การทบทวนวรรณกรรมเกี่ยวกับภาพรวมของวัณโรคชนิดดื้อยาและนโยบายป้องกันและควบคุมการแพร่ระบาดของวัณโรคในประเทศไทย

A literature review: Overview of drug-resistant tuberculosis and preventive and control policies of tuberculosis transmission in Thailand

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บทคัดย่อ

วัณโรคคือหนึ่งในสาเหตุหลักที่ทำให้เกิดการเสียชีวิตมาเป็นระยะเวลานาน โดยเฉพาะในประเทศที่กำลังพัฒนาซึ่งมีวัณโรคชนิดดื้อยาปรากฏร่วมด้วย ในปัจจุบันมีข้อจำกัดหลายประการที่ขัดขวางความสำเร็จของการรักษาวัณโรค ดังนั้นทุกปัญหาที่เกิดขึ้นและนโยบายในการป้องกันและควบคุมวัณโรคของยุคปัจจุบันจำเป็นต้องมีการตรวจสอบเพื่อลดสิ่งที่เป็นอุปสรรคต่อผลลัพธ์ที่ดีในการรักษาวัณโรค การศึกษานี้มีวัตถุประสงค์เพื่อพิจารณาภาพรวมของข้อมูลที่เกี่ยวข้องกับวัณโรคชนิดเชื้อดื้อยาในประเทศไทยและเพื่อเสนอแนวทางในการลดการแพร่ระบาดของวัณโรค โดยใช้วิธีการทบทวนและพิจารณาวรรณกรรมทางวิชาการและงานวิจัยที่เกี่ยวข้องกับวัณโรคด้วยวิธีการสืบค้นจากแหล่งข้อมูลที่เป็นทางการและฐานข้อมูลเกี่ยวกับวารสารทางการแพทย์และบทความการศึกษาทางวิชาการที่เผยแพร่ระหว่างปี 2553 จนถึงปี 2565 โดยมีประเด็นสำคัญคือ นิยามของวัณโรค สาเหตุการเกิดวัณโรค ชนิดของวัณโรค ยาที่ใช้และแนวทางการรักษาวัณโรค การป้องกันการติดเชื้อวัณโรค และสาเหตุหลักที่เป็นส่วนหนึ่งของการเพิ่มขึ้นของจำนวนผู้ติดเชื้อและผู้เสียชีวิตจากวัณโรค จากการศึกษาพบว่ามีปัญหาหลายประการที่ทำให้วัณโรคแพร่กระจายในวงกว้างและมีการพัฒนาเป็นวัณโรคชนิดดื้อยา ปัญหาที่สำคัญซึ่งได้จากการวิเคราะห์ข้อมูลวิจัยและบทความได้แก่ การไม่ตระหนักรู้ถึงการติดเชื้อ การไม่ได้รับการรักษาที่เหมาะสมอย่างต่อเนื่องจากปัจจัยทางด้านสังคมและเศรษฐกิจ และการตัดสินใจยุติการใช้ยารักษาด้วยตัวผู้ป่วยเองโดยปราศจากคำสั่งของแพทย์ ดังนั้นการทำให้ผู้คนในสังคมตระหนักรู้ถึงวัณโรคโดยการให้ข้อมูลสำคัญที่เกี่ยวข้องจะทำให้ผู้คนเห็นความสำคัญของการป้องกันตัวเองซึ่งเป็นปัจจัยหนึ่งที่จะลดอัตราการแพร่ระบาดของวัณโรคได้ รวมทั้ง

นโยบายบางประการสามารถมีการปรับปรุงเพื่อทำให้ผลลัพธ์ดียิ่งขึ้น เช่น การสนับสนุนให้มีการฉีดวัคซีนป้องกันวัณโรคอย่างทั่วถึง การตรวจหาเชื้อแบบเชิงรุก การส่งตัวผู้ป่วยเข้าสู่ระบบการรักษา การให้ความรู้เกี่ยวกับวัณโรคแก่ประชาชน และการสวมหน้ากากอนามัยทางการแพทย์เมื่ออยู่ในพื้นที่แออัด
คำสำคัญ: วัณโรค, การป้องกัน, ภาพรวม, วัณโรคชนิดดื้อยา, การแพร่ระบาด

