

High rate of transmission in a pulmonary tuberculosis outbreak in a junior high school in China, 2020

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ABSTRACT

Background: School tuberculosis outbreaks are common in China. This study aimed to introduce a new screening process to help control outbreaks.

Methods: An epidemiological investigation into a school-based tuberculosis outbreak was conducted in order to identify the origin of the infection, and how it was transmitted.

Results: In total, 10 confirmed active tuberculosis cases were diagnosed among student contacts in the index case's class, giving an incidence rate of 19.2% (10/52). Three were found through a proactive visit and seven through screening. Of the nine secondary cases, two had purified protein derivation of tuberculin (PPD) ≥ 15 mm or blister (confirmed by computed tomography (CT) scan before preventive therapy), five had TST ≥ 10 mm and < 15 mm (two with abnormal chest radiography scan and three with positive T-SPOT tests, confirmed by CT) and two with PPD ≥ 5 mm and < 10 mm (confirmed by CT scan through proactive visit).

Conclusion: Further to our results based on this school outbreak, a new screening process is recommended that involves conducting interferon gamma release assays on those students with PPD ≥ 5 mm and < 15 mm if there are three or more active tuberculosis patients in the class with an epidemiological link. Furthermore, a CT scan is recommended for students who have had a recent tuberculosis infection before they have preventive therapy.

Background

The World Health Organization aims to end the global tuberculosis epidemic by 2035 (WHO, 2014). However, this goal so far seems unlikely given the current rates of decline in tuberculosis incidence (1–2% annually) (Chiappini et al., 2012). Diagnosis and treatment of individuals with latent tuberculosis infection (LTBI), who are at high risk to progress to tuberculosis, is a priority (Rangaka et al., 2015). Recommended populations for LTBI testing and preventive tuberculosis treatment in China involve mainly: (1) children younger than 5 years old who are household contacts of people with bacteriologically confirmed pulmonary tuberculosis and who have not been found to have active tuberculosis; (2) people who carry human immunodeficiency virus (HIV)

or who are HIV sufferers, or individuals who have a positive HIV infection for which the clinician considers treatment to be unnecessary, and who are unlikely to have active tuberculosis; (3) students who are in close contact with confirmed active tuberculosis patients who are newly infected with mycobacterium tuberculosis; and (4) people who are initiating anti-TNF treatment, or receiving dialysis, or preparing for an organ or hematological transplant, or who have silicosis, among whom students are prioritized. In developed countries with a low tuberculosis burden, clustered tuberculosis outbreaks often occur in schools (Faccini et al., 2013; Norheim et al., 2017). Similarly, tuberculosis outbreaks have been common in Chinese institutional settings, including kindergartens, primary schools, high schools, and colleges (Abubakar et al., 2011; Ma et al., 2015). China has made great

Abbreviations: TST, tuberculin skin testing; CXR, chest radiography; CT, computed tomography; PPD, purified protein derivation; CDC, Center for Disease Control and Prevention; HIV, human immunodeficiency virus.

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advances in controlling tuberculosis; however, tuberculosis outbreaks in schools are of concern, and occur frequently. China has carried out a large amount of work on tuberculosis prevention and control in schools in recent years, but this remains far from enough. Our study focused on a school tuberculosis outbreak in Jiangsu Province, China to help encourage the authorities to pay more attention to the control of tuberculosis outbreaks in schools.

Methods

Epidemic summary

On September 19, 2020, one 17-year-old male student tested positive for bacteria tuberculosis, with a sputum smear microscopy result of 1+. Subsequently, staff in the Center for Disease Control and Prevention (CDC) conducted an epidemiological investigation for the index case and contact investigation relating to his close contacts. In total, 10 students in his class were confirmed as having active tuberculosis.

