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Prevalence and associated risk factors of drug-resistant tuberculosis in Thailand: results from the fifth national anti-tuberculosis drug resistance survey

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Abstract

OBJECTIVE To assess the prevalence and risk factors of drug-resistant tuberculosis (TB), the fifth national anti-TB drug resistance survey was conducted in Thailand.

METHODS A cross-sectional study was conducted by stratified cluster sampling with probability proportional to size of TB cases from public health facilities in 100 clusters throughout Thailand from August 2017 to August 2018. Susceptibility testing of TB isolates to first- and second-line anti-TB drugs was performed on Löwenstein–Jensen medium using the indirect proportion method. Multiple imputation was done for handling missing data using Stata 16. The proportion of TB cases with drug resistance was determined. The odds ratio was used to evaluate risk factors associated with drug-resistant TB.

RESULTS Among 1501 new TB and 69 previously treated TB cases, 14.0% [95% confidence interval (CI): 12.1–16.1] and 33.4% (95% CI: 23.6–44.8), respectively, had resistance to any anti-TB drug. Multidrug-resistant TB accounted for 0.8% (95% CI: 0.5–1.4) of new TB cases and 13.0% (95% CI: 6.5–24.4) of previously treated TB cases. Drug-resistant TB was associated with prior TB treatment [odds ratio (OR), 2.9; 95% CI: 1.6–5.0], age at 45–54 years (OR, 1.6; 95% CI: 1.0–2.4), male (OR, 1.5; 95% CI: 1.0–2.1) and human immunodeficiency virus (HIV) infection (OR, 1.6; 95% CI: 1.0–2.4).

CONCLUSIONS The burden of drug-resistant TB remains high in Thailand. Intensified prevention and control measures should be implemented to reduce the risks of drug-resistant TB in high-risk groups previously treated, especially individuals of late middle age, males and those with coinfection of TB and HIV.

keywords *Mycobacterium tuberculosis*, drug susceptibility testing, prevalence, risk factors, Thailand

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being), SDG 17 (partnerships for the goals)

Introduction

Anti-tuberculosis (TB) drug resistance survey is a global project initiated by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) [1]. Since 1997, Thailand has conducted a national survey of drug resistance in tuberculosis every 5 years [2–4]. Data from the 4th survey data showed that the percentages of multidrug-resistant tuberculosis (MDR-TB) in new TB cases and previously treated cases were 2.03% and 18.88%, respectively.

A continuous surveillance system based on routine drug susceptibility testing (DST) is the most effective mechanism for the systematic monitoring of drug-resistant TB; however, this system is only applicable to countries where the results of rifampicin (RIF) susceptibility testing should be documented for at least 75% of new pulmonary TB cases. These criteria are established on the basis of surveillance systems in Europe and North America [5]. In Thailand, universal access to DST is ongoing; therefore, a periodic survey of randomly selected TB

patients remains the basis of drug resistance surveillance. The survey can provide a nationwide burden of drug-resistant TB as an essential part of planning TB control in Thailand [1]. In addition, a standardised stratification of the survey results by patient characteristics can also provide information on the potential risk factors linked to drug-resistant TB [6].

To help Thailand develop a national response to drug-resistant TB and to avoid the further emergence of drug-resistant TB, in 2017, the Division of Tuberculosis, Department of Disease Control, Ministry of Public Health (MOPH), Thailand, conducted the fifth national survey of drug resistance in TB. The survey is aimed to determine the proportion of TB cases that are resistant to anti-tuberculosis drugs and to identify the risk factors associated with drug-resistant TB.

Methods

Sampling method

The survey was conducted by the National Tuberculosis Reference Laboratory (NTRL) of Thailand. The sample size for patients with new cases of smear-positive TB was calculated using the following formula (1).

$$n = \left\{ \frac{D*N*z^2*p*(1-p)}{\left(d^2*(N-1)\right)+(z^2*p*(1-p))} \right\} \times \left(\frac{1}{\text{recovery}}\right)$$

The sample size is represented as n, and N means 'number of new smear-positive pulmonary TB patients in public sector under MOPH registered in the TB Case Management (TBCM) database in fiscal year 2016 (as of 4 February 2017)'. The calculation is based on the assumption that 2% of the cases would be MDR-TB ($P = 0.02$) and that 30% of the culture samples would be lost owing to failure to recover the culture or due to contamination by growth of non-tuberculous mycobacteria (recovery = 0.7), with a precision of ±1.1% ($d = 0.011$) for the 95% confidence interval ($z = 1.96$) and a design effect ($D = 2$). Results from the calculation indicated a sample size of 1741 patients.