Abstract

Tuberculosis has been one of the major causes of death for a long period of time, mainly in underdeveloped nations, where drug-resistant tuberculosis is prevalent. There are numerous challenges in Thailand that obstruct the performance of tuberculosis treatment. As a consequence, all problems and contemporary tuberculosis transmission prevention and control policies in the country should be investigated in an attempt to lessen the impediments that prohibit beneficial results. The purpose of this study was to examine an overview of Thailand's drug-resistant tuberculosis data and to suggest strategies to minimize drug-resistant tuberculosis transmission. The study was conducted by reviewing the academic literature and research papers related to tuberculosis that published between 2010 and 2022 including definition, causes, types, regimens, preventions, and the main causes that contribute to the increase in infection rates and death tolls. As a result, there are several issues that cause tuberculosis to widely spread and develop to drug-resistant tuberculosis. Some of the most worrisome problems are the unawareness of being infected, detachment from the proper treatment associated with the socioeconomic factors, and the decision of patients themselves to cease the usage of anti-tuberculosis drugs without physicians' allowance. Consequently, Raising the awareness of the people in the public society, which can be done by providing the critical information about tuberculosis, will assist in increasing the personal protection that will help to dwindle the tuberculosis infection rate. Some of the policies can be improved for the best result. For example, the BCG vaccination supply, the active case finding, transferring the patients to the medication system, educating people about the danger of tuberculosis, and wearing masks whenever inhabiting in congested areas.
Keywords: Tuberculosis, Prevention, Overview, Drug-resistant Tuberculosis, Transmission

Introduction

For a long time, the rise in tuberculosis (TB) has been a public health concern, particularly in developing countries. Thailand, according to the World Health Organization, is one of the countries with a high prevalence of tuberculosis[1]; the country also has a high incidence of drug-resistant tuberculosis. (DR-TB).[2]

Poverty, malnutrition, a lack of medical personnel, and the difficulty in obtaining adequate medical care are the key factors that contribute to tuberculosis infection. More than one-third of tuberculosis patients in Thailand do not undergo adequate treatment, resulting in increase transmission and drug-resistant tuberculosis. According to Somsak Akksilp, deputy director-general of the Department of Disease Control, roughly 26,000 out of 80,000 cases were lost the tight adherence to treatments in 2012.[3]

The primary reasons why patients do not follow the regimens are that they are unaware that they are infected and do not know that they must continue the therapy even though they are feeling better. Furthermore, patients in low-income countries face socioeconomic challenges[2] that prevent them from receiving adequate care. As a result of incorrect antibiotic use, numerous new drug-resistant tuberculosis cases have emerged in recent years. To make matters worse, drug-resistant tuberculosis patients have the potential to transfer the drug-resistant strain to others. The cost of drug-resistant tuberculosis treatments is higher than the cost of drug-susceptible tuberculosis treatments, thus the government will struggle with the budget for health management.

This study aims to review the overview of drug-resistant tuberculosis in Thailand, including the unawareness of being infected with Mycobacterium tuberculosis, the guideline treatment for latent tubercul (LTBI) patients in Thailand, a summary of guidelines for programmatic management of Drug-Resistant TB, an example of adverse effects from medications, a concept that helps to increase the efficiency of the treatment, patient behavior in terms of sticking to the treatment, causes that make TB patients resistant to anti-TB drugs, how to reduce the spread of Tuberculosis, and current WHO policy on TB transmission control in practical ways. This study reviewed and gathered data from medical journals, academic paper, and official guidelines to make comprehensive TB data more accessible for wider group of people and intends to provide tuberculosis preventive and control policies based on the findings of the research and international guidelines as well.

