# Yield of tuberculosis contact investigation in a low-incidence country

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**INTRODUCTION**

Tuberculosis (TB) is the result of infection with *Mycobacterium tuberculosis* (*M. tuberculosis*), and remains a public health issue worldwide. Since the 1950s the incidence of TB has fallen dramatically in high- and middle-income countries (1, 2), while it has recently emerged as a public health concern in many low-income countries (3). The World Health Organization (WHO) estimated that globally in 2012 there were 8.6 million incident cases of TB, and 1.3 million deaths from the disease (4).

Public health measures to control the spread of TB infection have included different strategies focused on both prevalent and incident cases. The first priority of TB control programs is to identify and treat all individuals with active TB (5). Where adequate resources exist and when active TB cases are being successfully treated, efforts should be directed towards contact tracing strategies to allow the early identification of TB contacts, i.e., individuals exposed to someone who has been diagnosed with TB, and to offer appropriate treatment for both latent TB (LTB) infection and active TB (5, 6). TB contact tracing, and partner notification have been revealed as a valid tool to stem the tide of TB infection, in particular among disadvantaged groups (3, 7).

The transmission of *M. tuberculosis* depends on several factors such as the bacteriological status and contagiousness of the index TB case, the susceptibility and immune status of the exposed TB contact and the characteristics of the environment within which such contact occurs (8, 9). Under conditions particularly favorable for transmission, an individual with undiagnosed active TB may potentially cause a TB outbreak in confined settings such as schools, prisons and other congregate settings (7, 10).

Several studies have investigated the performance of TB contact tracing programs in selected populations, focusing in particular on multidrug-resistant TB (11), migrant subgroups (12, 13), or specific geographical areas (14). A meta-analyses investigated also the performance of TB contact tracing programs in low- and middle-income countries (3) and, to the best of our knowledge, only one study has reported on the country-wide performance of a TB contact tracing program from a high-income country (15).

The objectives of the present study were: to assess the yield of the Piedmont TB contact investigation program, and to evaluate both the role of its main determinants, and the role of selected risk factors for TB infection (such as TB case contagiousness, demographic and social TB case and contacts conditions, closeness of contact with the index TB case), among TB contacts identified in the city of Turin, a large metropolitan area in the north of Italy.

**METHODS**

The Region of Piedmont has been running since 1999 a TB contact investigation program for its territories in agreement with Italian Ministry of Health guidelines (16, 17) and according to the international guidelines for TB control strategies in the European region of the WHO (5, 18). The investigation is conducted for all new TB cases reported to the health authorities, with the aim of identifying potentially infected TB contacts in need of treatment (19) for a more precise description of the Piedmont TB surveillance system see Baussano et al, 2006 (20).

According to the stone-in-the-pond method, for each suspected or confirmed pulmonary TB case active TB contact investigation (by phone, mail, through personal invitation or inspections in congregate settings) was conducted among household members, close contacts, and regular contacts (21). Occasional contacts were investigated through passive investigation, (e.g. when requested by a general practitioner or when voluntarily presented) as per CDC guidelines (5).

TB data are kept in mandatory regional registries and no informed consent is required to obtain and store the information for public health and research purposes; an informed consent to collect clinical and demographical information on TB contacts was obtained. Encrypted personal identification codes guaranteed anonymisation.

*TB case definition*

The Regional Compulsory National Notification System and the Piedmont TB Surveillance System of Treatment Outcomes were used to identify pulmonary TB cases. The two systems together capture more than 80% of the TB cases occurring in the Piedmont Region (20).

The present study included TB cases residing in the metropolitan area of Turin (Piedmont Region) with a diagnosis of active pulmonary TB between 1 January 2002 and 31 December 2008. We included in the analyses all TB cases that were either confirmed by bacteriology/radiography or diagnosed by a clinician (22).

