RISK FACTORS FOR LATENT TUBERCULOSIS INFECTION IN CLOSE CONTACTS OF ACTIVE TUBERCULOSIS PATIENTS IN ALEPPO CITY

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ABSTRACT

The diagnosis and treatment of latent tuberculosis infection (LTBI) have become mandatory toreduce the burden of tuberculosis worldwide. Close contacts of active TB patients are at high risk of both active and LTBI. The aim of this study is to identify t risk factors of contracting LTBI, persons in close contact with TB patients were recruited. Close contacts of active pulmonary TB patients visiting local Tuberculosis Center were diagnosed for LTBI using TST. The association of positive TST with the following factors was estimated: age, gender, education, history of close contact, history of Bacillius Calmette-Guerin (BCG) vaccination. Of 210 subjects, 44.8% (94/210) were TST positive and. TST positivitywas significantly associated with medical history related to immunological case (OR: 3.278; 95% CI: 1.019-10.547, p =0.046) after adjustment for confounding variables. This study revealed a high prevalence of LTBI among close contacts of active pulmonary TB patients, having a medical history and being a household contact (number of family were risk factors of LTBI in the study population.

KEYWORDS: Latent Tuberculosis, Close Contact, TST, Prevalence, Risk factor.

1. INTRODUCTION

Tuberculosis (TB)remains a major global health challenge, affecting 2.8 million people each year, most of them live in low- and middle-income countries.[1] *Mycobacterium tuberculosis* is a prototypical airborne pathogen that is transmitted, almost exclusively, from person to person via shared air.[2,3] In 2010, the WHO estimates that nearly 1/3 of the world's population contracted LTBI, and that 10% of these carriers will develop an active TB infection.[1,2,4] The vast majority of these patients will become infectious and perpetuate the cycle of morbidity and mortality. Therefore, it is imperative to diagnose LTBI patients early and efficiently to reduce the global burden of TB.[5,6]

Several factors related to the source case, the organism, the environment, and the people who are exposed to the source case determine whether transmission will occur and establish a new infection. Nevertheless, people who are in close contact with an individual who has an infectious form of tuberculosis are at increased risk of acquiring the infection and, once infected, of progressing to active tuberculosis infection.[7,8] Contact investigation is the principal method used to detect additional TB patients and recently exposed persons with latent M. tuberculosis infection at risk for progression to TB.[9] TB detection programs have varying rates of success in eliciting, locating, and evaluating contacts of TB patients and initiating treatment for latent M. tuberculosis infection.[9]

There are several risk factors known to be associated with developing active TB in close contacts, including malnutrition, untreated LTBI, being a household contact, age under 5 years, acid-fast bacilli (AFB) positivity of source case, concomitant human immunodeficiency virus infection, and immunocompromised status.[10] However, there is limited data about risk factors for LTBI in close contacts.[11]

2. Objective

The present study was performed to determine the prevalence of tuberculosis infection(LTBI) among closed contact persons of pulmonary tuberculosis patients in Aleppo City and evaluate the effects of some host and environmental factors on the risk of TB infection.

3. MATERIAL AND METHODS
3.1. Subjects and study design
In this cross sectional study, close contacts of pulmonary TB patients who visited Tuberculosis Control Center and Chest Clinic of Aleppo University Hospital and Al-Razi

Hospitalwere prospectively enrolledbetween January and August 2015. All data presented in this study were acquired using a questionnaire by face-to-face interview filled by the author. Close contacts are recommended to visit a hospital because screening of close contacts is a national policy project carriedout by Aleppo Tuberculosis Center under the guidance of the World Health Organization.

Close contact was defined as exposure to AFB smear-positive and/or culturepositive active pulmonary TB patient during their infectious period before diagnosis and during treatment. Close Contact of AFB smear-negative active pulmonary TB patient was also included in this study due to inability to culture smear specimens in most times during the study period. Exclusion criterion was active TB identified by chest X-ray and sputum microscopic examination. The remaining subjects filled informed consent documents and were tested for LTBI by TST. We also documented seven potential risk factors for LTBI: gender, age, medical history, tobacco use, education, type of residence, number of family, history of Bacillus Calmette-Guerin (BCG) vaccination.