Material and method

This literature review gathered information related to TB from official guidelines, medical journals, academic research. All of which are conducted between 2010 and 2022 for the contemporary information. The review also consists of the information that contained relevant topics, which are definition, causes, types, regimens, preventions, and the main causes that contribute to the increase in infection rates and death tolls. The main resources are World Health Organization, New York State Department of Health, Centers for Disease Control and Prevention, The PLoS One journal, The Pediatric Infectious Disease journal, Department of Disease Control, BMC Public Health journal, General Hospital Psychiatry journal, Iranian Journal of Public Health, Clinics in Chest Medicine journal, Encyclopædia Britannica, Anales de Pediatría journal.

The definition of Tuberculosis and danger of drug–resistant tuberculosis.

Tuberculosis is a contagious infection caused by the bacteria *Mycobacterium tuberculosis*.[3] Tuberculosis can affect any area of the body, although it most commonly affects the lungs. There are two types of tuberculosis: latent and active.[4] LTBI occurs when a person has a TB infection but their immune system is still effective at disinfection. As a result, this group will exhibit no symptoms. However, medical care is required because it can progress to active TB. Coughing for more than 3 weeks, coughing up blood or mucus, having chest tightness and feeling the pain when inhaling or coughing, losing appetite and accidental weight loss, night sweats and exhaustion, and having a fever are all indicators of active tuberculosis.[5] In high-burden nations, three types of tb are found: TB, TB/HIV, and DR-TB. To begin, TB refers to patients with typical tuberculosis who do not have any comorbidities. Second, TB/HIV refers to tuberculosis patients who have HIV infection; this variety is more deadly than normal TB since HIV reduces the immune system's efficacy. Finally, the major issue of this study, DR-TB, is life-threatening since it does not react to normal medicines[6], which might result in medical treatment failure. DR-TB is a short for drug-resistant tuberculosis. This kind of tuberculosis does not react to at least the two most effective medications, isoniazid and rifampicin.[7] DR-TB is spreading because of a lack of medical control and care, as well as the easy transmission among people. TB patients must adhere to a 6-month medical regimen. The issue is many patients

misuse their medications. For example, not taking medications at the dosage prescribed by a doctor. Furthermore, improper storage can degrade the quality of the medications. The therapy for DR-TB is restricted and expensive in many developing nations. Furthermore, many people are suffering from side effects. For all of the reasons stated above, DR-TB is harmful since it elevates the risk of death.

Overview of DR–TB treatment and prevention

Treatment for DR-TB can last up to 20-24 months[8], which is substantially longer than the time required to cure conventional TB. Drugs used to treat tuberculosis are ineffective and have numerous side effects. Fortunately, a new medication known as Bedaquiline is quite successful. Bedaquiline, on the other hand, causes a number of side effects, including nausea, arthralgia, and chest pain. Furthermore, Bedaquiline is prohibitively expensive. In 2020, the Thai Tuberculosis Division spent 35,203 Baht on 188 tablets of Bedaquiline[9], resulting in a price per tablet of 187.25 Baht, whereas the minimum daily wage is less than 340 Baht. Tuberculosis is easily transmitted because it is an airborne illness. The germs are carried in TB patients' droplet nuclei, which are only 1-5 microns in diameter.[10] Thus, the best way to avoid contracting tuberculosis is to avoid staying in crowded settings. Furthermore, when exposed to patients, it is strongly advised to use a medical mask to avoid inhaling the droplets. To prevent normal TB from progressing to DR-TB, it is critical to rigorously adhere to medical treatments prescribed by physicians. Furthermore, health care practitioners must monitor patients while they are on TB treatment programs to ensure that they do not skip any medication doses. Vaccination, on the other hand, is the key to preventing tuberculosis infection. As a result, the public must receive the Bacille Calmette-Guérin (BCG) vaccine.

