Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Davit Baliashvili Date

Risk factors for active and latent tuberculosis (TB) among contacts of smear-positive index TB patients in the country of Georgia

By
Davit Baliashvili
Master of Science

Clinical Research

_____
Russell Ryan Kempker
Advisor

_____
Mitchel Klein
Committee Member

_____
Thomas R. Ziegler
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

Risk factors for active and latent tuberculosis (TB) among contacts of smear-positive index TB patients in the country of Georgia

By

Davit Baliashvili
MD, Tbilisi State Medical University, 2011

Advisor: Russell Ryan Kempker, MD, MSc

An abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Clinical Research

Abstract

Risk factors for active and latent tuberculosis (TB) among contacts of smear-positive index TB patients in the country of Georgia

By Davit Baliashvili

Introduction: Identifying and screening close contacts of patients with active tuberculosis (TB) is a TB control strategy that is uncommonly pursued in low-and middle-income countries. We carried out a population-based study to determine risk factors for latent TB infection (LTBI) and active TB among contacts of active TB cases.

Methods: Index patients included all smear-positive pulmonary TB cases diagnosed in Georgia between April-December 2012; eligible contacts included all close contacts identified by regional epidemiologists during household visits. Tuberculin skin tests (TST) were performed on contacts and a positive TST was defined as an induration of $\geq$10 mm. Active TB cases among contacts were determined by review of the Georgia National TB Program surveillance database.

Results: Among 896 index patients with active TB, 3133 contacts were identified and 1157 (37%) had a TST performed. Among those tested, 34% were positive. Most contacts (86%) were household contacts and 42.5% were male. Household contacts (OR=1.5, 95%CI 1.1-2.0) and contacts of male index patients (OR=1.5, 95%CI 1.1-2.0) were more likely to have positive TST. In multivariable analyses, household contacts were more likely to have a positive TST result (adjusted OR [aOR]=2.28, 95%CI 1.49-3.49) compared to non-household contacts. Those contacts whose index patient had a TB diagnosis in past and failed treatment (OR=6.4, 95%CI 1.9-21.8) or defaulted (OR=5.0, 95%CI 1.8-14.0) were more likely to have a positive TST compared to those with index cases who were previously cured. Overall, there were 111 active TB cases; the incidence rate was 1101 cases per 100 000 person-years. In multivariable analyses for active TB after 1-year follow-up period, Odds of having TB was significantly higher for household contacts among males (aOR 4.38, 95% CI 1.05-18.22), but it was not significant among females (aOR 0.76, 95%CI 0.35-1.67).

Conclusions: A high prevalence of TB was identified among contacts of active TB cases in Georgia. Contacts of index cases that defaulted or failed TB therapy were at increased risk of LTBI. Efforts aimed at reducing treatment default should enhance TB control efforts and may also decrease LTBI and active TB among contacts.

Risk factors for active and latent tuberculosis (TB) among contacts of smear-positive index TB patients in the country of Georgia

By
Davit Baliashvili, MD

Advisor:

Russell Ryan Kempker, MD, MSc

A thesis submitted to the Faculty of the
James T. Laney Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Clinical Research
2014

Table of Contents

INTRODUCTION

Tuberculosis (TB) is a major global public health problem and a leading cause of infectious disease-related morbidity and mortality worldwide. According to the World Health Organization (WHO), in 2012 there were an estimated 8.6 million incident cases of TB and 1.3 million deaths caused by TB worldwide (1). Tuberculosis remains a serious public health problem in the country of Georgia. After the breakup of the Soviet Union there was a rise in the TB prevalence in Georgia, which was caused by several factors including inadequate funding, poverty, increasing numbers of internally displaced persons and a collapse of public health infrastructure.

During recent years, TB incidence rates in Georgia have stabilized but remain high. According to WHO estimates, in 2012 the incidence rate of TB in Georgia was 116 cases per 100,000 persons. Moreover, Georgia is classified as a high-burden multidrug-resistant (MDR) TB country as designated by WHO; a designation that has been given to 27 countries. MDR-TB is defined by the resistance to the two most important first-line anti-TB drugs, isoniazid and rifampicin and is associated with higher morbidity and mortality. Treatment outcomes have also been shown to be much lower for MDR TB as compared to drug-susceptible TB (2).

The early diagnosis of pulmonary TB is of utmost importance in an effort to prevent TB transmission. Each untreated sputum smear positive patient with TB is estimated to infect 10 to 15 close contacts annually (3), thus making the early identification of sputum smear positive TB patients a critical priority in reducing transmission of *Mycobacterium tuberculosis*, the organism that causes TB. Close contacts of TB patients are at higher risk of becoming infected with TB and also developing active

TB disease (4). Therefore, investigating the contacts of patients with active TB may contribute to increased detection of disease in early stages and prevent further spread of infection among contacts.

The primary public health agency responsible for TB surveillance in the country of Georgia is the National Center for Disease Control and Public Health (NCDCPH). Another key national TB program provider is the Georgian National Center for Tuberculosis and Lung Diseases (NCTLD), the largest medical facility in Georgia specializing in TB and lung disease care. NCTLD collects clinical and demographic information on every patient diagnosed with TB from the entire country of Georgia.

Using data from the state contact investigation program of Georgia, the primary aim of this study was to estimate the risk of both active TB disease and latent TB infection among household and non-household contacts of active TB cases, and to assess the association between contacts' characteristics and the presence of active TB disease or latent infection. Based on our study results, we planned to provide recommendations regarding contact investigation activities and target groups of these studies, as well as methodologies that can provide improvements in TB control in the country. These recommendations could be useful in planning of future contact investigation studies, not only for Georgia, but also for other countries with similar profile of TB disease.