TB cases were classified into three main categories of contagiousness, according to laboratory or clinical results: i) sputum smear examination positive for acid-fast bacilli and culture positive (AFB+); ii) sputum smear examination negative, but sputum culture positive for *M. tuberculosis* complex (CULT+); and iii) 'other than defined' cases (OtD), i.e., both sputum smear and culture negative or missing, but clinically and/or radiologically diagnosed as being compatible with TB, and subsequently given a full course of anti-TB treatment. For each TB case included, information on sex, age, place of birth, social condition (such as homelessness or living in congregate settings), contagiousness and state of health was collected.

*TB contact definition*

Contacts for each TB case were identified through interviews with these cases, and were defined as anyone having had prolonged contact – i.e., at least 12 hours of exposure in a confined poorly

ventilated space – with an active TB case for. Following the international guidelines(5), we considered an infectious period of at least one month, in asymptomatic or AFB- cases, up to three months in symptomatic or AFB+ or cavitary TB cases. All identified TB contacts that could be traced were included in the present study. Information on gender, age, migration status, social and health condition (such as HIV status, diabetes, immunodepressive diseases or treatment with steroids, anti-TNF-alfa and so on) was collected. All traced TB contacts were checked for a previous BCG vaccination (through scar inspection, interview and vaccine certificate search) and screened for TB infection using the Tuberculin Skin Test (TST). TST was performed using tuberculin purified protein derivative (PPD) 5 UI according to the Mantoux method. The transverse diameter of induration was measured between 48 and 72 hours after the intradermal injection of 0.1 ml of tuberculin PPD in those contacts that returned to have their TST results evaluated. TB contacts were classified as infected if the induration was 5 mm or more regardless of a prior BCG vaccination (5). All subjects with a first negative TST who resulted to have had an exposure 10 weeks before the test, were submitted to a follow-up test. A conversion was considered in the occurrence of a tuberculin reaction > 5mm of induration after the window period (5). All positive TST subjects, household TB contacts aged 6 years or less, and subjects with symptoms of TB were submitted to clinical and radiographic examination to exclude active disease.

TB contacts were defined as having LTB infection when a subclinical infection with *M. tuberculosis* was present without clinical, bacteriological or radiological manifestations of disease. Preventive treatment was routinely offered to all LTB subjects, with an expected completion rate of about 74% (23, 24).

According to the closeness of contact with the index TB case, we classified contacts in: household contacts (relatives or similar); regular contacts (subjects having had regular or prolonged contact

with the index TB case in restricted and poor ventilated areas, e.g congregate settings) and occasional contacts.

*Data analyses*

To test if any of the TB index case characteristics was predictive for the number of possible contacts, the association between the TB index case's number of contacts and his characteristics (such as age, sex, nationality, living conditions) was tested using a Poisson regression model(25).

Logistic analysis was used to assess the potential role of some characteristics of TB contacts in determining the yield of the TB contact investigation program and a multilevel logistic regression analysis was performed to evaluate the predictors of TB, considering the effect of cluster by TB case. Odds ratios (OR) and their 95% confidence intervals (CI) were used as a measure of association.

Due to the observed non-linearity of the relationship between age and TST positivity in TB contacts, we stratified age into two categories, below and above the inflection point at 35 years of age ($\leq$35 years, >35 years), point in which the association between the considered variables (curve slope) changes dramatically (data not shown).

Analyses were performed using STATA 11.0 (STATA Version 11.0. In: StataCorp, ed. College Station, TX, 2010).

**RESULTS**

A total of 1099 pulmonary TB cases residing in the city of Turin were reported to the Piedmont TB notification systems, with an average incidence of about 20 cases in 2001 decreasing to 15 per 100.000 inhabitants in 2008. Among them, 266 (24.2%) had no identified TB contacts, including 107 (40.2%) AFB+ or CULT+ cases for which the epidemiological investigation was not able to identify any potentially infected contact, and 101 (59.8%) OtD cases (Table 1).