Overview of DR–TB regimens

Long-term DR-TB treatment requires at least 5 types of anti-TB medications in an intense phase and at least 4 types of anti-TB drugs in a continuous phase.[11] To reduce the potential of drug resistance, it is suggested that patients be prescribed medications that they have never taken before. If it is not possible to take 5 effective oral pills during an intensive phase, utilize Amikacin and Streptomycin as intravenous medications. Furthermore, if taking 5 effective oral medications during an intensive

period is not possible and users prefer oral pharmaceuticals, take Delamanid (available for patients over the age of 3), Pyrazinamide, and Ethambutol. If the above-mentioned medications are ineffective, use Ethionamide or Prothionamide (if there is no mutation at position inhA), imipenem-cilastatin/clavulanate or meropenem/clavulanate, *p*-aminosalicylic acid, or high-dose Isoniazid (in case of having resistance to Isoniazid at low-level). Furthermore, the use of capreomycin, kanamycin, amoxicillin/clavulanate (unless when combined with carbapenem), azithromycin, and clarithromycin is not advised. It is recommended that treating DR-TB take up to 5 months in an intense phase, or until culture conversion occurs. Importantly, Therapeutic Medication Monitoring is required for DR-TB patients since low drug levels in the blood will result in treatment failure. Furthermore, TDM can be used to monitor the negative effects of medications.[11] As a result, it is required for all DR-TB patients, particularly those with gastrointestinal absorption disorders and those with comorbidities such as HIV, diabetes, and renal insufficiency.

Unawareness of being infected with *Mycobacterium tuberculosis* has contributed to increasing infection and risk of death from tuberculosis

Many people who are exposed to the germs do not exhibit any symptoms, therefore they are unaware that they are afflicted with Tuberculosis. This form is known as Latent Tuberculosis Infection.

Tuberculin skin tests or IGRAs, which identify the presence of Mycobacterium tuberculosis, can be used to detect latent tuberculosis. When undergoing a Tuberculin Skin Test, 0.1 milliliters of Purified Protein derivative derived from Mycobacterium TB will be injected into the intradermal area of the forearm and the bulge size at the injection area will be measured 48 to 72 hours later.

Interferon-gamma release assays (IGRAs) are a blood test to measure the amount of Interferon-gamma (IFN-γ). There are two recognized IGRAs in Thailand: QuantiFERON-TB Gold Plus (QFT-Plus) and SPOT® TB test (T-spot). Both QFT-Plus and T-spot use ESAT-6 and CFP-10 as Mycobacterium tuberculosis antigens, with the difference being that the former uses Lithium heparinized blood to test within

12 hours at 25 degrees Celsius after taking a blood sample and measuring the IFN-γ secretions released from white blood cells (IU/ml), whereas the latter uses Heparinized peripheral blood Mononuclear cells (PBMCs) to test within 32 hours at 18 to 25 degrees Celsius. Positive, Negative, and Indeterminate interpretations are available in both QFT-Plus and T-spot. T-spot evaluates the borderline results as well. Overall, IGRAs are superior to Tuberculin Skin Tests because they are more precise and lower the possibility of false positives.

Although latent tuberculosis does not affect the human body, it can develop into active tuberculosis and endanger individuals. According to the Center of Disease Control and Prevention[12], more than 13 million Americans may be infected with latent tuberculosis. If these persons are not treated, one-tenth of them may develop active tuberculosis.

Active tuberculosis infection and severe symptoms are more likely in people who have comorbidities that impair immune system function, such as HIV. HIV individuals are 21 times[13] more likely than non-HIV patients to contract tuberculosis. Furthermore, more than 80% of active TB patients had latent TB but went untreated because they were unaware they were infected.

According to the World Health Organization, one-fourth of the world's population is infected with latent tuberculosis (LTBI). As a result, adequate medicines should be offered for LTBI patients in order to prevent them from developing active TB. Furthermore, active case detection is critical in congested locations, particularly in hospitals and prisons, because the faster cases are identified, the greater the likelihood of successful treatment.