The sampling frame consists of hospitals in the public sector under MOPH which registered 95% of new smear-positive cases registered in TBCM in fiscal year 2016 (as of 4 February 2017). A stratified cluster sampling with probability proportionate to the number of new smear-positive pulmonary cases was used to select 100 hospitals after excluding hospitals with less than 10 new smear-positive cases and categorising hospitals into five strata according to the number of their registered new smear-positive cases.

Eligible patients were smear-positive TB patients aged 18 years or older who had been newly diagnosed during the survey at the tuberculosis clinics selected as sample sites. Patients with TB that had never been treated with TB drugs or who had been treated for less than 1 month at the time of screening were considered new patients. Patients who had been treated for tuberculosis for 1 month or longer were considered previously treated patients.

Collection of patient information

Trained TB staff at the clinics interviewed each enrolled patient using a standard questionnaire to collect information regarding previous treatment for TB and sociodemographic data, including sex, age, nationality, human immunodeficiency virus (HIV) status, health insurance and imprisonment.

Microscopy examination and mycobacterial culture

Two sputum samples were obtained from each eligible patient, including the first morning sputum and second spot and/or morning sputum. Ziehl–Neelsen staining was used to differentiate acid-fast bacilli [7].

For culture isolation, each specimen was digested and decontaminated with *N*-acetyl-L-cysteine (NALC)/sodium hydroxide (NaOH) for 15 min. Centrifugation was used to concentrate the treated sputum specimen [8]. Then, 0.1- and 0.5-ml aliquots were inoculated into two tubes of Löwenstein–Jensen (LJ) medium and mycobacterial growth indicator tube (BD BBL™ MGIT™, Becton Dickinson, MD, USA). The cultures were incubated at 37 °C and assessed every week for 6 weeks for MGIT and every week for 8 weeks for LJ medium. Cultures with growing colonies were sent for identification and DST. The growth characteristics, morphological colony characteristics, inhibition test by *p*-nitrobenzoic acid and immunochromatography assay (ICA) were used to differentiate *Mycobacterium tuberculosis* (MTB) from other mycobacteria.

Drug susceptibility testing

DST was performed using the indirect proportion method on LJ medium for first- and second-line anti-TB drugs, with the following concentrations for four first-line drugs [9]: 0.2 μg/ml for isoniazid (INH), 40 μg/ml for rifampicin (RIF), 4 μg/ml for streptomycin (STM) and 2 μg/ml

for ethambutol (EMB), and for two second-line drugs [10]: 2 μg/ml for ofloxacin (OFX) and 40 μg/ml: for kanamycin (KAN). The cultures were incubated at 37 °C for 4 weeks. The critical growth proportion for resistance was 1% for all drugs.

GeneXpert MTB/RIF assay

The GeneXpert MTB/RIF assay was performed as described previously [11, 12]. Sample reagent was added in a 2:1 ratio to untreated sputum. The diluted sample was incubated for 15 min at room temperature. Two millilitre of each diluted sample was transferred into the test cartridge using a sterile pipette. The cartridge was inserted into the GeneXpert® system. Performance agreement in RIF resistance determination between drug susceptibility test and GeneXpert MTB/RIF assay was examined using Cohen's kappa.

Management and analysis of data

The laboratory form was the main data collection tool in this study. Information was collected at the health facility and laboratory levels using the form. Missing data among enrolled cases were (i) the number of missing mycobacterial culture data, (ii) the number of contaminated cultures, and (iii) the number of cultures with no DST results available. 'ice' command was implemented in Stata16 (StataCorp LLC, TX, USA) for multivariate imputation via chained equations [13]. Multiple variables in imputation included DST results of RIF, INH, STM, EMB, OFX, treatment history, age group, sex, and HIV status. Because only one resistance to KAN was observed, KAN was not imputed, and it was assumed that there was no KAN resistance among cases with missing DST results of KAN. MDR status was passively imputed. Status of resistance to any of six drugs and that of MDR with OFX and/or KAN was determined by combining drug susceptibility status of individual drugs after the imputations. 'mim: svey: logit' command on Stata for logit model incorporating clusters and weights was used to estimate proportion of drug resistance after multiple imputation. Clusters were defined by hospitals. Weights for each cluster were defined as allocated sample size of new smear-positive cased divided by the number of new smear cases included in analysis of proportion of drug resistance among new cases. Stratification was not incorporated in survey design specification ('svyset' command of Stata). For resistance to KAN and XDR-TB, the proportions of resistant TB cases were estimated without considering survey design and it is assumed there is only one case which are resistant to KAN and XDR-TB case. The observed DST results of the survey were used to determine proportion of pre-XDR-TB and XDR-TB among MDR-TB cases.

