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Transmissibility of tuberculosis among school contacts: An outbreak investigation in a boarding middle school, China

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ABSTRACT

Tuberculosis (TB) outbreak occurred in a boarding middle school of China. We explored its probable sources and quantified the transmissibility and pathogenicity of TB. Clinical evaluation, tuberculin skin testing and chest radiography were conducted to identify TB cases. *Mycobacterium tuberculosis* isolates underwent genotyping analysis to identify the outbreak source. A chain-binomial transmission model was used to evaluate transmissibility and pathogenicity of TB. A total of 46 active cases were ascertained among 258 students and 15 teachers/staff, an attack rate of 16.8%. Genetic analyses revealed two groups of *M. tuberculosis* cocirculating during the outbreak and possible importation from local communities. Secondary attack rates among students were 4.1% (2.9%, 5.3%) within grade and 7.9% (4.9%, 11%) within class. An active TB case was estimated to infect 8.4 (7.2, 9.6) susceptible people on average. The smear-positive cases were 28 (8, 101) times as infective as smear-negative cases. Previous BCG vaccination could reduce the probability of developing symptoms after infection by 70% (1.4%, 91%). The integration of clinical evaluation, genetic sequencing, and statistical modeling greatly enhanced our understanding of TB transmission dynamics. Timely diagnosis of smear-positive cases, especially in the early phase of the outbreak, is the key to preventing further spread among close contacts.

1. Introduction

Tuberculosis (TB), a respiratory disease transmitted mainly via the aerosol route, is caused by the acid-fast bacillus *Mycobacterium tuberculosis* (*M. tuberculosis*) (Fu and Fu-Liu, 2002). Although the annual incidence has been declining steadily over the past decade, on average by 3.4% per year since 1990 (WHO, 2015), China still ranks the second globally in terms of TB burden. In China, the Bacille Calmette–Guérin (BCG) vaccine is part of the national childhood immunization program which requires newborns to be vaccinated for free. The government-reported national BCG vaccine coverage of newborns has remained above 90% for most of the years since 1990 (WHO, 2014); however, local coverage rates vary substantially with urban/rural indicator, parental education level, and access to health services as strong predictors, especially in less-developed regions (Ciren et al., 2007; Xie and Dow, 2005). TB outbreaks usually occur in institutional settings and have been reported in kindergartens, primary schools, boarding schools, and colleges (1994; Hoge et al., 1994; Quigley, 1997). Boarding schools are subject to a higher risk of TB outbreaks, where adolescents often cluster under relatively overcrowded conditions (ATS, 2000; Cohn et al., 2000; Oelemann et al., 2007; WHO, 2009a,b). Because laboratory diagnostic approaches have low yield in teenagers (Wootton et al., 2005;

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You and Duanmu, 2006), the diagnosis of TB in this age group primarily relies on clinical manifestations.

We report here a TB outbreak from May to October of 2011 among students of a boarding school in Shijiazhuang City, Hebei Province. In September 2011, upon the reporting of culture positive pulmonary TB in three students from the same class, an epidemiologic investigation was carried out in the school by the municipal Center for Disease Prevention and Control (CDC) of Shijiazhuang. This effort of case finding and outbreak control was part of the CDC's responsibility, and was therefore not subject to institutional review.

This outbreak also provided a unique opportunity for evaluating the transmissibility of TB and associated risk factors such as smear positivity and BCG vaccination history in school mixing settings. Such evaluation will be extremely useful for future efforts in predicting the trend of TB transmission and assessing effectiveness of control programs using mathematical models (Abu-Raddad et al., 2009). Another goal of our study is to use molecular tools to identify the source of the outbreak. This school was relocated to Hebei from Yushu County of Qinghai Province in westerner China after an earthquake on April 14, 2010. The annual incidence rates of active TB in 2010 are 463 cases/100,000 persons in western China (where Qinghai is located) and 659 cases/100,000 in central China (where Hebei is located), a difference not very indicative of the geographic source of the outbreak. If the outbreak was introduced from the current local community, it would potentially affect future policies of disease prevention in migrating population of juveniles. For example, it may be necessary to migrate the juveniles to places with more resources for better hygiene practices, active surveillance and early diagnosis.

