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Abstract: OBJECTIVE: To determine the incidence of latent tuberculosis infection (LTBI), and risk factors for tuberculosis skin test (TST) conversion among Healthcare workers (HCWs) during a 20 year follow-up period.
DESIGN: Prospective cohort analysis. Surveillance was conducted from January 1, 1988, to December 31, 2007.
SETTING: 600-bed tertiary referral hospital in Barcelona, Spain.
PARTICIPANTS: HCWs in risk for occupational tuberculosis (TB) exposure, with negative baseline TST, direct contact with patients and/or biological samples and at least one follow-up visit with TST.
METHODS: TST is performed in HCWs with no previous history of TB or no previous positive TST. When TST is negative this test is performed once a year in high-risk workers, or at least every two years according to the hospital's guidelines. In all cases a interview questionnaire to gather information on possible risk factors was performed.
RESULTS: The study included 614 HCWs , 27% worked in areas of risk for TB exposure. Annual incidence rate had decreased from 46.8 per 100 person-years in 1990 to 1.08 per 100 person-years in 2007.
Cumulative incidence was higher in HCWs who work in high-risk areas ($p=0.0004$) and in time periods from 1990 to 1995, and from 1996 to 2001 ($p<0.0001$). Cox regression model showed a hazard ratio of 1.55 (CI 95%; 1.05-2.27) in high-risk workers, adjusted by gender, age and professional status.
CONCLUSIONS: Incidence of LTBI among HCWs is high, although it decreased throughout the follow-up period. It is crucial to maintain surveillance programs in HCWs.

Incidence of Tuberculosis Infection among healthcare workers: Risk Factors and 20-year evolution

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CONFLICT OF INTEREST
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INTRODUCTION

The risk for *Mycobacterium tuberculosis* transmission among healthcare workers (HCWs) has been well known for many years. The kind of job and the incidence of tuberculosis (TB) in the community conditions the risk of TB infection among HCWs(1-3). It is also important the introduction and compliance of TB prevention and control programs in health institutions. These programs must include a periodical medical surveillance of workers at risk (determining baseline risk and periodical follow-up), correct isolation measures and early diagnosis and treatment of patients with TB. Several studies confirm that the risk for TB infection among HCWs in hospitals in which these measures have been introduced is similar to that in general population(4,5).

In a recent review article of studies regarding tuberculosis infection (TI) among HCWs in countries with low incidence of TB, the authors concluded that there is still a high risk for TB among those who work in certain areas(6). One reason for this increase of risk for TB among HCWs in countries with low incidence of TB could be the delay in diagnosis(7,8). Another explanation could be an increase of immigrant HCWs who come from countries with a high prevalence of TB.

There is scant data about the incidence of latent tuberculosis infection (LTBI) in HCWs in Spain. Most studies have focused on prevalence, and have taken place in countries in which TB epidemiology differs from TB epidemiology in Spain. Introduction of a specific LTBI surveillance program among HCWs in our hospital has permitted us to analyse baseline LTBI prevalence, which has been 25.7%, ranging from 44.2% at the beginning of the study period (1988-1992) to 15.5 at the end of this period (2003-2007) (9)

The classical screening test in surveillance protocols for HCWs with workplace exposure to TB is tuberculin skin test (2). In the last years a new test appeared based on detection of interferon gamma (IFN-γ) released as a response to the *in vitro* stimulation of T cells from peripheral blood sensitized with specific antigens of *Mycobacterium tuberculosis*(10,11). In a previous study performed in our hospital we obtained a good agreement between two different tests based on IFN γ (T-SPOT.TB and QFN-G-IT) for the diagnosis of LTBI in HCWs. These tests are not influenced by previous BCG vaccination and were more related to workplace exposure than TST, thus being more useful to detect recent infection(12).

The surveillance program in our hospital is prospective, and HCWs with baseline negative TST are periodically evaluated with TST. The objective of this study is to determine the incidence of LTBI, to identify risk factors for tuberculosis skin test conversion among HCWs and to analyze the trends during a 20-year follow-up period.

METHODS

Study design: In the framework of a health surveillance programme we analyzed the data collected prospectively from a dynamic cohort of HCWs between January 1, 1988 and December 31, 2007.

Setting: Hospital Germans Trias i Pujol (HGTiP) is a 600-bed tertiary referral hospital near Barcelona (Spain)**,** with 3000 HCWs. It is referral hospital for more than 700,000 people. In 2009 there were 27,000 hospital admissions and 110,000 admissions in the emergency room. The number of patients admitted

with TB has changed over time. In the first years there were about 150 patients per year with TB, while lately there are about 50 per year. Incidence of TB in the community has also changed over the years, with an incidence of 45/100000 inhabitants in the year 1990 to an incidence of 25.1/100000 inhabitants in the year 2007(13,14) In our hospital, from the year 1994, coinciding with new CDC guidelines for prevention and control of nosocomial transmission of TB(15) a series of measures was reinforced. These measures included, among others, improvement of ventilation systems of several rooms for isolation of patients with TB, improvement of the protocol of action for the patients admitted in the emergency room (ER) and the promotion of use of personal high-efficiency particulate air masks.

