



## Outbreak, Surveillance and Investigation Reports

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### Identification of a Tuberculosis Cluster through Epidemiological and Geographical Tracing of a Patient with Multidrug-resistant Tuberculosis in Lopburi Province, Thailand, 2014

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#### Abstract

In May 2014, a suspected multidrug-resistant tuberculosis (MDR-TB) outbreak in Lopburi Province was investigated following the national guidelines for tuberculosis (TB) outbreak investigation and assessed the quality of patient care based on the International Standards for TB Care. The case finding focused on TB cases diagnosed during December 2012 to August 2014. Medical charts were reviewed at Khok Samrong Hospital and contacts of a MDR-TB case who was lost to follow up were traced back. Study findings found an epidemiologically linked cluster of TB cases with five geographically related cases and four cases were from the same family. Factors that might have contributed to this TB outbreak were identified as well, including delay in diagnosis and sub-standard care, low socioeconomic status, delay in conducting contact tracing, and an ineffective TB database system. Diagnosis, treatment and prevention activities should be improved to prevent further TB outbreaks in the communities.

**Keywords:** tuberculosis, multidrug-resistant, contact tracing, quality of care, Thailand

#### Introduction

Tuberculosis (TB) is an airborne infectious disease that can be transmitted by the bacterium *Mycobacterium tuberculosis*.<sup>1</sup> In 2015, Thailand was ranked in the top 22 high TB burden countries.<sup>2</sup> Multidrug-resistant TB (MDR-TB) is caused by a TB bacterium that is resistant to at least isoniazid and rifampicin, the two most potent first-line drugs for TB infection.<sup>3</sup> According to the information from Supranational Reference Laboratory in Thailand, MDR-TB was found among 2.0% of new cases and 18.8% of previously treated cases in 2012.<sup>4</sup>

During 2005, among immigrants in the United States, four MDR-TB cases who were Hmong refugees migrated from a refugee camp in Lopburi Province of Thailand were identified. Tracing back and screening

of 15,455 refugees in the camp resulted in 272 TB cases; of which, 24 (42.1%) out of 57 samples were MDR-TB.<sup>5</sup> Following another MDR-TB outbreak in 2010 which affected 15 cases in a community from the western part of Thailand<sup>6</sup>, the first national guideline for investigation of TB outbreaks was developed. The guideline recommends performing an investigation when there are at least two TB patients who share the same place or activity during a 3-month period; or at least one new or relapse MDR-TB case; or at least one extensively drug-resistant TB (XDR-TB) case in the community.<sup>7</sup> The guideline also suggests five steps for completing an investigation of a TB outbreak: first, perform a case review for diagnosis and outbreak verification; second, identify source and/or contact cases, and collect laboratory and environmental samples; third, conduct a descriptive

study of the outbreak; fourth, test the hypothesis for mode of transmission, source of infection and determine risk factors; and fifth, recommend specific control and prevention measures. At the national level, the Bureau of Tuberculosis and the Field Epidemiology Training Program in the Bureau of Epidemiology follow the guideline in respond to TB outbreaks. However, at the provincial and district levels, this guideline was not widely used or followed in a systematic way.

In May 2014, a MDR-TB patient from Khok Samrong Hospital in Lopburi Province had been lost to follow up for a year and currently, one of his family members and a neighbor were found to have TB. Hence, a joint investigation team from Bureau of Tuberculosis, Bureau of Epidemiology, Thailand MOPH - US CDC Collaboration, Office of Disease Prevention and Control for Region 4, Lopburi Provincial Health Office, Khok Samrong Hospital, and Dong Marum Health Promoting Hospital initiated an investigation to verify a possible MDR-TB outbreak following the national guideline on TB outbreak investigation and assess the quality of patient care based on the International Standards for TB Care (ISTC)<sup>8</sup>.