BACKGROUND

TB contact investigation is one of the most common strategies used in TB control efforts (5). It involves activities targeted to identify contacts with either active TB disease or latent TB infection as early as possible to avoid further spread of the disease and to increase case detection (6) because contacts of patients with active TB are at a much higher risk of exposure than the general population (7). Traditionally, contact tracing has been carried out in high-income countries, where the incidence and prevalence of tuberculosis is relatively low and resources are high (8-11). However, recent studies suggest that contact investigation can be an effective tool in high-incidence countries and in recent years interest to this activity has increased in low- and middle-income countries as well (12-14).

It is suggested that contact investigation is a high-yield intervention in contacts of multidrug-resistant tuberculosis for early detection of additional drug resistant cases (i.e., active case finding) and preventing further transmission of disease (15, 16). This is of particular interest in Georgia, which is a high-burden MDR TB country, according to WHO. A population-based study conducted in Georgia in 2009 showed that 7% of new TB cases and 27% of retreatment TB cases were MDR-TB (17). More recent data from the WHO Global Tuberculosis Report 2013, found current MDR TB rates to be higher, with an estimated 9% of new TB cases and 31% of previously treated TB patients in Georgia having MDR TB (1).

Contact investigation involves interviewing the TB case, identifying close contacts and then evaluating these contacts to detect if they have latent TB infection or active TB disease. The evaluation of contacts involves several activities, such as sputum evaluation

or chest radiography to detect active TB disease, or interferon-gamma release assay (IGRA) or tuberculin skin test (TST) to detect latent TB infection (LTBI). Both IGRA and TST are considered useful diagnostic tools to detect LTBI. It is suggested that TST can be useful diagnostic tool for detecting latent TB infection even in those children, who have received BCG vaccine in neonatal period (18). Diagnosis of latent TB infection is important because although patients with latent TB infection have no symptoms and are not infectious, they are infected with *M. tuberculosis* and are at risk for progressing from latent TB infection to active TB disease (1).

According to WHO, one third of the total world population has LTBI (1). Several TB contact investigation studies have reported that as compared to other groups of contacts of active TB patients, household contacts are at the highest risk of becoming infected with TB (4). For example, a study conducted in the USA found that 44% of household contacts were tuberculin skin test (TST)-positive compared to 29% of work contacts (19). Household contacts are also at higher risk of active TB disease compared to other close contacts(4).

A systematic review and meta-analysis of contact investigations published in 2013 showed that contacts of TB cases are at a high-risk of developing TB, particularly within the first year (4). According to this meta-analysis, in low- and middle-income countries, the prevalence of active TB disease in all contacts was 3.1% and the prevalence of LTBI was 51.5%. In high-income settings, the prevalence of active TB was 1.4% and the prevalence of LTBI was 28.1% (4). However, this meta-analysis did not provide information about risk of tuberculosis among non-household contacts, as a separate group. Children have also been identified to be at increased risk of developing active TB

after household contact with an index TB case (4, 20-22). Younger contacts are at higher risk of acquiring active TB compared to older contacts (21, 23).

There are very limited published data from contact investigations in the Caucasus region including Georgia. One study conducted in Turkey found that incidence of tuberculosis among household contacts was 2491 per 100,000 and the rates were highest in 15-24 and 25-34 year age groups (24). Previous studies of LTBI in contacts of TB cases in Georgia were limited to particular subgroups of the population (25, 26). The lack of contact transmission data coupled with a strong need of improved early diagnosis of TB triggered the creation of a national program to investigate contacts of TB patients in the country of Georgia. In 2012, the NCDCPH initiated a nationwide TB contact investigation. State epidemiologists of district public health centers from all regions in Georgia with the exception of Abkhazia and South Ossetia (conflict regions which are not under control of central government of Georgia) were trained at NCDCPH on how to perform a tuberculin skin test (TST) to detect whether a contact had latent TB infection. Patients with latent TB infection have infection with *M. tuberculosis*, have no symptoms and are not infectious but are at risk for progressing from latent TB infection to active TB disease. To our knowledge, this thesis presents data from the first nationwide TB contact investigation study in Georgia.

METHODS

The purpose of this study was to estimate the risk of both latent TB infection and active TB disease among household and non-household contacts of TB cases in Georgia. Using data from a nationwide contact investigation program and the clinical database of NCTLD, we also aimed to:

1) Estimate the association of type of contact (household vs non-household) and demographic characteristics with prevalent latent TB infection among contacts of active pulmonary TB cases.

2) Estimate the association of type of contact (household vs non-household) and demographic characteristics with risk of active TB disease among contacts of active pulmonary TB cases.

3) Assess whether type of contact modifies the effect of other risk factors for latent or active TB.

Study Design

A cohort study design was used in this study. Contacts who participated in the NCDC contact investigation from 2012 to 2013 were followed for ≥ 1 year and active TB disease status was determined by NCTLD clinical records and the national TB database.

Study Population

Our study population included contacts of active pulmonary TB cases who were diagnosed with AFB smear-positive TB between April and December 2012. The surveillance was carried out throughout the entire country of Georgia as part of the national TB contact surveillance program. An epidemiologist interviewed each index case within four days of TB diagnosis to determine possible contacts and subsequently used a standardized data form to interview each close contact that could be located. All contact investigations took place at either the contact's home or work place or at the epidemiologist's office. Tuberculin skin testing was carried out using the Mantoux method (27). Tuberculin skin testing using 0.1 ml tuberculin was performed on contacts of active TB cases. Induration size of ≥10mm was considered as a positive tuberculin skin test (TST). Latent TB infection was defined as a positive TST without prior diagnosis of active TB disease. Epidemiologists counseled contacts and recommended that they go to a TB physician to the nearest TB cabinet for TB screening. Contacts who had already been diagnosed with active TB disease at the time of contact investigation were not evaluated by epidemiologists, according to the study protocol.

Sources of Data

A contact database was created at NCDC and included information about contacts such as type of contact (household vs. non-household), TST induration result (positive ≥ 10 mm, negative < 10 mm) and demographic characteristics of contacts. It also included information about the index TB case for each contact, including the index case's name, age, region of residence and date of diagnosis.

