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Prevalence and risk of Latent Tuberculosis Infection among Internally Displaced people in Aleppo City Shelters

Alaa Almekhlef[1*], Abdullah Khouri[2] & Rawaa Al-Kayali[1,3]

[1]*Department of Biochemistry and Microbiology, Pharmacy Faculty/ Aleppo University, Syria*
[2]*Department of Thoracic Medicine, Faculty of medicine/ Aleppo University, Syria*
[3]*Department of Public Health, Center for Strategic Studies and Research/ Aleppo University, Syria*

Abstract:
Many factors may influence host susceptibility to tuberculosis (TB) infection, and increase the risk of developing the disease. The present study screened the residents of seven hostels to determine the prevalence of tuberculosis (TB) infection and disease among internally displaced persons residing in Aleppo City-Syrian Arab Republic and. Using a tuberculin skin test (TST) and a pretested structured questionnaire, Participation was voluntary. Approximately 5886 potential subjects, 7.1% participated in the screening program. Of these 96.6% who had a TST placed returned at 48–72 hours to have the skin test examined; The average mean age was 25 ± 17 years old, 48.6% of the TST positivity cases were male and 26.9% were female and 29.4% were TST-positive (≥ 10 mm induration). In multivariate analysis, risk factors for a positive TST included increasing age, ever having received BCG, close contact with a case of active tuberculosis, smoking and other medical conditions. Two patients with active TB were identified through this screening, giving a case rate of 493 per 100 000 population. Screening latent TB was valuable in case finding among this high prevalence population. However there is a need to perform a similar survey on a broader scale to obtain clearer figure.

Keywords **:** *Internally Displaced , Latent TB, Prevalence , Risk factor, Screening*.

1. Introduction

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. In 2015, an estimated 10.4 million people developed TB and 1.4 million died from the disease, 1.2million (11%) of whom were HIV-positive [1]. The infection is mainly transmitted from sputum smear positive pulmonary TB patients, who discharge droplets containing the bacterium when coughing, sneezing or talking [2]. Left untreated, a person with infectious pulmonary TB can infect an average of 10 – 15 people every year [3,4,5]. The risk of transmission is based on the degree of exposure (e.g. duration of time, proximity), how contagious the source is (e.g. smear status and degree of cavitations), and the vulnerability of the exposed [2,5].

Latent Tuberculosis Infection (LTBI) is the presence of *Mycobacterium tuberculosis* in the body without signs and symptoms, or radiographic or bacteriologic evidence of tuberculosis (TB) disease. Approximately one-third of the world's population is infected with *Mycobacterium tuberculosis*. It is estimated that more than 11 million people in the United States have LTBI, which is about 4% of the total population. While not everyone with LTBI will develop TB disease, about 5 – 10% of infected people will develop TB disease if not treated. The diagnosis of LTBI is based on information gathered from the medical history, TST or IGRA result, chest radiograph, physical examination, and in certain circumstances, sputum examinations [4,5,6].

The control strategies introduced by the WHO emphasize clinical solutions in the form of drugs, vaccines, and access to health care; but, despite the success of these programs, TB incidence and mortality have not decreased [7]. Syria has achieved public health gains in tuberculosis (TB) prevention, reducing annual TB prevalence from 85 TB cases per 100,000 persons in 1990 to 23 per 100,000 in 2011[8,9]. From March 2011 through 2016, the Syrian crisis has resulted in a regional humanitarian emergency with 4.8 million Syrian refugees [8]. Tuberculosis care in Syria was integrated in the healthcare system nationwide with specialty TB treatment facilities located in each governorate, including Aleppo and Homs, areas badly destroyed by crisis. As the conflict escalated, health infrastructure has been destroyed, drug supply chains have been interrupted, and healthcare workers have fled ; all negatively impacting TB diagnosis and treatment efforts [10].

