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Temporal trend of drug-resistant tuberculosis among Thai children during 2006–2021 ☆

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ABSTRACT

Background: The prevalence of drug-resistant tuberculosis (DR-TB) in adults has stabilized in the past decade. Our study aimed to describe the prevalence of DR-TB in Thai children between 2006 and 2021.

Materials and methods: Children younger than 15 years old who had culture-confirmed *Mycobacterium tuberculosis* complex (MTB), positive PCR-MTB, or positive Xpert MTB/RIF were included in this cohort. Drug susceptibility testing (DST) was performed using phenotypic and/or genotypic methods. The prevalence of DR-TB was compared using the chi-square test.

Results: Among 163 confirmed TB cases (44% as pulmonary TB, 27% as extrapulmonary TB, and 29% with both), the median age (IQR) was 12.2 (7.3–14.2) years. DST was performed in 139 cases (85%), revealing prevalences of all DR-TB, isoniazid-resistant TB (Hr-TB), and rifampicin monoresistant/multidrug-resistant TB (Rr/MDR-TB) of 21.6% (95% CI 14.7–28.4), 10.8% (95% CI 5.6–16.0%), and 2.9% (95% CI 0.1–5.7%), respectively. The DR-TB rates did not differ significantly between 2006–2013, 2014–2018, and 2019–2021 ($p > 0.05$). Two pre-extensively DR-TB (pre-XDR) cases with fluoroquinolone resistance were detected after 2014.

Conclusion: The prevalence of DR-TB in Thai children was stable. However, one-tenth of DR-TB cases confirmed with DST were Hr-TB, which required adjustment of the treatment regimen. The pre-XDR cases should be closely monitored.

Background

Over the past decade, although the global burden of tuberculosis (TB) has significantly decreased and the number of people who have access to TB treatment has increased, drug-resistant TB (DR-TB) continues to be a global health threat associated with high mortality (Lange et al., 2018; World Health Organization, 2021). Following advances in molecular technology, several tests, including Xpert MTB/RIF, have been widely implemented to diagnose TB and test for genotypic drug susceptibility in order to detect DR-TB early; however, phenotypic drug susceptibility testing (DST) by conventional culture remains the most commonly used method for detecting DR-TB (Dheda et al., 2019).

Globally, the burdens of multidrug-resistant TB (MDR-TB; defined as *Mycobacterium tuberculosis* strains with resistance to isoniazid and rifampicin) and rifampicin-resistant TB (RR-TB) are stable. For more than 10 years, the best estimate of the prevalence of MDR/RR-TB in newly diagnosed patients has been 3–4%, increasing to 18–21% in those previously treated for TB (World Health Organization, 2021). Recently,

Abbreviations: Hr-TB, Isoniazid-monoresistant tuberculosis; MDR-TB, Multidrug-resistant tuberculosis; Rr-TB, Rifampicin-monoresistant tuberculosis; Pre-XDR-TB, Pre-extensively drug-resistant tuberculosis; DR-TB, Drug resistant tuberculosis.

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antituberculosis regimens for DR-TB have changed, following the introduction of new and repurposed drugs. Among all DR-TB strains, those resistant to isoniazid and/or rifampicin are of the greatest concern.

In 2018, WHO recommended that isoniazid-monoresistant TB (Hr-TB) should be treated with a levofloxacin-containing regimen for 6 months to improve outcomes and prevent further drug resistance (Fregonese et al., 2018; WHO consolidated guidelines on tuberculosis 2020). In 2016, a 9–11-month injectable-based regimen (Bangladesh) for MDR-TB was implemented; then, in 2018, an all-oral bedaquiline-based regimen (9–12 months) was recommended. (WHO consolidated guidelines on tuberculosis, 2020; WHO rapid communication, 2018; WHO treatment guidelines for drug-resistant tuberculosis, 2016).