Additional information on TB index cases was obtained from the NCTLD TB surveillance database. This NCTLD database includes all TB cases diagnosed in the country of Georgia. For each index patient we retrieved additional demographic information, such as employment status, history of incarceration, whether the index case was an internally displaced person (IDP), past history of TB, as well as a drug susceptibility profile. Additionally, all contacts identified in the NCDC contact investigation program were cross-checked with the NCTLD surveillance database to determine which contacts developed active TB. The linking variables were name, age and region of residence. For those contacts we found to be diagnosed with active TB, we retrieved the date of diagnosis and additional TB-related information. The TB surveillance database was received from NCTLD on 15 April, 2014, providing at least 1-year follow-up period for all contacts. To improve accuracy, the cross-checking was conducted separately by two members of study team and the results were integrated. Contacts with active TB disease were defined as incident cases if they were diagnosed ≥ 60 days after date of diagnosis of their index patient, and defined as prevalent if they are diagnosed from 120 days before to < 60 days after date of diagnosis of their index patient.

Study definitions: The two primary outcomes of interest in our study were TST result and active TB disease status of contacts after 1-year follow-up. Both were dichotomous variables. The primary exposure of interest was type of contact (i.e, household vs. non-household contacts). A household contact was defined as a contact living in the same household as the index TB case and a non-household contact was

defined as close contact of an active TB case who did not live in the same household as the index case (e.g., friend, work colleague, neighbor, class-mate)

The merged database also included the following covariate information:

Index patients: Sex, date of birth, region, date of TB diagnosis, drug susceptibility to four first line anti-TB drugs (isoniazid, rifampicin, ethambutol, and streptomycin), past history of TB (yes/no) and outcome of treatment (cured, completed, defaulted, failed), employment status (yes/no), internally displaced person (yes/no), history of past incarceration (yes/no).

Contacts: Age, sex, type of contact (household vs. non-household) and TST result (positive ≥ 10 mm, negative <10mm). After checking all contacts in NCTLD database, for those who were found to be diagnosed with TB, this additional information was extracted: Date of diagnosis, employment status, internally displaced person (yes/no), history of past incarceration, disease location.

Database Management

Data was entered into Microsoft Office Excel 2013 database by an NCDC epidemiologist.

Data Analysis

Statistical analyses were performed using SAS version 9.3. To calculate confidence intervals for rates, OpenEpi, open source version 3.03 was used. We used bivariate

analyses and chi-square tests to examine the association between contact characteristics and 1) latent TB infection and 2) active TB disease. To estimate association between contact and index patient characteristics with risk of having active TB after 1-year follow up, we excluded from this analysis those contacts who were diagnosed after a1-year period from the date of diagnosis of their index patient. A multivariable logistic regression analysis was used to calculate odds ratios, adjusted odds ratios, and 95% confidence intervals for contact and index patient characteristics associated with active TB or latent TB infection among contacts of active TB cases. The primary exposure of interest was type of contact (household vs non-household). To control for confounding other covariates that changed the parameter estimate of the main predictor by more than 10% were included in the model. Model building and selection was based on purposeful selection of covariates strategy. A two-side p-value ≤ 0.05 was considered statistically significant for all analyses. Interaction was assessed using the Wald chi-square p-value for parameters of product terms. In order to estimate the association between outcome of previous TB episodes of index patients and the prevalence of latent TB infection among their contacts, we also conducted subset analyses on those contacts, whose index patients had a past history of TB.

IRB Approval

The study was approved by Emory University and Georgian National Center for Disease Control and Public Health (NCDC) Institutional Review Boards (IRBs).

RESULTS

Basic characteristics of study population

In total, there were 896 index TB cases who had at least one contact investigated. Among index TB cases, 675 (75%) were male, and the the mean age of index TB cases was 41 years (SD ± 16.7). 187 (22%) index patients had a previous history of TB and 762 (90%) were unemployed. Drug susceptibility testing results were available on *M. tuberculosis* isolates recovered from 742 (83%) of index TB cases. Among these, 87 (11.7%) were MDR-TB cases.

A total of 3133 contacts of 896 index cases were enrolled and investigated by epidemiologists from NCDC. Among the 3133 contacts, 1332 (42.5%) were male and the mean age of contacts was 32 years (SD ± 21.4). The type of contact was known for 2943 (94%) contacts; 2532 (86%) were household contacts and 411 (14%) were non-household contacts.

Latent TB infection

In total, 1157 (37%) contacts received a TST during the contact investigation. We conducted analyses to look at factors associated with receiving TST. The region with the highest proportion of contacts who received a TST was Achara (55.7%) and the region with the lowest was Racha-Lechkhumi (5.6%) (Figure 1). In bivariate analyses, factors associated with not receiving a TST included household contact (OR = 2.1, 95% CI 1.72-2.63), age (older people were more likely to not receive TST), and being an internally displaced persons (OR 1.8, 95% CI 1.03-3.03) (Table 1).

The prevalence of positive TST among contacts was 34%, 393 out of 1157 contacts had a positive TST result. The prevalence of a positive TST among contacts varied by region. The highest prevalence of LTBI was detected in region of Imereti where 86 (47.5%) contacts out of 181 who had received TST had positive result. The region with the second highest prevalence is Shida Kartli with 40 (43.5%) out of 92 contacts having positive skin test result (Figure 2).