The guideline treatment for LTBI patients in Thailand

The regulations after diagnosis with LTBI[13] are, first, taking a blood sample to examine the liver function in who are at risk in hepatitis, which are chronic alcoholism, hepatitis virus infection, HIV infection, malnutrition, people at age above 35 years old, and pregnant women or within 3 months after delivery both before and during use Isoniazid, Rifampicin, and Rifapentine. The second is taking blood samples to examine the kidney function in nephrotic syndrome or at risk in acute renal failure. Third, alcohol drinking must be discontinued. Lastly, the health care providers must inform LTBI patients that the efficiency of the treatment is up to the frequency of taking medicines. There are 4 most used

drug formulas to treat LTBI in Thailand.[13] First is giving only Isoniazid every day for 6 or 9 months in normal patients while giving Isoniazid daily for 9 to 12 months in children HIV patients. The second is giving only Rifampicin every day for 3 to 4 months. The third is giving Rifampicin with Isoniazid daily for 3 to 4 months. Fourth is giving Rifapentine together with Isoniazid once a week for 3 months.

Monitoring and evaluation in LTBI patients are made after finishing the treatment program. To begin, the contacts of TB cases' information and medical screening must be collected in the National Tuberculosis Information Program (NTIP).[13] Next, the registry in NTIP is necessary for all LTBI patients. It is mandatory to debrief and follow up the LTBI patients in case of taking only Isoniazid daily for 6 to 9 months, only Rifampicin for 3 to 4 months, Isoniazid with Rifampicin for 3 to 4 months, Isoniazid with Rifapentine 12 times in 3 months, or Isoniazid with Rifapentine once a day for a month. Within 2 years after finishing the LTBI medications, the patients must be tracked to ensure that they are completely discovered from LTBI and will not develop into active TB. The past report[13] said that some active TB cases are diagnosed with LTBI instead of active TB and follow LTBI treatment guidelines. Hence, the repeated chest radiograph check after 2 to 3 months after the beginning of LTBI treatment and 2 years monitoring after in contacts should be done. In addition, the health care providers must advise the patients to go to the hospital as soon as possible when having abnormal symptoms.

The summary of guidelines for programmatic management of Drug–Resistant TB

Drug-Resistant TB began in 1970 when there is Isoniazid and Rifampicin usage. Therefore, the Directly Observed Therapy; DOT11 is adopted to increase the efficiency of taking medicines and decrease the risk of DR-TB development.

DR-TB is one of the most problematic issues in many countries, especially in low-income and developing countries; DR-TB requires second-line anti-tuberculosis drugs that cost approximately 200,000 Baht in each patient while the normal TB patients can use first-line anti-tuberculosis drugs that cost less than the second-line about 100 times.[14] According to WHO, 3.5% of new TB cases and 20.5% of previously treated patients are diagnosed with MDR-TB.[15] In Thailand, the statics of MDR-TB cases tend to stay the same

The causes of Drug-Resistant TB can be a genetic mutation, but the most concerning reason is the human-made phenomenon in both clinical practice and programmatic TB management which causes ineffective TB medications and controls. The relevant factors can be divided into 3 main topics. To start with, healthcare-related factors such as giving improper doses of anti-TB (types of drugs, treatment duration, and false drug formulas), Inadequate management, and weak DOT system. Secondly, patient-related factors such as irregularly taking medicines because of adverse reactions or socioeconomic problems. Further, in some cases, mal-absorption also has a large impact on the treatment. Lastly, drug-related factors such as low quality of drugs due to impotent logistics and the condition of the storage.

The risk group of DR-TB is mainly in previously treated patients. First is that after the failure of retreatment regimen with first-line anti-tuberculosis drugs patients, this group has chronic cases, so if they are given retreatment regimen and put in DOT system and still fail to recover, the chance of MDR-TB will be up to 85%. Next is the after the failure of first treatment with first-line anti-tuberculosis drugs patients, this group still have *Mycobacterium tuberculosis* in the sputum after 5 months of the regimen, the range of MDR-TB is about 50%, but it can be varied from 10 to 90 % depending on the prevalence rate, quality of the DOT system, and the extent of disease. Third is relapse cases, which are recovered from TB and infected with TB again, can have DR-TB, especially in early relapse cases. If this group relapses after being treated by retreatment, the risk of DR-TB will be about 50%. On the other hand, if this group relapses after being treated with drugs for new cases, the risk of DR-TB will be 10% approximately.