Thailand has been one of the countries with a high burden of TB, DR-TB, and human immunodeficiency virus (HIV)/TB over the past two decades. However, the prevalence of TB declined from 172 per 100 000 population in 2015 to 150 in 2020, and, in 2021, Thailand was no longer on the MDR/RR-TB high-burden countries list (World Health Organization, 2021). MDR/RR-TB in the country had been stable at 5.7–6.6 per 100 000 population from 2015 to 2018 (World Health Organization, 2016). While the rate of MDR-TB is showing a decreasing trend, that for Hr-TB is increasing. A national DR-TB surveillance report showed that the prevalence of Hr-TB had been 5.7% in 2006–2007, compared with 9.7% in 2017–2018. However, the prevalence of MDR-TB declined slightly from 1.6% in 2006–2007 to 0.8% in 2017–2018 (Division of Tuberculosis, Department of Disease Control, Ministry of Public Health, 2015).

As children with TB usually reflect the recent transmission of TB, the prevalence of DR-TB in children can reflect the situation for DR-TB in the community (Schaaf et al., 2006). However, data relating to the pattern of DR-TB in children are limited. Data from Queen Sirikit National Institute of Child Health (QSNICH), a tertiary care center in Bangkok, showed prevalences of 11.5% for Hr-TB and 3.8% for MDR-TB in 78 cases aged under 18 years old in 2001–2010 (Vandepittel et al., 2015). Our study aimed to describe the temporal trends for DR-TB rates in Thai children from 2006 to 2021.

Materials and methods

Study population and design

This cohort study was conducted at two tertiary care centers in Bangkok, Thailand — the King Chulalongkorn Memorial Hospital (KCMH) and QSNICH. Data from KCMH, a university hospital with 300 children's beds, were collected from 2006 to 2021, while data from QSNICH, a referral hospital with a 426-bed capacity, were collected from 2019 to 2021. All data were divided into the following three groups according to testing period, study center, different research designs, and changes in laboratory assays for DST: (1) a retrospective study from 2006 to 2013, involving phenotypic DST only at the KCMH; (2) a retrospective study from 2014 to 2018, involving phenotypic DST and genotypic DST by Anyplex™ II MTB/TB at KCMH; and (3) a prospective study from 2019 to 2021 involving phenotypic DST and genotypic DST by Anyplex™ II MTB/TB or Xpert MTB/TB at KCMH and QSNICH. Genotypic DST by Anyplex™ II MTB/TB for both study sites was performed in the Department of Microbiology, KCMH. Phenotypic DST for DR-TB was performed in the Department of Microbiology, KCMH for cases from KCMH, and in the Department of Disease Control, Bangkok for those from QSNICH.

The study period was from 2006 to 2021, and therefore involved both retrospective and prospective data collection. First, the medical records of children aged 0–15 years who had been diagnosed with TB between 2006 and 2018, confirmed by mycobacterial culture or molecular diagnosis, were retrospectively reviewed. The cases were identified from ICD-10 and microbiological records from the Department of Microbiology, Faculty of Medicine, Chulalongkorn University. In addition, data on demographics, clinical diagnosis, treatments, and outcomes were collected. Second, a prospective study enrolled children aged 0–15 years with suspected TB, and involved the collection of specimens for acid-fast bacilli (AFB) staining, molecular techniques, and mycobacterial culture from two centers (KCMH and QSNICH) between 2019 and 2021.

Case definitions

According to WHO guidance on national TB programs for the management of TB in children in 2014, pulmonary TB refers to any bacteriologically confirmed TB with the involvement of lung parenchyma or the tracheobronchial tree, including intrathoracic nodes as well as miliary TB, while extrapulmonary TB refers to any bacteriologically confirmed TB with the involvement of organs other than lungs, such as pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, and meninges (World Health Organization. 2014). Treatment outcome definitions for drug-susceptible TB (DS-TB) and RR-TB are also defined by the same 2014 WHO guidance.

Case definitions of drug-resistant TB (DR-TB) and outcomes

The definition of DR-TB was adapted from the WHO 2020 drug-resistant tuberculosis treatment guidelines (WHO consolidated guidelines on tuberculosis, 2020). Drug resistance was categorized based on isoniazid and rifampicin DST as follows: Hr-TB if resistant to isoniazid and susceptible to rifampicin; Rr-TB if resistant to rifampicin but susceptible to isoniazid; RR-TB if resistant to rifampicin and either susceptible or resistant to isoniazid; MDR-TB if resistant to both isoniazid and rifampicin; pre-extensively drug-resistant (pre-XDR-TB) if resistant to isoniazid, rifampicin, and any fluoroquinolones or one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin); and extensively drug-resistant (XDR-TB) if resistant to isoniazid, rifampicin, any fluoroquinolones, and at least one of the three second-line injectable drugs. However, the pre-XDR-TB and XDR-TB definitions used did not comply with the WHO 2021 guidelines because DST for bedaquiline and linezolid was not assessed.