The prevalence of a positive TST was significantly higher among household contacts compared to non-household contacts (35.4% vs. 27.1%, OR 1.5, 95% CI 1.1-2.0) using a significance level of 0.05. In Bivariate analysis, the prevalence of positive TST was not significantly different between male and female contacts. However, contacts of male index TB cases had a higher prevalence of positive TST as compared to contacts of female index patients (318 out of 881 (36%) vs. 75 out of 276 (27%), OR 1.5, 95% CI 1.12-2.04) (Table 2). Contacts of employed index TB cases had higher prevalence of positive TST (OR 1.5, 95% CI 1.01-2.20). Past history of incarceration in index TB was not significantly associated with prevalence of LTBI in their contact (OR 0.75, 95% CI 0.44-1.30). Contacts of internally displaced persons had also not significantly different risk of positive TST (OR 1.26, 95% CI 0.46-3.28), as well as contacts of MDR index patients (OR 0.97, 95% CI 0.65-1.45) (Table 2).

There were 143 contacts who had an exposure to an index TB patient with a previous history of TB. Among These contacts, the risk of positive TST was significantly associated with the outcome of the previous TB episode of the index patient (Table 3). The prevalence of positive TST among contacts whose index patient was cured from the previous TB episode was 16.7% (9 out of 54); the prevalence of positive TST

was significantly higher among those contacts whose index TB patient completed treatment (18 out of 45, 40%, OR 3.33, 95% CI 1.31-8.46), defaulted (14 out of 28, 50%, OR 5.0, 95% CI 1.79-14.00) and failed (9 out of 16, 56%, OR 6.43, 95% CI 1.90-21.77) compared to those who were deemed to have been cured (Table 3). In multivariable analysis, independent risk factors for LTBI among contacts of an index TB retreatment case included being a contact of an index TB case that completed treatment, (aOR = 3.26, 95% CI 1.25-8.47), defaulted (aOR = 3.26, 95% CI 1.03-10.33) or failed treatment (aOR = 8.02, 95% CI 2.19-29.44) (Table 4).

In multivariable analysis, independent risk factors for positive TST among contacts who underwent tuberculin skin testing included being a household contact (aOR 2.3, 95% CI 1.49-3.49), being a contact to an index case that was employed, (aOR 1.66, 95% CI 1.10-2.52) and being a contact to a male index case (aOR 1.58, 95% CI 1.14-2.19) (Table 5). No interaction was detected (Table 6).

Active Tuberculosis

In total, 116 (3.5%) of 3133 contacts were determined to have active TB disease. Five persons listed as contacts were actually diagnosed with active TB more than 120 days before their index case and were excluded from further analyses. Among the remaining 111 cases, 53 were incident cases (i.e., diagnosed ≥ 60 days after date of diagnosis of their index patient) and 58 were prevalent cases (diagnosed from 120 days before to < 60 days after date of diagnosis of their index patient). The incidence rate of active TB disease among contacts was 1101 cases per 100 000 person-years.

The risk of active TB disease was not significantly different between household and non-household contacts (RR=1.23, 95% CI 0.49-3.12). Overall prevalence of active TB after 1-year of follow-up among all contacts, including both incident and prevalent cases was 3447 (95% CI 2850-4130) per 100 000. Among regions in Georgia, the highest prevalence of active TB among contacts after 1-year follow-up period was detected in Imereti where 34 (6.6%) out of 517 contacts had diagnosed TB during that period. The region with the second highest number is Guria, where 6.3% (7 out of 112) of contacts were diagnosed with TB.

In bivariate analysis, risk factors for developing active TB disease among contacsts included being a household contact, being male, younger age, having a positive TST or not having a TST performed (compared to those who were TST negative), and being a contact of an index TB case aged 15-44 years of age (Table 7). The Breslow-Day test for interaction revealed that association between type of contact and active TB was modified by a contact's sex (P-value<0.01). Therefore, association between type of contacts and active TB was estimated separately for males and females. The odds ratio among males comparing household vs. non-household contacts was 4.8 (95% CI 1.16-19.91); the odds ratio among females was 0.66 (95% CI 0.30-1.45).

In multivariable analysis, Logistic regression revealed that there is interaction between type of contact and contact's sex (P-value=0.04). Odds of having TB was significantly higher for household contacts among males (aOR 4.38, 95% CI 1.05-18.22), but it was not significant among females (aOR 0.76, 95% CI 0.35-1.67). Among household contacts, male sex was significant risk factor (aOR 1.7, 95% CI 1.09-2.67); however, it was not a risk factor among non-household contacts (aOR 0.3, 95% CI 0.06-

1.42). It was also detected that younger age is a significant predictor for having TB after 1-year of follow-up period and younger people are at higher risk (per 1-year increase aOR 0.98, 95% CI 0.97-0.99). Contacts of male and female index patients did not have significantly different risk of active TB (aOR 0.82 95% CI 0.52-1.29) (Table 8). Other variables in the model were also tested for interaction, but their parameter estimate was not significant (Table 9).

DISCUSSION

The results of our study suggest that household contacts have a higher prevalence of positive TST than non-household contacts. The results from this first nationwide contact investigation in Georgia shows that household contacts have higher risk than other groups of contacts or all close contacts (4, 19). We also found that association between type of contact and active TB is modified by sex of contact: Among males, household contacts have significantly higher risk of active TB after 1-year follow-up (OR 4.80, 95% CI 1.16-19.91) while among females, household type of contact is not a significant risk factor (OR 0.66, 95% CI 0.30-1.45).

To our knowledge, our study is the first to report that among contacts whose index patients had a past history of TB, risk of latent infection depends on the outcome of their index case's previous TB treatment. Risk is significantly higher among those contacts, whose index patients failed from treatment or were lost to follow-up compared to those whose index patients were cured. This novel result highlights the importance of completing treatment regimen, especially in the countries like Georgia, where the default rate among patients is high. Patients in which treatment is not successful or who are lost to follow-up create longer exposure period for their contacts. Therefore, efforts aimed at reducing treatment default should enhance TB control efforts and may also decrease LTBI and active TB among contacts.

LTBI prevalence among household contacts (35.4%) is relatively low, compared to other low- and middle-income countries (4, 13). One possible reason for this can be the conservative approach in the tuberculin skin test methodology that was used in tuberculosis contact investigation program of Georgia: To have higher specificity of the

test, induration size of 10 mm or more was considered as a positive result, while in majority of other studies common practice is to use 5 mm threshold for LTBI diagnosis.