A total of 833 index TB cases (75.8%) had at least one identified TB contact. The median number of TB contacts per index TB case was three (Inter Quartile Range [IQR]: 2-6), and the highest number of TB contacts (n=150) was recorded in a primary school outbreak. Of these 833 TB cases, the majority were male (58.9%), 47.7% of them were foreign-born, and their mean age was 45.7 years (±21.3). In terms of contagiousness, 489 of the 833 index TB cases (58.7%) were AFB+, 129 (15.5%) were CULT+, and 147 (25.8%) were OtD (Table 1).

We identified 4759 TB contacts (46.0% male) with a mean age of 35.4 years (±18.1); 1362 (28.6%) were foreign-born and 3511 (73.8%) were household contacts (Table 2). Female TB cases and TB cases living in congregate settings showed a significantly higher number of TB contacts than male TB cases and TB cases not living in congregate settings (rate ratio, RR=1.38; 95%CI 1.30-1.46 and RR=1.28; 95%CI 1.19-1.38, respectively), whereas homeless and foreign-born TB cases had a significantly lower number of TB contacts than TB cases who were not homeless and those born in Italy (RR=0.68; 95%CI 0.56-0.83 and RR=0.58; 95%CI 0.54-0.62, respectively - data not shown). Table 3 reports the yield of the regional TB contact investigation program stratified by the contagiousness of TB cases. The largest number of identified TB contacts were those of AFB+ cases (70.7%), with an average number of four contacts per index TB case (IQR: 2-7). For 22 TB cases contact screening was expanded due to a high attack rate in the inner circle. We traced 93.3% of all identified TB contacts, with a higher yield for TB contacts of AFB+ cases (94.4%). All traced TB contacts (4441) were screened for TB using TST, and 3942 (82.8%) of them returned to have their TST results evaluated. Among the latter, the prevalence of TBI infection was 45.0% (1773 TB contacts with an intradermal reaction ≥5 mm; 207 subjects converted during the 8-10 week window period). Twenty-eight contacts (0.7%) were found to have active TB (Table 3).

The main determinants of the yield of the TB contact investigation program are reported in Table 4: TB contacts aged 35 years or less had a higher likelihood of being evaluated than those over 35 years (OR=1.43; 95%CI 1.05-1.94), foreign-born TB contacts were evaluated significantly less often than TB contacts born in Italy (OR=0.55; 95%CI 0.41-0.75), and regular and household contacts were more easily evaluated than occasional contacts (OR=4.74; 95%CI 2.98-7.54 and OR=4.04; 95%CI 1.81-9.03, respectively).

Results of the multilevel analysis, stratified by the age of TB contacts, are shown in Figure one.

Among contacts aged 35 years or less contagiousness of the index TB case (TB contacts of CULT+ and AFB+ cases) and closeness of contact (household contacts) were significantly associated with TB infection. In both age groups, foreign-born TB contacts showed a higher risk of TB infection compared to TB contacts born in Italy (OR=4.79, 95%CI 3.55-6.47 and OR=4.82, 95%CI 3.47-6.69 for ≥35 and <35 years of age, respectively). The statistically significant interaction found between the contagiousness of TB cases (both AFB+ and CULT+) and age of TB contacts (test for interaction: p=0.024 and p=0.025, respectively) disappeared when stratification by age group was performed.

**DISCUSSION**

Since the risk of infection with *M. tuberculosis* is directly related to the intensity and duration of exposure to an individual with active TB, close TB contacts are at the highest risk of being infected. Thus TB contact tracing, in particular of household contacts, should be considered a mainstay of TB control strategies, contributing to the early detection of new TB cases and to prevention of TB through early treatment of LTB infection (26).

