Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

An Investigation of Extensively Drug-resistant Tuberculosis: Revealing Potential Improvements for Tuberculosis Control Program

Suphanat Wongsanuphat[1]*, Charuttaporn Jitpeera[1], Orathai Suwanchairob[1], Wannisa, Theprongthong[2], Patcharin Tantiworrawit[3], Panithee Thammavijaya[1]

1 Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand

2 Division of Tuberculosis, Department of Disease Control, Ministry of Public Health, Thailand

3 Division of Innovation and Research, Ministry of Public Health, Thailand

*Corresponding author email: suphanat.wong@gmail.com

Abstract

On 31 May 2019, the Division of Epidemiology (DoE) was notified of a confirmed extensively drug-resistant tuberculosis (XDR-TB) case in Bangkok. The DoE and local teams conducted a joint investigation to describe the epidemiological characteristics of the case, identify possible source cases and contacts, and implement control measures. A descriptive study was performed among cases and close contacts by interviewing and reviewing the medical records using a standard case definition. An environmental study was performed at the case's house, workplaces, and tuberculosis (TB) clinic. The TB drugs were tested to analyze the content of active ingredients and dissolution. The case was a 36-year-old Thai male. In 2011, he was diagnosed with pulmonary tuberculosis and had received inappropriate treatment. He developed multidrug-resistant tuberculosis (MDR-TB) eight months later and XDR-TB in May 2019 with delayed hospital admission. Two possible source cases, both co-workers of the index case, were identified. Of 21 contacts, 13 were screened with a chest x-ray and found to have no abnormality. At the TB-clinic, drugs were stored in a room with inappropriate levels of temperature and humidity; however, the content of active ingredients and dissolution of TB drugs were within normal limits. Early hospital admission and monitoring of drug stockpile environments according to standard guidelines are recommended.

Keywords: extensively drug-resistant tuberculosis, XDR-TB, health insurance, drug quality

Background

The emergence of drug-resistant tuberculosis (DR-TB), a form of tuberculosis (TB) which is resistant to at least one first-line anti-TB drug, is a recent and major threat to global TB control. The treatment duration is substantially longer and more expensive and, compared with drug-susceptible TB (DS-TB), side-effects are more harmful.[1–6] DR-TB can be categorized into three groups, mono-resistant (rifampicin-resistant tuberculosis; RR-TB), multidrug-resistant tuberculosis (MDR-TB), which means resistant to isoniazid and rifampicin, and extensively drug-resistant tuberculosis (XDR-TB) which means MDR-TB with additional resistance to fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin).[7]

In Thailand, 106,000 new TB cases were identified in 2018, which is approximately 153 cases per 100,000 population.[8] Of these, around 26% consisted of MDR/RR-TB, which caused various outbreaks in both the community and health care facility settings.[8–10] In addition, XDR-TB was decided as a dangerous communicable disease in Thailand.[11]

On 31 May 2019, the Department of Disease Control (DDC) received notification of a newly identified confirmed XDR-TB case in Bangkok. The DDC and the Public Health Nurse Division conducted a joint investigation during 31 May to 6 Jun 2019. The objectives of the investigation were to verify the diagnosis, describe clinical and epidemiological characteristics of the case, identify possible source cases and secondary cases, and provide recommendations for disease control.

Methods

Descriptive Study

A descriptive study was conducted among the index case, contacts and possible source case(s) by interviewing and reviewing medical records. The case and contact definition followed National Tuberculosis (NTB) Control Programme guidelines, which are shown in Table 1.[12] A possible source case is a contact who had been diagnosed with TB within two years prior to the index case's symptoms onset.

Table 1. Definition of tuberculosis cases and contacts

Type	Definition
Tuberculosis case	
Presumptive case	A person who met at least one of the following criteria: (i) cough ≥2 weeks (ii) hemoptysis (iii) cough <2 weeks plus fever or unexplained weight loss
Probable case	A person diagnosed with tuberculosis and treated with tuberculosis drugs but with no bacteriologically confirmed laboratory results.
Confirmed case	A person with bacteriologically confirmed tuberculosis based on laboratory results.
Contact	
Contact	All persons with a history of contact with the index case during 3 months before the index case developed symptoms to 2 weeks after adequate treatment
Household contact	A person living with the index case within the same place of residence.
Close contact	A person who associated, socialized or interacted with the index case for more than 8 hours per day or 120 hours per month but did not live in the same house

