Concurrent Outbreaks of Tuberculosis in a School and the Wider Community in Macau

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Between 2009 and 2012, 22 adolescents of age 15–20 from a day school in Macau were diagnosed with tuberculosis. Detection of multiple molecular clusters may suggest the presence of concurrent outbreaks, and could reflect also ongoing transmissions in the community. Careful interpretation of molecular epidemiology data is crucial in contact investigations.

Key words. contact investigation; molecular epidemiology; RFLP; school; tuberculosis.

Tuberculosis (TB) in schools is a public health concern because of the potential risk of outbreaks in children and adolescents. School outbreaks have been sporadically reported in low burden countries [1–3], where the tuberculin skin test (TST) was a common tool for contact investigation to detect latent TB infection (LTBI) [1, 2, 4]. The situation in countries with a higher TB prevalence in the community is less well understood. The application of TST in such settings should be approached with caution because reactions arising from previous or repeated Bacille Calmette-Guerin (BCG) vaccinations may make disease interpretation difficult. In this study, we report the investigation of a TB outbreak in a school in Macau, a city with intermediate TB burden. With a population of 0.58 million in 2012 and an area of 29.9 km², the city of Macau (a Special Administrative Region of China) has the highest population density in the world. The proportion of Macau’s population aged 20 or below was 20.3% in 2011. These unique characteristics prompted us to analyze the transmission dynamics of TB by observing epidemiologic patterns of the infection in a school setting.

PATIENTS AND METHODS
In the last 5 years, 400 TB cases (69/100 000) were reported annually to the Health Department in Macau. Less than 10% of these cases were school-aged children and teenagers or related cases detected after contact investigations. In January 2009, a 15-year-old girl (no. 1) presented with cough and weight loss, and she was subsequently diagnosed with smear-positive pulmonary TB in a secondary day school in Macau. Contact investigations, comprising symptom screening, TST (single test), and chest radiography were conducted for classmates, teachers, interest group (Chinese Calligraphy) schoolmates, and close friends in the school. Together with family members, they were defined as close contacts. In view of concern for rapid expansion of the outbreak, a school-wide screening program, using chest radiography, was conducted in January 2010. To characterize the outbreaks, restriction fragment length polymorphism (RFLP) analyses were retrospectively performed, illustrated in phylogenetic tree, on positive isolates obtainable in the course of the investigations [5, 6].

RESULTS

Epidemiological and Clinical Presentations
The TB outbreak occurred in a coeducational school for junior secondary (J1–J3, age 13–15) and senior secondary (S1–S3, age 16–18) students. The school campus, located in Central District of Macau, was an old one where some
2000 students attended class regularly. After report of the first case, follow-up investigation led to the diagnosis of 1 classmate (no. 2) with active disease in the following month. TST for classmates and close-contact students yielded 26 LTBI of 56 screened (46.4%), using 15 mm as the cutoff for positivity [7]. Within a 5-month period, 5 other students (nos. 3–7) from different classes in the same school presented with various forms of TB disease. Four more classmates (no. 12, no. 16, no. 17, and no. 19) of student no. 6 were further identified as disease cases after contact tracing. After the school-wide screening program, 7 TB disease cases (nos. 8–11, nos. 13–15) were identified, all of whom were either family members, students in same class of previously diagnosed cases, or were their close friends. No new TB case was detected from August 2010 until June 2011, when 1 more symptomatic student was identified (no. 19) during contact tracing. He had previously shared the same classroom with case no. 6. Thereafter, 4 more students (no. 18, no. 20, no. 21, and no. 22) were diagnosed with TB disease within a 13-month period between August 2011 and September 2012. They did not have any close relationship with previously diagnosed students, except 1 (no. 18), who was in the same class as 2 known TB cases (no. 3 and no. 14) in the school.

Between January 2009 and December 2012, a total of 22 students were diagnosed with TB disease, the social and temporal relationship of whom is depicted in Figure 1. No TB diagnoses were made among teachers and staff. Clinically, 10 (45.5%) students presented with respiratory symptoms.