Study definitions

All cases were diagnosed according to the Chinese Guidelines for Tuberculosis Prevention and Treatment (Wu et al., 2018; You et al., 2019). Tuberculosis cases in China are divided into three categories, namely, bacteriologically diagnosed patients, clinically diagnosed patients, and tuberculosis suspects. Bacteriologically diagnosed patients are those with positive tests via, for example, sputum smear, culture, GeneXpert MTB/RIF (Xpert, Cepheid, USA), or pathological diagnosis of pulmonary lesions. Clinically diagnosed cases apply to those who meet three of the following criteria: (1) negative sputum smear, culture, or GeneXpert MTB/RIF, and without a pathological diagnosis of pulmonary lesions; (2) examination of CXR demonstrating pathological changes in accord with active tuberculosis; (3) cough and expectoration for ≥ 2 weeks, hemoptysis, and other suspected symptoms of tuberculosis, or TST ≥ 10 mm, or with positive interferon gamma release assay (IGRA) test, or positive for antituberculosis antibodies. Suspected cases refer to those who meet one of the following criteria: (1) examination of CXR demonstrating pathological changes in accord with active tuberculosis; (2) children ≤ 5 years old who have cough and expectoration for ≥ 2 weeks, hemoptysis, and other suspected symptoms of tuberculosis, and with TST ≥ 10 mm, or with positive IGRA test, or positive for antituberculosis antibodies.

Close contacts in this context involve students and teachers who study/teach in the same classroom or live in the same dormitory as the tuberculosis patient (for at least seven consecutive days, or for a total of at least 40 hours within 3 months of diagnosis and within 14 days of initiating therapy). LTBI refers to individuals with a positive TST (PPD ≥ 10 mm) or IGRA test. Epidemiological links refer to definite close contacts between the index and secondary cases, or where it has been proved by laboratory evidence that the TB strains share the same genotype.

Field investigation

After identifying an active tuberculosis case among students, staff from the CDC conducted epidemiological field investigations and close-contact investigations immediately. Close contacts were asked whether they had suspected symptoms of tuberculosis, such as cough, expectoration, and hemoptysis, and to undergo a TST and CXR scan. Students with TST < 5 mm and normal CXR scan were advised to retake the TST after 2–3 months; students with TST ≥ 5 mm and < 15 mm and normal CXR scan were advised to retake the CXR after 3 months; and students with TST ≥ 15 mm and normal CXR scan who were considered as having a recent LTBI were recommended to receive preventive

treatments. Individuals with abnormal CXR scans were transferred to local hospitals designated for treating tuberculosis, for further diagnosis. Acid-fast staining (Ziehl–Neelsen method) and/or cultures (Lowenstein–Jensen media) and GeneXpert MTB/RIF were conducted on suspected cases. If participants were microbiologically negative on all these tests, they received anti-inflammatory therapy (not including antituberculosis drugs) as a diagnostic treatment. If participants failed to respond to this therapy, they were given antituberculosis therapy for 1–2 months. For clinically diagnosed tuberculosis, a diagnosis was given retrospectively, based on the participant's response to antituberculosis therapy, which was confirmed by a panel of experts consisting of two physicians, three radiologists, and one laboratory expert. TSTs were performed using the Mantoux method. An intradermal injection of 0.1 mL of 5 tuberculin units of purified protein derivative was used. After 48–72 hours TST results were read. (Huebner et al., 1993). T-SPOTs were performed immediately after the TSTs. Spots were counted with a magnifying glass and expressed as the number of spots per million peripheral blood mononuclear cells.

According to Chinese guidelines, in addition to meeting the aforementioned definition, a clinically diagnosed student case should also satisfy the following conditions: (1) at least three negative sputum smear microscopy assessments; (2) at least one negative culture or *Mycobacterium* nucleic acid test (such as GeneXpert MTB/RIF); (3) diagnosis by a panel of experts.

Statistical analysis

Standard 2×2 contingency tables were used to summarize the categorical variables. The frequencies of categorical variables were compared using Pearson χ^2 and Fisher exact tests, as appropriate. Data were analyzed using SPSS software (version 23.0, IBM Corporation, Armonk, NY), as described previously (Lu et al., 2020).

Ethical considerations

The CDC of Jiangsu Province reviewed and approved this study. All eligible participants signed the written informed consent.