Face-to-face interviews were conducted using a semi-structured questionnaire of Thailand's tuberculosis case investigation form-02 and -03 for TB cases and contacts, respectively.[13] For the case, data collected included demographic characteristics, past and present illnesses and a list of possible source cases and contacts. In addition, the risk of developing DR-TB and potential strategies to combat this risk was evaluated using a patient-centered approach (PCA), which is a method for quality improvement of TB treatment recommended by World Health Organization and the Thai Division of Tuberculosis.[12,14] PCA can be defined as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions".[14] For contacts, data collected included demographic characteristics, contact category (household or non-household), and underlying diseases and symptoms.

Environmental Study

We conducted an environmental study at the index case's house, workplaces and affected TB-clinics using face-to-face interviews and direct observation. For the index case's house, we directly observed the type of building and physical structure, sputum disposal locations, and presence of air ventilation. For workplaces, we interviewed personnel concerning the type of activity, duration of employment, health screening, and number of co-workers and position, and observed the index case's working zone and presence of air ventilation. For TB-clinic, we interviewed personnel concerning clinic workflow, type, and number of health care providers. The temperature and relative humidity of all TB stockpiles were recorded using a standard thermohydrometer, three times per day, at 9:00 AM, 12:00 AM and 3:00 PM during 6 to 10 Oct 2019.

Laboratory Study

Chest radiography was done among all contacts. If any abnormality of chest imaging was detected, sputum for TB and DR-TB using GeneXpert MTB/RIF was performed.[15] In order to assess the active ingredients and dissolution of tuberculosis drugs in the TB clinic, we purposively collected the oldest batch of first-line TB drugs from a selected stockpile and sent it to the Bureau of Drug and Narcotic, Department of Medical Sciences for processing.[16]

Results

Descriptive Study

Index case description

The index case was diagnosed with XDR-TB in Bangkok and reported to the DDC on 31 May 2019. The case was a 36-year-old Thai male living in Bangkok with a history of MDR-TB. He had health insurance under the Universal Coverage Scheme and was registered at his home town (400 kilometers from Bangkok).[17]

In July 2011, he visited a private hospital after experiencing unexplained weight loss and was diagnosed with TB based on chest imaging without an acid fast bacilli (AFB) test or drug susceptibility test (DST). After two months of medication prescription, he was lost to follow up.

In April 2012, his symptoms worsened and, after visiting a general practitioner, he was referred to a TB clinic. He reported that at the TB clinic, the multidisciplinary team, which used a patient-centered approach, could support him by increasing his awareness and improving his understanding on the importance of treatment.

In May 2012, based on his first DST, his disease was found to be resistant to first-line drugs. He was diagnosed with MDR-TB and was prescribed five TB drugs of which only two, namely kanamycin and ethionamide, were active. One year later, he obtained culture conversion and was treated monthly for another six months. At the end of this treatment, he had had treatment for a total of 45 months, meaning that his final status was "completed treatment".

On 16 May 2019, he re-visited the same TB clinic due to chronic cough and was diagnosed with relapsed TB by positive sputum AFB results.

On 31 May 2019, he was diagnosed with XDR-TB. However, he was not hospitalized until 5 June due to problems with his health insurance. During the admission period, patient-centered approaches were not performed.

Results of the DST, diagnosis, drug regimens received and critical points at each treatment place are shown in Table 2.

Table 2. Timeline of index case from medical record review showing place of treatment, drug sensitivity test, diagnosis, drug regimen and critical points

	July 2011	April 2012	May 2012	October 2014	May 2019
Place of Treatment	Private Hospital D	TB-clinic	TB-clinic	TB-clinic	TB-clinic
DST (Resistant to)	No initial AFB No DST	I, R, Z, Ofx, PAS	I, R, Z, Ofx, PAS, Lfx	Sputum negative for 6 months	I, R, FQs, AG/CP (Genotypic DST)
Diagnosis	New TB	MDR-TB	MDR-TB	Improved	XDR-TB
Treatment	I, R, Z, E	Km, Eto, Ofx[a], PAS[a], Z[a]	Km, Eto, Ofx[a], PAS[a], Z[a]	Discontinue drug	Start XDR regimen
Critical points	No initial AFB and DST No PCA -> poor compliance	Inappropriate diagnosis Inadequate drug regimen	Inadequate drug regimen		Delayed hospital admission process due to health insurance problem

