

## Role of casual contacts in the recent transmission of tuberculosis in settings with high disease burden

W. Wang<sup>1,2</sup>, B. Mathema<sup>3,4</sup>, Y. Hu<sup>1,2</sup>, Q. Zhao<sup>1,2</sup>, W. Jiang<sup>1,2</sup> and B. Xu<sup>1,2</sup>

1) Department of Epidemiology, School of Public Health, Fudan University, 2) Key Laboratory of Public Health Safety (Ministry of Education), Shanghai, China, 3) Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY and 4) Tuberculosis Center, Public Health Research Institute, Newark, NJ, USA

### Abstract

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. It is expected that combining multiple molecular methods will further help in focusing contact investigations. We performed a population-based molecular epidemiological study in six sites in China between 1 June 2009 and 31 December 2010. A genotyping method combining 7-loci MIRU-VNTR and IS6110-based RFLP was employed to determine predictors of recent transmission. A second interview was performed with the clustered patients to identify potential epidemiological links. The molecular clustering analysis revealed that 187 isolates (15.3%) were clustered by sharing identical VNTR-IS6110 combined patterns, with an estimated recent transmission index being 8.9%. None of these patients reported having contacts with other members within the same cluster. Nineteen of 121 reported having a history of contact with a TB case within 2 years before the current TB diagnosis. Additionally, geographical correlation was established for 19 cases in nine clusters, while only one possible epidemiological link was established in secondary interview. The results underscore the role of casual contact or reactivation of latent TB as a driving factor maintaining the current endemicity in rural China, with high disease burdens of tuberculosis.

**Keywords:** Casual contacts, clustering, contact investigation, recent transmission, tuberculosis

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**Corresponding author:** B. Xu, School of Public Health, Fudan University, 138 Yi Xue Yuan Road, Shanghai 200032, China  
E-mail: bxu@shmu.edu.cn

Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. Particularly worrisome is the worldwide emergence of multidrug-resistant (MDR) and extensively resistant forms of *Mycobacterium tuberculosis* (*Mtb*) strains that are difficult to treat and associated with poor therapeutic outcomes [1].

Globally in 2012, data from drug resistance surveys and continuous surveillance among notified TB cases suggest that 3.6% of newly diagnosed TB cases and 20% of those previously treated for TB had MDR-TB [2]. China has the second highest burden of TB worldwide, with c. 1.3 million new TB cases detected annually [3]. Additionally, China is one of the hot spots of MDR-TB, with a prevalence of MDR-TB of 5.7% and

25.6% among new and previously treated cases according to the latest national TB survey in 2008 [4].

Molecular tools have enhanced our understanding of TB epidemiology by providing insight into the transmission dynamics, source and spread of *Mtb* [5,6]. Moreover, molecular epidemiological methods have refined the estimates of recent transmission so that they are important indicators in assessing the effectiveness of TB control programmes [7,8] and identifying previously unrecognized epidemiological links [9,10].

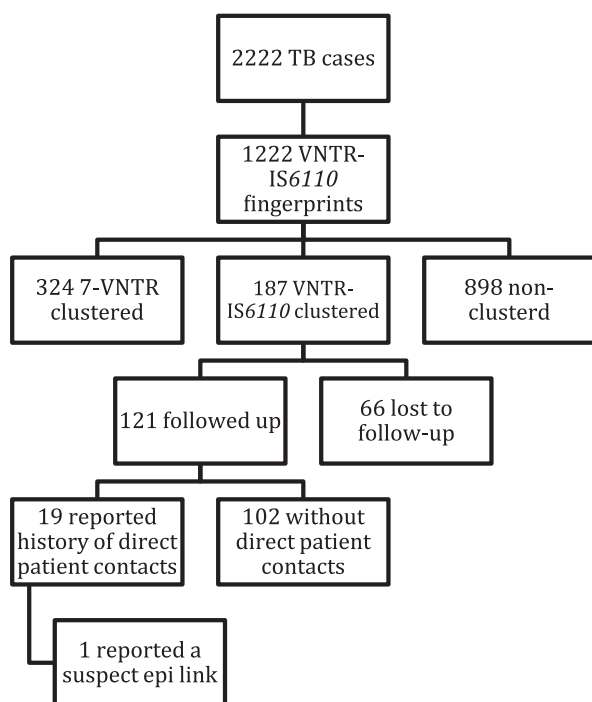
Conversely, genotyping has highlighted some limitations of conventional contact investigations to identify recent transmission. For instance, a molecular epidemiological study suggested that interventions only for close contacts might be inadequate to identify recently infected patients if contact occurs outside the household or close relatives/friends [11]. In Rotterdam, molecular typing identified widespread transmission from multiple sources among drug users, illustrating the limitations of contact investigation in high-risk populations and