2. Materials and methods

2.1. Case definition and clinical outcomes

A "TB case" was defined according to the diagnosis criteria published by the World Health Organization (WHO) (WHO, 2002). Briefly, laboratory-confirmed cases were defined as those with *M. tuberculosis* present in sputum smear or culture. Clinical cases were defined as those for which *M. tuberculosis* or other pathogens could not be cultured but that were characterized by a radiologic, pathologic, or therapeutic response, and/or a positive tuberculin skin test (TST) that was consistent with active tuberculosis. The criteria for positivity of TST will be given in Section 2.2. On the basis of clinical presentation and/or laboratory results, cases were also classified as pulmonary and extra-pulmonary, and pulmonary was sub-classified as pulmonary alone or with extra-pulmonary diseases. Treatment outcomes were classified according to the WHO criteria (WHO, 2002).

2.2. Case detection and epidemiological investigation

Systematic TB screening of contacts, defined as all teachers and students from this school, was performed by clinical evaluation, TST, and/or chest radiography (CXR). TST was performed by the Mantoux method using PPD tuberculin with 48–72 h to assess the reaction. The TST positivity was defined as $\geqslant$15 mm of induration if BCG vaccinated and $\geqslant$5 mm if unvaccinated. TST-positive persons were referred for further clinical assessment. Persons with chest radiograph abnormalities compatible with TB underwent further diagnostic evaluation. Diagnosis of latent or active tuberculosis was made by a consultant physician specialized in respiratory diseases.

Each case was interviewed by a CDC staff to collect information on close contacts, personal and family history of TB disease and treatment, and recent symptoms. Medical records of each patient were carefully reviewed to verify the recent history of symptoms and diagnosis for other diseases.

2.3. Genomic investigation of *M. tuberculosis*

The 24-loci MIRU-VNTR (Oelemann et al., 2007) and spoligotyping was performed on 13 outbreak isolates (coded as MT001–MT013) and 20 historic isolates. Of the historic isolates, six (HB001–HB006) were collected from Shijiazhuang, Hebei Province (where the outbreak occurred) and 14 (QH001–QH014) from the Yushu County, Qinghai Province (from where the students originally came). A total of 17 *M. tuberculosis* isolates (13 outbreak and 4 historic strains from Shijiazhuang) were sequenced with Ion Torrent (Life Technologies, San Francisco, CA). Phylogenetic trees

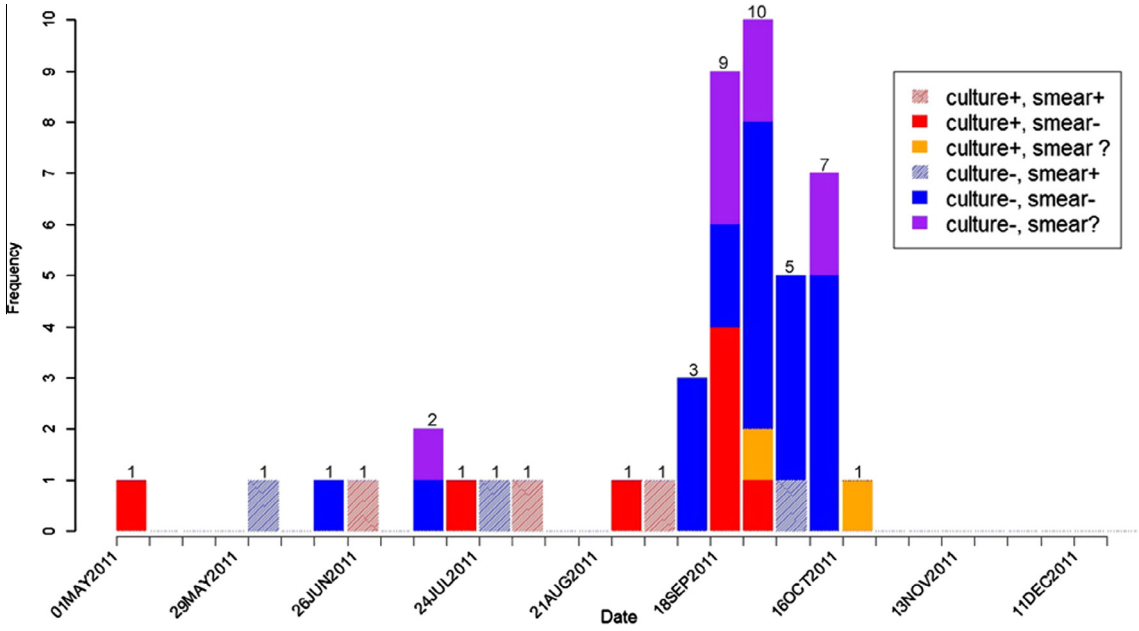

Fig. 1. Epidemic curve for the TB outbreak among students and staff attending a boarding middle school in China. The question marks represent indetermination of sputum smear status.