Note: [a]TB drugs that the patient received while already being resistant to them. I: Isoniacid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutal, PAS: Para-aminosalicyclic acid, Ofx: Ofloxacin, Lfx: Levefloxacin, Eto: Ethionamide, Km: Kanamycin (Km), PCA: Patient-centered approach, FQs: Fluoroquinolones, AG/CP: Aminoglycosides/Cyclic polypeptide

Identification of contacts and possible source case

There were 21 reported contacts, as shown in Table 3. We screened 13 of these, all three household contacts and 10 of the 18 close contacts. Only one of his four close friends were screened because he preferred not to tell them all due to fear of stigmatization and some of his old contacts during his first episode of TB were not contactable. However, no additional case among the screened contacts was detected. All had normal chest imaging and no abnormal symptoms. Therefore, sputum GeneXpert MTB/RIF was not performed.

Table 3. Contact screening of index case and demographic characteristics of contacts

Type of contact (number)	No. of contacts screened (%)	Median age (range)
Household contacts (3)	**3 (100%)**	**11 (4–34)**
Close contacts (18)	**10 (56%)**	**34 (22–44)**
• 2009–2014 colleagues (10)	6 (60%)	32 (26–44)
• 2015–2019 employees (4)	3 (75%)	26 (22–30)
• 2009–2019 friends (4)	1 (25%)	35

For possible source case, two suspected persons were identified, both from a restaurant where the index case worked. The first case was a 26-year-old male co-worker, treated at the TB clinic. He was diagnosed

with DS-TB in 2005 and MDR-TB in late 2005. His illness persisted during 2005–2013. While working at the restaurant in 2009, his sputum culture remained positive with a high concentration of the Mycobacterium organism. He worked in the kitchen with the index case for almost two years, spending more than eight hours per day together in close proximity.

The second case was a male co-worker who the index case reported having a chronic cough during 2009–2011. He died from TB (presumptive) in 2011. However, we could not identify the hospital or clinic where he was diagnosed or treated and therefore could not review his medical record.

Environmental Study

Index case house

The house of the index case was a two-story townhouse consisting of two bedrooms and two bathrooms, one bedroom had an air-conditioner, and each had two windows which were rarely opened. The index case reported that he usually disposed of his sputum in the toilet bowl.

Previous workplace (2009–2015)

From 2009 to 2015, the index case worked at a restaurant where his major duties involved preparing and cooking food in the kitchen, which had an air-conditioner. His workspace was located next to an MDR-TB patient's workspace (approximately two meters away). From an interview with the restaurant owner, health screening was not provided for restaurant employees until 2012.

Current workplace (2015–2019)

The index case's main work activities involve preparation of ingredients at his house and distribution of ingredients to vendors under his employment.

TB-clinic

This clinic was a major public TB clinic located in Bangkok. It consisted of two outpatient department (OPD) rooms and one directly observed treatment (DOT) room. All three rooms had adequate natural air ventilation. More than 20 multidisciplinary health care providers were employed. The clinic serviced approximately 50 TB cases per day.

Three medication stockpiles were identified: a main stockpile, an OPD stockpile and a DOT stockpile. The main stockpile was kept in a room with adequate temperature (<30°C) and humidity control (<60%). It contained most of the TB drugs including second-line drugs which were transferred to the OPD stockpile once a month. The OPD stockpile was stored in a room with an air-conditioner which was turned on only during working hours. It stocked TB drugs for six months without temperature or humidity control. The DOT stockpile was a medication stockpile for DOT which was transferred from the OPD stockpile once a week. It was stored in a room without temperature and humidity control. Relative humidity and temperature ranged from 36–55% and 24.4–27.0°C, 44–54% and 25.0–29.4°C, and 45–64% and 27.2–33.5°C in main, OPD and DOT stockpile, respectively. For drug quality, samples of active ingredients and dissolution were all within normal levels (Table 4).