Results

Analysis of the epidemic

In total, 10 confirmed active tuberculosis cases were diagnosed among those in the same class as the index case, giving an incidence rate of 19.2% (10/52). LTBI rates among close contacts of the index case, contacts of secondary cases, and total contacts were 16.8% (20/119), 9.0% (50/558), and 10.3% (70/677), respectively (Tables 1 and 2). As shown in Supplementary Figure 1, most of the student cases were those seated adjacent to the index case. According to the field epidemiology, there was a strong possibility that the tuberculosis cluster epidemic in this school was a homologous outbreak.

Description of the index case

On September 19, 2020, one 17-year-old male student tested positive for bacterial tuberculosis, with sputum smear microscopy result of 1+. According to his self-report, he had been coughing and expectorating for 1 week, with hemoptysis, but did not have any suspicious symptoms prior to this. The patient had developed paroxysmal non-irritating cough after feeling cold 1 week previously, with a little white sputum, no fever, no sore throat, and no joint pain. On September 17, 2020 he attended hospital for a computed tomography (CT) scan, which showed scattered miliary, nodular, and patchy high-density shadows in both

Table 1
Screening of close contacts between teachers and students of index case

Class	Occupation	Screening items		Results					
		Chest X-ray	TST	Abnormal X-ray	Abnormal CT scan	PPD (mm)			
						≤ 5 N (%)	≥ 5 and <10 N (%)	≥ 10 and < 15 N (%)	≥ 15 or blister N (%)
Senior one	Students	52	52	0	None	40 (76.9)	10 (19.2)	2 (3.8)	0
Senior one	Teachers	10	10	0	None	3 (0.3)	5 (50.0)	2 (20.0)	0
Junior Three A	Students	50	50	2	9	29 (0.6)	7 (14.0)	11 (22.0)	3 (6.0)
Junior Three A	Teachers	7	7	0	0	4 (0.6)	1 (14.3)	1 (14.3)	1 (14.3)
Total		119	119	2	9	76 (63.9)	23 (19.3)	16 (13.4)	4 (3.4)

TST = tuberculin skin test; PPD = purified protein derivation of tuberculin; CT = computed tomography

Table 2
Screening of close contacts between teachers and students of secondary cases (n = 9)

School	Case	Numbers who should have been screened	Numbers screened	Results					
				Tests		PPD (mm)			
				N of TST	N of chest X-ray	≤ 5* N (%)	≥5 and < 10* N (%)	≥ 10 and < 15* N (%)	≥ 15 or blister* N (%)
School B	Case 1	62	62	62	62	52 (83.9)	7 (11.3)	1 (1.6)	2 (3.2)
School C	Case 2	67	67	66	67	54 (81.8)	9 (13.6)	3 (4.5)	0
School B	Case 3	65	65	63	65	41 (65.1)	4 (6.3)	10 (15.9)	8 (12.7)
School D	Case 4	60	60	59	60	49 (83.1)	6 (10.2)	4 (6.8)	0
School E	Case 5	63	63	62	63	45 (72.6)	13 (21.0)	2 (3.2)	2 (3.2)
School A	Case 6	62	62	61	62	48 (78.7)	8 (13.1)	3 (4.9)	0
School A	Case 7	63	62	62	62	51 (82.3)	7 (11.3)	4 (6.5)	0
School F	Case 8	65	65	62	65	56 (90.3)	1 (1.6)	5 (8.1)	0
School F	Case 9	64	64	61	64	55 (92.0)	0	0	6 (9.8)
Total		571	570	558	570	451 (80.8)	55 (9.9)	32 (5.7)	18 (3.2)

TST = tuberculin skin test; PPD = purified protein derivation of tuberculin

lungs, after which he was advised to attend a municipal hospital designated for treating tuberculosis, for further diagnosis. After undergoing sputum smear microscopy (1+), he was confirmed as having active tuberculosis on September 19.

Contact investigation

After the tuberculosis case had been confirmed, local staff from the CDC immediately conducted an initial contact investigation in the same (senior) class of the index case on September 19. In total, 62 close contacts, including 52 students and 10 teachers, were asked to undergo TST and CXR. None of the close contacts had abnormal CXR, while the rates of positive PPD ≥ 5 mm, ≥ 5 mm and < 10 mm, and ≥ 10 mm and < 15 mm were 24.2% (15/62), 6.5% (4/62), and 0, respectively (Table 1). None of these close contacts had an induration diameter of PPD ≥ 15 mm.