Outcomes for TB patients were adapted from the WHO Definitions and Reporting Framework for Tuberculosis 2013 revision (updated December 2014 and January 2020). World Health Organization. 2013 revision. Treatment outcomes for TB patients, excluding cases of RR- or MDR-TB, were as follows: 'cured' referred to a pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment, but who was subsequently smear- or culture-negative in the last month of treatment and on at least one previous occasion; 'treatment completed' referred a TB patient who completed treatment without evidence of failure. If a patient had no records of sputum smear or culture results in the last month of treatment, and no reported negative results on at least on the previous occasion, either because of no tests performed or unavailable results, then there was no evidence of failure.

Treatment outcomes for RR-TB, MDR-TB, and XDR-TB patients treated using second-line treatments were as follows: 'cured' referred to treatment completed as recommended by the national policy without evidence of failure, with three or more consecutive cultures taken at least 30 days apart being negative after the intensive phase; 'treatment completed' referred to treatment completed as recommended by the national policy without evidence of failure, with no records that three or more consecutive cultures taken at least 30 days apart after the intensive phase were negative; 'lost to follow-up' referred to patients whose treatment was interrupted for 2 consecutive months or more. Treatment success included both 'cured' and 'treatment completed'.

Mycobacterial culture and identification

Mycobacterium tuberculosis complex (MTBC) was isolated from clinical specimens (pulmonary and extrapulmonary) by conventional mycobacterial culture. The clinical specimens were processed using a digestant-decontaminant solution (3% NaOH and 1.45% sodium citrate)

Table 1
Baseline characteristics of confirmed tuberculosis cases

Characteristics	2006–2021	2006–2013	2014–2018	2019–2021	*p*-value
Total confirmed — TB	*N* = 163	*N* = 46	*N* = 45	*N* = 72	
Sex (female)	92 (56%)	23 (50%)	18 (40%)	51 (71%)	0.008
Age (years), median (IQR)	12.2 (7.3–14.2)	12.4 (7.7–14.0)	12.0 (7.1–14.4)	12.4 (7.7–14.1)	0.94
0 to < 5 years, *N* (%)	31 (19%)	10 (22%)	9 (20%)	12 (17%)	
5 to < 10 years, *N* (%)	29 (18%)	6 (13%)	10 (22%)	13 (18%)	
10–15 years, *N* (%)	103 (63%)	30 (65%)	26 (58%)	47 (65%)	
Underlying diseases, *N* (%)	42 (26%)	18 (39%)	13 (29%)	11 (15%)	0.04
HIV	6 (4%)	4 (9%)	2 (4%)	0	0.33
History of TB contact and source persons	51/153 (33%)	10/38 (26%)	10/43 (23%)	31/72 (43%)	0.12
Parents (mother/father)	27 (53%)	5 (50%)	6 (60%)	16 (52%)	0.99
Grandparent	13 (25%)	2 (20%)	2 (20%)	9 (29%)	
Other	11 (22%)	3 (30%)	2 (20%)	6 (19%)	
Tuberculin test ≥ 10 mm	77/109 (70%)	27/30 (90%)	22/32 (69%)	28/47* (60%)	0.03
History: treatment of TB infection	3/158 (2%)	0/43	0/44	3/71 (4%)	0.48
Previous TB treatment	7/158 (4%)	6/43 (14%)	1/44 (2%)	0/71	0.007
Sites of infection, *n* (%)					0.38
Pulmonary	72 (44%)	19 (41%)	15 (33%)	38 (53%)	
Extrapulmonary	44 (27%)	16 (35%)	13 (29%)	15 (21%)	
Both	47 (29%)	11 (24%)	17 (38%)	19 (26%)	

Abbreviations: TB, tuberculosis; LTBI, latent TB infection

* Among 19 patients who had negative tuberculin test (<10 mm), the interferon-gamma released assays were performed in 5 patients, which 2 patients had positive results.