There are 2 laboratory TB tests; First is a smear microscope, which can be both Ziehl-Neelsen (ZN) dye method with light microscope method and fluorescent microscope method. The smear test is the fundamental TB test that is positive when detecting 5,000 to 10,000 bacteria per 1 milliliter. However, it is not possible to identify DR-TB with this method. The second is a screening test that can detect DR-TB. For instance, Xpert MTB/RIF, one of the real-time PCR methods, can detect TB and Rifampicin-resistant TB at the same time within 100 minutes. Further, it can be used in both positive and negative sputum smear tests but must have at least 131 bacteria in 1 milliliter of sample. However, the Xpert MTB/RIF is still not accepted as the standard test because it

can examine only Rifampicin-resistant TB. From the meta-analysis study of the Xpert MTB/RIF in adult patients, the pulmonary TB test and Rifampicin-resistant TB test have sensitivity and specificity rates at 95 and 98% respectively. Additionally, from the meta-analysis study of the Xpert MTB/RIF in children patients, testing Rifampicin-resistant TB from sputum have pooled sensitivity and pooled specificity rates at 86 and 98% orderly. There are 5 anti-TB drugs groups. Group 1 is first-line anti-tuberculosis drugs (i.e. Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol). This group has the best potential and lessen severe side effects. Thus, it is recommended to use this drug group if the Drug Susceptibility Testing indicates that patients can respond to the medication. Group 2 is injectable anti-tuberculosis agents (i.e. Capreomycin, Kanamycin, Amikacin, and Streptomycin). The two most commonly used drugs are Kanamycin and Amikacin because they are affordable, efficient, and demonstrate less ototoxicity than Streptomycin. Additionally, Capreomycin will be used if the patients are resistant to Kanamycin and Amikacin. Group 3 is Fluoroquinolone anti-TB drug (i.e. Levofloxacin, Moxifloxacin, Ofloxacin), which are the main anti-DR-TB drugs. Levofloxacin and Moxifloxacin have more potential than Ofloxacin. At present, Ciprofloxacin is not recommended for use in drug-susceptible or drug-resistant patients because it increases the rate of relapsing compared with other drugs in the same groups. Group 4 is oral bacteriostatic second-line anti-tuberculosis agents (i.e. *para*-aminosalicylic acid, Cycloserine, Terizidone, Ethionamide, and Prothionamide), whereas Ethionamide is most chosen because it has a reasonable price. Group 5 is anti-tuberculosis agents with unclear efficacy in the treatment of DR-TB (i.e. Clofazimine, Linezolid, Amoxicillin/Clavulanate, Thioacetazone, Meropenem/Clavulanate, Imipenem/Cilastatin, high-dose Isoniazid[16-20 milligrams per kilogram per day], and Clarithromycin). Because of unclear efficiency, WHO does not recommend the usage of this group as the main drug in the regimen. However, it can be used in the case that groups 1 to 4 of anti-TB drugs cannot be applied. The current study about using Linezolid with other drugs for treating MDR-TB and XDR-TB found that the success rate of the treatment is 80% in MDR-TB and 50% in XDR-TB. In Thailand, the usage of 600 milligrams of Linezolid with other drugs(i.e. Clofazimine, Imipenem/Cilastatin, Clarithromycin, Amoxicillin/Clavulanate, Thioacetazone, and high-dose Isoniazid orderly) once a day is suggested for

Pre-XDR-TB and XDR-TB patients. Since DR-TB treatment takes a long period of time, the adverse effect (e.g. inhibiting bone marrow function, neuropathy or numbness, etc.) must be closely monitored. Nowadays, WHO suggests the addition of Bedaquiline and Delamanid in adult pulmonary DR-TB patients, but have some regulations; the proper patient inclusion consists of non-pregnant and non-breastfeeding TB patients at age 18 or above, have the informed consent from the patients, and have the active pharmacovigilance system[16] to prevent the danger related to adverse reactions from the medicine, namely rash, digestive system problems (e.g. nausea, vomiting, diarrhea, etc.), psychiatric problems (e.g. depression, panic disorder, etc.), jaundice, ototoxicity, neuropathy, electrolyte wasting, and hypothyroidism.