Table 4. Environmental and Laboratory study of quality of four different drugs from OPD stockpile

Drug	Environmental Study			Laboratory Study	
	Detail of samples / storage duration at OPD stockpile (suggested duration)	Storage at OPD stockpile		Standard Identification[2]	
		Temp (Standard Level)	Humidity (Standard Level)	Concentration (Normal range)	Dissolution
Rifampin	In Packages / 3 months (<1 month)	During 6–10 October, Working hour 25.0–29.4°C (<30°C)	During 6–10 October, Working hour 44–54% (<60%)	97.4 (90.0–110.0% la.)	Passed
Isoniazid	In Bottles / 3 months (<1 month)			98.6 (90.0–110.0% la.)	Passed
Ethambutol	In Packages / 3 months (<1 month)			96.5 (95.0–105.0% la.)	Passed
Pyrazinamide	In Packages / 5 months (<1 month)			99.7 (93.0–107.0%% la.)	Passed

Note: % la.: % label claim

Action Taken

Five days after confirmation of XDR-TB, the index case was admitted to a hospital and started on a regimen two days later. He remained in hospital for two months until sputum conversion. After discharge, he attended the TB clinic and opted for DOT at a healthcare service near his home. We suggested to his wife to clean the entire house thoroughly, change the bedding set regularly, open the windows every day to improve air ventilation, and identify a proper sputum disposal area. We planned to follow up the contacts every six

months for the next two years and encouraged them to see a doctor if suspicious symptoms developed. At the TB clinic, we advised health personnel to monitor the temperature and humidity levels of all stockpile rooms.

Discussion

This DR-TB investigation illustrated several gaps in TB control in Thailand. Here, we discuss the TB control gaps in four perspectives including; patient perspective (risk of developing DR-TB), healthcare provider perspective (lack of DST during first period of treatment and inadequate treatment), TB clinic and health system (inadequate drug storage and problem with health insurance), and employer perspectives (pre-working health screening and sick leave).

From the patient perspective, the index case had a history of working with a confirmed DR-TB case which was a risk factor for DR-TB.[18] Infection with MDR-TB had a direct impact on the poor end-of-treatment outcome.[19] Another contributing factor was that he was a relapsed case who had a history of having taken TB drugs in the past.[20] Moreover, his poor drug adherence during the initial treatment period could be one of the factors associated with DR-TB.[21–23] In Bangkok, the rates of lost to follow-up and relapse were higher than the national level during 2016–2019.[24] Lost to follow-up might be the result of associated factors such as remoteness of an accommodation to the nearest healthcare facility, living in an urban area and having a regular occupation, which were factors found in this case.[25,26] Moreover, lost to follow up is known to be associated with poor drug adherence and relapse, which are known key risk factors for developing secondary DR-TB.[21] PCA performed by a multidisciplinary team at the TB clinic appeared to improve his drug compliance and adherence to follow up. However, the PCA approach can only be well-organized in TB clinics which have a large number of healthcare providers and is not isolated from a medicine dispensary and family medicine unit.[27,28]

From the health care provider perspective, we could not determine whether the index case was a primary or secondary DR-TB case due to a lack of DST during the first period of treatment. This issue was also mentioned in a previous case investigation.[29] DST can provide a definitive diagnosis and proper treatment of DR-TB, which can improve the treatment success rate.[30] In addition, the index case received the adequate dosage and duration of TB drugs, but his disease was resistant to two drugs during the MDR-TB treatment period. According to NTB and the U.S. Centers for Disease Control and Prevention recommendations, patients should receive at least four different drugs that are active against tuberculosis.[31,32] Therefore, the index case received an inadequate drug regimen during his MDR-TB treatment period. Inadequate drug treatment for MDR-TB could amplify XDR strains (secondary XDR-TB), which could eventually be transmitted to contacts, who then develop primary XDR-TB.[22,23,29,33]

From the health system perspective, drug quality is another risk factor explored in this study. In the TB clinic the room containing the DOT stockpile during the day-time had inadequate temperature and humidity levels, which could affect the quality of drugs leading to treatment failure.[34–39] Nevertheless, the concentration and dissolution of all drugs tested among the standard TB regimen were within normal ranges based on independent laboratory tests. Despite the fact that XDR-TB patients are designated by law to be isolated with compulsory hospitalization, the identification process of the hospital in isolating the index case and providing timely treatment was delayed due to a health insurance issue.[2] This can lead to further problems including treatment failure and disease spreading.[18,21,27,40]

