

Prevalence of cutipositivity in a sample of homeless shelter population in Rome in the course of Latent Tuberculosis Infection surveillance plan. Preliminary results

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Abstract

Background: in Europe homelessness is a known risk factor both for active and latent tuberculosis (TB). In Rome 409 cases of TB were notified in 2004, but the real occurrence among homeless people is unknown. Tuberculosis surveillance has been organized with the aim to develop an integrated model for the risk evaluation and management of both Latent Tuberculosis infections (LTBI) and TB in Rome homeless people.

Methods: the eligible individuals have been recruited in the homeless' refuges. The Tuberculin Mantoux test has been used to evaluate the infection prevalence; in case of a positive result, the individual's expectorate has been collected and the chest X-ray has been performed. A collecting data form has been filled in for evaluating some risk factors. Multiple logistic regression models have been carried out to find statistically significant determinants of infection.

Results: out of 120 subjects recruited, 108 came back for the evaluation of the skin test; the prevalence of LTBI was 43.5% (47/108 subjects); no active TB cases were found. According to the multivariate analysis, factors significantly associated to LTBI are gender (for males OR = 4.94; 95% CI: 1.46 – 16.67, 1st model; OR 5.84; 95% CI: 1.26 – 21.10, 2nd model), birth place (for Europe: OR 3.05; 95% CI: 1.02 – 9.13, 1st model; OR 3.12; 95% CI: 1.10 – 8.88, 2nd model; for East Mediterranean native Region OR = 4.34; 95%CI: 1.15-16.39); Body Mass Index class (for obesity OR = 3.34; 95% CI:1.31-8.51).

Conclusions: these preliminary results have demonstrated a high prevalence of LTBI among homeless people. Male gender, birth place (Europe and East Mediterranean native Region) and obesity were found to be significant risk factors. The surveillance system allowed positive patients for LTBI to be rapidly directed to a specialized centre for the clinical evaluation and the appropriate therapy in order to prevent the evolution of disease.

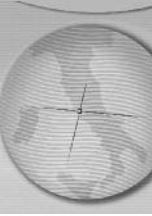
Key words: homeless, Italy, Latent Tuberculosis infections, surveillance, tuberculosis,

Introduction

Tuberculosis (TB) incidence is still increasing in three endemic areas of the world: in African countries with high prevalence of HIV (estimated impact rate: 400 cases/100,000 per year); in African countries with low prevalence of HIV (incidence rate around 200 cases/100,000 per year); and in Eastern Europe (TB incidence

doubled since 1990) [1]. In the United States of America, as an example of developed countries, foreigners and racial/ethnic minority populations continue to be affected disproportionately by TB [2].

In WHO European Region, 422,830 TB cases were notified in 2006 [3], with an incremental west-to-east-gradient in recent years.



The trend in big cities is interesting, too: in London, over the past 15 years, the incidence has doubled to 41.3/100,000 per year and continues to rise [4] and an extremely high TB prevalence was seen in homeless people (788/100,000) [5].

In early 2001 there were indications that TB was increasingly becoming a problem among drug addicts and homeless people in Rotterdam, too [6].

In France (5,374 notified cases in 2005) the notification rates were higher in some groups such as people born abroad (41.5/100,000), especially those born in sub-Saharan Africa (160/100,000) and those recently (<2 years) arrived in France (251/100,000), in homeless people (214/100,000) and in the eighties and over (21.7/100,000) [7].

In Germany, 7,515 new cases were reported to the Robert Koch Institute in 2001 and 7,684 cases in 2002, corresponding to an incidence of 9.1 (2001) and 9.3 (2002) per 100,000 inhabitants (as per 1 October, 2003) [8]. However, in 2004 an incidence rate of 12.0 cases/100,000 was documented in Hamburg [9].

In Hungary, although the cases' number is showing a steady decline since 1996 (42.6/100,000; 4,278 cases), TB continues to have a great public health impact since the notification rates by country shows significant geographic differences in particular areas of the country [10, 11].

