborative TB/HIV activities, and management of comorbidities
   - D. Preventive treatment of persons at high risk, and vaccination against TB
2. **BOLD POLICIES AND SUPPORTIVE SYSTEMS**
   - A. Political commitment with adequate resources for TB care and prevention
   - B. Engagement of communities, civil society organizations, and public and private care providers
   - C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   - D. Social protection, poverty alleviation and actions on other determinants of TB
3. **INTENSIFIED RESEARCH AND INNOVATION**
   - A. Discovery, development and rapid uptake of new tools, interventions and strategies
   - B. Research to optimize implementation and impact, and promote innovations

Source: The Global TB report 2016