Therefore defining the prevalence of infection at a global and a regional level is critical to understanding the potential size of the reservoir of infection and planning intervention strategies [11].Targeted testing is an essential TB prevention and control strategy that is used to identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection (LTBI) or at high risk for developing TB disease once infected with *Mycobacterium tuberculosis*. Identifying persons with LTBI is important to the goal of TB control and elimination because treatment of LTBI can prevent infected persons from developing TB disease and stop the further spread of TB [4].

2. Objective

The present study was performed to determine the prevalence of tuberculosis infection(LTBI) among internally displaced persons residing in Aleppo City shelters and evaluate the effects of some host and environmental factors on the risk of TB.

3. Materials and Methods

3.1. Study Design and Setting:

This active – finding strategized study preformed in 7 shelters in Aleppo city from October 2015 to June 2016 and Tuberculosis Control Center in Aleppo city. Each household was visited by the author and all permanents residents of the hostels were offered the opportunity to have TST performed. The data were collected using a pretested structured questionnaire by face-to-face interview. Informed written consent was obtained from The Department of Social Affairs. The patients' private details were kept strictly confidential.

3.2. Study Population and Area:

The study took place in areas controlled by the Syrian government in Aleppo City. Study subjects' were made up of permanent residents of 7 hostels; University Dormitory (4 housing units), schools and other shelters. A positive TB disease was confirmed by a positive sputum smear, chest X-ray, and clinical manifestations as diagnosed by a physician. Residents participated by voluntary. All TST screening, chest radiography, and sputum examination were provided free of charge.

3.3. Measured Risk Factors and Equipment:

The information collected included host factors (sex, age, weight, medical history) and additional factors (contact with active TB, symptoms suggestive of active TB). History of Bacilli Calmette-Guérin (BCG) vaccine was obtained and BCG scar was inspected by physical examination for the presence or absence. Residents currently undergoing treatment for active TB disease were not included in the study.

3.4.Tuberculine test:

Tuberculin skin testing was performed using the Mantoux method; a 0.1 mL (5-TU) solution of purified protein derivative (PPD; Tuberculin Mammalian For human use, BB-NCIPD Ltd.Sofia.Bulgaria). A dose of exactly 0.1 ml was slowly injected on the volar surface of the forearm, and the reaction to the test was read by the author 48–72 hours later[12,13]. If an induration was present its limits were determined and its largest transverse diameter measured in millimeters with a transparent flexible ruler [13,14].

A positive TST was defined as induration of ≥ 10 mm. Two-step TST was not performed. Any subject with a TST ≥ 10 mm was referred to the national centers for tuberculosis and lung Disease (Tuberculosis Control Center and Chest Clinic of Aleppo University Hospital) for chest radiography to exclude active disease. Expenses for public transportation were provided. Subjects with cough, fever, or night sweats of more than 2 weeks' duration were instructed on the collection of three early-morning sputum specimens. All specimens were brought to the Aleppo Tuberculosis Control Center laboratory for acid-fast bacilli (AFB) smear microscopy. Specimens were processed using standard methodology[4,12,15].

3.5. Statistical Analysis:

X^2 test was performed with SPSS software (IBM® SPSS® Statistics 23) to assess associations between all continuous (e.g., age, number of people living in apartment) 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

The combined population of internally displaced persons in the seven hostels was approximately 5886. Tuberculin skin tests were placed on 419 internally displaced persons at the seven hostel locations, of whom 405 (96.6%) returned to have the TST read at 48–72 hours after placement. The demographic characteristics of the 405 subjects are shown in Table 1. Participants in the screening had been internally displaced for a mean of 2 year (range 2 months –3 years), and had lived in their current hostel for a mean of 1 year (range 1–3). Mean age was 25 years (range 4 month –85 years). The mean number of persons living in a subject's apartment were respectively 7.6 (range 2–37; standard deviation [SD] 5.9). Of 405 internally displaced persons who returned to have their TST read, 119(29.4%) were TST positive.