A concept that helps to increase the efficiency of the treatment

All TB patients, especially DR-TB patients who must stay on the pharmaceutical regimen for up to 24 months, must closely adhere to the treatment requirements. There are a multitude of reasons why people are unable to follow all of their healthcare professionals' recommendations, for instance, the adverse effect of the medicines, the cost of the medications, the effect on mental health, etc. The research, which is mentioned below, supports the aforementioned reasons.[17]

First of all, hepatotoxicity is the most common effect from anti-TB drugs among all serious adverse effects in children, about 11 of 599 TB children patients were diagnosed with this symptom. The hepatotoxicity is related to Isoniazid, Rifampicin, and Pyrazinamide, whereas the first two mentioned drugs are the main regimens in the treatment[18].

Next, the drop in budget for health facilities in China[19] in the 1990s caused all patient to be charged with medical fee regardless of the disorders they are afflicted with. In the same period of the change, there is rural-urban migration which was related to TB incidence. Thus the government decided to provide free treatment to all TB patient; including free TB diagnosis, free TB drugs for 6 months and 8 months for new patients and previously treated patients, respectively, and free X-ray examination together with a free sputum smear test at the first visit. As a result, healthcare assistants were required to refer TB patients and people in contact with TB to health centers for diagnosis, confirmation, and treatment. This program helped to notice more than 55,213 new cases at that time. Moreover,

more than 70% of TB patients[20] were diagnosed with mental health issues. Many drugs used in TB treatment were possible to have adverse psychiatric effects on the patients such as Cycloserine which was associated with depression development. In addition, anti-TB drugs (i.e. Isoniazid and Linezolid) reacted with depression treatment drugs and Rifampicin may reduced the efficiency of antipsychotic doses. As stated by the report, obviously, mental health is one of the crucial factors to complete the TB treatment successfully. Consequently, the people-centered care method[21] must be adopted. This method will make TB care more accessible. To make people-centered TB care, the authorities must provide psychosocial support to both patients and their families. Additionally, there must be support to make patients follow a full treatment program; one of the most important is to educate patients about the essentials of being treated properly. Furthermore, the public society must be informed that TB is curable and is not a despicable disease to protect patients from a mental breakdown and encourage them to receive health care as well.

The behavior of the patients about being consistent with the treatment

The main factors which obstructed the TB treatment from success[22] were the socioeconomic factors which consisted of the shortage of transportation cost and social support, insufficient communication between the patients and health-care providers. The behavioral factors, for example, cease to take medicines without physicians' allowance; consumption of alcoholic drinks and usage of cigarettes; inadequate knowledge about treatment interval and consequences of non-compliance, and abandoning the appointment also have an impact on the treatment. Consequently, minimizing the socioeconomic and behavioral factors will enhance the quality of the treatment. In Thailand, the main struggling factors are alcohol usage, discontinuing taking medicines after feeling better, severe adverse effects from drugs, and the lack of treatment support.

There is a report about factors that affect the success of anti-TB treatment.[23] To begin with, treatment-related factors were reported in 50% of the studies. These consist of people's reactions toward the number of tablets, the sophistication of regimens, treatment period and adverse reactions, and potential interactions

between TB and other pharmaceuticals. All factors destroy the daily routine of the patients and make them feel forced. Second of all, personal factors were reported in 75% of the studies. The main hindrance is many patients feel like they are disempowered because of being blamed for unintentional evidence such as forgetting to take medicines since there are many kinds of drugs in the regimen. However, some patients are strategically forgetting to take medicines to regain control and return to their normal lives. These factors show that the communication between patients and healthcare workers plays an important role since no one wants to be forced to do something.