Study population: HCWs attended a health examination at the Preventive Medicine Service, and met the following inclusion criteria: negative TST at the first visit, direct contact with patients and/or biological samples and at least one follow-up visit with TST. The clerical, maintenance and laundry workers were not included in the study.

Skin testing: Since 1988 our hospital has had a TB surveillance program for HCWs. In an initial health examination by the Preventive Medicine Service (either in the first visit when they start working at the hospital, or at any moment of their working life), HCWs with no previous history of TB or no previous positive TST, TST was performed. The test is administered by a trained nurse using the Mantoux method i.e 0.1 ml of 2 T.U of Tuberculin PPD RT 23. The test is read 48 to 72 hours after application. When TST is negative and there is risk for occupational TB exposure, this test is performed once a year in high risk workers, or at least every two years according to the hospital's guidelines. TST

were performed and read at workplaces and self-reporting of results was not allowed. Every worker with positive TST undergoes a chest X ray to detect TB. In all cases an interview questionnaire to gather information on possible risk factors was performed (sociodemographic, work history, history of previous TB or exposure to people with active TB, previous TST and BCG vaccination) .

Study variables:

Dependent variables: time (in months) between the first negative TST and LTBI (positive TST, assuming that probability is constant over time) or total follow-up time if the last TST remains negative. A positive TST was defined as a skin induration of at least 5 mm, and a skin induration of at least 15 mm in those people with a history of BCG vaccination (according to the Spanish Society of Lung Diseases, SEPAR)(3).

Independent variables: age at the time of the last TST (<26, 26-35, >35 years), gender, working place at the time of the last TST (with at least 3 months duration). Four professional categories were established: physicians, residents, nurses and others (technicians and orderlies). Workers were divided into high and low risk group based on the risk of exposure to patients with active TB (from data on professional categories and workplace collected in the questionnaire). The high-risk group was comprised by workers of: emergency , pulmonology, internal medicine services, HIV unit, microbiology, bronchoscopy, and pathology(16) services. The low risk group was comprised of the rest of workers. All medical residents were considered to be at high risk. Other variables such as duration of employment or BCG vaccination were also analysed. Time periods were classified into: 1990-1995, 1996-2001 and 2002-2007.

Statistical analysis: The Kaplan-Meier method was performed to estimate cumulative probability of LTBI at 48 months (4 years) with a 95% confidence interval. The explanation of this 48 month analysis is, first of all, that there is a large staff turnover, especially in the case of residents. Secondly, that it is interesting to know recent TST conversions, in which the risk of TB is higher. Global cumulative probability and cumulative probability for each variable were calculated. Survival comparison between different groups were analysed with the log-rank test and the Breslow test. Finally we performed a Cox proportional regression model to estimate the hazard ratio (HR) of LTBI with 95% interval confidence to determinate the contribution of each independent variable adjusted by all the other variables. We checked the proportionality of the hazards during the follow-up.

Analysis was done using SPSS, version 14 (SPSS Inc).

RESULTS

Figure 1 shows the results of TST of HCWs. Of the 1597 with negative baseline TST 614 workers met all the inclusion criteria (38,5%). Of those 31.6% had only 2 TST, 35.2% had 3, 17.4% had 4, 7.5% had 5 and 8.3% had more than 5. The reasons for not inclusion are specified in Figure 1.

Description of study population. During the follow-up period (median 50 months) of these 614 HCWs, there were 145 TST conversions in 44805 person-month at risk, which represents 3.8 per 100 person-year (CI 95% 3.7 to 4.0) (26.7% conversions). Follow-up period median was 53 months for those who

still had negative TST at the end of this period, and 41 months for those with a positive TST.

Table 1 shows the characteristics of the population. Most were women (74,6%) with mean age of 31.6 years (SD 7.7). As for profession, 58.3% were nurses, 23,8% physicians (13,4% residents), 11.9% technicians and 6% orderlies. Mean years working at the hospital at the moment of inclusion was 9.4 years (SD 6.9), and 27% worked in areas with high risk of TB exposure. Only 8.3% of workers had BCG vaccination and the 98.7% of workers were born in Spain.

Tuberculosis infection incidence.

The annual incidence rate decreased from 46.8 per 100 person-year in 1990 to 1.08 per 100 person-year in 2007.

Global cumulative probability of LTBI (positive TST) at 48 months was 15.5% (CI del 95% 1.6 -18.5%) (Figure 2). At the end of the 48 months, 81 workers had LTBI.

A differential characteristic between censored and non-censored cases with an incomplete time of observation before the 48 months was analysed, in order to detect differences among the variables of the study. Censored cases before the 48 months represent 18% of cases. The only statistically significant differences found were age at the moment of the last TST and the duration of employment at the beginning of the follow-up. Both mean of age or mean of the duration of employment were higher in non-censored cases than in censored ones before 48 months (33 vs. 30 years, and 10.5 vs. 7.0 respectively). This could be due to staff turnover, which is especially high in younger workers and those with shorter duration of employment. This makes it difficult to periodically perform

TST. Despite the differences found, they do not preclude the utilization of survival analysis.