Figure 1. Categorization of cases by different modes of tuberculosis diagnosis and their temporal and social relationships in a school outbreak in Macau (n = 22). RFLP, restriction fragment length polymorphism.
symptoms, of whom 5 of 22 (23%) were smear-positive. Treatment with standard anti-TB regimen (comprising isoniazid, rifampicin, pyrazinamide, and ethambutol) was given, and 21 (95%) students eventually completed the full course of therapy. One student, an 18-year-old boy, died of aggressive pulmonary TB. Overall, TST had been performed on 484 students (median age, 16; inter-quartile range, 15–17), of whom 172 (35.5%) tested positive using a cutoff of 15 mm, compared to that of 58.9% (33 of 56) in teachers and staff. Among the students, testing in 2009 (compared to 2010 and 2011) and history of previous testing were associated with a higher rate of positive results. A total of 120 (69.8%) of the TST-positive students subsequently received LTBI treatment, and all except 11 eventually completed the course.

Molecular Characterization
RFLP analyses were performed on 14 microbiologically confirmed cases with available isolates. For comparison, 47 community cases diagnosed during the same period and residing in the same districts in Macau were concurrently evaluated (see Supplementary Figure 1). Three genetically related clusters could be delineated among the students (Figure 1): Cluster A (n = 3), B (n = 3), and C (n = 4), alongside 4 additional cases with different genotypes who were nonclustered. Cluster A comprised the first case diagnosed in January 2009, one of her classmates in J3 (no. 11), and her sister (no. 15), both siblings were detected on school screening. Cluster B comprised 3 students in the same class in S1, but the classroom was located on a different floor from students of Cluster A. Two of them presented with disease for consultation, whereas a third one was diagnosed only upon school screening. Cluster C was made up of 4 students, 3 of whom were from the same class in S2 but separate from those of Clusters A and B. The fourth student (no. 20) was in J1 and belonged to a class on the same floor as the 3 senior students. There were 4 other cases that showed RFLP patterns completely different from the 3 clusters: one came from the same class as cases of Cluster A, 2 were from 1 class not associated with any cluster, and the remaining one was from yet another class where a student with culture-negative isolate was diagnosed. Three consecutive cases diagnosed from May to July 2010 did not belong to the same molecular cluster. Of the 47 background community cases, I had an RFLP pattern identical to Cluster C. He was a 53-year-old male unrelated to the school or family of the outbreak students.

DISCUSSION
Although school outbreaks of TB have been sporadically reported in the literature, these often represented common source outbreaks with the index cases traceable to students [1, 8], teachers and staff [2, 4], or school bus drivers [3]. The current outbreak involved multiple sources in a high-density susceptible population. The school environment might have been one of the predisposing factors [9, 10], because the small congested classrooms could lead to close contacts with contagious adolescent cases. The TB incidence of the school was high at 0.59% in 2010. The outbreak took place when the school was planning to be relocated. Further transmissions seemingly subsided in the first quarter of 2011, 1 year after closure of the old campus. On the other hand, TB might have been introduced through repeated exposure in some families, because 4 of the 22 cases were family members of diagnosed cases. The identification of 1 background case in the community showing identical RFLP with 1 of the clusters but without demonstrable epidemiologic linkages suggested concurrent transmission of the genotypically specific Mycobacterium tuberculosis in the society [11]. The school TB outbreak in Macau was therefore likely part of a larger network of community transmissions. The high population density of this small city and its close proximity to high TB burden (prevalence and incidence) areas, alongside the heavy population flows, could have fuelled its spread. The school population constituted a particularly susceptible community that heralded the larger outbreak, which might otherwise not be uncovered.

In conducting contact investigation, the high background BCG vaccination coverage in Macau could have resulted in a high TST positivity rate, despite the adoption of a high cutoff [7]. In the current outbreak, over one-third of the student contact cases were diagnosed as LTBI, a figure that was higher than an average of 20% among TB contacts in other schools in Macau (statistical data not shown) in the same years. The over 50% positive rate in staff and teachers could have been a cohort effect because older people had a higher chance of previous exposure to Mycobacterium tuberculosis, especially in intermediate or high burden localities. The effect of repeat testing cannot be excluded. The high prevalence of LTBI in students in the school reflected enhanced exposure to TB, which in turn supports the occurrence of ongoing transmission within the school. To overcome the shortcoming of TST, interferon-γ release assays (IGRA) might play a role for confirming LTBI in school outbreaks in high BCG-vaccinated populations [12]. The specific role of IGRA however needs to be evaluated in larger studies in localities with different levels of TB burden.

Finally, our investigations suggest that molecular typing, supplemented with standard contact investigations with radiography [11], is useful in the public health control of TB
spread in school in intermediate burden localities. However, careful interpretation of molecular data in a broader context is crucial.

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