According to the definition of close contacts, 50 students and 7 teachers in Junior 3 (who were in the same class with the index case before the senior one) were screened by TST and CXR. Of these, two had abnormal CXR scan (nodular and patchy high-density shadows) and induration diameters of PPD of 12.5 mm and 13.0 mm, respectively. After CT scan, sputum smear, and GeneXpert MTB/RIF testing, both individuals were diagnosed as active tuberculosis cases, with negative bacteria, on October 5 and 10, respectively.

Of the four students with PPD ≥ 15 mm or blistering, who needed to have preventive treatments, two were diagnosed as suspected tuberculosis following CT scans. After sputum smear and GeneXpert MTB/RIF tests, both were diagnosed with active tuberculosis on October 12 (one with a negative bacteria result and one with a positive GeneXpert MTB/RIF). Of the other two with PPD ≥ 15 mm or blistering, one received preventive treatment, while the other (a teacher) refused treatment, with both due to undergo CXR after 3, 6, and 12 months.

Of the 12 contacts with PPD ≥ 10 mm and < 15 mm, two were the confirmed tuberculosis cases with abnormal CXR. Nine of the others underwent T-SPOT testing, of whom five returned positive results. Three of these produced abnormal CT scans, and were diagnosed as active tuberculosis cases after sputum smear and GeneXpert MTB/RIF tests. The other two underwent preventive treatment.

Thirty-three of the 57 students had PPD ≥ 5 and < 10 mm. Two of these decided to attend hospital to undergo CT scans, and both were diagnosed as having active tuberculosis with negative bacteria tests on October 24 and November 11, respectively (Figures 1 and 2). Thus, in Junior 3, the positive rates for TST ≥ 5 mm and < 10 mm, ≥ 10 mm and < 15 mm, and ≥ 15 mm or blistering were 14.0% (8/57), 21.1% (12/57), and 7.0% (4/57), respectively (Table 1).

In total, 10 students in Junior 3 were diagnosed with active tuberculosis cases. These 10 students were located in six different high schools, where a new contact investigation was conducted for 571 close contacts, of whom 570 (99.8%) were investigated. None of the 570 students had an abnormal CXR scan, and none was diagnosed as a tuberculosis case (Supplementary Figure 2). Positive rates among student and teacher contacts for TST ≥ 5 mm and < 10 mm, ≥ 10 mm and < 15 mm, and ≥ 15 mm or blister were 0–21.0%, 0–15.9%, and 0–12.7%, respectively (Table 2). Positive rates among just student contacts for TST ≥ 5 mm and < 10 mm, ≥ 10 mm and < 15 mm, and ≥ 15 mm or blister were 0–17.3%, 0–10.0%, and 0–8.0%, respectively (see Supplementary Table 1).

Given that teachers spend less time in contact with patients, and considering other confounding factors, it was decided to compare the positive rates for TST between student contacts. As shown in Figure 3, the positive rates for of TST ≥ 10 mm and < 15 mm and ≥ 15 mm or blister in contacts of the index case were much higher than those for secondary cases (p < 0.001 and p = 0.020, respectively). The same result was found for contacts in different classes of the index (p = 0.145

