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Original Research

The prevalence of latent tuberculosis infection in rural Jiangsu, China

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ABSTRACT

Objectives: Diagnosis and interventional treatment of latent tuberculosis (TB) infection (LTBI) are important components in tuberculosis control. But systematic studies regarding the epidemic of LTBI are still rare in China. The objective of this study was to assess the prevalence and risk factors associated with LTBI based on the results of a domestic TB-specific gamma interferon (IFN-γ) release assay (TB-IGRA) in rural Jiangsu, China.

Study design: Cross-sectional study of subjects registered in eight villages in Jiangsu, China.

Methods: This study was conducted in 2012 in eight villages. After recruitment, individuals with active TB or a history of TB were excluded. The TB-IGRA was performed for diagnosis of LTBI.

Results: 2169 of 2185 subjects met the requirement and were analysed in this study. 524 (24.3%) had a positive result, and positive rate gradually increased with age (P for trend <0.001). Multivariate analyses showed that increasing age, male gender and a history of TB exposure were risk factors associated with LTBI. Bacillus Calmette-Guérin (BCG) vaccination did not reduce the risk of TB infection in participants (aged ≥20 years).

Conclusions: The findings of this study demonstrate that the prevalence of LTBI in China might be overestimated by tuberculin skin test compared with IFN-γ release assay (IGRA). The degree of TB exposure is related to *Mycobacterium tubercuium* (MTB) infection, and BCG vaccination offers little protection against MTB infection in adults. The early and effective detection and treatment of active TB patients, and screening and intervention for LTBI patients with a high risk of developing active TB could be cost-effective methods for TB control in China.

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Introduction

Tuberculosis (TB), caused by *Mycobacterium tubercuium* (MTB), remains a major cause of mortality and morbidity worldwide, with approximately 8.6 million new cases and 1.3 million deaths in 2012.[1] It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis*. China is one of the 22 countries with a high TB burden, and in 2012, an estimated 0.9 million new TB cases occurred. The prevalence of LTBI is 45% in China according to a nationwide survey in 2000 using the tuberculin skin test (TST).[2] Although the Directly Observed Therapy, Short-course (DOTs) strategy for treatment of active TB in patients has currently proven to be a successful approach to TB control in countries such as China,[3] the growing latent TB population will contribute to a large pool of TB; an estimated 5–10% of LTBI will become active and cause TB disease in a patient's lifetime. The intervention treatment of LTBI has been shown to be an important strategy for eliminating tuberculosis in some developed countries.[4–6] LTBI screening and prophylactic treatment may be an effective method to control the TB epidemic in China.

Because there is no diagnostic gold standard to detect MTB infection, it is difficult to accurately evaluate the prevalence of LTBI. This is in contrast to the methods for the diagnosis of active TB, which relies on the detection of *M. tuberculosis* and/or clinical symptoms. LTBI is indirectly diagnosed by the adaptive cell-mediated immune response toward specific mycobacterial antigens. There are two approaches currently used to determine the adaptive immunity: the TST and the gamma interferon (IFN-γ) release assay (IGRA). The TST measures delayed-type hypersensitivity reactions to a crude mixture of MTB antigens, which are also present in Bacillus Calmette-Guérin (BCG) and non-tuberculosis mycobacteria. In 1978, national BCG vaccination was introduced in the China National Childhood Vaccination Programme. Because BCG vaccination in China was extensive, the diagnostic results of TST may not accurately reflect the prevalence of LTBI and the effect of BCG vaccination against *M. tuberculosis* infection according to previous studies.[7,8] IGRA is based on the measurement of IFN-γ secreted from T-cells previously exposed to MTB when stimulated *in vitro* with MTB-specific antigens such as ESAT-6 and CFP-10. Both antigens are encoded by RD1, a genomic region present in *M. tuberculosis* but lacking in all *Mycobacterium bovis* BCG vaccine strains and most of the non-tuberculous *Mycobacterium*.[9] IGRA use has increased in recent years, work performed on IGRAs has suggested it may be a suitable alternative method to diagnose LTBI.[10–12] Several LTBI prevalence studies based on IGRAs have been reported in China; investigated populations included new army recruits, students and health care workers.[13,14] These studies limited by sample size and the lack of applicability to the general population. Between July 1, 2013 and September 30, 2013, Gao et al. rolled 21,022 participants and assessed the prevalence of latent tuberculosis using IGRAs in rural populations in China.[15] There is a great need to understand the true prevalence of latent TB infection in China. Therefore, we investigate the prevalence of LTBI by IGRA in the general population and to evaluate the risk factors associated with *M. tuberculosis* infection. This study provided additional evidence to the existing body of literature using IGRAs to examine LTBI prevalence in the Chinese context.

Methods

Study design

Jiangsu is a province located in the eastern coastal centre of mainland China. The number of registered TB cases was 46,476 in 2008. In China, rural areas have a higher TB burden than urban areas. In this study, participants residing in eight villages in rural Dongtai, Jiangsu were randomly recruited. The villages were selected on the basis of socioeconomics, demographics and tuberculosis epidemiology. The sampling method was cluster in this study. Eligible participants were identified by door-to-door survey; inclusion criteria included household registration or residence permit for that village, ability to complete the investigation and provision of written informed consent. The sample size designed was based on the formula ($N = [z^2PQ]/d^2$) of cross-sectional study and the prevalence of TB infection reported by the forth national TB survey in China. On the basis of the fourth national TB survey that the prevalence of LTBI in the general population was 31.7% (TST $\geq$10 mm), with a significant level of 0.01, a simple size of 1436 was calculated. This was increased to 2000 to avoid the participants who did not have the TB-IGRA results or failed to be interviewed. All participants were interviewed for history of BCG vaccination, history of tuberculosis and active tuberculosis. Individuals with active TB, history of TB, or pregnancy were excluded from this study.

Study procedures and data collection

All participants were initially screened with clinical consultation and chest radiographs. Anyone with clinical symptoms of pulmonary disease or chest radiological abnormalities was transferred to Dongtai Center for Disease Control and Prevention (CDC) for active TB confirmation. Individuals confirmed as having active TB by microbiological or clinical symptoms were not included in the analysis of LTBI.

Every participant completed a standardised questionnaire. Data obtained included age, gender, history of TB, and history of TB exposure. A TB exposure history included individuals with no TB who lived in the same household with a TB patient, and we verified the information about living with a TB patient according to the national active tuberculosis case report system. Weight and height were also measured to calculate body mass index (BMI = weight in kg/height^2 in m). BCG status was determined by the scar of vaccination by doctors in physical examination.

A domestic TB-specific whole-blood IFN-γ release assay (TB-IGRA) approved by China Food and Drug Administration (CFDA) was employed to test LTBI. TB-IGRA demonstrated comparable clinical performance with QuantiFERON-TB Gold In-Tube (QFT-GIT) when evaluated by several studies.[18,19] According to manufacturer instructions, 4 ml of venous whole blood anticoagulated by heparin was collected from