according to previous studies Global Laboratory Initiative, 2014. The mycobacteria were recovered in liquid media (MGIT, Becton Dickinson, USA), and incubated in an MGIT 960 system (Becton Dickinson, USA) with solid medium — LJ medium, Biomedia, or Ogawa medium (in-house preparation) at 37°C for 6–8 weeks. The mycobacteria were identified by the GenoType MTBC (Hain Lifescience GmbH, German), according to the manufacturer's instructions (Hain Lifescience, 2015). The phenotypic DST for isoniazid (H), rifampicin (R), ethambutol (E), and streptomycin (S) was performed using the MGIT 960 DST method Global Laboratory Initiative, 2014. Furthermore, the MTBC and genotypic drug resistance were directly identified in clinical specimens using the Anyplex™ II MTB/MDR Detection assay, targeting *katG* and *inhA* (for isoniazid resistance) and *rpoB* (for rifampicin resistance), according to the manufacturer's instructions (from 2014) (Chumpa et al., 2020).

Statistical analysis

Data were analyzed using descriptive statistics. The primary outcomes were drug resistance patterns. For clinical and outcome variables, median (interquartile range/IQR) values were calculated for continuous variables and frequencies for categorical variables. Comparisons of prevalence for each peroid were analyzed using the chi-square test. All analyses were performed using Stata version 13.1 (StataCorp, College Station, Texas, USA).

Results

Patient demographics

From 2006 to 2021, 163 children were diagnosed with bacteriologically confirmed TB; of these, 105 children were confirmed by culture and genotypic method, 37 children by culture only, and 21 children by genotypic method only. Baseline characteristics of confirmed TB cases, including age, history of TB contact, history of the treatment of TB infection, and sites of infection, did not differ significantly among the three study periods (Table 1). The median age (IQR) of children was 12.2 (7.3–14.2) years old, and 42 (26%) children had underlying medical conditions, including six (4%) cases of HIV infection. Fifty-one (33%) of children had a history of TB contact, with most of the source persons being family members (including parents and grandparents).

The sites of infection were pulmonary TB in 72 (44%) children, extrapulmonary TB in 44 (27%), and both pulmonary and extrapulmonary TB in 47 (29%). All three cases of congenital TB had lesions in the lungs, liver, and spleen; one of them exuded pus from the ears. The sites of extrapulmonary TB included lymph nodes (37 cases), pleura (15 cases), osteoarticular (10 cases), disseminated (10 cases), central nervous system (six cases), abdomen (four cases), skin and soft tissue (three cases), pericardial (two cases), and kidney (one case). Among six children living with HIV infection, the median (IQR) age was 14.2 (12.8–15.3) years, and the median (QR) CD4 count was 285 (67–544) cells/mm^3.

Between 2019 and 2021, 25 of 72 cases were from KCMH, and all underwent DST, while the other 47 cases were from QSNICH, with 42 (89%) undergoing DST. Baseline characteristics and the prevalences of Hr-TB, Rr-TB, MDR-TB, and pre-XDR-TB did not differ statistically between the two centers ($p > 0.05$).

Drug-resistant tuberculosis

Among 163 confirmed TB cases, 139 (85.3%) had either phenotypic or genotypic DST. From 2006 to 2018 (the retrospective study period), 72/91 (79.1%) cases underwent DST, and from 2019 to 2021 (the prospective study period), DST was applied to 67/72 (93.1%) cases (Table 2). Of 15 Hr-TB cases, five had discordant DST results, of which four cases were detected by phenotypic DST only (with negative genotypic DST), and vice versa for the fifth case. Among 11 Hr-TB cases detected by genotypic DST, *katG* gene mutation was detected in eight cases, with three cases showing an *inhA* gene mutation. However, all six cases of Rr-TB/MDR-TB had concordant genotypic and phenotyphic DST results. Two cases of Rr-TB were confirmed susceptible to isoniazid by phenotypic DST. The prevalences of DR-TB, Hr-TB, Rr-TB, MDR-TB and pre-XDR-TB are shown in Table 2 and Figure 1; these did not differ significantly among the three study periods, except for MDR-TB.