4.1. Age and Sex distribution:

The age distribution showed an increase in numbers of children under 10 years old and those between 21 – 40 years old (25.9% and 34.8% respectively). Proportion of females was higher in all age groups (range 53% to 61.7%). The Most of the population studied were lateral (69.3% of adults) and unsmokers (73.1%). 17% of study subjects' had a medication such as anemia (4.9%), diabetes (2.5%), arthritis (3.7%) and other disease.

4.2. BCG vaccine and scar:

385 (95.1%) of subjects were vaccinated and BCG scar was visible in 73% of them. History of BCG vaccinated persons was almost 98.2% in children and youngs, then started decreasing in persons above 40 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 (P > 0.05).

Table 1: Risk factors of having positive TST among internally displaced people living in Aleppo Shelters.

Demographic characteristic	*n* (%)	TST positive n (%)	*P* value
Total	405 (100%)	119 (29.4%)	-
Sex :			
Female	234 (57.8%)	63 (26.9%)	0.204
Male	171 (42.2)	56 (48.6%)	
Age :			
< 10	105 (25.9)	19 (18)	0.001
11-20	84 (20.7)	18 (21.4)	
21-40	141 (34.8)	58 (41.1)	
41-60	66 (16.3)	21 (31.8)	
> 60	9 (2.2)	3 (33.3)	
Education:			
Child	167 (41.2%)	32(19.1%)	0.001
Uneducated	73 (18 %)	30 (41.1%)	
Average educated	60 (15.1%)	22 (36.6%)	
educated	105 (25.7%)	35 (33.3%)	
History of tobacco use:			
Yes	109 (26.9%)	50 (47.6%)	0.000
No	296 (73.1%)	69 (23.3%)	
Number of family:			
1-5	167 (41.2)	53 (31.7)	0.335
6-10	197 (48.9)	51 (25.8)	
11-20	27 (6.7)	11 (40.7)	
> 20	13 (3.2)	4 (30.7)	
Medical history:			
Yes	69 (17%)	31 (26.1%)	0.002
No	336 (83 %)	88 (26.2)	
History of close contact:			
yes	161 (39.8%)	87 (54%)	0.000
no	244 (60.2%)	32 (15%)	
History of BCG vaccination:			
Yes	385 (95.1%)	114 (29.6%)	0.649
No	20 (4.9%)	5 (25%)	
BCG scar :			
Yes	296 (73%)	78 (26.4%)	0.027
no	109 (27%)	41 (37.6%)	

4.3.TST reaction:

In our population males were more likely than females to have a positive TST (56/ 171 [48.6%] vs. 63/234 [26.9%]) without any significance (OR: 0.835; 95% confidence interval [CI] 0.465-

1.499; P= 0.204). Subjects over 20 years of age had a significantly higher rate of positive TST (Table 1). Of 189 persons aged 1–20 years, 37 (19.5%) were TST positive compared to 82 (37.9%) of 216 adults (P = 0.001). Among adults, the rate of TST positivity did not increase with increasing age (Table 1). Educated persons are less likely to have a positive TST (57/165 [34.5%] vs. 30/73[41.1%]; P = 0.01). Other variables associated with an increased risk of having a positive TST in univariate analysis included tobacco use and history of medication (Table 1,2). Smokers were more likely than unsmokers to have a positive TST (50/ 109 [47.6%] vs. 69/296 [23.3%]; OR: 2.328; 95% confidence interval [CI] 1.167– 4.648; P= 0.000).As well as the prevalence of a positive TST was associated with presence of medication history (31/69 [26.1];OR: 2.385; 95%CI: 1.228– 4.626; P=0.01).

Additionally the positivity of TST was associated with close contact (87/161[54%] vs. 32/244[15%], OR: 10.36; 95% confidence interval [CI] 5.969–17.997; p=0.000). In contrast number of family individuals didn't affect on the TST positivity, although the families compounded of more than ten persons were more likely to have a positive TST (15/40[37.5%] vs. 104/364(28.5) ; p = 0.335).

Above all TST positivity was not significantly associated with a history of BCG vaccination unlike the presence of BCG vaccine scar (Table 1).Neither of history of BCG vaccination or BCG scar could be a risk factor for having a positive TST (Table 2, p > 0.05).