## Methods

After notification of the MDR-TB patient in May 2014, information was reviewed and consulted between the local health personnel and the central teams. A descriptive epidemiological study was conducted on 28-29 Aug 2014. Diagnosis of the notified patient (Patient B) was confirmed to be MDR-TB by drug susceptibility result at the TB clinic in Phuket Province. An investigation was carried out to identify the source and contacts of Patient B using case and contact record forms following the national guideline<sup>7</sup>.

## Case Finding

The case finding focused on the TB cases that were diagnosed during December 2012 to August 2014 in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province. In addition, medical charts in Khok Samrong Hospital were reviewed according to the standard forms described in the national guideline<sup>7</sup>.

A suspected TB case was defined as a person living in the same village with an index/source case and had a cough lasting two weeks or more, or hemoptysis, or at least two of the following symptoms: cough less than two weeks, fever, weight loss and abnormal night sweats during 2012 to 2014. A probable TB case was a suspected case who had an abnormal finding in chest X-ray compatible with TB and did not improve

after treatment with antibiotics for two weeks. A confirmed TB case was a person who was diagnosed as TB by sputum smear, culture, or molecular testing such as Xpert MTB/RIF and line probe assay.

Latent TB infection (LTBI) is a state of persistent immune response to stimulation by *M. tuberculosis* antigens without clinical manifestation of active TB disease. The diagnosis is based on a positive result of either a skin (tuberculin skin test) or blood (interferon-gamma release assay) test, indicating an immune response to *M. tuberculosis* with negative mycobacteriological test of *M. tuberculosis*<sup>8</sup>. An MDR-TB case was a patient who had laboratory-confirmed *M. tuberculosis* resistance at least to isoniazid and rifampicin. Probable and confirmed (TB and MDR-TB) cases were regarded as cases in this study.

An index case was defined as a confirmed or suspected case of new or recurrent TB infection first identified in a specific household or workplace. A source case was defined as a case or a person who might be the source of TB infection for index cases and secondary cases. In this investigation, Patient B could not be traced back; therefore, contact tracing was initiated from Patient A (father of Patient B).

## Contact Tracing

A contact list of Patient A, containing information such as place and duration of contact, was created. Types of contact included household members and close contacts. Household contacts were those who shared the same enclosed living space with Patient A for one or more nights. Close contacts were people who were not in the household, yet shared an enclosed space with a TB patient for extended periods (>8 hours/day or >120 hours/month)<sup>1</sup>. The team then interviewed all the names on this list. To assess the possibility of TB transmission in the community, patients were asked about their social links to other persons and genograms were generated.

Data were analyzed and collated, including demographic information, date of onset and treatment, clinical characteristics, laboratory results, treatment outcome, and clinical and laboratory information of contacts. Attack rates among household and close contacts were calculated using number of probable and confirmed TB cases as the numerator and number of all household contacts and close contacts as the denominator.

## Laboratory Testing

Sputum specimens were collected from four household contacts and submitted for molecular testing using Xpert MTB/RIF assay at the National

TB reference laboratory in Bangkok. The Xpert MTB/RIF assay was approved by the World Health Organization in 2013 to diagnose pulmonary and extra pulmonary specimens in adults and children<sup>9</sup>. This assay is a rapid and polymerase chain reaction (PCR)-based TB diagnostic test that was being incorporated into the recommendations for diagnosing MDR-TB in programmatic settings of Thailand.

The Xpert MTB/RIF can be used to identify both the presence of *M. tuberculosis* and rifampicin resistance in less than two hours. It has high sensitivity and specificity for both smear-positive and smear-negative diseases.<sup>10,11</sup> Any specimen diagnosed as rifampicin-resistant TB by Xpert MTB/RIF would additionally be confirmed as MDR-TB by line probe assay at the national TB reference laboratory.

Line probe assay is a deoxyribonucleic acid strip assay that uses PCR and hybridization to detect genetic mutations in specific genes that confer rifampicin-resistance and isoniazid-resistance from *M. tuberculosis* cultured isolates and acid-fast bacilli (AFB) smear positive specimens. A published case series of TB patients in Thailand confirmed that mutations in the *rpoB* gene were specific to rifampicin-resistance.<sup>12</sup> Resistance to isoniazid has been demonstrated to be significantly associated with mutations in the *katG*, *inhA* and *ahpC* genes.<sup>13</sup> It has been proven to diagnose MDR-TB within 24 hours in several controlled laboratory studies.