Analysis of factors associated with drug-resistant TB was carried out by using observed DST results. In this analysis, drug-resistant TB cases were defined as cases resistance to any of the 6 drugs even if DST results of some other drug were missing and pan-susceptible TB was defined as those with TB susceptible to all six drugs. 1485 of enrolled cases met with the definitions. A multivariate logistic random effects regression model was used to investigate associations with drug-resistant TB. The odds ratio (OR) adjusted for treatment history, age group, sex and HIV status were determined. Statistical analysis was performed using the 'lme4' package and 'broom.mixed' package in R software [14] to get OR with CIs. Interactions between variables were not considered in the analysis.

Ethical approval

The study was approved by the Ethics Review Committee of the Department of Diseases Control, Ministry of Public Health. Written informed consents were obtained from each participant. All the authors vouch for the completeness and accuracy of the data presented.

Results

Patient enrolment and mycobacterial culture

Patient recruitment across 60 out of 77 provinces of Thailand (Figure 1) began in August 2017 and ended in August 2018. A total of 1728 smear-positive patients aged 18 years or over with TB diagnosis were enrolled in the study; 1628 patients (94.2%) were new TB cases, and 100 patients (5.8%) were previously treated TB cases. While overall achievement of enrolment defined as ratio of number of enrolled cases to planned sample size is high, the enrolment situation, such as proportion of enrolled cases from eligible cases, varied by hospital. There was no new case enrolled from one hospital. Mycobacterial culture was not performed in nine cases. Fifty-six positive cultures (3.2%) were identified as non-tuberculous mycobacteria. Of 1663 cases with *M. tuberculosis* complex, 1561 cases (93.9%) were culture-positive, 102 cases (6.1%) were culture-negative, and 18 cases (1.1%) were contaminated. DST results were not available for 40 cases of culture-positive cases (2.6%). Overall, the survey obtained 1501 cases with DST results from 1441 new TB cases (96.0%) and 60 previously treated TB cases (4.0%) as shown in Figure 2.

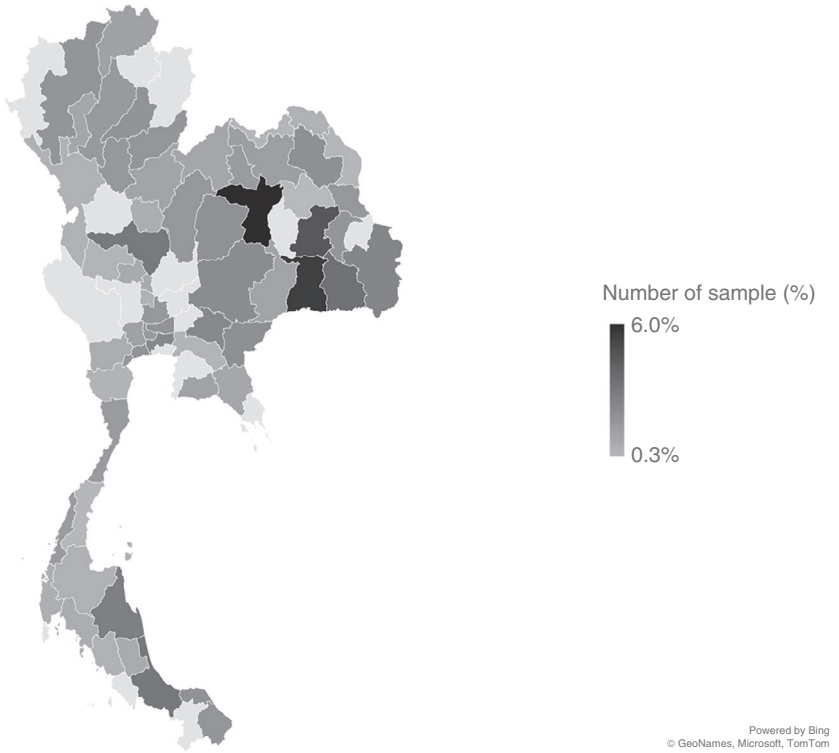

Figure 1 Distribution map of sample collection for the fifth national anti-TB drug resistance survey.