Management of children with DR-TB and the outcomes

Of the 30 cases of DR-TB, 15 were Hr-TB, two Rr-TB, two MDR-TB, and two pre-XDR-TB, for which the treatment regimens had to be changed (Table 3). Among the 15 cases of Hr-TB, five cases before 2016 received an ofloxacin-containing regimen, eight cases after 2016 received a levofloxacin-containing regimen, and the other two cases received RZE regimens. Two cases of MDR-TB were resistant to streptomycin but sensitive to the second-line aminoglycosides, including kanamycin and amikacin. These two MDR-TB cases developed due to

Table 2
Prevalence of drug-resistant tuberculosis in children

Type of resistance	Overall 2006–2021	Phenotypic resistance in KCMH 2006–2013	Phenotypic and genotypic resistance in KCMH 2014–2018	Phenotypic and genotypic resistance in KCMH and QSNICH 2019–2021	*p*-value*	*p*-value**
TB confirmed by culture or PCR	*N* = 163	*N* = 46	*N* = 45	*N* = 72		
By both	105 (64%)	24 (52%)	32 (71%)	49 (68%)		
By PCR only	21 (13%)	0	6 (13%)	15 (21%)		
By culture only	37 (23%)	22 (48%)	7 (16%)	8 (11%)		
Drug susceptibility test	139 (85.3%)	28 (60.9%)	44 (97.8%)	67 (93.1%)		
Prevalence of drug-resistant TB, *N* (%, 95% CI)						
Any drug-resistance	30/139 (21.6%, 14.7–28.4)	6/28 (21.4%, 10.2–39.5)	13/44 (29.5%, 16.1–43.0)	11/67 (16.4%, 7.6–25.3)	0.26	0.98
Hr-TB	15/139 (10.8%, 5.6–16.0)	1/28 (3.6%, 0.6–17.5)	7/44 (15.9%, 5.1–26.7)	7/67 (10.4%, 3.1–17.8)	0.26	0.30
Rr-TB	2/139 (1.4%, −0.05–3.4)	0	1/44 (2.3%, −2.1–6.7)	1/67 (1.5%, −1.4–4.4)	0.73	0.47
MDR-TB	2/139 (1.4%, −0.05–3.4)	2/28 (7.1%, 2.0–22.6)	0	0	0.04	0.04
Pre-XDR-TB	2/139 (1.4%, −0.05–3.4)	0	1/44 (2.3%, −2.1–6.7)	1/67 (1.5%, −1.4–4.4)	0.73	0.30
Rr-, MDR-, Pre-XDR-TB	6/139 (4.3%, 0.09–7.7)	2/28 (7.1%, 2.0–22.6)	2/44 (4.6%, −1.6–10.7)	2/67 (3.0%, −1.1–7.1)	0.57	0.61
Other (mono S, mono Z-TB)	9/139 (6.5%, 2.4–10.6)	3/28 (10.7%, 3.7–27.2)	4/44 (9.1%, 0.6–17.6)	2/67 (3.0%, −1.1–7.1)	0.23	0.39

Abbreviations: PCR, polymerase chain reaction; Hr-TB, isoniazid-resistant tuberculosis; Rr-TB, rifampicin-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis; pre-XDR-TB, pre-extensively drug-resistant tuberculosis; mono S, mono-streptomycin-resistant tuberculosis; mono Z, mono-pyrazinamide-resistant tuberculosis

* Comparison of prevalence among three periods — 2006 to 2013, 2014 to 2018, and 2019 to 2021.

** Comparison of prevalence between two periods —2006 to 2013 and 2014 to 2021.

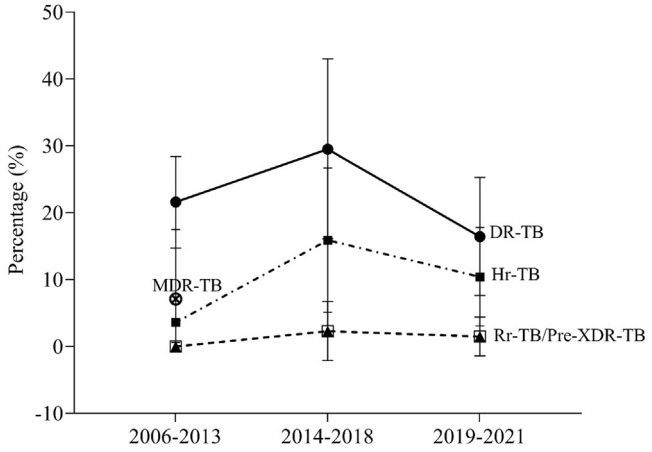

Figure 1. The prevalence of DR-TB, Hr-TB, Rr-TB, MDR-TB, and pre-XDR-TB, 2006–2021

