Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(1) 1–5

DOI: 10.1177/0300060519869715
journals.sagepub.com/home/imr
SAGE

Prevalence of multidrug-resistant tuberculosis in suspected childhood tuberculosis in Shandong, China: a laboratory-based study

Xiao-Lin Zhou[1], Qiao-Pei Chen[2] and Mao-Shui Wang[1]

Abstract

Objective: Currently, the prevalence of multidrug-resistant tuberculosis (MDR-TB) in childhood tuberculosis (TB) in Shandong, China remains unclear. We retrospectively conducted laboratory-based surveillance in a high TB burden district, to analyze the local prevalence of MDR-TB in childhood TB.

Methods: We collected data, including microbiological results and demographic and disease information, using a questionnaire and medical records. We used the chi-squared test to compare the prevalence of MDR-TB in childhood TB between two periods: 2008 to 2013 and 2014 to 2018.

Results: In Shandong, the prevalence of MDR-TB in childhood TB was low, at 5.6%. Between 2008-2013 and 2014-2018 among children with TB, the prevalence of MDR-TB remained unchanged, the proportion with pulmonary TB decreased from 78.3% to 64.9%, and the proportion with a TB contact history decreased from 20.5% to 9.9%.

Conclusions: The prevalence of MDR-TB among childhood TB in Shandong, China was low and has remained stable over the past years. However, non-tuberculous mycobacterial diseases may be a new challenge in the management of suspected childhood TB.

[1]Department of Lab Medicine, Shandong Provincial Chest Hospital, Shandong University, Jinan, Shandong, China
[2]Department of Clinical Laboratory, Guangxi Maternal and Child Health Hospital, Nanning, Guangxi, China

Corresponding authors:
Qiao-Pei Chen and Mao-Shui Wang, Department of Clinical Laboratory, Guangxi Maternal and Child Health Hospital, Nanning 530002, Guangxi, China;
Department of Lab Medicine, Shandong Provincial Chest Hospital, 46# Lishan Road, Jinan 250013, China.
Emails: chenqiaopei@163.com; wangmaoshui@gmail.com

Keywords
Childhood tuberculosis, multidrug-resistant tuberculosis, China, non-tuberculous mycobacteria, prevalence, surveillance

Date received: 15 May 2019; accepted: 24 July 2019

Background

Tuberculosis (TB) is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 10.4 million TB cases and 1.6 million TB deaths. Childhood TB has been neglected by health professionals because children frequently have paucibacillary disease that is thought to be noninfectious. According to a World Health Organization (WHO) report in 2017, children account for 6.9% of new TB cases globally. The global health community has not set pediatric-specific targets for reducing the disease burden owing to the absence of clear pediatric targets; perceptions of low public health importance; and challenges in presentation, diagnosis, treatment, and reporting.[1] Furthermore, the disease burden has not been well characterized, such as the prevalence of multidrug-resistant TB (MDR-TB).

Until now, several studies have investigated the prevalence of MDR-TB among children in China; however, the figures are highly unreliable and variable. According to previous reports, the prevalence of MDR-TB in childhood TB was between 4.6% and 22%.[2–5] However, the prevalence of MDR-TB among children in Shandong Province, China remains unclear. Therefore, we conducted laboratory-based surveillance in Shandong to evaluate the prevalence of MDR-TB among children age $\leq$15 years old, from 2008 to 2018.

Patients and methods

This retrospective study was conducted at Shandong Provincial Chest Hospital (SPCH), which has about 800 beds and attends approximately 1000 patients with culture-confirmed TB every year. Mycobacterial culture was performed using Löwenstein–Jensen medium, and drug susceptibility assay was performed as previously reported.[6] We used the absolute concentration method (isoniazid: 1 μg/mL, rifampin: 50 μg/mL, ethambutol: 5 μg/mL, and streptomycin: 10 μg/mL) on Löwenstein–Jensen medium to screen *Mycobacterium tuberculosis (MTB)* isolates. Quality control was conducted using inter-laboratory confirmation testing at reference laboratories recognized by the WHO in South Korea and Hong Kong, China. Non-tuberculous mycobacteria (NTM) were identified using p-nitrobenzoic acid and thiophene-2-carboxylic acid hydrazide tests and further identified with a Mycobacteria Identification Array Kit (CapitalBio, Beijing, China).