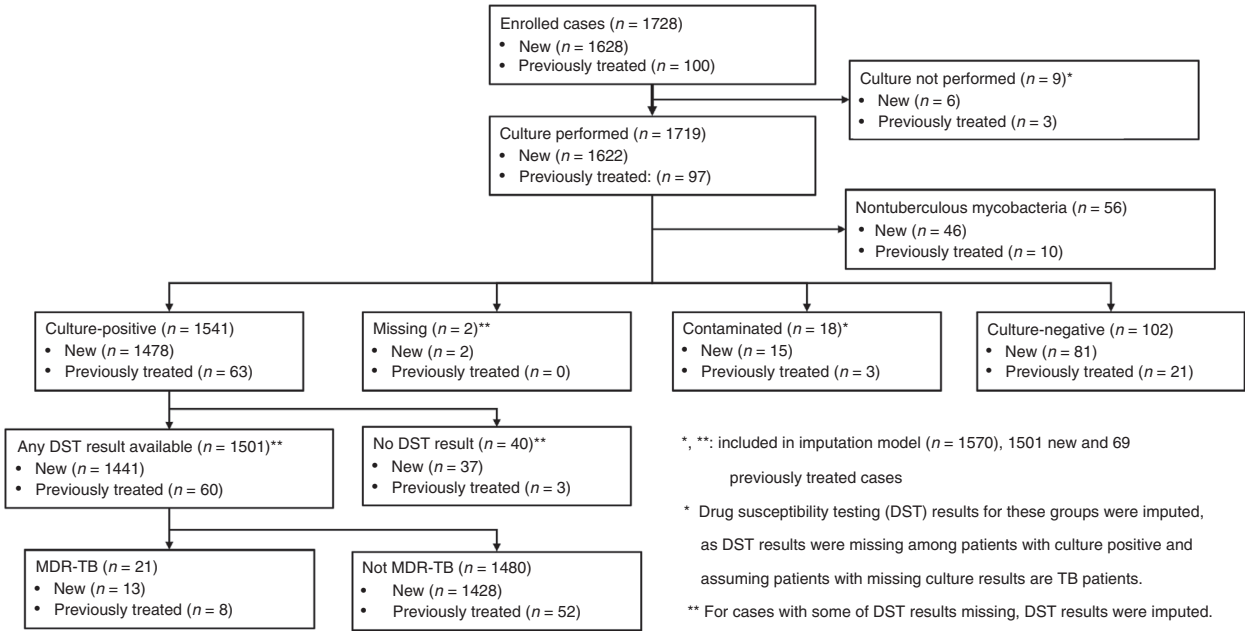

Figure 2 Flow chart of analysis based on phenotypic DST results of enrolled cases.

The proportion of patients with drug-resistant tuberculosis

Estimates of resistance TB without imputation were also carried out. In this analysis, prevalence of each drug was estimated separately because the number of cases with DST results varied by drug as shown in Table 1. New cases were weighted in the same way as described in the Methods. The results are shown in Table 1. The analysis with multiple imputations included 1570 cases consisting of the cases with DRS results, and the cases indicated with asterisk (*, **) in Figure 1 assuming the cases without culture results (*) were TB cases. After performing the multiple imputation and applying the weights, the proportions of patients with drug resistance tuberculosis were estimated for 1501 new TB cases and 69 previously treated TB cases. Resistance to any anti-TB drug was found in 14.0% (95% CI: 12.1–16.1) of new cases and 33.4% (95% CI: 23.6–44.8) of previously treated TB patients. In this survey, the burden of INH-resistant TB was the highest with 9.7% (95% CI: 8.2–11.5) of new TB cases and 21.3% (95% CI: 13.0–32.9) of previously treated TB cases. Patients with resistance to RIF (RR-TB) were detected 1.3% (95% CI: 0.8–2.0) in new TB patients and 19.6% (95% CI: 11.6–31.3) in previously treated TB patients as shown in Table 1. Multidrug-resistant TB (MDR-TB) accounted for 0.8% (95% CI: 0.5–1.4) of new TB cases and 13.0% (95% CI: 6.5–24.4) of previously treated TB cases. Considering the actual proportion of previously treated patients, approximately 1 of 2 patients had resistance to INH, RIF, or both, and 1 of 10 patients had MDR-TB. Resistance to OFX was 1.3% (95% CI: 0.7–2.6) of new TB cases and 3.9% (95% CI: 1.0–14.3) of previously treated TB cases.