In Italy, from the second half of the eighties, TB cases have been constantly decreasing. The incidence rate in the general population is extremely low; however, the most TB cases were observed among certain risk groups (alcohol and drug users, homeless people, HIV-infected people, young foreign people aged 25-34) and in certain groups such as migrants, drug resistant forms may be higher. From 1999 to 2005, TB cases reported in foreign citizens represented 32% of the total cases reported in Italy, with a steady increase from 22% in 1999 to 44% in 2005, especially in the young and those of adult age, with a peak in the age group 25-34, which are the most represented among foreigners living in Italy [12]. In developed countries TB cases increase is related to different factors, including HIV epidemic and growing number of immigrants from countries with high TB incidence and other important socio-economic problems [13]: the TB incidence rate correlates well with measures of poverty [14].

In Rome, from 1996 to 2004, each year on average 359 cases were notified, with a range of 355-443 [12]; a considerable increase of people living on the road has been reported in recent

years: in 1998, it was estimated that there were 5,000 homeless people but nowadays the expected number is 10,000-12,000 [15]. Homelessness is a problem correlated to migration in metropolis and one of the greatest risk factors to contract both LTBI and TB [16]. This diagnosis should be considered in any homeless individual with fever and persistent productive cough [17]. On this basis, the present study was carried out with the aim of:

- estimating cutipositivity prevalence in a sample of homeless shelter population (Italian and foreigners) in Rome;
- founding socio-demographic, behavioural and clinical variables associated to LTBI risk;
- preventing the spread of LTBI and TB risk among homeless shelter population, through a diagnostic-therapeutic pathway and an active guidance to specialized reference Hospitals.

In this paper, preliminary results are presented and discussed relatively to the first and second aims.

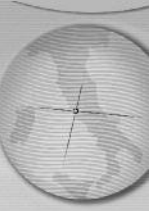
Methods

Population and setting

The eligible individuals - male and female, Italians and foreigners, adults ≥ 18 years old - were recruited in Caritas and Acisel homeless refuges in Rome, between November 2006 and March 2007. These two shelters - 2 among many others existing in Rome - were selected as previous contacts with these two refuges existed before this study. The only important difference existing between these shelters is that Acisel is open exclusively to male and foreign homeless people. Individuals were recruited according to HUD (U.S. Department of Housing and Urban Development) homeless definition, as "an individual who lacks a fixed, regular... and adequate night-time residence..." [18].

With the aim of making our sample representative of the homeless shelter population in Rome, the sample size was calculated using 2004 available data, the most recent ones existing when the protocol of the study was drafted: the homeless number was about 2,000 units in Rome (1,588, June 2000) [19]; the confidence level was fixed equal to 95%; in a similar population living in a city, the LTBI prevalence was estimated as 25% [20] and, considering 20% as the worst expected result, the sample size resulted in 251 units. We increased the sample size to 276 units considering a 90% study compliance.

A detailed anamnesis was collected using a surveillance form to record information about markers and risk factors: gender, age, height and



weight (BMI as index of over weight or obesity), native land, past TB diagnosis and therapy, regularity of immigration condition (entry permit or not), smoking habits, alcohol abuse (according to *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*, 4th edition, Text Revision. Washington, DC: American Psychiatric Association; 2000) or drugs use.

The operative units participating in the investigation are Hygiene, Microbiology and Radiology Institutes of Catholic University in Rome. Before starting the study, training meetings were carried out to standardize all the procedures.

The protocols of this research were cleared by the local ethical committee.

TST and other laboratory tests

The Mantoux Tuberculin Skin Test (TST) (Biocine test PPD® 5 UI) was performed by medical physicians at homeless' refugees surgeries after informing the subjects about the study and obtaining their written consent by collecting their signatures on a form (translated in the proper languages).

TST was read after 72 hours. According to the standard of the American Thoracic Society, who provided news recommendations for targeted tuberculin testing and treatment regimens for person with Latent Tuberculosis Infections (LTBI), we considered positive reactions the ones with induration diameter >10 mm. [21] and we classified this as LTBI to train to a clinical pathway, managed by specialized hospital.

Only the positive subjects were invited to undertake a chest X-ray and to collect three sputum samples on alternate days. The chest X-ray was performed with a MPX+ (GE Healthcare, Italy) portable equipment for radiography and read by 2 independent readers. The sputum was collected with a safe disposable device (Sputum Collection System, Becton Dickinson U.S.A.).