Our results suggest that TST result is associated with active TB. This might indicate that TST is a valuable tool in predicting progression to active TB and, therefore, usage of tuberculin skin tests, for predicting active TB disease among contacts, should be considered during planning of future contact investigation studies. We can assume, that treatment for latent TB infection could potentially avert some proportion of active TB disease among contacts. Currently, treatment of latent TB infection is not usually conducted in Georgia.

According to our results, Imereti and Guria regions have almost two times the prevalence of active TB among contacts compared to other regions. This result suggests that national authorities might need to consider some additional activities in these regions to improve early detection of disease.

Our study has several limitations. First, large proportion of contacts did not receive a tuberculin skin test (TST). Therefore, we have information about LTBI status only for limited portion of the total population. Additionally, epidemiologists did not record a measurement of induration, which precluded us to look at a more sensitive cut-off of 5 mm induration. Another limitation of the study is that the detection of active TB disease among contacts was a passive process; we did not follow them actively. We used a clinical database for the country to identify those contacts, who had diagnosed TB. However, according to WHO, the case detection rate in Georgia in 2012 was 78% (1). Moreover, although we did not actively check contacts for TB disease, during their visits

epidemiologists counseled them to go to a physician for TB screening. Therefore, we assume that we have found more than 80% of active TB cases among contacts.

In conclusion, our results suggest that contacts of active pulmonary smear-positive patients are at higher risk of both active and latent TB, furthermore, household contacts have higher risk compared to non-household contacts. To better understand risk factors for LTBI and active TB among contacts, future studies should be conducted. These studies should include screening not only for latent TB infection, but also for active TB disease through chest X-ray or sputum microscopy. This will allow us to increase case detection through active case finding, as well as to evaluate factors that are associated with progression from latent TB infection to active TB disease. Therefore, With well-planed and managed activities, contact investigation has potential to contribute to better understanding of disease transmission and progression patterns and can become a powerful tool in decreasing TB incidence and prevalence in the country of Georgia.

REFERENCES

1. World Health Organization. *Global tuberculosis report 2013 (in IRIS)*. Geneva: World Health Organization; 2013.
2. World Health Organization. *Multidrug-resistant tuberculosis (MDR-TB) indicators: a minimum set of indicators for the programmatic management of MDR-TB in national tuberculosis control programmes*. Geneva: World Health Organization; 2010.
3. Lomtadze N, Aspindzelashvili R, Janjgava M, et al. Prevalence and risk factors for multidrug-resistant tuberculosis in the Republic of Georgia: a population-based study. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2009;13(1):68-73.
4. Herrera M, Bosch P, Najera M, et al. Modeling the spread of tuberculosis in semiclosed communities. *Computational and mathematical methods in medicine* 2013;2013:648291.
5. Fox GJ, Barry SE, Britton WJ, et al. Contact investigation for tuberculosis: a systematic review and meta-analysis. *The European respiratory journal* 2013;41(1):140-56.
6. World Health Organization. *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries*. Geneva: World Health Organization; 2012.
7. Rieder HL. Contacts of tuberculosis patients in high-incidence countries. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2003;7(12 Suppl 3):S333-6.
8. Greenaway C, Palayew M, Menzies D. Yield of casual contact investigation by the hour. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2003;7(12 Suppl 3):S479-85.
9. Control and prevention of tuberculosis in the United Kingdom: code of practice 2000. Joint Tuberculosis Committee of the British Thoracic Society. *Thorax* 2000;55(11):887-901.
10. Rose CE, Jr., Zerbe GO, Lantz SO, et al. Establishing priority during investigation of tuberculosis contacts. *The American review of respiratory disease* 1979;119(4):603-9.
11. Erkens CG, Kamphorst M, Abubakar I, et al. Tuberculosis contact investigation in low prevalence countries: a European consensus. *The European respiratory journal* 2010;36(4):925-49.
12. Hsu KH. Contact Investigation: A Practical Approach to Tuberculosis Eradication. *American journal of public health and the nation's health* 1963;53:1761-9.
13. Fox GJ, Nhung NV, Sy DN, et al. Contact investigation in households of patients with tuberculosis in Hanoi, Vietnam: a prospective cohort study. *PloS one* 2012;7(11):e49880.

14. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *The Lancet infectious diseases* 2008;8(6):359-68.
15. Hwang TJ, Ottmani S, Uplekar M. A rapid assessment of prevailing policies on tuberculosis contact investigation. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2011;15(12):1620-3.
16. Shah NS, Yuen CM, Heo M, et al. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;58(3):381-91.
17. Becerra MC, Appleton SC, Franke MF, et al. Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study. *Lancet* 2011;377(9760):147-52.
18. Militao de Albuquerque Mde F, Ximenes RA, Campelo AR, et al. Neonatal BCG vaccine and response to the tuberculin test in BCG vaccinated children in contact with tuberculosis patients in Recife, Brazil. *Journal of tropical pediatrics* 2004;50(1):32-6.
19. Marks SM, Taylor Z, Qualls NL, et al. Outcomes of contact investigations of infectious tuberculosis patients. *American journal of respiratory and critical care medicine* 2000;162(6):2033-8.
20. Triasih R, Rutherford M, Lestari T, et al. Contact investigation of children exposed to tuberculosis in South East Asia: a systematic review. *Journal of tropical medicine* 2012;2012:301808.
21. Singh M, Mynak ML, Kumar L, et al. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. *Archives of disease in childhood* 2005;90(6):624-8.
22. Guwatudde D, Nakakeeto M, Jones-Lopez EC, et al. Tuberculosis in household contacts of infectious cases in Kampala, Uganda. *American journal of epidemiology* 2003;158(9):887-98.
23. Borraccino A, Migliore E, Piccioni P, et al. Yield of tuberculosis contact investigation in a low-incidence country. *The Journal of infection* 2014.
24. Kilicaslan Z, Kiyan E, Kucuk C, et al. Risk of active tuberculosis in adult household contacts of smear-positive pulmonary tuberculosis cases. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2009;13(1):93-8.
25. Weinstock DM, Hahn O, Wittkamp M, et al. Risk for tuberculosis infection among internally displaced persons in the Republic of Georgia. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2001;5(2):164-9.
26. Whitaker JA, Mirtskhulava V, Kipiani M, et al. Prevalence and incidence of latent tuberculosis infection in georgian healthcare workers. *PloS one* 2013;8(3):e58202.
27. Nayak S, Acharjya B. Mantoux test and its interpretation. *Indian dermatology online journal* 2012;3(1):2-6.