**Assessing Quality of Care**

Informal interviews were carried out with Patient B’s family members and neighbors about their treatment experiences, how they took medication and cared for themselves, and basic knowledge of TB. Information obtained from interview and records review were used to assess the quality of care by four dimensions (diagnosis, treatment, TB co-infection with human immunodeficiency virus (HIV) and other co-morbid conditions, and public health and prevention) as stated in the ISTC guidelines<sup>14</sup> as well as explore the impact of TB on socioeconomic status.

At the end of the investigation, preliminary results were disseminated and practical recommendations were provided to the local health care staff and all stakeholders. A report was also submitted to the Provincial Health Office and the Department of Disease Control, Ministry of Public Health.

**Results**

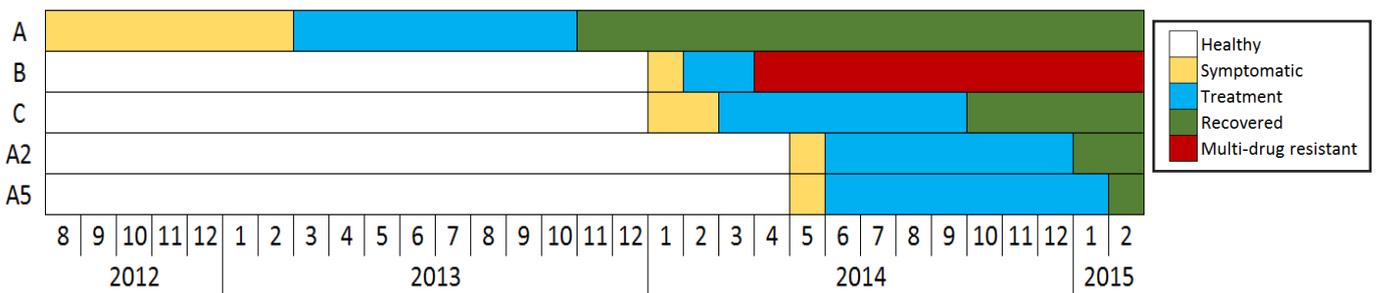
The case investigation revealed five TB cases from a cluster with epidemiological and geographical linkage, including three confirmed cases (Patients A, B and C) identified by reviewing medical records in the TB clinic of Khok Samrong Hospital during February 2013 and June 2014, and two more probable cases discovered in Patient A’s family through contact tracing. Evidence from the investigation implied that Patient A was likely to be the source and spread the disease to the other four cases as he was the first one who developed the symptoms one year earlier than others (Figure 1).

**Case Description**

Patient A was the first TB case in this outbreak. He started to have TB symptoms while staying with his son (Patient B) in Phuket during August 2012. Patient A returned to Lopburi in February 2013, and was diagnosed with TB and received treatment there. In January 2014, Patient B was diagnosed with TB and started treatment in Phuket. After receiving treatment for two months, results of his sputum AFB still revealed 3+. Patient B went to Lopburi during the second month of TB treatment to visit his mother who developed acute respiratory failure with suspected TB and eventually died. After his mother’s funeral, Patient B returned to Phuket, yet did not visit the hospital again for TB treatment.

**Contact Tracing**

As Patient B’s sputum was tested to have *M. tuberculosis* resistant to isoniazid and rifampicin, TB clinic staff in Phuket tried to contact him. However, he could not be traced back for further investigation since the TB database systems across the country



**Figure 1. Timeline of confirmed (Patients A, B and C) and probable (Patients A2 and A5) TB cases in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2012-2014**

were not properly linked. Nonetheless, his deceased mother was suspected of having TB and his father was diagnosed as having TB. Hence, his father (Patient A) was regarded as the source case and the contact tracing was initiated from Patient A.