The bacterioscopic analysis (Ziehl-Nielsen staining) and cultures in solid (Lowenstein-Jensen) and liquid media (an automatized system MGIT, Becton Dickinson U.S.A.) were performed by the Microbiology unit, according to internal QC procedures.

Moreover, PCR was prepared to identify and confirm *M. tuberculosis* (Probetec, Becton Dickinson U.S.A.).

In case of *M. tuberculosis* isolates a phenotypic study of drug resistance to streptomycin, isoniazid, ethambutol and rifampicin and the genetic typing with Random Amplification of Primers Designed Technique (RAPD), based on PCR technique, were prepared.

The positive subjects to TST were referred to INMI (National Institute for Infectious Diseases "Lazzaro Spallanzani") in Rome for clinical evaluation.

Statistical analysis

Univariate analysis was performed using the chi-square test and the Mann-Whitney test for assessing differences between groups for categorical and quantitative variables, respectively.

A multivariate analysis was performed using the dichotomous variable LTBI risk as the dependent variable and the following variables as independent variables: gender (female as reference group), marital status (single as reference group), nationality (foreigners as reference group), nutritional status (no obesity as reference group) and age category (age under 60 as reference group). Multiple logistic regression analysis was chosen as the most appropriate statistical method in order to study the statistical significant determinants of the LTBI risk; the results are presented as odds ratios (OR) and 95% Confidence intervals (95% CI). Two different multiple logistic regression models were performed; in the first one, the influence of some risk markers was investigated; three variables were selected for the model: 3 modalities (two dummy variables) related to native land (WHO African or Asian; WHO Eastern Mediterranean Region; WHO European Region according to the WHO profiles of environmental burden of disease by regions), age and gender.

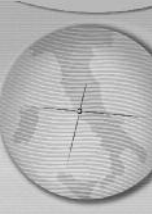
The second multivariate approach was performed in order to evaluate simultaneously the influence of some risk markers and risk factors assumed to affect the LTBI risk. This multiple logistic regression model was performed using as covariates nine variables: age, gender, WHO region, immigrant condition; employment condition; obesity (BMI ≥ 30); educational level and marital status (married or widowers).

A stepwise approach (backward elimination) was followed, using the method suggested by Hosmer and Lemeshow. The variables went out of the model until a p value > 0.10. The goodness of fit of the model was assessed using the Hosmer and Lemeshow test.

The statistical significance was set at $p \leq 0.05$. The statistical analysis was conducted using SPSS software (release 12.0).

Results

During the time period November 2006-March 2007, 120 individuals were recruited in the



homeless' refugees; for each subject a data collection form was completed and a Mantoux test was performed. Among all of the recruited subjects, 108 came back for the reading of the Mantoux tuberculin skin test, with a compliance of 90% (power of the pilot study equals to 46%). Among these, 61 (56,5 %) subjects were negative and 47 (43,5 %) were positive. In the same period, 133 expectorates were collected, with an average of 2.82 samples per person (not all positive provided 3 sample, as stated) and 46 chest X-rays were then performed (1 person escaped).

No individuals with active TB were identified.

Among responders (Table 1) 86 subjects (79,6 %) were male and 22 (20,4 %) female; 19 (17,5 %) were over 60 years old. As far as marital status is concerned, 52 subjects (48,5 %) were single, 25 (23,4 %) married, 23 (21,5 %) divorced or separated and 7 (6,6 %) widowers.

58 (54,7 %) were immigrants and 19 (17,5 %) worked during the recruitment period.

Among them 53 (50,5 %) declared that they

were registered within the Italian National Health Service, 8 (20,5 %) reported to be temporary present foreigners. With regard to their educational level, 4 (3,7 %) of them had no instruction title, 63 (58,3 %) completed elementary or middle schools, 37 (34,3 %) completed high schools and 3 (2,7 %) had a University degree (for one of the recruited subject it was impossible to determine their level of study).

Two subjects (1,9 %) reported a previous TBC diagnosis. As far as smoking habits are concerned, 66 (61,1 %) were smokers, 40 (37 %) were non-smokers and only 2 (1,9 %) ex-smokers.