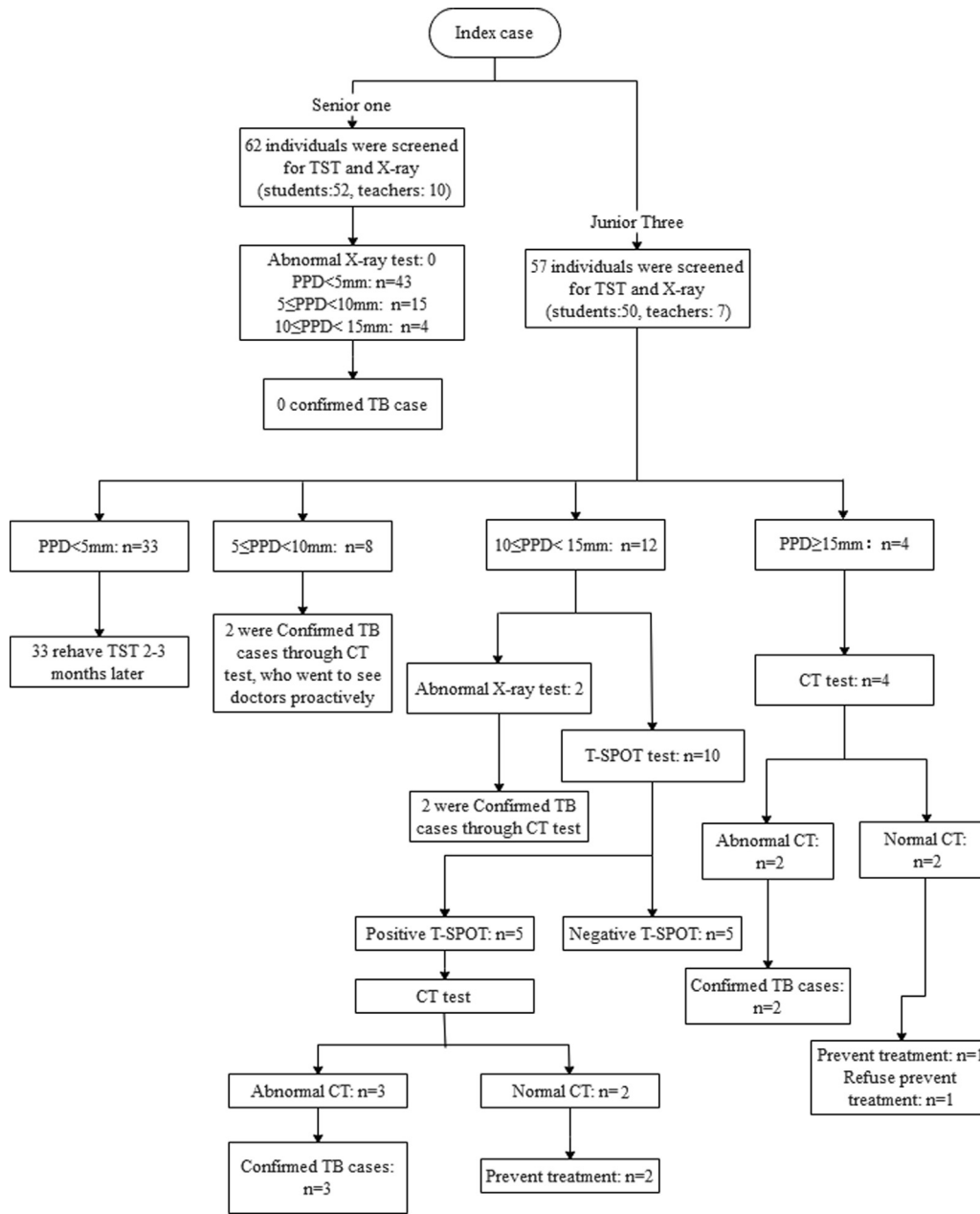


Figure 1. Diagnosis and exclusion of all suspected cases found during the whole investigation of close contacts in the school