The investigation team found eight household contacts (Patients B and A1-7) and three close contacts (A8, A9 and C) of Patient A. Expanding the investigation through a genogram revealed that one of the household contacts (A5) was related to two more household contacts (A5-x and A5-y) who were the parents of A5. Thus, total ten household contacts and three close contacts were identified from Patient A.

Patient C was a confirmed TB case with human immunodeficiency virus (HIV) co-infection. Tracing of Patient C from a separate genogram observed two more household contacts (C1 and C2), however, only one of them (C2) who was staying at home was included in the study (Table 1).

Among all contacts, Patient B was diagnosed with MDR-TB and Patient C was recently confirmed to have pulmonary TB in March 2014. The investigation team found two more probable TB cases: Patient B's son who developed pleural effusion with HIV co-infection (A2), and Patient B's great grandson who had perihilar infiltration based on a chest X-ray (A5).

Assuming that Patient A was the source case, the attack rate of contacts from Patient A was 30.0% (3/10) for household contacts and 33.3% (1/3) for close contacts.

### Social Determinants

The family genograms highlighted the geographical and relationship linkages of a TB cluster. In Patient A's family, early marriages and history of divorce with remarriage were observed. Patient A's house had limited ventilation and lighting, and there were no windows. The house was crowded with eight family members. Patients A5 (aged 3 years) and A6 (aged 1 year with LTBI) stayed in Patient A's house during the day-time while their parents (A5-x and A5-y) who lived in another house went to work. Patient C's house, a noodle shop frequently visited by Patient A, was across the road (Figure 2).

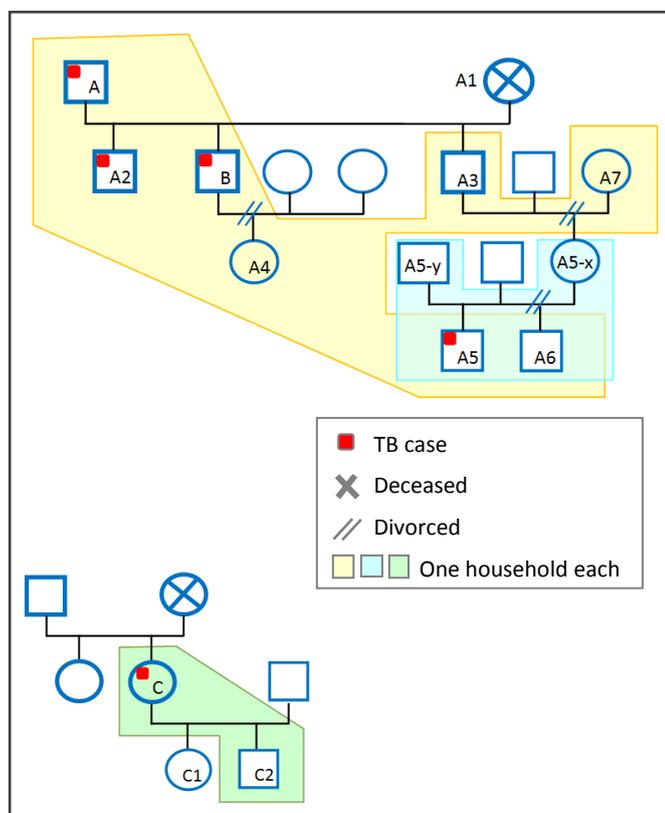
Patient A sought medical care seven months after onset of symptoms. When interviewed, he and his family members had a low education level and lacked of knowledge on TB infection, symptoms and preventive measures such as the wearing of a protective face mask. Patient A perceived that TB could be cured by taking one tablet of a drug per day, could not be transmitted to others, and did not relapse. He was a heavy tobacco smoker and consumed alcohol every day.