poor compliance with first-line drug treatment, with DS-TB being confirmed by phenotypic DST at the first diagnosis. The first case was a 10-year-old girl with pulmonary TB, for which the directly observed therapy (DOT) did not apply in DS-TB. After 6 months, sputum AFB remained positive and mycobacterial culture with DST reported the MTB as being MDR-TB. She had a successful treatment outcome with the new 18-month regimen. The second case was a 10-year-old HIV-positive boy (CD4 of 32 cells/μL) with pulmonary TB; after 10 months, his sputum AFB remained positive and mycobacterial culture with DST reported MDR-TB. During admission, the boy developed seizures and pneumonia, and died before the DST was reported. Two cases of pre-XDR-TB were resistant to fluoroquinolones, and both were newly diagnosed TB with no history of DR-TB contact. All except three cases of DR-TB had successful outcomes (86%); two cases of Rr-TB were lost to follow-up, and one case of HIV infection with MDR-TB died (Table 3). As of March 2022, there had been no reports of relapse cases.

Discussion

This study demonstrated that the prevalence of DR-TB in children was stable from 2006 to 2021. The majority of DR-TB cases were Hr-TB, for which the recommended treatment regimen is fluoroquinolone-based. The prevalences of Rr-TB, MDR-TB, and pre-XDR-TB did not differ among the three study periods. Overall, the outcomes of DR-TB cases in this study were favorable.

The prevalence of Hr-TB in Thai adults has remained stable since 2006, at approximately 10% (Kamolwat et al., 2021). Our study reported that the prevalence of Hr-TB in Thai children was 10.8% — comparable with previous studies in Thailand (11.5% in 2001–2010 and 13% in 2008–2011) (Lapphra et al., 2013). This differed from the prevalence reported among South African children, which decreased from 5.6–7.7% in 2003–2013 to 2.5–3.6% in 2013–2017 (Schaaf et al., 2020) However, our rate was similar to the global estimation of Hr-TB prevalence in children (12.1%, 95% CI 9.8–14.8%), with the majority of cases occurring in the Western Pacific and Southeast Asia regions (Yuen et al., 2015).

According to WHO and Thai recommendations, the standard regimen for TB in children is 2HRZE/4-10HR if there is no history of contact with DR-TB cases. Therefore, the children would have received only one effective drug (rifampicin) during the continuation phase in Hr-TB cases, which may have further increased the risk of developing new RR/MDR-TB and a treatment failure phase (Lew et al., 2008).

In this study, some children underwent genotypic DST before the treatment initiation or had no history of Hr-TB case contact; therefore, the fluoroquinolone-containing regimen was prescribed (Table 3). Since 2018, the WHO has recommended that Hr-TB should be treated with levofloxacin-containing regimens for 6 months to improve outcomes and prevent the development of resistance (WHO consolidated guidelines on tuberculosis, 2020). Therefore, DST by genotypic (a line probe assay for isoniazid and rifampicin resistance or a PCR-TB to detect isoniazid and rifampicin resistance) or phenotypic (liquid culture) methods should be applied in all cases. Moreover, the result should be reported as early as possible, and no later than 2 months after diagnosis.

Table 3
Characteristics, management, and treatment outcomes for Hr-TB, RR/MDR-TB and pre-XDR-TB