We collected data, including demographic and diseases information, using a questionnaire and medical records. The chi-squared test was used to compare the prevalence of MDR-TB in children between two periods: 2008 to 2013 and 2014 to 2018. This study was approved by the Human Research Ethics Committees of SPCH (ethics approval number: SPCHEC 2018-03-02). Written informed consent was waived owing to the retrospective design

of the study and anonymous nature of the data collection.

Results

Between February 2008 and January 2018, we obtained 14,840 *MTB* isolates. A total 314 isolates (2.12%) were collected from children, and 222 isolates (70.7%) were submitted for drug susceptibility testing, including 214 *MTB* and 8 NTM isolates (Table 1). The mean age of children was 10.7 ± 4.8 years (range from 3 months to 15 years), and 60.8% were male. Thirty patients (13.5%, 29 household contacts and one school contact) had a TB contact history. Treatment outcomes were as follows: 210 patients (94.6%) cured, 7 (3.2%) failed treatment, 1 (0.5%) interrupted treatment, 3 (1.4%) lost to follow-up, and 1 (0.5%) transferred out. Among the 214 *MTB* isolates, the overall proportion of first-line drug resistance (at least 1 drug) was 15.9% (34/214). Streptomycin showed the highest rate of resistance (12.6%), followed by isoniazid (10.3%), rifampin (7.9%), and ethambutol (2.3%). Twelve (5.6%) *MTB* isolates were MDR-TB. Two (0.9%) *MTB* isolates were resistant to all first-line drugs; none were extensively drug-resistant TB. It is worth noting that NTM isolates were obtained from eight children, and six of these were confirmed as NTM diseases. Among the isolates, five were collected from tissues, two from sputum, and one from pleural effusion; two isolates were defined as *M. fortuitum* and one as *M. scrofulaceum*. The rates of first-line anti-TB drug resistance among NTM isolates were 100% (8/8) for isoniazid, 100% (8/8) for streptomycin, 87.5% (7/8) for rifampin, and 37.5% (3/8) for ethambutol.

Table 1. Comparison of demographic profiles and drug susceptibility pattern of mycobacterial isolates collected from children between 2008–2013 and 2013–2018.

	2008–2013 (N)	2013–2018 (N)	Total (N)	P
Cases	85	137	222	
Sex (male)	47	88	135	0.185
Age (years)	10.3 ± 5.0	11.0 ± 4.7	10.7 ± 4.8	0.202
Non-tuberculous mycobacteria	2	6	8	0.714
TB contact history	17	13	30	0.03
MDR-TB	6	6	12	0.412
Mono-resistant TB	13	21	34	0.943
Isoniazid	10	12	22	0.498
Rifampin	7	10	17	0.833
Streptomycin	12	15	27	0.519
Ethambutol	1	4	5	0.651
Forms of TB				
Pulmonary TB	65	85	150	0.037
Extrapulmonary TB	18	46	64	0.037
Pulmonary + extrapulmonary TB	32	36	68	0.09
Primary TB	4	4	8	0.714
Disseminated TB	5	7	12	0.816
Pleural TB	25	48	73	0.376
Tuberculous meningitis	10	10	20	0.267
Tuberculous lymphadenitis	12	11	23	0.154

TB, tuberculosis; MDR-TB, multidrug-resistant TB.

To check for variation in the prevalence of MDR-TB among children in Shandong, China, we performed a comparison between the periods 2008 to 2013 and 2014 to 2018. Statistical analysis showed that among children with TB between 2008-2013 and 2014-2018, 1) the proportion with a TB contact history decreased from 20.5% (17/83) to 9.9% (13/131, $P < 0.05$); pulmonary TB (PTB) decreased from 78.3% (65/83) to 64.9% (85/131, $P < 0.05$); and extrapulmonary TB (EPTB) increased from 21.7% (18/83) to 35.1% (46/131, $P < 0.05$) and 2) the proportion of MDR-TB among children with TB decreased from 7.2% (6/83) to 4.6% (6/131) and the prevalence of NTM isolates increased from 2.4% (2/85) to 4.4% (6/137); however, no statistical significance was found between the two periods.

Discussion

In the current study, we found that the overall rate of PTB among childhood TB decreased between 2008-2013 and 2014-2018. There are three reasons for this. First, although TB remains a major public health problem in China, the prevalence has steadily decreased. China has now fallen to second place worldwide in TB prevalence.[7] Second, as an important cause of PTB, the TB contact history was lower during 2014 to 2018 than in 2008 to 2013. Third, we found that the percentage of cases of EPTB has increased in recent years; this may have a large impact on the balance between PTB and EPTB.