**Table 1. List of contacts of Patient A and contact tracing results in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2013-2014**

ID	Status	Age (year)	Result of Acid-fast bacilli	Xpert MTB/RIF Result*
A	Source case, Confirmed TB	65	3+/3+/3+	Not detected
<i>Household</i>				
B	Notified case, Confirmed MDR-TB	35	3+/3+/1+	N/A
A1	Dead (respiratory failure), Suspected TB	59	Not found	N/A
A2	HIV Probable TB	39	Not found	Not detected
A3	TB Negative	33	Not found	Not detected
A4	TB Negative	16	Not found	Not detected
A5	Probable TB	3	Not collected	N/A
A5-x	TB Negative	20	N/A	N/A
A5-y	TB Negative	22	Not found	N/A
A6	Latent TB	1	Not collected	N/A
A7	TB Negative	43	Not found	Not detected
A8	TB Negative	67	Not found	N/A
A9	TB Negative	72	Not found	N/A
<i>Community</i>				
C	Confirmed TB	37	1+/1+/1+	N/A
C1	N/A	18	N/A	N/A
C2	TB Negative	8	N/A	N/A

\*Tested in September 2014

N/A = not available



**Figure 2. Genograms of tuberculosis cases and their contacts in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2014**

### Quality of Care

Quality of patient care was assessed for five TB cases (A, B, C, A2 and A5) in this outbreak. Strengths and weaknesses in the quality of care linked to the ISTC guidelines were observed and compared (Table 2). A delay in diagnosis of TB was found for Patient A and diagnostic testing such as gastric aspirate was not performed to confirm TB in children under five (A5). Taking a sub-optimal dosage of anti-TB drugs by Patient A and misconceptions about TB care were identified as well.

At the end of second and third months of treatment, Patient B had a positive result for *M. tuberculosis* by culture, and resistance to isoniazid and rifampicin by drug susceptibility testing while Patient A had no growth in culture. Patient A was treated for eight months before being cured; however, Patient B traveled to Phuket and Chumphon Provinces, and refused to receive any treatment. In February 2015, Patient B was admitted to Chumphon Hospital with pneumonia and started treatment as an MDR-TB patient in March 2015.

From public health and prevention perspectives, although the staff in the TB clinic conducted the second step of the investigation by interviewing Patient A about household contacts in his family, they did not complete the clinical evaluation process at the

very beginning. However, they performed all steps of contact investigation by June 2014. For TB infection control in Khok Samrong Hospital, the TB clinic was separated from the general out-patient department. There was also a 'fast track' infection control system in the TB clinic for suspected patients. Moreover, all TB cases in this hospital were recorded in an electronic database system and reported in a timely manner.

### Discussion

This outbreak investigation revealed an epidemiologically linked cluster of TB cases. Out of five geographically related cases identified, four cases were from the same family. We found the practices that did not follow the ISTC guidelines which negatively impacted on the quality of patient care. Potential factors contributing to this community TB outbreak were delay in diagnosis of the source case, sub-standard care, low socioeconomic status, delay in conducting contact tracing, and an ineffective national TB database system. Elimination of these contributing factors could help TB-related health personnel achieving their ultimate goal to eliminate TB in the community.

The source case spent six months in a private clinic before being diagnosed with TB. This delay in diagnosis and sub-standard care led to a prolonged period of possible TB transmission. Furthermore, no specimens were collected from the source's two grandchildren, who were diagnosed with probable TB and latent TB infection, and no pediatric anti-TB drug was given to them. Sputum specimens of the source's contacts were sent to Bangkok for Xpert MTB/RIF testing. As Thailand is a middle income country, case finding and diagnosis remain major challenges to TB control. In 2013, the Global Fund and National Health Security Office supported the use of Xpert MTB/RIF and line probe assay for early detection of *M. tuberculosis* and diagnosis of drug resistance in high risk MDR-TB groups, people living with HIV/AIDS and MDR-TB suspected cases<sup>1</sup>. The Xpert MTB/RIF is a rapid test and should be installed at or near the point of care.

However, many challenges existed in district hospitals with limited staff and infrastructure. We recommended the Ministry of Public Health to ensure a good logistics for accurate diagnoses and proper management of TB in district hospitals by allocating up-to-date equipment in TB laboratories.