3.2. Measurements
Index cases were evaluated with a medical history and physical examination performed by Aleppo University and Tuberculosis Center Physicians. Sputum samples were collected for microscopic examination. Chest radiographs were taken and tuberculin skin testing were performed. Tuberculin skin testing was performed on all studysubjects by placing 0.1 ml of 5 tuberculin units of purifiedprotein derivative (PPD; Tuberculin Mammalian For human use, BB-NCIPD Ltd. Sofia. Bulgaria) on one of the forearm using the Mantoux method. After 48–72 hours, the diameter of palpable induration was recorded using standardized procedures.[12,13] A tuberculin skin test wasconsidered positive if it was 10 mm or greater.

3.3. Statistical analysis
X2 test was performed with SPSS software (IBM® SPSS® Statistics 23) to assess associations between all continuous (e.g., age, number of family) and categorical (e.g., sex, education, history of close contact) variables and TST positivity. The prevalence odds ratio was performed to measure the association between the whole demographic characteristics and having positive TST by using multivariate logistic regression. Given the relatively high prevalence of positive TSTs among the population assessed in the study, the odds ratio overestimates the risk ratio. A value of P < 0.05 was considered to be statistically significant

4.   RESULTS AND DISCUSSION
The review of 45 cases of active TB patients identified a total of 210 close contact individuals (91 males and 119 females) confirmed not to have active TB by chest Xrays (Table 1). Subjects were household or work contacts of patients with confirmed active pulmonary TB.

Tuberculin skin tests were placed on all subjects, who returned to have the TST read at 48–72 hours after placement. The demographic characteristics of subjects are shown in Table 1.

Mean age was 19 ± 16.7 years (range 4 month –76 years). The mean number of persons living in a subject's apartment were respectively 7.3 (range 2–18; standard deviation [SD] 3.4). Of 210close contacts who returned to have their TST read, 94(44.8%) were TST positive.

4.1. Subjects distributions
The age distribution showed an increase in numbers of children under 10 years old and those between 21 – 40 years old (28.1% and 34.3% respectively). Proportion of females was higher in all age groups (range 66.6% to 48.8%). The Most of the population studied were educated (76% of adults) and unsmokers (79.5%). 9% of study subjects' had a medication such as anemia, diabetes, arthritis, and other diseases. More than 93% of the subjects had a BCG vaccination and 71.9% of them BCG scar was visible. 100% of children had BCG vaccinated, then the proportion started decreasing in persons above 21 years old, BCG scar decreased with increasing age, reflecting increasing BCG vaccination coverage in Syria in the last decades. The distribution of subjects with BCG vaccine and scar by age was approximately equal in both males and females.

4.2. TST reaction results
A total of 44.8% subjects had TST positivity and females were more likely than males to have a positive TST (47%). The distribution of TST indurations is shown in Figure 1. The mean TST induration diameter (10 mm) increased with age; 49.6% in subjects above 20 years old. The prevalence of LTBI increased with age, from 28.9% in children < 10 years of age group to 56.2% in the oldest age group above 40 years old. Among adults, the rate of TST positivity did not increase with increasing age. The prevalence tended to be higher among subjects with low levels of education, table1.

The prevalence among individuals who had medication and smokers was greater than the prevalence among healthier and nonsmokers (68.4%, 48.8% vs 42.4%, 43.4% respectively). In contrast TST positivity individuals didn't increasewith increasing.
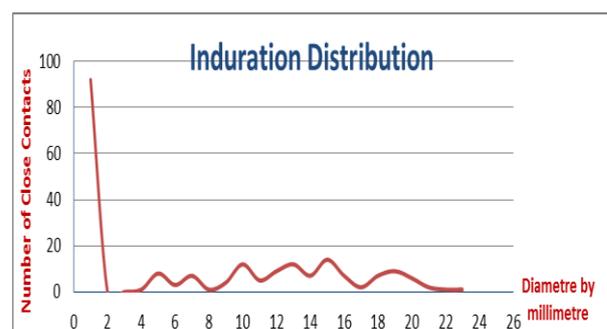

Figure 1: Frequancy distribution of Tuberculin reaction size.