Considering cases with DST results of RIF, INH, OFX and KAN from the observed survey data, among the 13 MDR-TB patients with new TB cases, 15.4% (95% CI: 2.7–46.3) had pre-extensively drug-resistant TB, which was defined as MDR-TB with resistance to either OFX or KAN; in addition, 7.7% (95% CI: 0.4–37.9) had extensively drug-resistant TB (XDR-TB), which was defined as MDR-TB with resistance to OFX and KAN. Because the number of MDR-TB cases is small, these proportions do not consider sampling.

Performance agreement between phenotypic DST and GeneXpert MTB/RIF assay

Against DST as a gold standard for detection of RIF resistance in MTB, GeneXpert had a sensitivity, specificity, positive predictive value and negative predictive value of 87.5%, 99.0%, 65.1% and 99.7%, respectively. GeneXpert had performance agreement at 98.5% with a substantial agreement (Kappa = 0.73, 95% CI: 0.62–0.84).

Factors linked to drug-resistant tuberculosis

There were 1485 cases (1426 new and 59 previously treated cases) with DST results from observed survey data with drug-resistant tuberculosis status mentioned in the Methods. Of these, 227 cases (207 new and 20 previously treated cases) were drug-resistant TB. Among 1485 cases, sex of two cases was unknown and these cases were removed from the analysis. They were new cases of whom one was drug-resistant TB. Among the remaining 1483 cases, 248 had 'Unknown HIV status' and were combined with HIV-negative cases. There were 10 cases with unknown imprisonment status, who were combined with the cases with 'no imprisonment'. Table 2 shows results of the multivariate analysis of risk factors for drug-resistant TB for 1483 cases. After adjusting for treatment history, sex, age, HIV and imprisonment, there were four variables: treatment history (OR = 2.9; 95% CI: 1.6–5.0; $P < 0.001$), female *vs.* male (OR = 1.5; 95% CI: 1.0–2.1; $P < 0.05$), age 65 years or over *vs.* age at 45–54 years (OR = 1.6; 95% CI: 1.0–2.4; $P < 0.05$) and HIV-negative/unknown *vs.* HIV-positive (OR = 1.6; 95% CI: 1.0–2.4; $P < 0.05$) were significantly associated with drug-resistant TB.

Patients who had been previously treated for TB were a leading risk factor for drug-resistant TB. In addition, late middle age, male patients and patients with HIV coinfection were at higher risk of having drug-resistant TB than female patients and those without HIV infection.

Discussion

This is the fifth national drug resistance survey. The prevalence of MDR-TB among new TB cases observed from this survey (0.8%; 95% CI: 0.5–1.4) was lower than those of previous surveys such as 1.7% (95% CI: 1.1–2.6) observed in 2006 [15] and 2.0% observed in 2012 (unpublished). However, it may be due to random error because of overlapped confidence interval and/or due to limitations of the survey as mentioned below. Therefore, the judgement should be made carefully, and it is necessary to monitor prevalence of RR/MDR-TB continuously in future to determine the trend.

The proportion of any resistance to INH among new TB cases was remained the same in this survey compared to the proportion reported in a previous survey in 2006 (9.7% *vs.* 9.7%, respectively) [4]. This finding has implications for appropriate empiric treatment regimens and

Table 1 Summary of the proportion of patients with resistance to anti-TB drugs in Thailand