Nine subjects (8,6 %) declared to be alcohol abusers, only one (0,9 %) referred to be an ex-alcohol abuser. Most study participants declared not to be drug-users, two subjects (1,9 %) declared to be drug-users and 3 (3,1 %) ex-drug users. Among those who tested positives 9 (19,1 %) were over 60 years old, 5 (10,6 %) were female and 42 (89,4 %) were male.

Table 1. The most important characteristics of the study participants according to TST status.

Variable	TST positive Number (%) or Median (interquartile range)	TST negative Number (%) or Median (interquartile range)	P
<i>To be Immigrant</i>			
Yes	28 (48,3 %)	30 (51,7 %)	0,265
No	18 (37,5 %)	30 (62,5 %)	
<i>Italian National Health Service</i>			
No	21 (42,0 %)	29 (58,0 %)	0,440
Yes	24 (45,3 %)	29 (54,7 %)	
Not Known	0 (0 %)	2 (100 %)	
<i>Temporary Present Foreigners</i>			
No	14 (48,3 %)	15 (51,7 %)	0,492
Yes	2 (25,0 %)	6 (75,0 %)	
Not Known	1 (50 %)	1 (50 %)	
<i>previous TBC diagnosis</i>			
No	44 (44,4 %)	55 (55,6 %)	0,205
Yes	2 (100 %)	0 (0 %)	
<i>Smoking habit</i>			
No	16 (40,0 %)	24 (60,0 %)	0,805
Yes	30 (45,5 %)	36 (54,5 %)	
Ex-smoker	1 (50,0 %)	1 (50,0 %)	
<i>Alcohol abuse</i>			
No	39 (41,5 %)	55 (58,5 %)	0,495
Yes	5 (55,6 %)	4 (44,4 %)	
Ex-alcohol abuser	0 (0 %)	1 (100 %)	
<i>Drug use</i>			
No	39 (43,8 %)	50 (56,2 %)	0,439
Yes	0 (0 %)	2 (100 %)	
Ex-drug user	1 (33,3 %)	2 (66,7 %)	
<i>Obesity</i>			
No	23 (37,1 %)	39 (62,9 %)	0,120
Yes	23 (52,3 %)	21 (47,7 %)	

Note - missing data: 1 for immigrants; 3 for Italian National Health Service; 69 for temporary present foreigners; 7 previous TBC diagnosis; 4 for alcohol abuse; 14 for drug use.

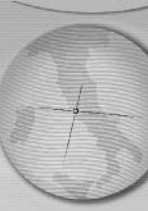


Table 2. Results of the multivariate approaches performed in order to find statistically significant determinants of LTBI.

	Univariate analysis	Multivariate analysis	Multivariate analysis
		1st model	2nd model
	OR (95%CI)	OR (95%CI)	OR (95%CI)
<i>Native land</i>			
African/Asian (referent)	1	1	1
EstMed	2.83 (0.76-10.59)	3.07 (0.79 – 11.97)	4.34 (1.15 -16.39)
Europe	3.06 (1.01-9.25)	3.05 (1.02 – 9.13)	3.12 (1.10 – 8.88)
<i>Gender</i>			
Females	1	1	1
Males	4.39 (1.33-14.48)	4.94 (1.46 – 16.67)	5.84(1.26 – 21.10)
<i>Age</i>	1.00 (0.97 – 1.03)	1.021 (0.988 – 1.054)	
<i>Immigrant status</i>			
No	1		
Yes	1.30 (0.59-2.85)		
<i>Employment condition</i>			
Unemployed	1		
Employed	0.44 (0.12-1.65)		
<i>Obesity</i>			
No	1		1
Yes	3.04 (1.10-8.41)		3.34 (1.31-8.51)
<i>Educational level</i>			
Lower (less than high school)	1		
High (high school or university degree)	1.40 (0.47-4.18)		
<i>Marital status</i>			
Single	1		
Married	2.12 (0.67-6.67)		
Divorced, separated or Widowers	2.90 (0.41-20.40)		
<i>Hosmer and Lemeshow test –p-value</i>		0.766	0.865