4.4. ARTI:

Based on the TST survey data, The annual risk of tuberculosis infection (ARTI) was calculated from the estimated prevalence of infection (P) by using the following equation, where A = mean age of test-read subjects [16]: $ARTI = 1 – (1–P)^{1/A}$

The ARI was 2.14% in all population studied, The findings of the study showed that the annual risk of tuberculosis infection was found to be close among both sexes, higher among subjects with close contact (2.17%) than others without (2.11%) and higher in adults (those over 20) without any increasings. The ARTI was similar among unvaccinated and vaccinated people (2.14%) but slightly lower in people with BCG-vaccinated scar (2.13%) than those without(2.16%). Therefore, it should be feasible to carry out ARI studies among BCG vaccinated in other areas or shelters with similar characteristics of BCG vaccinated group as in the present study.

4.5.Active tuberculosis:

Six(2%) of the subjects reported cough, fever, or night sweats of at least 2 weeks' duration. Of these, 5 provided sputum samples for AFB smear microscopy to the TCC laboratory. One specimen from the 5 patients were positive ; and had a positive TST (22 mm induration).The four others were negative TST, unfortunately specimen culturing was not available in the period of the study. Of the 119 subjects with a positive TST, 87(72.3%) underwent chest radiography. One (1.1%) of the 87 had evidence of active tuberculosis and the clinical diagnosis of TB disease was made by the local Tuberculosis Center staff. His AFB smear was negative. Combining the case diagnosed by AFB smear microscopy with the case of active TB which diagnosed by chest radiography among the 119 subjects screened, giving a rate of 493 cases/100 000.

Discussion

There are no accurate figures for the displaced people inside Syria and refugees abroad, but we can determine in cross-data that the number of internally displaced persons (IDPs) exceeds 6 million who are deployed throughout Syria, particularly semi-safe areas[8,17]. In Aleppo, The number of displaced people approximate to 133 thousand in 2012, most of them residents of Aleppo and its countryside. By October 2014, the IDP largest population reported by ACAPS was in Aleppo[17].Poor living conditions, crowding, malnutrition and concomitant disease among displaced people set this population at risk for tuberculosis and infectious diseases[18]. The result of current study showed a relatively high prevalence of latent TB infection (LTBI) and disease among internally displaced persons living in shelters in Aleppo City.

In our population TST positivity was not associated with male sex, number of persons in a family. This result didn't correspond with the study conducted in Georgia (2001).In contrast, TST positivity among shelters residents was higher among those > 20 years of age, and decreased for the rest adults (those > 40 years old); this was compatible with study conducted in Georgia (2001)[19]. Such result could be interpreted that most TB exposure in our population occurred recently during living in refugee housing since their displacement 1-3 years ago. If this is the case, most of the TB infection is recently acquired, especially among adults.

In addition, our study showed that TST positivity was associated with close contact with active TB, tobacco use and medical history of infectious and immunity disease (Table 2). Undoubtedly close contact with infectious TB patient is the most risk factor of having latent TB [20,21]; close contact increase the probability ten times in our study (Table 2). This result reconcile with the study carried out in Georgia (2010)[22]. Cigarette smoking was an important risk factor associated with a higher prevalence of LTBI; Smoking doubles the opportunity of having positive TST (Table 2). Smokers should be considered as a high-risk population for LTBI and potential candidates for LTBI prophylaxis treatment [19, 23]. Medical history of infectious and immunity disease could reflect the effect of malnutrition and poor living conditions on transmission and developing TB among this group[11].

There was a clear increase in the proportion of infected persons and the prevalence of active TB among the hostel residents screened who had no prior history of TB was quite high, at 493/100 000. This rate is more than twice that reported for the entire Syrian population, of approximately 20/100 000 in 2016 [24]. Therefore the prevalence of TST positivity among internally displaced persons may be higher than estimated among other Syrians in other regions. We cannot comment on any change from the previous epidemiological status of tuberculosis, because unfortunately no previous data on risk of infection have been available for Aleppo City.