	New TB cases			Previously treated TB cases		
Drug susceptibility	No. of cases/Total cases with DST results (%)	Estimated prevalence without imputation % (95% CI)	Estimated prevalence with imputation % (95% CI)	No. of cases/Total cases with DST results (%)	Estimated prevalence without imputation % (95% CI)	Estimated prevalence with imputation % (95% CI)
Any resistance to six drugs	204/1423 (14.3)*	13.5 (11.7–15.5)*	14.0 (12.1–16.1)	20/59 (33.9)	33.9 (24.5–44.8)	33.4 (23.6–44.8)
Any resistance to RIF	20/1441 (1.4)	1.2 (0.8–1.9)	1.3 (0.8–2.0)	12/60 (20.0)	20.0 (11.9–31.7)	19.6 (11.6–31.3)
Any resistance to INH	143/1441 (9.9)	9.6 (8.1–11.4)	9.7 (8.2–11.5)	13/60 (21.7)	21.7 (13.2–33.4)	21.3 (13.0–32.9)
Any resistance to STM	81/1441 (5.6)	5.1 (4.0–6.5)	5.2 (4.1–6.6)	9/59 (15.3)	15.3 (8.4–26.1)	15.0 (8.1–26.2)
Any resistance to EMB	8/1441 (0.6)	0.5 (0.2–1.0)	0.5 (0.3–1.1)	1/59 (1.7)	1.7 (0.2–12.2)	2.0 (0.3–13.7)
Multidrug resistance	13/1441 (0.9)	0.8 (0.5–1.3)	0.8 (0.5–1.4)	8/60 (13.3)	13.3 (6.6–25.1)	13.0 (6.5–24.4)
Any resistance to OFX	18/1423 (1.3)	1.1 (0.7–1.8)	1.3 (0.7–2.6)	2/60 (3.3)	3.3 (0.9–11.9)	3.9 (1.0–14.3)
Any resistance to KAN	1/1423 (0.1)	0.1 (0.0–0.4)	0.1 (0–0.4)‡	0/60 (0.0)	0.0 (NA)§	0.0 (NA)§
Pre-extensive drug resistance	2/1423 (0.1)†	0.1 (0.0–0.5)†	0.1 (0–0.5)	0/60 (0.0)	0.0 (NA)§	0.0 (NA)§
Extensive drug resistance	1/1423 (0.1)†	0.1 (0.0–0.4)†	0.1 (0–0.4)‡	0/60 (0.0)	0.0 (NA)§	0.0 (NA)§

*Cases with all DST results of 6 drugs were included.
†Cases with all DST results of RIF, INH, OFX and KAN were included.
‡They are not based on multiple imputation as mentioned in the Method.
§The proportions are based on cases with observed DST results, and CI was not calculated.

INH preventive therapy. In addition, the high proportions of any resistance to OFX in new and previously treated cases of TB give rise to concerns about the empirical use of fluoroquinolones for treating respiratory tract infections linked to poor treatment outcomes and drug-resistant TB [16].

This survey shows that primary XDR-TB is also a crucial issue in the TB control programme, as evidenced by the fact that one new TB case had XDR-TB. These findings indicate ongoing transmission of primary drug-resistant TB. Household or close contacts with drug-resistant TB cases is a major cause of primary transmission [17–19]. Therefore, policymakers need to understand whether additional resources should be allocated for transmission-interrupting interventions.

Prevention of drug-resistant TB, especially MDR-TB, is an essential part of the TB control programme. In this survey, there were 42.9% of MDR-TB cases who had undergone prior treatment. This finding points to the need for interventions that will improve TB treatment compliance,

Table 2 Multivariate analyses of risk factors for drug-resistant tuberculosis among 1483 smear-positive cases after removing 2 cases with unknown sex

Variable	Drug-resistant tuberculosis (%) $N = 226$	Pan-susceptible tuberculosis (%) $N = 1257$	Drug-resistant TB *vs.* Pan-susceptible TB OR (95% CI)
History of treatment			
New	206 (91.2)	1218 (96.9)	Reference
Previously treated	20 (8.8)	39 (3.1)	2.9** (1.6–5.1)
Sex			
Female	43 (19.0)	328 (26.1)	Reference
Male	183 (81.0)	929 (73.9)	1.5* (1.0–2.1)
Age			
18–24 years	12 (5.4)	64 (5.1)	1.4 (0.7–2.7)
25–34 years	29 (12.8)	131 (10.4)	1.3 (0.8–2.3)
35–44 years	43 (19.0)	244 (19.4)	1.1 (0.7–1.8)
45–54 years	63 (27.9)	269 (21.4)	1.6* (1.0–2.4)
55–64 years	40 (17.7)	270 (21.5)	1.0 (0.6–1.6)
≥65 years	39 (17.3)	279 (22.2)	Reference
HIV status			
Negative/unknown	191 (84.5)	1135 (90.3)	Reference
Positive	35 (15.5)	122 (9.7)	1.6* (1.0–2.4)
Imprisonment			
Non-imprisonment// unknown	222 (98.2)	1231 (97.9)	Reference
Imprisonment	4 (1.8)	26 (2.1)	0.7 (0.3–2.2)