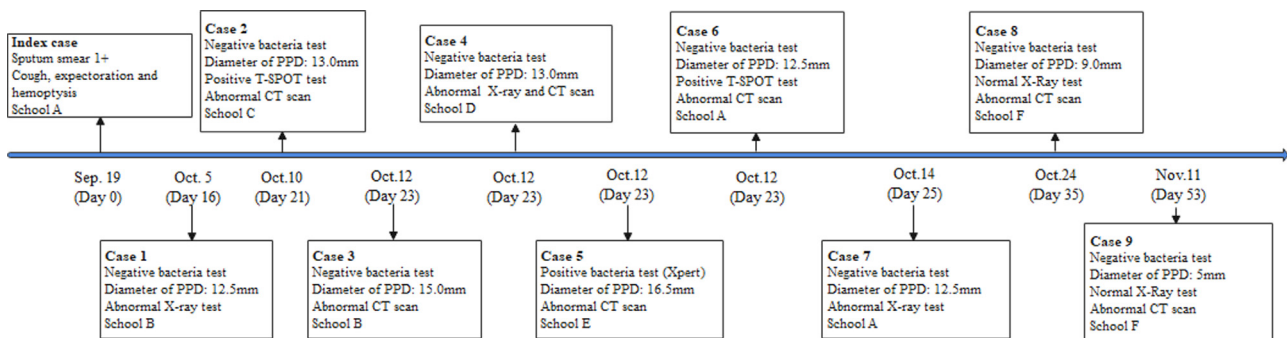


Figure 2. Timeline of confirmed tuberculosis cases, Jiangsu Province, China

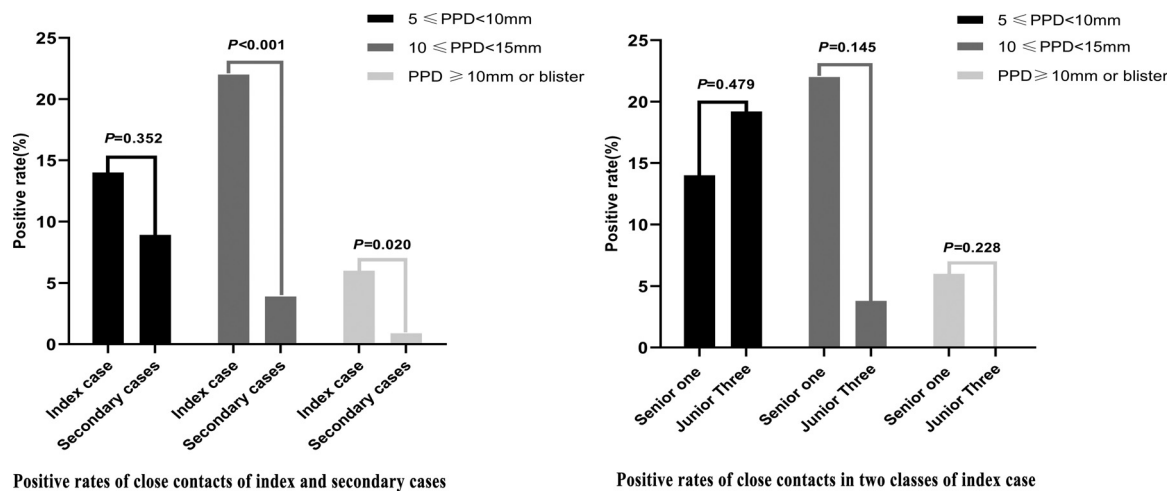


Figure 3. Positive rates for close contacts of the index case in different classes and secondary cases

Table 3

Characteristics of active tuberculosis cases identified during a school outbreak, Jiangsu, China, 2020 (n = 10)

Case	School	Sex	Symptoms	Discovery approach	PPD (mm)	Chest X-ray	T-SPOT	CT scan	Microscopy	Xpert	Date of diagnosis
Index case	School A	Male	Cough, expectoration, hemoptysis	Proactive visit	None	Abnormal	None	Abnormal	1+	Positive	September 19
Case 1	School B	Female	None	Screen	12.5	Abnormal	None	Abnormal	Negative	Negative	October 5
Case 2	School C	Female	None	Screen	13.0	Normal	Positive	Abnormal	Negative	Negative	October 10
Case 3	School B	Female	None	Screen	15.0	Normal	None	Abnormal	Negative	Negative	October 12
Case 4	School D	Female	None	Screen	13.0	Abnormal	Positive	Abnormal	Negative	Negative	October 12
Case 5	School E	Female	None	Screen	16.5	Normal	None	Abnormal	Negative	Positive	October 12
Case 6	School A	Female	None	Screen	12.5	Normal	Positive	Abnormal	Negative	Negative	October 12
Case 7	School A	Male	None	Screen	12.5	Normal	Negative	Abnormal	Negative	Negative	October 14
Case 8	School F	Female	None	Proactive visit	9.0	Normal	None	Abnormal	Negative	Negative	October 24
Case 9	School F	Male	None	Proactive visit	5.0	Normal	None	Abnormal	Negative	Negative	November 11

TST = tuberculin skin test; PPD = purified protein derivation of tuberculin; CT= computed tomography

and p = 0.228, respectively), although the results were not statistically significant, probably due to the small sample size.