Therapeutically, there is no evidence to support the efficacy of taking rifampicin for three times a week as recommended by WHO. In addition, a sub-optimal

**Table 2. Comparison between the guideline and actual practices during a tuberculosis outbreak in Village 8, Dong Marum Sub-district, Khok Samrong District, Lopburi Province, Thailand, 2013-2014**

<b>Guideline from the International Standards for Tuberculosis Care<sup>14</sup></b>	<b>Actual practice in a tuberculosis outbreak</b>
<b>Diagnosis (standard 1-3 and 6)</b>	
To ensure early diagnosis, all clinically suspect patients, including children, should be evaluated for tuberculosis (TB).	Patient A did not seek appropriate health care and the provider at a private clinic did not suspect the disease for six months, leading to ongoing transmission.
All patients should have at least two specimens for smear microscopy or one specimen for Xpert MTB/RIF, and all children should have bacteriological confirmation.	All adult patients had at least two specimens. However, no specimen was tested for a pediatric case (Patient A5) since health staff were not familiar with collecting specimens from children.
<b>Treatment (standard 7-11 and 13)</b>	
Prescribe an appropriate regimen. The dose and regimen of anti-TB drugs should conform to the recommendation from World Health Organization.	All adult patients received an appropriate regimen from health care staff (fixed dose combination of HRZE three tablets/day). Patient A5 took rifampicin 25 mg/kg/day three times weekly.
A patient-centered approach to treatment should be developed in order to promote adherence, improve quality of life and relief suffering.	Patients lived with poverty and lack of basic knowledge on TB disease. Though Patient A took medicine every day, he took only one tablet which was considered as sub-optimal.
Response to treatment should be monitored by sputum smear microscopy at the time of completion of the initial phase. Smear-positive cases should be assessed for drug resistance.	Regular follow up with smear microscopy was performed. At the end of third month, if acid-fast bacilli (AFB) was still positive, sputum was sent for culture.
Records of all medication given, bacteriological response, outcomes and adverse reactions should be accessible and systematically maintained.	There were individual folders for each patient and each contained complete information.
<b>Addressing human immunodeficiency virus (HIV) infection and co-morbid conditions (standard 14-15 and 17)</b>	
All providers should conduct a thorough assessment for co-morbid conditions and other factors that could affect TB treatment response or outcome.	Patient A had alcohol dependence and was a heavy tobacco smoker.
HIV testing and counseling should be conducted for all patients. For all patients with HIV and TB, antiretroviral therapy should be initiated within two months.	Patient C received anti-retroviral therapy within two weeks after confirmation for HIV infection by laboratory result.
<b>Public health and prevention (standard 18-21)</b>	
Persons in close contact with patients who have infectious TB should be evaluated and managed in line with the recommendation.	There was no evaluation for contact cases after Patient A was diagnosed with TB.
Children less than five years of age who are close contacts of a person with infectious TB, and who do not have active TB should be treated as presumed latent TB infection.	Children under five were evaluated and treated for TB and latent TB infection, but no pediatric formula was provided.
Each health care facility should develop and implement an appropriate TB infection control plan to minimize possible transmission.	The TB clinic was isolated from the general out-patient department for minimizing possible transmission.
Providers must report about new and relapse cases, and their treatment outcomes to local public health authorities.	Neat and systematic recording and reporting was observed.

HRZE = Isoniazid, rifampicin, pyrazinamide and ethambutol

dosage of anti-TB drugs can lead to drug-resistant strains of *M. tuberculosis*. These problems suggest that both public and private health care systems need more supervision in TB diagnosis, especially in obtaining gastric aspirate in children who have close contact with MDR-TB cases for identifying their drug resistant status. Members of a family with a low socioeconomic status, living in congested and crowded conditions with poor ventilation, and having personal behaviors of smoking may increase susceptibility to TB as well as more negative treatment outcomes<sup>15</sup>.