Number of family; families compounded of less than 5 persons were more likely to have a positive TST (51.3%). In addition, displacement in our study population didn't affect on the prevalence of latent TB infection (Figure 1, Table 1).

4.3. Risk factors for LTBI

Multivariate logistic regression was performed with TST positivity as the dependent variable and the risk factors as independent variables. The potential risk factors that were not associated with TST- positivity were as follows: sex, age, education, residence, smoking, history of BCG vaccination and BCG scar. Based on an unadjusted logistic regression analysis, the risk factors of having an LTBI among close contacts we remedication and number of family. Occurrence of positive TST was higher in females than in males butgender was not associated with a positive test result (p=0.271). Although Increasing age increase the prevalence of TST positivity, age didn't increase the risk of having LTBI in our population. Education, type of residence, smoking affected the prevalence of LTBI but didn't considered as risk factors in close contacts (p > 0.5). Controversially, Number of family had associated with TST positivity stratified less 10 individuals, when returning to the data, TST positivity was higher in couples in small and bigger families. This result reflect the importance of proximity to an Infectious Case. Medication was significantly associated with the TST positivity (p=0.46). These results suggest that being a household contact are the predominant risk factors for LTBI.

4.5. DISCUSSION

To the best of our knowledge, this was the first study in which the diagnoses have been reported for whom contracted LTBI after having close contact with active pulmonary TB patients in Aleppo City. The result of current study showed a relatively high prevalence of latent TB infection (LTBI) among close contacts living/handling with active pulmonary tuberculosis patients in Aleppo City. The prevalence of LTBI expected to be high in close contacts of active TB patients due to increased probability of acquiring the infection with Mycobacterium bacilli, in a variety of settings, and increased substantial risk to develop active TB.[7,8,14] The incidence of new cases is highest in the first year and remains above background incidence for at least 5 years after exposure to a patient with TB,[1,3,15] In this study the prevalence of LTBI among contacts in Aleppo City, which was 44.8% had great difference from the results of contact tracing conductedin Sudan (2017), Taiwan (2010), Australia (2013) that revealed prevalence 6.5%, 19 and 28.1% respectively of LTBI among household contacts.[16-18] Our study result was considered to be a lower prevalence compared to those reported in Uganda, South Africa and high burden countries, where prevalence among contacts was 66% ,89% and 93%, respectively.[7,18-20] Given that Syria has an intermediate burden of TB cases and almost every child receives BCG vaccination at birth, the positive rates of TST (diameter > 10 mm) in this study was considerably highand theincidence of LTBI in close contacts of active TB patients is quite high.[who].There areseveral studies which reported different prevalence of T.B among householdcontact, this leads to the assumption that many of these current cases were actually infected by a member of their own family.[21]

History of medication was significantly associated with the risk of TST positivity. The potential risk of LTBI increases in those who had diseases such anemia, diabetes, arthritis, kidney disorders and asthma.

Table 1: Table 2: Risk factors of having positive TST among close contact people in Aleppo City.