O.R. = Odds Ratio; C. I. = Confidence Interval

As far as the results of cutireactions by the native land are concerned, data are as follow: most people were Italian (residents: 50 subjects, 38% Mantoux +) and Romanian (immigrants: 24 subjects, 58,3% Mantoux +). Among the other study participants, 9 were from Afghanistan (55,6% positive), 7 from Eritrea (42,9% positive), 5 from Poland (all negative), 2 from Sudan (negative) and 2 from Turkey (1 positive and 1 negative) with only 1 subject from all others country (Algeria, Bosnia, Bulgaria, Egypt, Ethiopia, Philippines, Morocco, Somalia and Ukraine).

The preliminary results for the LTBI risk, according to the two multiple logistic regression analysis, performed in order to discover the relationship between the risk markers, risk factors and the outcome, are showed in Table 2.

Male gender, coming from East Mediterranean Region of Europe and Europe (including Italy and Romania according to WHO World Region classification) and obesity are factors significantly associated with the development of LTBI.

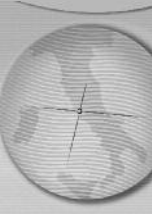
Discussion

Our results show an high prevalence of TST positivity (that we assumed as LTBI in risk categories studied), especially in males.

Both univariate and multivariate analysis showed male gender as a risk marker for LTBI. Concerning this risk marker there is no agreement in the literature, since different papers highlight the role of female gender as risk marker associated with the delay in the diagnosis and treatment of Tuberculosis with Extra Drug Resistant TB [22, 23] and with a high mortality rate during follow-up of smear positive TB patients [24].

Nevertheless, no significant differences were reported by other authors [25].

According to an analysis of risk factors carried out by Lefebvre and Falzon [26] on European Surveillance data, in our investigation the prevalence of male gender could be attributed to the male habits of alcohol abuse, cigarette smoking and homelessness, as shown in 2006 by



Rydzewska [27] et al., who studied the socioeconomic factors of 1991-2000 Kalisz pulmonary Tuberculosis incidence appraisal. Other experiences [28, 29] confirm that smoke is a risk factor, as represented in our sample [30 subjects among 47 positives - 63,8 % - were smokers) even if lacking of statistic significance, especially on account of the high number of persons who were non responders to specific questions regarding alcohol or drugs misuse.

The association with male gender could be a consequence of repeated short treatment interruptions among males, as it has been documented in different settings, especially if coming from high prevalence countries [26].

Regarding the gender, the results of Ganapathy et al. [30] are very interesting and to investigate: in 2008 they observed that gender differences in community perceptions on TB seem to be critical in issue related to marriage. The stigma of TB is more visible in women than men when they come to marriage. Men and children were perceived to get preferential attention by their families during illness, highlighting the need for gender specific intervention strategies to enhance better access of TB services.

Despite that in our survey age does not appear as a statistically significant risk marker, the age is a well known risk marker for TB and LTBI (the risk of infection increase with age); to be greater than 60 years old is the major risk marker both in Levevre and Falzon investigations [26] which demonstrated that death remained significantly associated with increasing age. A systematic review carried on by Faustini et al. [31] in 2006 showed a clear association between Multi drug Resistant Tuberculosis (MDR -TB) and those under 65 years of age, but the association was weak and heterogeneous; this result reflects the year in which effective anti tuberculosis drugs such as rifampicin were introduced. Risk markers such as age and gender show a stronger association than smoking and alcoholism with pulmonary tuberculosis [32].

A possible interesting result of the multivariate approach performed could have been that to be married is a risk factor; anyway, the univariate analysis showed an Odds Ratio of 2.12, but not statistically significant (C.I.: 0.67-6.67). As far as concern the marital status, Jurj et al. (2006) investigation [33] is interesting because they highlighted a statistically significant husband - wife disease association for Tuberculosis: wife and husband share common lifestyle habits and risk, supporting the hypothesis that the shared marital environment may contribute to similarities in

lifestyle and morbidity in married couples. Moreover they provided a basis for health promotion and prevention strategies that target married patients. In 2005 Nissaptorn et al. [34] showed that, in a Malaysian study, married females had an higher TB rate than males, in part agreeing with the previously discussed conclusion of Ganapathy [30] about perceptions of gender and Tuberculosis in a south Indian urban community.