Table 1. Comparisons of contact who did and did not undergo tuberculin skin testing.

Characteristics		**TST[a] done N (%)**	**TST not done N (%)**	**OR[b]**	**95% CI[c]**	**P-value**
Type of Contact	***Non-household***	210 (51.1)	201 (48.9)	1.00		
	Household	834 (32.9)	1698 (67.1)	2.13	1.72-2.63	<0.01
Contact Sex	***Male***	497 (37.3)	835 (62.7)	1.00		
	Female	660 (36.7)	1141 (63.3)	1.03	0.89-1.19	0.73
Contact Age Category	***0-4***	120 (44.4)	150 (55.6)	1.00		<0.01
	5-14	250 (53.3)	219 (46.7)	0.70	0.52-0.95	
	15-44	468 (34.5)	890 (46.5)	1.52	1.17-1.98	
	45-64	200 (29.5)	479 (70.5)	1.92	1.43-2.56	
	≥65	82 (31.8)	176 (68.2)	1.72	1.20-2.45	
Index TB case Employment Status	***Employed***	116 (28.9)	285 (71.1)	1.00		
	Unemployed	963 (37.7)	1594 (62.3)	0.67	0.54-0.85	<0.01
Index TB case history of prison	***No***	999 (36.5)	1741 (63.5)	1.00		
	Yes	67 (39.2)	104 (60.8)	0.89	0.65-1.22	0.47
Index TB case history of TB	***No***	903 (36.9)	1544 (63.1)	1.00		
	Yes	215 (36.9)	368 (63.1)	1.00	0.83-1.21	0.99
Index TB case IDP[d]	***No***	1044 (37.1)	1768 (62.9)	1.00		
	Yes	18 (25.0)	54 (75.0)	1.77	1.03-3.03	0.04
Index TB case MDR[e] Status	***No***	659 (34.6)	1247 (65.4)	1.00		
	Yes	126 (38.2)	204 (61.8)	0.89	0.67-1.09	0.21
Index TB case Sex	***Male***	856 (37.8)	1406 (62.2)	1.00		
	Female	255 (35.5)	464 (64.5)	1.05	0.93-1.32	0.25
Index TB case Age Category	***0-4***	18 (45.0)	22 (55.0)	1.00		<0.01
	5-14	57 (69.5)	25 (30.5)	0.36	0.16-0.78	
	15-44	705 (38.2)	1138 (61.8)	1.32	0.70-2.48	
	45-64	283 (32.1)	599 (67.9)	1.74	0.91-3.28	
	≥65	94 (32.9)	192 (67.1)	1.65	0.86-3.27	

[a] Tuberculin skin test

[b] Odds ratio

[c] Confidence interval

[d] Internally displaced person

[e] Multidrug-resistant

Table 2. Bivariate analysis of demographic characteristics and tuberculin skin test (TST) result.

Characteristics		**TST[a] Positive N (%)**	**TST Negative N (%)**	**OR[b]**	**95% CI[c]**	**P-value**
Type of Contact	***Non-household***	57 (27.1)	153 (72.9)	1.00		
	Household	294 (35.35)	540 (64.75)	1.46	1.05-2.04	0.02
Contact Sex	***Male***	169 (34.0)	328 (66.0)	1.00		
	Female	224 (33.9)	436 (66.1)	0.99	0.78-1.27	0.95
Contact Age Category	***0-4***	48 (40.0)	72 (60.0)	1.61	0.89-2.94	
	5-14	83 (33.2)	167 (66.8)	1.32	0.79-2.20	
	15-44	165 (35.3)	303 (64.7)	1.04	0.59-1.82	
	45-64	60 (30.0)	140 (70.0)	1.20	0.70-2.07	
	≥65	24 (29.3)	58 (70.7)	1.00		0.33
Index TB Case Employment Status	***Unemployed***	317 (32.9)	646 (67.1)	1.00		
	Employed	49 (42.2)	67 (58.8)	1.49	1.01-2.20	<0.05
Index TB case history of TB	***No***	306 (33.9)	597 (66.1)	1.00		
	Yes	75 (34.9)	140 (65.1)	1.05	0.77-1.43	0.78
TB Index case history of incarceration	***No***	344 (34.4)	655 (65.6)	1.00		
	Yes	19 (28.4)	48 (71.6)	0.75	0.44-1.30	0.30
Index TB Case IDP	***No***	350 (33.5)	694 (66.5)	1.00		
	Yes	7 (38.9)	11 (61.1)	1.26	0.49-3.28	0.64
Index TB Case MDR[e] Status	***No***	274 (33.95)	533 (66.05)	1.00		
	Yes	40 (31.75)	86 (68.25)	0.97	0.65-1.47	0.90
Index TB Case Sex	***Female***	75 (27.2)	201 (72.8)	1.00		
	Male	318 (36.1)	563 (63.9)	1.51	1.12-2.04	<0.01
Index TB Case Age Category (in years)	***0-4***	6 (33.3)	12 (66.7)	1.00		
	5-14	19 (33.3)	38 (66.7)	1.00	0.32-3.08	0.08
	15-44	252 (35.7)	453 (64.3)	1.11	0.41-3.00	
	45-64	96 (33.9)	187 (66.1)	1.03	0.37-2.82	
	≥65	20 (21.3)	74 (78.7)	0.54	0.18-1.62	