No.	Year	Age	Sex	U/D	Source person	Site	DST result	Regimen	Total duration of treatment	Outcome
Newly diagnosed TB										
1	2013	4	M	VUR	No	Pulmonary	Hr	2HRZE/4HR/3ROfx	9 months	Complete
2	2014	3	M	No	No	Disseminated	Hr	2HRZE/4RZEOf/9ROfx	15 months	Complete
3	2015	14	M	HIV	No	Pulmonary and lymph node	Hr (*InhA*)	2RZEOfx/4REOfx	6 months	Complete
4	2015	14	M	No	No	Pulmonary and central nervous system	Hr (*KatG*)	2RZEOfx/10REOfx	12 months	Complete
5	2015	0.1	F	No	Mother	Pulmonary	RR (*rpoB*)	HRZE	2 months	LTFU
6	2015	0.4	M	No	No	Pulmonary	Pre-XDR (*KatG, rpoB*, FQ)	Ethio,Z, Lfx,CS,PAS, Km	18 months	Complete
7	2016	0.2	M	No	Mother	Congenital TB	Hr (*InhA*)	1EAmOfx/3RZEOf/8RE	12 months	Cured
8	2016	5	M	Down syndrome	No	Pulmonary	Hr (*KatG*)	2RZELfx/4RLfx	6 months	Complete
9	2016	14	M	No	No	Pulmonary and pleura	Hr (*KatG*)	RZE	6 months	Complete
10	2018	8	F	Down syndrome	No	Disseminated	Hr	RZELfx	12 months	Complete
11	2019	2	F	No	No	Miliary	Hr (*KatG*)	12HRZELfx	12 months	Complete
12	2019	4	M	No	Father	Osteoarticular	Hr (*KatG*)	12RZELfx	12 months	Complete
13	2019	11	F	No	Mother	Pulmonary	Hr (*KatG*)	6RZELfx	6 months	Complete
14	2019	8	F	Down syndrome	Father	Pulmonary and lymph node	Hr	2HRZE/6RZE	8 months	Complete
15	2019	3	M	No	No	Lymph node	Hr (*InhA*)	3HRZE/4HR/6RZELfx	13 months	Complete
16	2020	14	F	No	No	Pleura	Hr	6RZELfx	6 months	Complete
17	2020	12	F	No	No	Lymph node	RR (*rpoB*)	Shorter regimen (Bdq,Pto,Cfx,Lfx,H,Z,E)	4 months	LTFU
18	2020	10	F	No	No	Pulmonary and lymph node	Hr (*KatG*)	6RZELfx	6 months	Complete
19	2020	13	F	No	Father	Pulmonary	Pre-XDR (FQ)	Bdq,LZ,Cfz,Cs,Am,Eto	18 months	Complete
History of previous TB treatment										
1	2006	10	F	No	No	Pulmonary	MDR, Strep	EKmLfxCsPAS	18	Complete
2	2008	10	M	HIV	No	Pulmonary	MDR, Strep	HRZE	–	Died

VUR = vesicoureteral reflux; HIV = human immunodeficiency virus infection; Hr-TB = isoniazid-resistant tuberculosis; RR-TB = rifampicin-resistant tuberculosis; MDR-TB = multidrug-resistant tuberculosis; pre-XDR-TB = pre-extensively drug-resistant tuberculosis; U/D = underlying disease; LTBI = latent TB infection; DST = drug susceptibility test; H =isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; FQ = fluoroquinolone; Ofx = ofloxacin; Lfx = levofloxacin; Bdq = bedaquiline; LZ = linezolid; Cfz = clofazamine; Cs = cycloserine; Am = amikacin; Km = kanamycin; Eto = ethionamide; Pto = prothionamide; PAS = para aminosalicylic acid; LTFU = lost to follow-up

Currently, the Xpert MTB/RIF, which is widely used worldwide, is not able to detect isoniazid resistance. Several manufacturers have developed a new class of moderate-complexity automated NAATS for the detection of TB and resistance to rifampicin and isoniazid on high-throughput platforms, which are suitable for areas with a high population density and rapid sample referral systems. Hopefully, the early and efficient detection of Hr-TB will improve treatment outcomes and reduce further development of DR-TB (WHO consolidated guidelines on tuberculosis, 2021). In our study, Hr-TB children were treated with fluoroquinolones — ofloxacin until 2015 and levofloxacin thereafter.

Currently, ofloxacin and ciprofloxacin are no longer recommended for use in DR-TB care (WHO treatment guidelines for drug-resistant tuberculosis, 2016). In addition, the high prevalence of Hr-TB raises concerns regarding the effectiveness of 6–9 months of isoniazid daily (6-9H) as a preventive therapy; however, the 2022 WHO recommendation for TB preventive therapy in children is a 3-month isoniazid and rifampicin regimen or a 3-month isoniazid and rifapentine regimen for children aged more than 2 years old among DS-TB contact cases (WHO operational handbook on tuberculosis, 2022). In Thailand, the National TB guidelines recommend the 3HR, 3HP, or 6-9H regimen if there is no history of DR-TB case contact, and the 4R regimen if there is a history of Hr-case contact.