From the employer perspective, of the two possible source cases, one co-worker did not leave his job during the period when the index case was still working at the restaurant. His sputum culture remained positive which could increase the risk of transmission to the index case.[18] According to NTB guidelines, patients should leave their job until sputum conversion occurs in order to prevent disease transmission.[13] Furthermore, the co-worker did not have chest imaging performed before beginning their employment in the restaurant. All employees should have adequate health checks before starting employment.[41]

Limitations

Firstly, we could not interview the first of the two possible sources. However, a two-year period of daily and prolonged contact with the index case and the high concentration of Mycobacterium organism meant that he was the most likely source of infection. Secondly, we could not interview all contacts of the index case due to insufficient contact information. Thirdly, we did not have information why the first doctor did not take DST during his first visit and the other doctor prescribed four drugs that only two drugs were active during his treatment for MDR-TB. And lastly, we could not perform any tests on MDR-TB or XDR-TB drugs, which are known to degenerate more quickly than the standard TB drugs and evaluate the temperature and humidity of the stockpile rooms during the night-time.[42]

Recommendations

For National TB Control Agency

A number of recommendations can be made from the results of our investigation. Firstly, identification and clarification of the health insurance status of TB cases, especially DR-TB cases, and an additional consensus on the healthcare facilities available for admission of index cases who lack health insurance, are needed. Secondly, sputum specimens, especially among DR-TB cases, should be kept until completion of treatment. Thirdly, encouraging an annual health check-up policy, including chest imaging, among employees and workers should be reemphasized. Strengthening the patient-centered approach, not only to DR-TB patients but also to those with DS-TB, is suggested, contingent on the availability of human resources. Lastly, enhancing the co-operation between TB clinics and family medicine units is recommended.[14,28]

For Tuberculosis Clinics

Appropriate diagnostic methods, including a requirement to perform AFB testing and DST, and the prescription of appropriate drug regimens, especially among DR-TB patients, should be reemphasized to attending physicians.[12,13] Establishing a protocol to reassure physicians of the appropriate diagnosis and drug regimen is also suggested. Additionally, the humidity and temperature of stockpile rooms should be checked regularly. Lastly, an adequate sick leave period for all new TB cases should be reemphasized to attending physicians.

Conclusion

We identified a TB outbreak involving three cases, including one confirmed XDR-TB (index case) and two possible source cases who were co-workers of the index case. No TB was detected among any of the index case's contacts. Close and prolonged contact with a confirmed DR-TB case, poor drug compliance, and prescription of an inappropriate drug regimen were factors related to XDR-TB development. Early clarification of health insurance status, provision of an adequate sick leave period, use of a patient-centered approach, and regular monitoring of standard TB drug stockpiles are strongly recommended.

Acknowledgements

We would like to acknowledge the support from Dr. Petchawan Pungrassami, Senior Expert in Preventive Medicine from the Department of Disease Control, Division of Tuberculosis, the Institute of Urban Disease Control and Prevention, Bamrasnaradura Infectious Disease Institute, the Drug and Narcotic Division in the Department of Medical Sciences, and the Public Health Nurse Division, Bangkok.

Suggested Citation

Wongsanuphat S, Jitpeera C, Suwanchairob O, Theprongthong W, Tantiworrawit P, Thammavijaya P. An investigation of extensively drug-resistant tuberculosis: revealing potential improvements for tuberculosis control program. OSIR. 2022 Sep;15(3):91–8.

References

1. World Health Organization. Tuberculosis (TB) [Internet]. World Health Organization; [cited 2019 Nov 8]. <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>
2. Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martin-Casabona N, et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis. 2007;13(3):380–7.
3. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: The new XDR-TB threat. Is "science" enough to tackle the epidemic? Eur Respir J. 2007;29(3):423–7.
4. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, et al. Global incidence of multidrug-resistant tuberculosis. J Infect Dis. 2006 Aug 15;194(4):479–85.
5. Matteelli A, Migliori GB, Cirillo DM, Centis R, Girardi E, Raviglione MC. Multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis: epidemiology and control. Expert Rev Anti Infect Ther. 2007 Oct;5(5):857–71.
6. World Health Organization. Drug-resistant TB: XDR-TB FAQ [Internet]. Geneva: World Health Organization; 2018 [cited 2019 Nov 8]. <https://www.who.int/tb/areas-of-work/drug-resistant-tb/XDR-TB-faq/en/>
7. World Health Organization. TB drug resistance types [Internet]. Geneva: World Health Organization; 2015 [cited 2019 Nov 8]. <https://www.who.int/tb/areas-of-work/drug-resistant-tb/types/en/>
8. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. 231 p.