Causes that make TB patients resistant to anti–TB drugs

Normally, TB patients have to follow the treatment guideline for approximately 6 months. This long duration of treatment causes some problems that can lead to more severe types of TB. Many patients forget to take drugs because there are many kinds of medicines they have to take each day; anti-TB drugs are antibiotics that can make the patients resistant to the drugs if not taken regularly or completely. Further, patients can be resistant to anti-TB drugs because of infection with drug-resistant *Mycobacterium tuberculosis*. Therefore, all TB patients must be tested with Drug Susceptibility Test (DST), which separate the bacteria from patients' sputum and conduct culture-based (phenotypic) method by placing the bacteria in anti-TB drugs then observing the growth of bacteria, to diagnose the type of TB that patients are infected with. 5 main kinds of TB[24] are identified by WHO. Firstly, monoresistance is TB patients who are resistant to one of the first-line anti-tuberculosis drugs (i.e. Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol) only. Secondly, polydrug resistance in TB patients who are resistant to more than one of the first-line anti-tuberculosis drugs, excluding both Isoniazid and Rifampicin. Thirdly, Multidrug resistance (MDR) is TB patients who are resistant to at least both Isoniazid and Rifampicin. Fourthly, Rifampicin Resistance(RR) is TB patients who are resistant to Rifampicin, detected by phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. RR-TB includes any resistance to Rifampicin. Lastly, Extensive drug resistance (XDR) is TB patients who are resistant to any Fluoroquinolone anti-TB drug (i.e. Levofloxacin, Moxifloxacin, Ofloxacin) and at least one of injectable anti-tuberculosis agents (i.e. Capreomycin, Kanamycin, and Amikacin), in addition to MDR.

How to decrease the spread of Tuberculosis

The first is to ensure that everyone gets BCG (Bacille Calmette-Guérin) vaccination, the only licensed vaccine against TB used worldwide since 1921 that derived from a strain of the weakened *Mycobacterium bovis*.[25] However, there is TB incidence every year because BCG has about 80% efficiency in the prevention of TB for 15 years and has limited effectiveness in people of age 35 and above.[26] On the other hand, BCG injection is beneficial to prevent many children from being infected with TB since it is more challenging for treating children TB patients. Next, early diagnosis and treatment are the potential methods to decrease TB spread. TB patients can indeed spread the disease to 10 to 15 other people per year,[27] but once diagnosed and following the treatment guidelines, the majority of patients will no longer spread the disease after 2 weeks of the medications.[27] Third, active case finding is necessary to inform people about TB symptoms and encourage them to be treated after being diagnosed with TB. This is not only beneficial for the patients but also their families and the whole society. Moreover, the active case finding in the crowded areas must be done because the earlier cases are found, the more chance of recovery will occur. Fourth is managing the accommodations and surroundings. Since TB is an airborne infection, intensive hygiene care must be highly considered. The effective ways are to have appropriate air ventilation by opening the window frequently and ensuring that the natural sunlight can reach inside the house because Ultra Violet in the sunlight can cease the growth cycle of the bacteria. Fifth is using a medical face mask when being in a crowded area and do not forget to cover mouth and nose when coughing and sneezing. Moreover, TB screening should be provided to medical workers as much as possible.

Conclusion

Currently, Thailand has fairly good policies for prevention and control of Tuberculosis. However, the results will come out with a better quality if there are any improvements. For instance, encouraging and providing the BCG vaccination nationwide will minimize risk of infection in Thai citizens. In addition, the cases must be actively investigated and transferred to medical cares as soon as possible to reduce the transmission among people in the general public and to lessen the risk of severe development. Further, the officers and relevant authorities should inform the population about the impotance

of hygiene in their own residences. Finally, the certified medical face mask must be worn in case of staying in the crowded area or among the risk groups. Altogether, everyone in the society must be educated about the vital data about tuberculosis to protect themselves and others.

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