Tuberculosis contact investigation in an intermediate burden setting: implications from a large tuberculosis contact cohort in Taiwan

To the Editor:

There are still several unanswered research questions regarding tuberculosis (TB) contact investigations [1–4]. For example, up-to-date epidemiological studies regarding TB contacts in the area of intermediate incidence are not readily available [5]. The long-term risk of TB, especially beyond 5 years, remains undetermined [6]. Risk factors for TB development among contacts are also not well defined [2]. To expand current understanding and knowledge of TB contact investigation, we recruited a population-based TB contacts cohort utilising the National Health Insurance Research Database of Taiwan, which included medical care claims data of 99% Taiwan residents [7].

Taiwan is a country with an intermediate TB burden. The incidence rate of TB was 72.5 per 100 000 population in 2005 and decreased gradually to 45.7 in 2015 [8]. Supported by the national budget and a single, government-sponsored insurance medical service system, the completion rate of TB contact investigation has reached more than 95% [9]. Participants were included if they had an outpatient diagnosis of International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) code of V01.1 or 795.5. At the same time, the participants should also fulfil the criteria of co-payment exemption. Under the National TB Program of Taiwan, TB contacts were exempt from a certain fraction of the actual cost of using the medical services, the so-called co-payment exemption, since July 2007. The date of this outpatient visit was set to be the cohort entry date. Contacts were followed until December 31, 2013. The primary outcome was development of active TB.

Early adherent isoniazid preventive therapy (IPT) was defined as starting isoniazid within 180 days after the entry date and lasting for at least 180 days. Non-adherent IPT was defined as starting isoniazid within 180 days of the entry date but lasting for fewer than 180 days. Contacts with ICD-9 code 795.5 or a prescription for IPT within 6 months after the entry date were defined as having latent tuberculosis infection (LTBI).

The Cox proportional hazard regression model was used to analyse factors associated with development of TB. Adjusted covariates included age, gender, medical visits within 3 months prior to the cohort entry date, contact area TB incidence, urban contact area, economic status, underlying diseases and steroid usage.

A total of 312 322 participants were recruited in the cohort (figure 1). The median follow-up time was 955 days (IQR 468–1476 days). Among the 312 322 TB close contacts, 0.7% developed active TB during follow-up (n=2322). Among all TB close contacts, 140 849 (45.1%) were male and the median age was 36 years (IQR 21–52 years). The most common comorbidities were diabetes mellitus (5.8%), chronic obstructive pulmonary disease (2.1%), malignancy (1.6%) and end-stage renal disease (1.2%). Of the overall contacts, 88.6% had no previous underlying diseases and were considered to be healthy.

A total of 32 474 contacts with LTBI were included. Among them, 1346 (4.1%) developed active TB during follow-up; of these, 98.4% (n=1324) developed LTBI within 1 year of contact. The median age of contacts with LTBI was 12 years old (IQR 7–25 years). The vast majority of LTBI contacts had no comorbidities
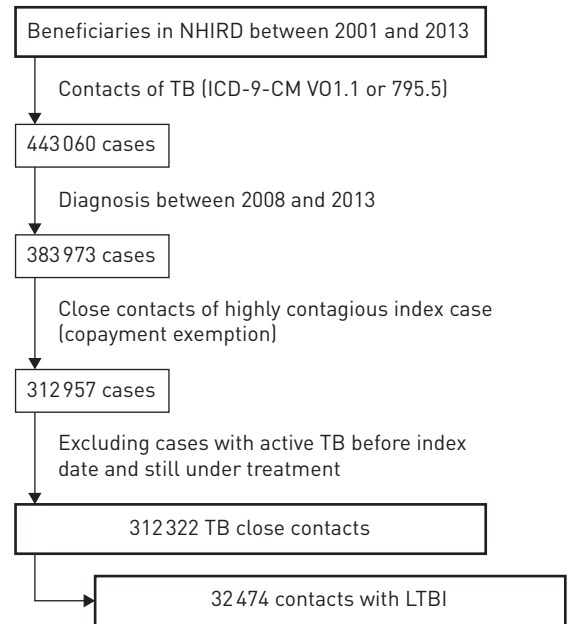
FIGURE 1 Flowchart of patient recruitment. NHIRD: National Health Insurance Research Database; TB: tuberculosis; ICD-9-CM: International Classification of Diseases, 9th Edn, clinical modification; LTBI: latent tuberculosis infection.

Beneficiaries in NHIRD between 2001 and 2013

Contacts of TB (ICD-9-CM V01.1 or 795.5)

443 060 cases

Diagnosis between 2008 and 2013

383 973 cases

Close contacts of highly contagious index case (copayment exemption)

312 957 cases

Excluding cases with active TB before index date and still under treatment

312 322 TB close contacts

32 474 contacts with LTBI

(95%). 41% of all LTBI contacts received early adherent IPT with 0.2% (25/13 435) of them developing active TB during follow-up, while 31% received non-adherent IPT with 0.7% (73/10 032) developing active TB.