In 2012, WHO stated that a person with TB could infect up to 10-15 people through close contact over the course of a year.<sup>16</sup> For MDR-TB transmission, a study on household contacts suggested that circulating MDR-TB strains in Peru were less likely to result in the disease among household contacts compared to drug-sensitive strains.<sup>17</sup> A mathematical model demonstrated that even when the most fit MDR-TB strain was assumed to be less fit than the drug-sensitive strain. However, the MDR strain would eventually outcompete the drug-susceptible strain.<sup>18</sup> In our study, the delay in conducting contact tracing increased the likelihood of disease transmission from Patient A. He had only been asked about the number of members in his family and none had been contacted for a clinical evaluation until his son (Patient B) was diagnosed with MDR-TB merely 16 months later. Due to this time lapse, the investigation team could not find additional TB cases and this might have potentially promoted further transmission. Treatment of contacts with latent TB infection is recommended for individuals at increased risk of developing TB such as those with HIV.<sup>19</sup> Therefore, actions should be taken to limit the transmission of not only drug-sensitive strains, but also drug-resistant strains by conducting contact tracing as early as possible and giving treatment to TB cases as a prevention measures.

Lastly, from public health and prevention perspectives, ineffectiveness in the national TB database system allowed Patient B to avoid receiving treatment. At the time of his initial diagnosis, he was not required by law to receive treatment. The stand-alone database system, which was not linked with other surveillance databases, was a major reason behind the fact that other hospitals were not informed about MDR-TB. Implementation of a national-linked database system would enable health care providers to aware of the patient's status and trace the history of all suspected TB cases. Policies and laws should be advocated for regulation of

persons with serious communicable diseases such as MDR-TB.

### Limitations

Two TB cases (Patients B and A2) could not be traced or interviewed. Thus, identification of their contacts was not possible. This probably resulted in under-reporting of actual TB cases in this outbreak. In addition, we used clinical criteria to diagnose TB in two patients (A2 and A5) since the sputum result was cultured negative for one and could not be collected from the other. However, based on the guidelines of Thai National TB Control Programme in 2013<sup>1</sup>, pulmonary TB could be diagnosed with a negative or unknown smear result. In the process of contact tracing, sputum samples from four contacts were sent for molecular testing using Xpert MTB/RIF in order to increase the sensitivity of TB diagnosis and early detection of resistant to rifampicin if TB developed.

### Public Health Recommendations

Our study suggested that there was an opportunity to prevent future TB outbreaks by addressing the short and long-term public health responses to TB. This included improving access to care, upgrading TB laboratory equipment in clinics and hospitals, improving adherence to TB follow up, and advocating an inclusive and shared national database system for tracing TB patients in Thailand. To reduce the transmission of *M. tuberculosis*, the following specific interventions should be implemented. First, community awareness could be raised by promoting social campaigns on important occasions such as the World TB Day. Moreover, regular trainings for all health personnel from both public and private sectors should be provided to improve the quality of care. Conducting a contact investigation for every TB case, especially for MDR-TB, should be the first priority for TB clinics in order to receive accreditation. Lastly, a national database for TB, based on the current system for the National AIDS Programming which facilitates health personnel to track patients for early treatment and follow-up, should be established.

### Acknowledgements

The authors would like to thank the staff from Field Epidemiology Training Program, Thailand. We also appreciate Patama Monkongdee, Michael Martin and TB program staff from the Thailand MOPH – US CDC Collaboration (TUC) for editing the laboratory information. Additionally, we acknowledge the support of the staff from Office of Disease Prevention and Control for Region 4, Lopburi Province, Khok

Samrong Hospital and Dong Marum Health Promoting Hospital. We are also grateful to Dorothy L. Southern (US CDC) for reviewing and editing this manuscript.

### Suggested Citation

Soontornmon K, Aye YM, Phankhor N, Watanatorn S, Modmoltin W, Jiraphongsa C. Identification of a tuberculosis cluster through epidemiological and geographical tracing of a patient with multidrug resistant tuberculosis in Lopburi Province, Thailand, 2014. OSIR. 2017 Jun;10(2):14-22.

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