Characteristics of active tuberculosis

In total, 10 active tuberculosis cases (including the index case) from the same junior high school and six other high schools were found in this outbreak. Among these 10 cases, three (30%) were male and seven (70%) were female; two (20%) had positive bacteria tests and eight had negative bacteria tests diagnosed by CT scan; three (30%) were found through proactive visits and seven (70%) through screening. Among the nine cases found in the secondary school, two (22.2%) had TST ≥ 15 mm or blister, five (55.6%) had TST ≥ 10 mm and < 15 mm, and two (22.2%) had TST ≥ 5 mm and < 10 mm (Table 3).

Discussion

School tuberculosis outbreaks are of particular concern for public health (Bran et al., 2006; Phillips et al., 2004; Rodríguez et al., 2007; Tagarro et al., 2011). Such outbreaks have been reported previously in countries with low endemicity, such as the UK, Italy, Ireland, and the USA (Cinquetti et al., 2019; Ridzon et al., 1997; The Lodi Tuberculosis Working Group, 1994; Stein-Zamir et al., 2006). However, they have become more common in China due to the specific educational environment in which students experience much pressure from the exam system (e.g. nationwide college entrance examinations), and are often exposed

to poor living conditions (e.g. crowded conditions with poor ventilation) and diagnostic delays (Faccini et al., 2013; Toyota and Morioka, 2001).

Our findings from this school tuberculosis outbreak suggest that more attention should be paid to students with PPD ≥ 5 mm and < 15 mm when their class includes three or more active tuberculosis cases who have epidemiological links. IGRA tests could be used on these individuals to find more recently infective cases, and CT scans could be used to confirm whether they are potential active tuberculosis cases before having preventive therapies.

TST and IGRA are the two tests recommended by WHO for testing LTBI (WHO, 2020). High-risk groups with positive TST (PPD ≥ 5 mm or 10 mm) or IGRA tests should have preventive therapies. However, in China, students with PPD ≥ 15 mm or positive IGRA test and normal CXR scan are classed as recent LTBI, and are required to receive preventive treatment. For students with PPD ≥ 5 mm and < 15 mm, no further treatment is required, except for reinforcing postoperative follow-ups or performing CXR 3 months after the first screening.

In this outbreak, after conducting T-SPOT on individuals with PPD ≥ 10 mm and < 15 mm, three additional tuberculosis cases were found with normal CXR scans, while CT scans revealed two extra tuberculosis patients among students with PPD ≥ 5 mm and < 10 mm. Because BCG vaccination has been widely applied in China, 10 mm is used as the cutoff value for a positive TST test (Lu et al., 2020). With regard to students, who are considered as a distinct group in China, there is no test available that distinguishes recent from remote tuberculosis infections, and students with PPD ≥ 15 mm are recommended to have preventive treatment. Our study supports this strategy, yet in certain

conditions, such where there are three tuberculosis cases who have an epidemiological link in one class, it is important to consider students with PPD ≥ 5 mm and < 15 mm. If there are three or more confirmed tuberculosis cases in one class, this indicates that the transmission is not recent, emphasizing the impact of a delay in diagnosis, which is one of the most important factors behind tuberculosis outbreaks. Regarding the index case's denial of having suspicious symptoms, such as cough, sputum, and hemoptysis, this was probably due to the non-specific nature of these clinical symptoms, which may be caused by other conditions, leading to possible confusion.

Another factor requiring more attention is that tuberculosis is a chronic infectious disease, with a window period (time between infection and when the immunological response becomes measurable) of up to 8 weeks; this means that extra time is needed to test a case's infection status. Since both TST and IGRA have window periods (Anibarro et al., 2011; Menzies, 1999), misclassification of infection status might occur, which may categorize recent infection cases as remote or non infections. To increase sensitivity, some countries (Canada, Italy, Spain, and Saudi Arabia) have introduced a two-step approach, whereby individuals with negative TST undergo an IGRA test (Denkinger et al., 2011). Considering the high cost and the complexity of these processes, this new two-step approach is recommended for students with PPD ≥ 5 mm and < 15 mm, following the TST test, when there are three tuberculosis cases with an epidemiological link within the same class.