9. Jiraphongsa C, Wangteeraprasert T, Henpraserttae N, Sanguanwongse N, Panya L, Sukkasitvanichkul J, et al. Community outbreak of multiple drug resistance tuberculosis, Kanchanaburi province, Thailand on 2002–June 2010. Journal of Preventive Medicine Association of Thailand. 2011 Sep–Dec;1(3):261–71. Thai.

10. Oeltmann JE, Varma JK, Ortega L, Liu Y, O'Rourke T, Cano M, et al. Multidrug-resistant tuberculosis outbreak among US-bound Hmong refugees, Thailand, 2005. Emerg Infect Dis. 2008 Nov;14(11):1715–21.

11. Communicable disease act B.E. 2558 (2015), Royal Thai Government Gazette [English version on the Internet], Volume 132, part 86 Kor (Dated 2015 Sep 8) [cited 2019 Nov 8]:26–44. <https://ddc.moph.go.th/uploads/ckeditor/c74d97b01eae257e44aa9d5bade97baf/files/001_2gcd.pdf>

12. National Tuberculosis control programme guidelines, Thailand, 2018. Bangkok: Division of Tuberculosis, Department of Disease Control; 2018. 120 p.

13. Tuberculosis investigation and control guidelines, Thailand, 2018. Bangkok: Division of Tuberculosis, Department of Disease Control; 2018. 80 p.

14. World Health Organization. A patient-centred approach to TB care [Internet]. Geneva: World Health Organization; 2018 [cited 2019 Nov 17]. 2 p. <https://apps.who.int/iris/bitstream/handle/10665/272467/WHO-CDS-TB-2018.13-eng.pdf?ua=1>

15. Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention. A new tool to diagnose tuberculosis: the Xpert MTB/RIF assay [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2020 Apr 11]. 2 p. <https://www.cdc.gov/tb/publications/factsheets/pdf/xpertmtb-rifassayfactsheet_final.pdf>

16. Pharmapproch. Quality control tests for tablets [Internet]. [place unknown]: Pharmapproach.com; 2019 [cited 2019 Oct 23]. <https://www.pharmapproach.com/quality-control-tests-for-tablets/>

17. Sumriddetchkajorn K, Shimazaki K, Ono T, Kusaba T, Sato K, Kobayashi N. Universal health coverage and primary care, Thailand. Bull World Health Organ. 2019 Jun 1;97(6):415–22.

18. Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention. Tuberculosis: Drug-resistant TB [Internet]. Atlanta: Centers for Disease Control and Prevention; 2017 [cited 2018 Jun 10]. <https://www.cdc.gov/tb/topic/drtb/default.htm>

19. Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Byrnes G, et al. Tuberculosis recurrence and mortality after successful treatment: Impact of drug resistance. PLoS Med. 2006 Oct;3(10):e384. doi:10.1371/journal.pmed.0030384.

20. Bestrashniy JRBM, Nguyen VN, Nguyen TL, Pham TL, Nguyen TA, Pham DC, et al. Recurrence of tuberculosis among patients following treatment completion in eight provinces of Vietnam: A nested case-control study. Int J Infect Dis. 2018 Sep [cited 2020 Apr 11];74:31–7. <https://www.sciencedirect.com/science/article/pii/S1201971218344485>

21. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaout I, et al. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. BMC Pulic Health. 2011 Feb 28;11:140.

22. Raviglione MC, Smith IM. XDR tuberculosis—implications for global public health. N Engl J Med. 2007 Feb 15;356(7):656–9.