prompting an active case-finding programme [12]. In various settings, a substantial proportion of household contacts were infected with a different strain to that of the index case: 30% in California [13] and 54% in Cape Town [14]. The utility of molecular methods in clarifying transmission patterns was heavily dependent on the half-life of biomarker(s) used [15]. As such, it is expected that combining multiple molecular methods such as restriction fragment length polymorphisms (RFLP) typing with biomarkers including mycobacterial interspersed repetitive unit-variable number of tandem repeats (MIRU-VNTR) will further help in focusing contact investigations.

In the present work, we used MIRU-VNTR and IS6110-based RFLP genotyping to understand the transmission of TB in rural China by examining circulating *M. tuberculosis* strains and to determine the predictors of recent transmission.

## Materials and Methods

We performed a population-based molecular epidemiological study at six sites in China between 1 June 2009 and 31 December 2010 (Fig. 1). The field sites cover a total population of about 5.8 million inhabitants; 67% of them were part of a rural population, including three counties (Changshan [CS], Tengzhou [TZ] and Shenxian [SX]) in Shandong Province and three counties (Jianhu [JH], Guanyun [GY] and Ganyu [GYu]) in Jiangsu Province.



**FIG. 1.** Number of cases with different epidemiological contact histories during the follow-ups.

## Study population

Inclusion criteria were patients who had active TB that was bacteriologically confirmed by sputum culture and who provided informed consent for this study. Extra-pulmonary TB cases were excluded from the study. Ethical approval was given by the Ethics Committee of the School of Public Health, Fudan University.

## Data collection

Subjects were interviewed at the time of TB diagnosis at the county TB dispensaries (CTDs) by physicians who underwent a 2-day training course for the interview. A semi-structured questionnaire was developed that covered general demographic and socio-economic characteristics, clinical symptoms and disease history at TB diagnosis. BCG vaccination was determined by self-reporting and confirmed by the presence of a scar at interviewing. Family income was self-reported; the products that families produced during the same time were converted and added to the total income.

A second interview was performed only with clustered patients to identify potential epidemiological links. Each of the clustered patients was interviewed again to obtain more-detailed data that were not recorded at the first interview (e.g. data regarding jobs, detailed migration/relocation information before the onset of TB, entertainment activities and related locations) and more information about known contacts with TB. Finally, the patients were asked whether they could recognize some or all of the patients clustered with them.

During the interview, we asked the participants to give their oral consent to divulge their identity to other TB patients in their cluster. When patients were absent or refused to come, we telephoned the patients or their families to obtain their permission for the disclosure of their identity.

## Molecular characterization

The sputum samples of patients were sent to the reference laboratory in the Shandong Provincial TB Center for culture and drug susceptibility testing. Drug susceptibility testing was performed for isoniazid, rifampin, pyrazinamide and ethambutol on Lowenstein-Jensen solid medium. Drug-resistant TB refers to TB that is resistant to any of the four first-line anti-tuberculosis drugs. MDR-TB is defined as TB that is resistant to at least isoniazid and rifampicin.

*Mycobacterium tuberculosis* genomic DNA was extracted in the laboratory by standard methods [16] and then shipped to Fudan University to genotype the *M. tuberculosis* isolates using a high-resolution 7-loci variable number of tandem repeats (7-VNTR) method that was described by Zhang et al. [17], showing sufficient discriminatory power to differentiate prevalent W-Beijing genotype strains in the Chinese popula-

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