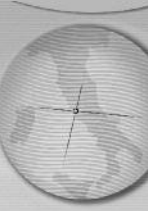
On the other hand, in 2006 Valim et al. [35], identified that unmarried patients were more likely to develop TB due to recent transmission than married patients.

The results of the second multiple logistic regression model applied show significant association with obesity, to be native from Eastern Mediterranean Region and Europe and to belong to male gender. The major risk in obese people can biologically be explained with a low respiratory capacity, that characterize some respiratory diseases; diabetes can often coexists together with a sedentary life style and a fall in immune response.

However, these data don't agree with the ones published previously by Leung et al. [36] in 2007 who studied the association of TB with obesity, well knowing the association with under-nutrition in China, where the incidence of TB is approximately 90 per 100,000 inhabitants. In his experience, the association studies with body mass index (BMI) demonstrated that obese (BMI ≥ 30) and overweight (BMI $25 < 30$) individuals were at significantly lower risk of active pulmonary TB than normal weight individuals (BMI $18,5 > 25$). Low BMI is moreover one of the four nutritional factors that define the Nutritional Risk Score (NRS) as, if insufficient, a negative prognostic factor in patients with miliary Tuberculosis [37].

The association with native land appears very important: the risk is greater in person native from Eastern Mediterranean Region and from European Region that include both Italy and Romania. Our data agree with the ones coming from Euro TB Surveillance, which covered the WHO European Region where, in 2006, TB notification rates (17/100,000 overall) were highest in Romania (127) and Bulgaria (42) - which joined the EU in 2007 - and in the Baltic States (34-75).

In the European Region, FSU (Former Soviet Union) countries have high TB notification and mortality rates, as well as a high burden of TB cases and MDR-TB. The FSU remains the regional priority for TB control, which is often complicated by inadequate information and resources necessary to mount the best-suited response.



Together with the social emergency in large urban areas such as the city of Rome where Caritas estimate 6000-9000 homeless persons in 2007, these preliminary results make the TB surveillance a public health priority with high social implication.

In fact, around 7,000 homeless people are currently sleeping on the streets of Rome, according to city council estimates. This shows an increase of 3,000 people on the streets since 2003, based on figures from the Catholic relief, development and social service organization Caritas. However in Rome the actual number of homeless is likely to be much higher than the council figure due to the difficulty of obtaining a realistic estimate.

The performed study has some limitations well known to the authors.

First, the homeless subjects evaluated were recruited in only 2 shelters in Rome.

These two shelters, in the same manner of all other shelters, guarantee a place where is possible to consume a simple meal and to sleep.

This aspect could represent an important question for the generalization of the study results. Considering that the authors are not able to determine if there are important differences in the sociodemographic and socioeconomic characteristics of the homeless populations of the 2 recruited shelters and all the other shelters in Rome, it is believed that the study findings probably could not be generalized to all homeless

shelters in Rome.

Last, in this paper have been presented the study findings related only to 108 people, as preliminary results of the performed surveillance. The results on this sample population (108 persons: 39% of total sample estimated) are obviously preliminary, since it is foreseen that at the end of the study 280 persons were to be enrolled; actually, our experience shows that the pathway provided for an active search of person at risk to direct to a specific evaluation and treatment, can be affected by high compliance, that can represent a first step to ensure success in TB control in high risk people, in low prevalence countries.

In conclusion, Tuberculosis surveillance, based on early case detection and ensuring patient complete at least 6 months of regular treatment in high risk people (i.e. migrants from endemic countries that come often homeless in big urban areas, increasing the risk of disease spreading) is a public health and social priority.

No data about TB in homeless people are available in Italy, therefore our investigation adds original information because it estimates not only TB but also LTBI (Latent Tuberculosis infections) among this socially vulnerable group.

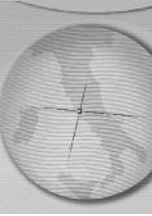
Acknowledgements

The study was carried out with the funding of Italian Ministry of University and Research.

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