Table 2 : Factors associated with positivity TST in multivariate analysis.

Demographic characteristic	Odd ratio	95% CI confidence Lower	Upper	P value
Sex	0.835	0.465	1.499	0.546
Tobacco use	2.328	1.167	4.648	0.017
Medical history	2.385	1.228	4.626	0.010
Close contact	10.36	5.969	17.997	0.000
History of BCG	2.866	0.750	10.956	0.124
BCG scar	0.78	0.429	1.420	0.417

Although the diagnosis and treatment of active disease should be the highest priority for control programs according to guidelines from the American Thoracic Society and the US Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO)[25], screening is increasingly framed as a potential part of the remedy for stalled case detection rates and diminishing returns from the traditional methods of passive detection of tuberculosis (TB) that rely upon health seeking by symptomatic individuals. Indeed TB screening has been shown to detect additional TB cases in several controlled trials. Moreover, its effectiveness in routine use among certain key populations is also suggestive of benefit, though the overall evidence base remains very weak (Kranzer et al 2012). Screening strategies present both opportunities and challenges for the health system. Screening may identify earlier TB disease and a different sort of TB patient than the traditional approaches [25,26].

This tuberculin survey have some general limitations: **a)** First limitation identified was related mostly to sampling in this survey; study participation was voluntary and the number of subjects included was small. Furthermore many replaced people leave the shelters during the later months. However, the low rate of participation may also reflect a participation bias. Those residents concerned about the possibility of tuberculosis may have been more likely to participate. On the other hand, unhealthy hostel residents or those fearing the stigma of being diagnosed with TB may have avoided screening. **b)** Not all internally displaced persons had a chest radiograph performed, it is possible that additional persons had active tuberculosis that was not detected. Only , 87(72.3%) of the 119 TST-positive subjects followed up for chest radiography. If cases of active TB exist among the remaining 32 TST-positive subjects, the prevalence of active TB for the entire screened population may be significantly higher than the 493/100 000 documented in this study. **c)** Because two-step testing was not performed , it could be additional cases of active disease among the 286 who had a negative tuberculin skin test and were not referred for a chest radiograph. Therefore, we may have underestimated the prevalence of TST positivity, especially among older individuals[12,15,16].

Furthermore in this study, applying cut-off of 10 mm overestimated the ARTI. This may be due to limited specificity with this cut-off as a result of high prevalence of infections with nontuberculosis mycobacteria (NTM) [12,27]. Over 95% of our study population reported a history of at least one BCG vaccination. Significant debate exists over the interpretation of a positive TST in the setting of BCG vaccination. TST reactivity after BCG varies depending on the strain, dose, method of vaccination, time since vaccination, number of BCG administered, age, nutritional status, and perhaps geographic latitude[27,28]. BCG scars are usually taken as proxy for BCG vaccination status. As subjects vaccinated at birth may not develop a scar, vaccination coverage was probably higher than the proportion of subjects with BCG scar observed in this survey (73% vs 95%). Among adults who received a single BCG vaccination as an infant, a positive TST may be more likely to represent true infection, as the TST reactivity due to BCG wanes with time[12,28,29]. However, it remains more difficult to interpret the result of the TST among those who have been BCG vaccinated. Of note, a history of BCG vaccination was an independent risk factor for a positive TST in our population.

Conclusion

Many useful results have become available through this survey; we found high rates of both TB infection and disease among internally displaced persons living in hostels in Aleppo . The risk of testing TST positive did not increase with age among adults, and the annual risk of infection was greatest for adults suggesting high rates of transmission among this group since their displacement. The likelihood of infection is ten times higher when there was a close contact with active TB patients . Tuberculin skin testing with a symptom questionnaire proved a useful mechanism for active case finding in this population with extremely high rates of TB. Identifying persons with latent TB infection is important to the goal of TB elimination because treatment can prevent these persons from developing TB disease and thereby stop the further spread of TB to others.

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