In our study, the overall prevalence of MDR-TB among children in Shandong, China was 5.6%, similar to the findings of a previous data[2] and lower than that reported in another study (10.8%).[2,6] Moreover, we observed no substantial variations in the prevalence of MDR-TB among children between the two study periods. This is in contrast to the results of a previous study,[2] which showed that the percentage of MDR-TB in childhood TB increased significantly from 2006 to 2015. This difference may be owing to limitations in the previous research. First, the age criteria in that study was higher, from 15 to 18 years old, and most patients (76.1%) were $\geq$15 years old. Second, few MDR-TB cases were reported each year (usually $<$10 cases), so the prevalence could easily fluctuate because of the small sample size. Third, the statistical methods used in that previous study were inappropriate. In fact, only in the last 3 years (2012–2015), the prevalence of MDR-TB seemed to be increasing among children.[2] Therefore, assessing the prevalence rate over a longer period may provide better understanding regarding the situation of MDR-TB in children.

Our results indicated a decreasing trend in the prevalence childhood MDR-TB, although not statistically significant. This phenomenon may be explained by the contribution of recent transmission during an MDR-TB epidemic in China and the impact of TB contact on the risk of TB diseases.[8,9] Remarkably, a previous study showed an increasing prevalence of NTM infections in China.[10] In the present study, NTM isolates were detected in eight patients and the first isolate was detected in 2012. As far as we know, most NTM isolates were resistant to first-line anti-TB drugs. Therefore, greater attention must be given to this situation for better management of these infections in children.

Although we revealed important information in this study, some limitations exist. In our study, 12 MDR-TB patients were included, and the average annual number of patients with MDR-TB was fewer than two. If comparing results in each year from 2008 to 2018, statistical significance may never be achieved. For this reason, we divided the study into two periods: 2008 to 2013 and 2014 to 2018.

Conclusions

In Shandong, China, although the proportion of PTB among cases of childhood TB has decreased, the proportion of EPTB cases increased from 2008-2013 and 2014-2018. Moreover, the local prevalence of MDR-TB among children was not very high and remained unchanged between the two periods. However, NTM diseases may be a new challenge in the management of suspected childhood TB.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Mao-Shui Wang https://orcid.org/0000-0001-6046-3953

References

1. Dodd PJ, Gardiner E, Coghlan R, et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; 2: e453–e459.
2. Tao NN, He XC, Zhang XX, et al. Drug-resistant tuberculosis among children, China, 2006–2015. *Emerg Infect Dis* 2017; 23: 1800–1805.
3. Yang Y, Zhou C, Shi L, et al. Prevalence and characterization of drug-resistant tuberculosis in a local hospital of Northeast China. *Int J Infect Dis* 2014; 22: 83–86.
4. Guo Q, Pan Y, Yang Z, et al. Epidemiology and clinical characteristics of pediatric drug-resistant tuberculosis in Chongqing, China. *PLoS One* 2016; 11: e0151303.
5. Jiao WW, Liu ZG, Han R, et al. Prevalence of drug resistant Mycobacterium tuberculosis among children in China. *Tuberculosis (Edinb)* 2015; 95: 315–320.
6. Deng Y, Wang Y, Wang J, et al. Laboratory-based surveillance of extensively drug-resistant tuberculosis, China. *Emerg Infect Dis* 2011; 17: 495–497.
7. Wang L, Zhang H, Ruan Y, et al. Tuberculosis prevalence in China, 1990-2010; a longitudinal analysis of national survey data. *Lancet* 2014; 383: 2057–2064.
8. Yang C, Luo T, Shen X, et al. Transmission of multidrug-resistant Mycobacterium tuberculosis in Shanghai, China: a retrospective observational study using whole-genome sequencing and epidemiological investigation. *Lancet Infect Dis* 2017; 17: 275–284.
9. Soysal A, Millington KA, Bakir M, et al. Effect of BCG vaccination on risk of Mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005; 366: 1443–1451.
10. Xu D, Han C, Wang MS, et al. Increasing prevalence of non-tuberculous mycobacterial infection from 2004–2009 to 2012–2017: a laboratory-based surveillance in China. *J Infect* 2018; 76: 422–424.