Among overall TB close contacts, the incidence of active TB was 3236, 889 and 415 (per 100 000 person-years) in the first, second and third months, respectively. At 1 year, the incidence decreased to 202 (per 100 000 person-years), and at the third year the rate decreased to 119 (per 100 000 person-years). The incidence rate remained stable within the third to fifth year (143 per 100 000 person-years) (figure 2), but always higher than the baseline population in Taiwan (the incidence rate of TB was 33.6 per 100 000 person-years for those aged between 45 and 55 in 2015 in Taiwan) [8]. The highest TB incidence group was among those aged more than 65 years (634 at first year and 403 at the fifth year per 100 000
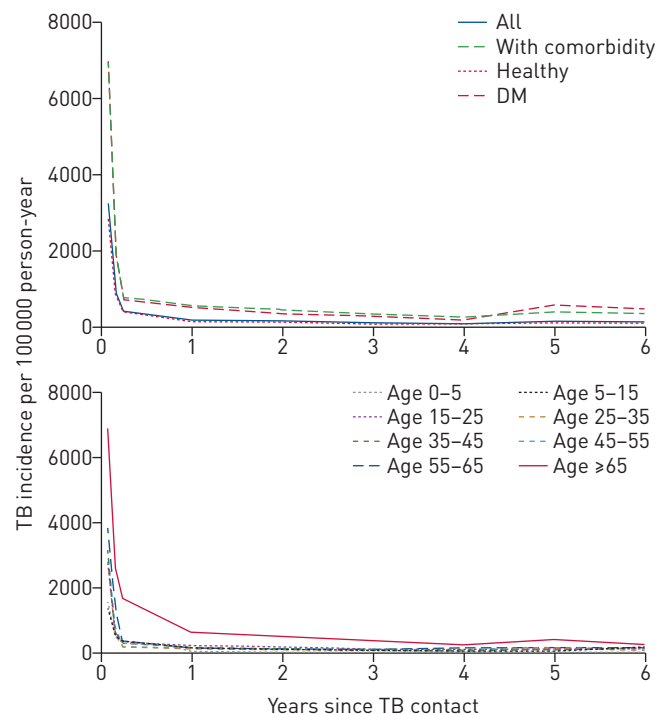

FIGURE 2 Incidence of tuberculosis (TB) among contacts of major entities (overall, diabetes mellitus (DM), healthy, with comorbidity) and different age groups with time.

person-years) (figure 2). The cumulative percentage of active TB for all contacts was 35.4%, 45.0% and 49.4% at the first, second and third months after contact, respectively.

Among all TB contacts, major risk factors associated with active TB development in the Cox regression model included age (with age less than 5 years as the reference group, the risk was highest in contacts aged ⩾65 (HR 26.10, 95% CI 17.37–39.23), and aged between 55 and 65 (HR 12.50, 95% CI 8.26–18.91)), LTBI (HR 65.45, 95% CI 60.02–71.37) and AIDS (HR 4.79, 95% CI 2.14–10.71).

Among contacts with LTBI, the major risk factors associated with TB development included age (with age less than 5 years as the reference group, the risk was highest in contacts aged ⩾65 (HR 22.19, 95% CI 14.4–34.19)), AIDS (HR 7.10, 95% CI 2.62–19.29) and high contact area incidence (HR 2.94, 95% CI 1.45–6.00).

Among contacts with LTBI, early adherent IPT was associated with a lower risk of active TB development (HR 0.02, 95% CI 0.02–0.03) while non-adherent IPT remained associated with a lower risk of active TB development (HR 0.11, 95% CI 0.09–0.14).

The long-term risk of TB among close contacts remained undetermined since most studies conducted previously were limited by the case number and follow-up period (usually less than 5 years) [3, 6]. Our study revealed that the TB risk was still higher than the general population 5 years after TB contact. While it can be impractical in public health policy to regularly follow such a large number of contacts for years, integrating contact history (even beyond years) as a risk factor for tuberculosis into routine clinical practice may be considered.

In a meta-analysis pooling five randomised control trials, those who received IPT had a relative risk of 0.31 of developing active TB [10]. Our study revealed a stronger association between IPT and TB risk reduction. This interpretation should be taken with caution because of the observational nature of our study. For example, after contacts were coded as LTBI because of positive tuberculin skin tests and referred, IPT would not be given for those suspected to have coprevalent TB.

In addition to what was already included in the guidelines, we found that older age, especially those above 65 years old, was associated with a significant risk for TB (HR 26.1, 95% CI 17.37–39.23). The fact that older age was associated with significantly higher risk does not equal the necessity of treatment of LTBI among elderly people. The risk of TB drug-related hepatotoxicity and systemic drug reaction remains a concern, especially in the elderly population [11, 12]. If elderly contacts had some underlying comorbidities such as diabetes mellitus, however, the risk may be further elevated [13, 14]. Careful selection of patients is mandatory before initiating LTBI treatment among elderly people.

Our study also has limitations. We did not have data on an index case, especially sputum mycobacterial study results. Second, not until 2016 was universal screening for LTBI performed in Taiwan TB contact investigations. Also, the identification of LTBI is through a diagnosis code or use of IPT and has not yet been validated.

In conclusion, we found that under a setting of intermediate TB incidence, TB contact investigation resulted in 0.5% yield with a 1-year follow-up. TB risk among contacts remained higher than the general population after a 5-year interval. Specific subgroups of contacts (*e.g.* age⩾65, AIDS) were at higher risk for developing TB and warrant special attention.

Meng-Rui Lee[1,2,3], Cheng-Maw Ho[4], Chih-Hsin Lee[5,6], Ming-Chia Lee[7,8], Lih-Yu Chang[1,2], Kai-Lun Yu[1,2], Jen-Chung Ko[1], Jann-Yuan Wang[2], Jann-Tay Wang[2] and Li-Na Lee[2,9]
[1]Dept of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsin-Chu, Taiwan. [2]Dept of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan. [3]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan. [4]Dept of Surgery, National Taiwan University Hospital, Taipei, Taiwan. [5]Division of Pulmonary Medicine, Dept of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan. [6]Division of Pulmonary Medicine, Dept of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan. [7]Dept of Pharmacy, New Taipei City Hospital, New Taipei, Taiwan. [8]School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan. [9]Dept of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan.

Correspondence: Jann-Yuan Wang, Dept of Internal Medicine, National Taiwan University Hospital, #7, Chung-Shan South Rd, Zhongzheng Dist., Taipei 10002, Taiwan. E-mail: jywang@ntu.edu.tw

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