23. Ebrahim GJ. Drug resistance in tuberculosis. J Trop Pediatr. 2007 Jun;53(3):147–9.

24. Division of Tuberculosis. Tuberculosis Case Management [Internet]. Bangkok: Division of Tuberculosis, Department of Disease Control; [cited 2019 Dec 15]. <https://tbcmthailand.ddc.moph.go.th/uiform/>

25. Santos E, Felgueiras O, Oliveira O, Duarte R. Factors associated with loss to follow-up in Tuberculosis treatment in the Huambo Province, Angola. Pulmonology. 2019 May–Jun;25(3);190–2.

26. Abubakar I, Lipman M. Reducing loss to follow-up during treatment for drug-resistant tuberculosis Ibrahim. Eur Respir J. 2019 Jan 10;53(1):1802268.

27. McMullen CK, Safford MM, Bosworth HB, Phansalkar S, Leong A, Fagan MB, et al. Patient-centered priorities for improving medication management and adherence. Patient Educ Couns. 2015 Jan;98(1):102–10.

28. Gargioni, G. Role of communities in tuberculosis care and Prevention [Internet]. [place unknown]: Z-Library; 2009 [cited 2019 Nov 19]. p. 660–7. doi:10.1016/b978-1-4160-3988-4.00064-0.

29. Araujo-Filho JA, Vasconcelos AC Jr, Sousa EM, Silveira Cd, Ribeiro E, Kipnis A, et al. Extensively drug-resistant tuberculosis: a case report and literature review. Braz J Infect Dis. 2008;12(5):447–52. doi:10.1590/s1413-86702008000500019.

30. World Health Organization. Implementing tuberculosis diagnostics: a policy framework [Internet]. Geneva: World Health Organization; 2015 [cited 2020 Jan 3]. <https://apps.who.int/iris/handle/10665/162712>

31. Reechaipichitkul W, Netniyom S, Pungrassami P, editors. Guideline for programmatic management of drug-resistant tuberculosis. Bangkok (TH): Division of Tuberculosis, Department of Disease Control; 2015 May. 97 p. Thai.

32. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR Recomm Rep. 1998 Oct 30;47(RR-20):1–58.

33. Lawn SD, Wilkinson R. Extensively drug resistant tuberculosis. BMJ. 2006 Sep 16;333(7568):559–60.

34. Cao K, Yang K, Wang C, Guo J, Tao L, Liu Q, et al. Spatial-temporal epidemiology of tuberculosis in Mainland China: An analysis based on bayesian theory. Int J Environ Res Public Health. 2016 May 5;13(5):469.

35. Onozuka D, Hagihara A. The association of extreme temperatures and the incidence of tuberculosis in Japan. Int J Biometeorol. 2015 Aug;59(8):1107–14.

36. Rao HX, Zhang X, Zhao L, Yu J, Ren W, Zhang XL, et al. Spatial transmission and meteorological determinants of tuberculosis incidence in Qinghai province, China: A spatial clustering panel analysis. Infect Dis Poverty. 2016 Jun 2;5(1):45.

37. Yanagawa H, Hara N, Hashimoto T, Yokoyama H, Tachibana K. Geographical pattern of tuberculosis and related factors in Japan. Soc Sci Med Med Geogr. 1981 Feb;15(1):141–8.

38. World Health Organization. Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union [Internet]. Geneva: World Health Organization; 2012 Feb 4 [cited 2019 Nov 11]. <https://www.who.int/news/item/04-02-2012-survey-of-the-quality-of-anti-tuberculosis-medicines-circulating-in-selected-newly-independent-states-of-the-former-soviet-union>

39. Burugina Nagaraja S, Satyanarayana S, Chadha SS, Kalemane S, Jaju J, Achanta S, et al. How do patients who fail first-line TB treatment but who are not placed on an MDR-TB regimen fare in South India? PLoS ONE. 2011 Oct 11;6(10):e25698. doi:10.1371/journal.pone.0025698.

40. Reid MJA, Goosby E. Patient-centered tuberculosis programs are necessary to end the epidemic. J Infect Dis. 2017 Nov 6;216(Suppl 7):S673–4.

41. Ministerial regulations: the criteria and procedure for medical examination of employees, and submission of examination result to Labor Official, B.E. 2547 (2004), Royal Thai Government Gazette Volume 122, part 4 Kor (Dated 2005 Jan 13):19–22. <http://www3.mol.go.th/sites/default/files/laws/th/00151640.pdf>

42. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014. 403 p.