[a] Tuberculin skin test

[b] Odds ratio

[c] Confidence interval

[d] Multidrug-resistant

Table 3. Association of index patients' previous TB treatment outcome and risk of positive TST among their contacts

	TB Treatment Outcome	TST[a] positive	TST negative	OR[b]	95% CI[c]	P-value
Outcome of previous TB treatment	***Cured***	9 (16.7)	45 (83.3)	1.00		<0.01
	Completed	18 (40.0)	27 (60.0)	3.33	1.31-8.46	
	Default	14 (50.0)	14 (50.0)	5.00	1.79-14.00	
	Failure	9 (56.25)	7 (43.75)	6.43	1.90-21.77	

[a] Tuberculin skin test

[b] Odds ratio

[c] Confidence interval

Table 4. Multivariable analysis in subset of contacts of index patients with previous history of TB.

Characteristic	**aOR[a]**	**95% CI[b]**
Outcome Completed vs Cured	3.26	1.25-8.47
Outcome Defaulted vs Cured	3.26	1.03-10.33
Outcome Failure vs Cured	8.02	2.19-29.44
Household vs Non-household	3.44	0.87-13.64
Male vs Female	1.64	0.74-3.64

[a] Adjusted odds ratio

[b] Confidence interval

Table 5. Multivariable analysis of risk factors for positive tuberculin skin test among contacts of index TB cases.

Characteristics	**aOR[a]**	**95% CI[b]**	**P-value**
Household contact (vs. Non-household Contact)	**2.28**	**1.49-3.49**	**<0.01**
Male Contact	1.02	0.75-1.33	0.99
Age of contact (per 1 year increase)	1.00	0.99-1.00	0.21
Index Case Employed	**1.66**	**1.10-2.52**	**0.02**
Index TB Case - Age	0.99	0.98-1.00	0.15
Index TB Case - Male	**1.58**	**1.14-2.19**	**<0.01**

[a] Adjusted odds ratio

[b] Confidence interval

Table 6. Testing of Interaction between Type of Contact and other variables in the final model.

Interaction	**Variable**	**P-value**
Type of Contact	Contact's Sex	0.39
	Contacts Age	0.48
	Index patient's Employment status	0.92
	Index Age	0.10
	Index patient's Sex	0.40

Table 7. Bivariate analysis of risk factors for having active TB disease after 1-year follow-up period among contacts of smear-positive index patients.

Characteristic		Active TB N=103 N(%)	No Active TB N=3030 N(%)	OR[a]	95% CI[b]	P-value
Type of Contact - males	***Non-household***	2 (1.1)	185 (98.9)	1.00		
	Household	53 (4.9)	1019 (95.1)	4.80	1.16-19.91	0.03
Type of Contact - females	***Non-household***	8 (3.6)	216 (96.4)	1.00		
	Household	35 (2.4)	1425 (97.6)	0.66	0.30-1.45	0.30
Contact Sex	***Male***	59 (4.4)	1273 (95.6)	1.85	1.24-2.75	
	Female	44 (2.4)	1757 (97.6)	1.00		<0.01
Contact Age Category	***0-4***	18 (6.7)	252 (93.3)	3.61	1.32-9.88	
	5-14	27 (5.8)	442 (94.2)	3.09	1.18-8.13	
	15-44	38 (2.8)	1320 (97.2)	1.46	0.57-3.74	
	45-64	13 (1.9)	666 (98.1)	0.99	0.35-2.80	
	≥65	5 (1.9)	253 (98.1)	1.00		<0.01
TST[c] Result	***Negative***	12 (1.6)	752 (98.4)	1.00		<0.01
	Positive	33 (8.4)	360 (91.6)	5.75	2.93-11.26	
	TST Not Done	58 (2.9)	1918 (97.1)	1.90	1.01-3.55	
Index TB case employment status	***Employed***	14 (3.5%)	387 (96.5%)	1.00		
	Unemployed	86 (3.4%)	2471 (96.6%)	0.97	0.55-1.73	0.90
Index TB case history of Incarceration	***No***	92 (3.4%)	2648 (96.6%)	1.00		
	Yes	8 (4.7%)	163 (95.3%)	1.41	0.67-2.96	0.40
Index TB case history of TB	***No***	83 (3.4)	2364 (96.6)	1.00		
	Yes	19 (3.3)	564 (96.7)	0.96	0.58-1.59	0.87
	Favorable outcome	7 (2.6)	260 (97.4)	1.00		
	Unfavorable outcome	4 (2.5)	154 (97.5)	0.96	0.28-3.35	0.95
Index TB case IDP[d]	***No***	93 (3.3%)	2719 (96.7%)	1.00		
	Yes	2 (2.8)	70 (97.2)	0.84	0.20-3.46	0.8
Index TB case MDR[e] Status	***No***	73 (3.2)	2200 (96.8)	1.00		
	Yes	10 (3.0)	320 (97.0)	0.94	0.48-1.84	0.86
Index TB	***Male***	75 (3.2)	2193 (96.8)	1.00		

case Sex	***Female***	28 (3.7)	737 (96.3)	1.16	0.75-1.80	0.5
Index TB case Age Category	***0-4***	0 (0.0)	40 (100.0)	-		
	5-14	0 (0.0)	82 (100.0)	-		
	15-44	79 (4.3)	1764 (95.7)	6.56	1.60-26.85	
	45-64	21 (2.4)	861 (97.6)	3.10	0.71-13.38	
	≥65	3 (1.1)	283 (98.9)	1.00		<0.01

[c] Tuberculin skin test

[a] Odds ratio

[b] Confidence interval

[d] Internally displaced person

[e] Multidrug-resistant

Table 8. Multivariable analysis of risk factors for having active TB disease after 1-year follow-up period among contacts of active TB cases in Georgia.