*P-value < 0.05 and **P-value < 0.001.

especially among adult male TB patients and HIV-infected patients with TB. WHO describes factors influencing adherence to TB treatment as follows: economic factors, patient-related factors, regimen complexity, relationships between the health provider and the patient, and pattern of healthcare delivery [20]. Analysis of national survey data revealed that gender could influence adherence to the treatment since there was a significant gender-related difference in the proportion of drug-resistant TB. Based on a previous study, male sex has other predictors of non-compliance to TB treatment, for example, smoking history and drug abuse [21], while women have higher accessibility to TB care than men [22]. Treatment complexity is a primary consideration of poor compliance in TB/HIV coinfection [23, 24]. Improvement in TB care in HIV patients could be achieved through mentoring and training programmes [25].

There are several limitations in this survey. First, clusters were selected from public health facilities under MOPH and did not include private healthcare sectors and non-MOPH public sectors (e.g. university hospitals). In fiscal year 2017, registration of TB cases in the private and non-MOPH public sectors in the National Tuberculosis Information Program (NTIP) was voluntary. The proportions of registered TB cases in the private sectors were 2.1%. Excluding private sectors is unlikely to affect prevalence of drug resistance significantly among the registered cases in Thailand. Almost all patients have access to public health service with universal health coverage. However, selection biases might occur in identification of the survey population due to non-registered cases probably mainly from private and non-MOPH public sectors in Bangkok. Second, there was potential for misestimation of drug resistance proportions among previously treated TB cases because the sample size was calculated on the basis of prevalence of MDR-TB in new TB cases. Third, although the number of enrolled new smear-positive samples reached 93.5% of the target sample size, DST results were not available for 226 samples (13%) due to contaminated culture, loss of culture sample and positive culture without DST results. Fourth, while multiple imputations were carried out to handle missing DST data, there was some uncertainty due to imputations. Missing mechanism may not be suitable for multiple imputations, and there may be limitation of covariates adopted in imputation model. Because the results from different sets of the multiple imputations are slightly different, there is also some uncertainty which may be due to instability of the imputation model. Fifth, there was missing information on risk factors. We combined unknown HIV status with HIV-negative and unknown imprisonment with no

imprisonment. There may be influence of misclassification on the observed association. Regarding sex, if we combine unknown sex with female, statistically significant is marginal ($P = 0.05$). 95% lower limits of ORs is close to 1 for age group and HIV status. There may be other real risk factors. Further studies, therefore, may be required to confirm the risk factors. Finally, there may be potential selection bias due to incomplete ascertainment of cases because laboratory-based diagnosed case data suggested that some cases including RR cases were not enrolled. The real prevalence may be higher than the observed. To estimate prevalence of drug-resistant TB, weight adjustment was made only for the number of cases included in the analysis at hospital while there may be factors associated with drug resistance and there may be significant differences in their distribution between enrolled cases and the whole of eligible patients. It might be possible to reduce influence of some of limitations by utilising other information such as TB surveillance data, DST results of unenrolled cases examined by the regular laboratory service and from private and non-MOPH public sector hospitals. In 2019, the National TB Control Programme (NTP) implemented a supply management system for anti-TB drugs. Registration of TB cases in the NTIP was required for procurement of anti-TB drugs; consequently, every healthcare facilities including public and private sectors had to make obligatory TB case registration. This mechanism could improve data collection on TB cases in Thailand.

This survey presents, for the first time, a comprehensive view of the nationwide epidemic of drug-resistant TB in Thailand. Division of Tuberculosis as the NTP of Thailand should focus on the early detection of drug resistance in TB using molecular techniques and should improve universal access to DST. In addition, strengthening contact tracing capacity should be achieved to halt the transmission of M/XDR-TB and a systematic approach to manage TB treatment should also be considered to minimise patient non-compliance.

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