In total, seven students with normal CXR were diagnosed by CT scan. The diagnosis of tuberculosis in children is often challenging because their clinical symptoms are not obvious, resulting in difficulty in providing specimens, and they often have a low bacillary load (Heuvelings et al., 2019; Marais and Schaaf, 2014; Sodhi et al., 2017). Only 20–50% of children are diagnosed microbiologically with tuberculosis (Bélarde et al., 2018; Sodhi et al., 2017). The CT scan is superior to CXR in terms of recognizing radiological signs of tuberculosis, due to its higher resolution and sensitivity in distinguishing non-specific and interobserver variability in imaging manifestations (Andronikou et al., 2009; George et al., 2017; Heuvelings et al., 2019). Furthermore, tuberculous lymphadenopathy is a primary disease that occurs among children, and yet CXR scan has poor sensitivity in detecting mediastinal and hilar lymphadenopathy (Bhalla et al., 2015; Concepcion et al., 2017; Nachiappan et al., 2017). In contrast, CT has been regarded as the gold standard for demonstrating the presence of lymphadenopathy in children with primary tuberculosis, and can distinguish early features of the disease (lymphadenopathy, nodules, small pleural effusions) before these can be detected by CXR (Concepcion et al., 2017; George et al., 2017; Sodhi et al., 2017). Therefore, CT scans are recommended for individuals with recent infections, before beginning preventive therapy.

Delayed diagnosis is a major factor in the emergence of school tuberculosis outbreaks, combined with the prolonged exposure of school children (Cinquetti et al., 2019; Wu et al., 2018). This is fully demonstrated by the high infection rates among index and secondary cases, and the high incidence among students in the same class. The short distance between contacts and index cases plays an important role in causing *M. tuberculosis* transmission. This was demonstrated by our study, whereby most secondary cases were seated adjacent to the index case, according to the seat map for the index patient's class. Thus, prolonged exposure of contacts to the index case aggravated the tuberculosis outbreak. The index case continued to attend classes and stay in school after consulting a doctor, which would have increased the transmission risk (Black et al., 2018). Measures such as morning check-ups, registration of absenteeism due to illness, and tracking systems should be reinforced by schools.

The results of this school outbreak study reinforce the need to conduct contact screening as soon as possible. Furthermore, it is important to distinguish the different contact groups. According to Chinese guidelines, the time required to confirm contacts is 3 months. Thus, given that fresh graduates from the same junior middle school may move up to different schools, it remains necessary to continue to trace them in order to avoid new school outbreaks.

The main limitation of our study was that sputum cultures were not collected. Without isolates of *Mycobacterium tuberculosis*, it was not possible to conduct genome-wide sequencing analysis to confirm the transmission network between index and secondary cases.

Conclusions

As a result of this specific school outbreak, a new screening process is recommended that involves conducting IGRA tests on those students with PPD ≥ 5 mm and < 15 mm if there are three or more active tuberculosis patients with an epidemiological link in one class. Furthermore, CT scans are recommended for students with a recent tuberculosis infection, before they undergo therapy.

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Availability of data and materials

Please contact the first author for data requests.

Ethical approval and consent to participate

The CDC of Jiangsu Province reviewed and approved this study. All eligible participants signed the written informed consent.

Consent for publication

All coauthors consent to this submission.

Competing interests

The authors declare no conflicts of interest.

Authors' contributions

Peng Lu conceived the study, analyzed the data, and drafted the manuscript; Limei Zhu, Qiao Liu, and Wei Lu participated in the study design; Feng Lu and Ling Tang implemented the field investigation; Xiaoyan Ding and Wen Kong participated in the study design. All authors contributed to the study and have read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijregi.2021.10.012](https://doi.org/10.1016/j.ijregi.2021.10.012).

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