Our findings on the yield of the TB contact investigation are consistent with estimates reported in other countries(3, Etkind, 2000 #24, Mulder, 2009 #12). In particular, a systematic review of TB

contact investigation programs in high- and middle-incidence settings reported a pooled yield among household contacts of 4.5% (4.3-4.8) for all active TB cases and of 51.4% (50.6-52.2) for LTB cases (3). In low-incidence settings an average of 5 to 10 TB contacts for each incident TB case were identified and evaluated. About 30% of these contacts had LTB and 1 to 4% had active TB (27). In our study 45.9% (95%CI 44.0-47.7) of the contacts of AFB+ cases had LTB infection and 0.8% (95%CI 0.49-1.19) had active TB. The estimated TB incidence among evaluated TB contacts (7/1000) implies a relative risk of TB infection around 40 times higher than the incidence reported from the same geographic area in the general population (10-16/100.000) (20).

The median number of identified household contacts collected in this study was lower than the median/mean number of contacts reported in the Etkind review (27), possibly due to the different family size and household composition in the northern Italian population (the average number of children in each family is estimated to be 1.5 (28)). Moreover, the average household size of foreign-born traced TB contacts was most likely small as well, as immigrants were more likely to be illegal and/or have migrated recently (demographic data show that migrants are likely to run their migration project alone. They usually gather their family several years after their arrival in Italy(29)). This hypothesis seems to be confirmed by the results of our Poisson regression analysis.

The major determinants of TBI (contagiousness and closeness of contact) seem to play a different role depending on the age of the TB contact. In particular, in the group aged 35 years or less, household contacts and contacts of AFB+ cases showed the higher risk of TB infection. Furthermore we also found that contacts of CULT+ cases had a high risk of being infected, while having a lower bacterial load.

In the older age group the effects of contagiousness and closeness of contact disappeared, while the effect of place of birth of TB contacts and the cohort effect persisted. It is likely that in this age group

the incidence of TB was hidden by a higher prevalence of previous TB infection. This finding was confirmed by the significant interaction found between the age of TB contacts and the main determinants of TB infection (contagiousness and closeness of contact).

The weakness of the contact tracing strategy lies in the yield of TB contact investigation among migrants. In fact, as also confirmed in a review by Mulder (12), regardless of age, migrants remain the group with the highest burden of TB in all the industrialized countries. More than 50% of the identified TB infections, indeed, are prevalent ones since acquired likely outside Italy. Namely, in order to improve the outcomes of TB control programs, contact tracing strategies should be combined to active case finding and screening programs in migrants(30).

Furthermore, the advantages of treating high-risk foreign-born TB contacts are potentially higher when compared with those born in the reference country. In fact, due to the high relative risk estimated in foreign-born persons with a low risk of TB exposure (approximately 5-fold the baseline risk) and to the lack of interaction between the contact's place of birth and both the index TB case and the TB contact's risk factors, the resulting risk model is multiplicative.

A number of limitations must be considered when interpreting our results. First, both active TB cases and TB contacts were tested for infection using PPD 5 UI. Interferon-γ release assay (IGRA) was not performed, as contact tracing protocols were introduced in Turin before IGRA was made available. The higher specificity of the IGRA method could have improved the detection of LTB infection, in particular among BCG-vaccinated subjects (31). Second, place of birth of the foreign-born subjects included in the study was not considered in the analyses to avoid the effect of small numbers on the power of our estimations. Finally, health professional commitment in information retrieval among the different contagiousness categories is far from equal, having an impact in the quality of data available for less symptomatic subjects.

In conclusion, our results suggest that TB contact investigation programs should be seriously considered as a valid tool to improve TB case detection and TB prevention also in low-incidence areas. Moreover, in line with CDC priorities, more effort should be put into the younger population, in accordance with the stone-in-the-pond method. Furthermore, an effort should also be made to extend TB contact tracing to the contacts of CULT+ index cases, as they are responsible for at least the same number of new TB cases as AFB+ index cases (51.9% vs 59.3% of new cases), despite a negative sputum smear examination (32).

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