In our study, the prevalence of Rr/MDR/pre-XDR-TB in Thai children was stable over the study period (2006–2021), which was in line with previous studies (5.1% during 2001 and 2010, 5.7% during 2008 and 2011) (Lapphra et al., 2013; Vandepittel et al., 2015). The rate of RR-TB in Thailand was 2%, comparable with South Africa. Though the rate of MDR-TB/pre-XDR-TB in Thailand was lower than in South Africa, pre-XDR-TB with fluoroquinolone resistance should be carefully monitored (Schaaf et al., 2020).

Globally, the number of pre-XDR-TB cases increased (World Health Organization, 2021). Therefore, children with detected rifampicin resistance should be further investigated using DST, using either line-probe assay or liquid media, to detect possible resistance to other second-line drugs, including fluoroquinolones. The result of fluoroquinolone DST is crucial for treatment decision making in MDR-TB children, because in pre-XDR-TB with fluoroquinolone resistance, a regimen combining bedaquiline, linezolid, clofazimine, and cycloserine has been proposed (WHO operational handbook on tuberculosis, 2022). However, a new regimen for pre-XDR-TB, including bedaquline, linezolid, and pretomanid, has been proposed for adolescents aged 14 years and over (Conradie et al., 2020).

In this study, discrepant results between genotypic and phenotypic methods were observed in the Hr-TB cases, indicating that not all drug-resistant genes can be detected by multiplex real-time PCR (Anyplex^{TM} II MTB/MDR Detection). However, this multiplex real-time PCR still had high sensitivity, specificity, PPV, and NPV for Hr-TB (85.3%, 99.5%, 93.5, and 97.2%, respectively) (Chumpa et al., 2020). The most common mutations for Hr-TB were located in *katG* and *inhA* promoter regions, with other mutations reported in *aphC, fabG1*, and *furA* genes (Seifert et al., 2015). On the other hand, no such discrepancies were reported for RR-TB, in which the most common mutation gene was *rpoB* (He et al., 2022).

One strength of this study was that it was based on data for TB cases over a 16-year period, confirmed by culture or molecular diagnosis, which provided great accuracy in terms of rates of resistance. Moreover, the PCR was performed using the Anyplex^{TM} II MTB/MDR Detection kit, which can detect isoniazid and rifampicin resistance.

In terms of limitations, firstly, this was largely a retrospective study — from 2004 to 2018 — which may have resulted in incomplete data acquisition. However, data from both laboratory and medical records were collected. Furthermore, after 2018, the prospective part of the study was conducted in two referral centers, which revealed no difference in DR-TB rates between the two centers. Secondly, since our study was conducted in a tertiary care hospital, the external generalizability of results regarding treatment outcomes might be limited. However, the prevalence of DR-TB could be representative of Thai children generally because more than 95% of cases were treatment naïve. Thirdly, in the period between 2006 and 2013, only phenotypic DST (i.e. no genotypic DST) was performed, which might have affected the rates of DR-TB found. However, for the rates of DR-TB during 2014–2021, the results of phenotypic DST were highly concordant with those of genotypic DST, which might support the accuracy of the data for 2006–2013, based on phenotypic DST only.

Conclusion

The prevalence of DR-TB in Thailand was shown to be stable, with Hr-TB predominant, accounting for approximately one-tenth of cases during 2006–2021. However, pre-XDR-TB cases with fluoroquinolone resistance have emerged. Therefore, both phenotypic and genotypic DST should be performed in all children with TB, while the rate of DR-TB in children should continue to be monitored.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

Study design: WJ, PS, and TP. Data collection: WJ, PSNA, NT, JM, PK, and MT. Data analysis: WJ and TP. Laboratory: SR, NU. Writing — original draft preparation, WJ and SR. Writing — review and editing: PS, TS, and TP.

Ethical review

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB No. 526/61) and the Queen Sirikit National Institute of Child Health (No. 104/62). Written informed consents were obtained from the parents, and children aged ≥ 7 years were asked to provide assent if appropriate. Informed consent was waived for the retrospective part of the study.

Conflicts of interest

The authors have no conflicts of interest to declare.

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