Characteristics	**aOR[a]**	**95% CI[b]**	**P-value**
Household (vs. Non-household) Contact – among males	**4.38**	**1.05-18.22**	**0.04**
Household (vs. Non-household) Contact – among females	0.76	0.35-1.67	0.49
Male Contact (Household)	**1.70**	**1.09-2.67**	**0.02**
Male Contact (Non-household)	0.30	0.06-1.42	0.13
Age (per 1 year increase)	**0.98**	**0.97-0.99**	**<0.01**
Contact of Male Index Case	0.82	0.52-1.29	0.40

[a] Adjusted odds ratio

[b] Confidence interval

Table 9. Testing for interaction between type of contact and other variables in the final model

Interaction	**Variable**	**P-value**
Type of contact	Contact's Sex	0.03
	Contact's Age	0.88
	Index patient's Sex	0.25

Figure 1. Percentage of contacts with a tuberculin skin test (TST) performed by region in the country of Georgia (n=total number of contacts).

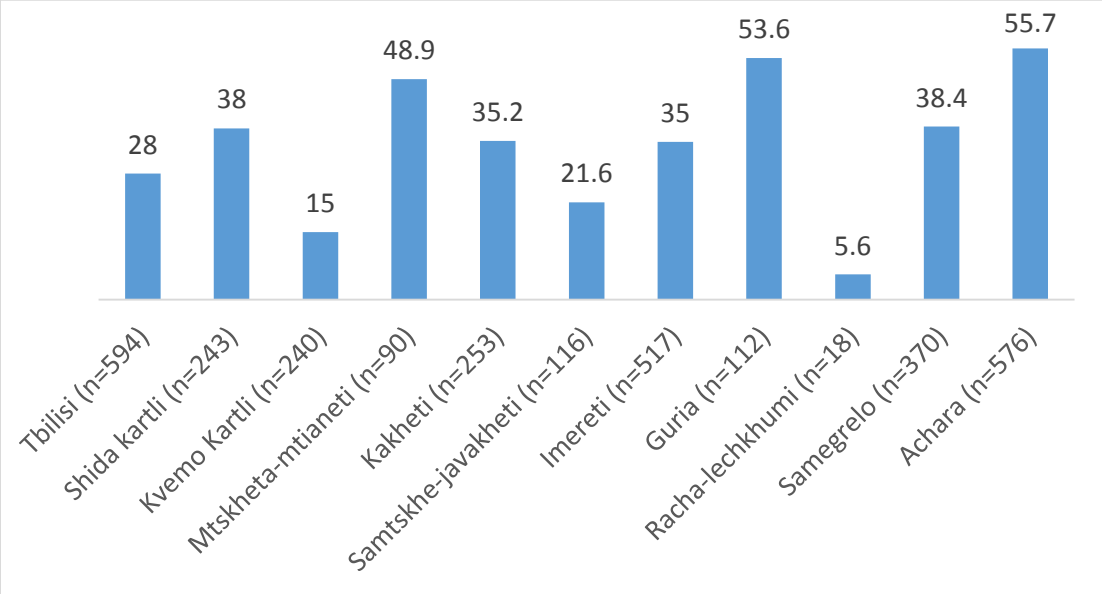

Figure 2. Percentage of contacts with positive TST by region (n=number of contacts with TST performed)

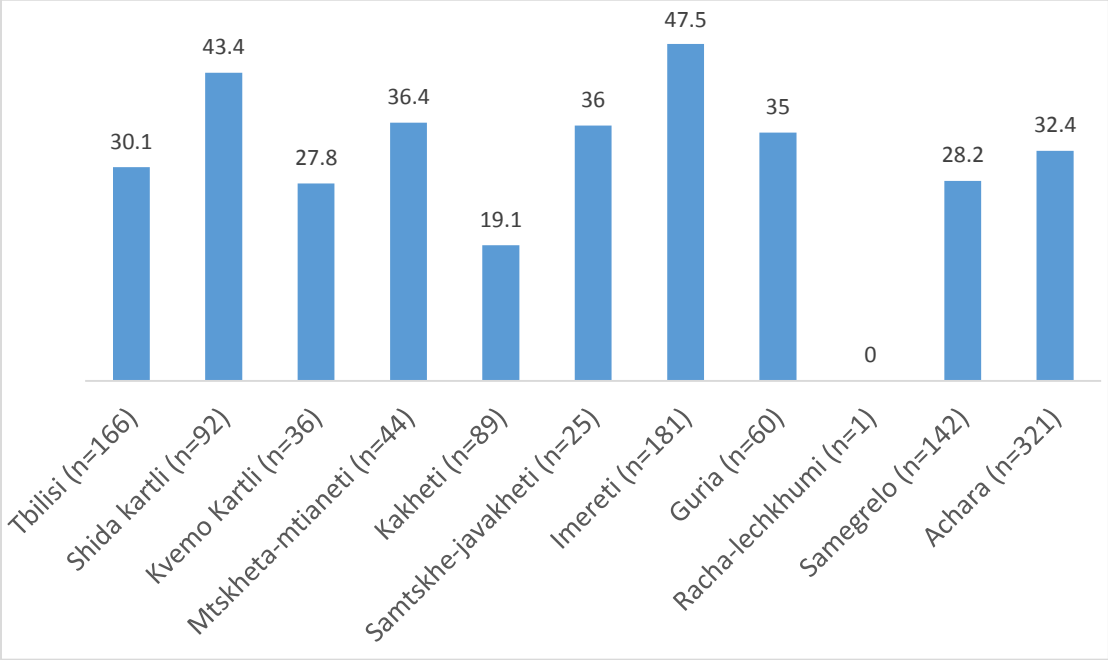

Figure 3. Percentage of contacts with active TB after 1-year follow-up by region (n=total number of contacts)