Demographic characteristic	*n*(%)	TST positive n (%)	P value (χ^2)	95% confidence interval for Exp(B)		Exp(B)= Odd ratio	P value (L.R.)
				lower	*upper*		
Total	210 (100%)	94 (44.8%)	-	-		-	-
Sex Female Male	119 (56.7) 91 (43.3)	56 (47) 38 (41.7)	0.444	0.645	2.734	1.328	.442
Age < 10 11-20 21-40 41-60 > 60	59 (28.1) 43 (20.5) 72 (34.3) 32 (15.2) 9 (1.9)	23 (38.9) 18 (41.8) 34 (47.2) 18(56.2) 4 (25)	0.635	0.006	4.178	0.160	0.271
Education Child Uneducated Average educated educated	89 (42.4) 29 (13.8) 38 (18.1) 54 (25.7)	36(40.4) 18 (62) 17 (44.7) 23 (42.5)	0.232	0.075	1.557	0.341	0.165
Residence: Displaced Urban	156(74.3) 32(15.2)	68(43.5) 13(40.6)	0.344	0.761	11.002	2.894	0.119

Rural	22(10.5)	13(59)					
Number of family 1-5 6-10 11-15 15	76(36.2) 113(53.8) 8(3.8) 13(6.2)	39(51.3) 48(42.4) 2(25) 5(38.4)	0.387	0.111	1.528	0.411	0.041
History of tobacco use Yes No	43 (20.4) 167 (79.5)	2 (48.8) 73(43.7)	0.547	0.714	5.290	1.944	0.193
Medical history Yes No	19 (9) 191 (91)	13 (68.4) 81(42.4)	0.843	1.019	10.547	3.278	0.046
History of BCG vaccination Yes No	197 (93.5) 13 (6.2)	84 (42.6) 10(76.9)	0.016	0.064	1.453	0.306	0.136
BCG scar Yes no	151 (71.5) 59 (28.1)	63(41.7) 31(52.5)	0.156	0.278	1.218	0.582	0.151

In our population LTBI was not associated with male sex. This result didn't correspond with the study conducted in Georgia (2001), South Korea (2014), Australia (2013) results that considered male sex as a risk factor.[7,11,18,22] Although TST positivity was higher among those > 20 years of age, increasing age was not significantly associated with latent infection. It is uncertain whether increased age is the risk factor of contracting LTBI or whether increased cumulative exposure to *Mycobacterium tuberculosis* as people grow older increases positivity of TST.

Educational status and residence related to confirmed pulmonary TB among household contacts showed that illiterate and displaced/rural contacts constituted more occurrence versus educated and urban contacts without any significant value (P = 0.165, 0.119 respectively). Smoking was not significantly associated with LTBI among close contacts (P = 0.193). These result doesn't correspond with the global researches that consider urbanization as a risk factor.[1,23] On the other hand, This study showed that number of family had associated with TST positivity stratified less 10 individuals (P = 0.041). Women as housewives, in term of occupational aspect, have accounted for the highest percentage of 25% compared to all contacts (data was not showed), that explained by the prolonged time spent with the pulmonary T.B patient at household level; that increases the likelihood of T.B disease, This finding reflects the role and importance of degree of closeness with the index case for accruingthe disease.[8,16]

Above all TST positivity was not significantly associated with a history of BCG vaccination and the presence of BCG vaccine scar. Neither of history of BCG vaccination or BCG scar could be a risk factor for having a positive TST (Table 1, p > 0.05).

The design of our study (cross sectional design) have some limitations: a) We conducted this study in specific population of close contacts of pulmonary TB patients who visited Tuberculosis Control Center and Chest Clinic of Aleppo University Hospital and Al-Razi Hospital; they may not represent all other regions of Aleppo Governorate. b) Because two-step testing was not performed, it could be additional cases of positivity or active disease among the 116 who had a negative TST. Therefore, we may have underestimated the prevalence of TST positivity,[13,24]

5. CONCLUSION
LTBI is prevalent in close contacts of active pulmonary TB patients in an Aleppo City and prevalence of LTBI among contacts in this study was 44.8%, which is high if compared to similar studies in different countries. Results suggest that contact tracing, if conducted well, will be a powerful means of improving case detection rates for active TB disease. Close contacts of patients with TB are a well-recognized group that is likely to benefit from preventive therapy. Yet a considerable proportion of contacts miss out on the opportunity to receive treatment.

6. ACKNOWLEDGEMENTS

7. Conflicts of interest
Author had no conflicts of interest to declare in relation to this article.

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