Comparison of survival curves.

Table 2 shows the probability of LTBI according to different independent variables. Incidence is higher in women (17.2%; CI 95% 13-20.9) than in men (11.4%; CI 95% 5.1-16.8). According to the working area, the incidence is significantly higher in HCWs at high risk (21.2%; CI 95% 15.1-26.8) than in those at low risk (12.3%; CI 95% 8.0-15.9).

No significant differences were found according to age group, BCG vaccination or professional group, but the incidence was higher in the age range from 26 to 35 years (16.1%; CI 95% 12-19.9) and in residents (19.3%; CI 95% 9.2-28.8). According to the period of time of the last TST, the incidence is higher in the period from 1990 to 1995 (57.3%; CI 95% 39.4-74.6) and in the period from 1996 to 2001 (20.4%; CI 95% 16.1-23.9), while is lower in the period from 2002 to 2007 (6.1%; CI 95% 4.0-7.9) ($p<0,0001$).

Figures 3 to 5 show Kaplan Meier curves with the probability of LTBI, according to gender, working area and time period.

Cox regression.

Hazard ratio (HR) of LTBI covering all the follow-up period has been analysed (Table 3). Significant variables in the univariate analysis were included. Age and professional status were also included regardless of their statistical significance. In the final model we found that high-risk workers have a risk of LTBI 1.55 times greater than those who work in low risk areas (CI 95% 1.05-2.27). Medical residents and nurses, when compared to technicians and orderlies, have a non-

significant higher risk of LTBI (HR= 1.27; CI 95% 0.68-2.60, and HR=1.20; CI 95% 0.69-2.07, respectively). We found no significant differences according to age or gender.

DISCUSSION

This study shows, in the HCWs of our hospital, an incidence of LTBI at 4 years the 15.5%, (CI 95%; 12.6 to 18.5). In those countries with low incomes, annual mean incidence of LTBI is 5.8% in health care workers (range 0-11%) while in those countries with higher income it is 1.1% (0.2-12%)(17). This variability can be due to a different level of exposure to patients with TB, which is estimated by the number of patients with TB admitted each year in each hospital, and by the existence or not of proper control measures in each institution. A recent review conducted by Baussano et al (18) estimated a LTI rate of 3.8% (95% CI 3.0%-4.6%) for countries with a low TB incidence (<50 cases/100.000 population), and 6.9% (3.4%-10.3%) for countries with intermediate TB incidence (50-100 cases/100.000 population).

In our study the risk of TST conversion was significantly higher in those who work at high-risk areas for TB (emergency, pulmonology, internal medicine, microbiology and pathology services and HIV, bronchoscopy units). This association has been previously described (19-21), where authors also found association with professional status. In our present study, risk has also been higher, though not significant, in medical residents and nurses. An explanation to this finding could be that these are the groups that spend more time with patients and/or perform procedures that can generate aerosols. In the case of residents, they also spend more time in the emergency room, where undiagnosed patients are seen, and they work under stressful conditions that

can produce a certain immunosuppression. Incidence of LTBI was higher in initial periods of the study, and similar to other data from our country (22). This situation could reflect the high number of TB patients seen in our hospital at the beginning of the 90s. The decline in the incidence may be due to two possible reasons. First, this may be partly due a decrease in the number of patients with TB admitted at the hospital over time (with about 150 patients per year at the beginning of the study and about 50 per year at the end of the study) and a decrease of the incidence of TB in the general population. Moreover in the first years of the study, AIDS has contributed substantially to the increase of TB cases in Spain. In Catalonia (Spain), from 1987 to 1993 the crude annual TB incidence rate increased by 50% to a rate of 49.7 per 100,000 inhabitants, with a least 60% of the increase directly due to AIDS(23) . A total of 7,010 AIDS cases were diagnosed between 1988 and 1994, of which 24.3% had TB. Second, the decrease in incidence in HCWs could also be explained by a new, improved measures against nosocomial TB that were adopted in our institution throughout the studied period, as other authors have previously reported(19,24,25). These measures were reinforced since 1994 and mainly included improvement of ventilation system, reduce emergency stay, avoid unnecessary admissions and improvement of the compliance with personal protective equipment (PPE).

On the other hand, it has also been described that a diagnostic delay occurs as the number of patients with TB admitted to the hospital decreases (26). We must also bear in mind the role immigration may play in the incidence of TB in the general population, and this may have been present among HCWs. This occurred in the United States, where some authors found that not being born in

the US and getting a TST done and making a contact study at work was an independent risk for TST conversion (27). Nevertheless, in our hospital the number of immigrant HCWs is low, although it has increased in recent years.

Although it was not an objective of our study, we can state that during this period 22 HCWs have been diagnosed as having TB(28). Pulmonary disease was the most frequent type (62%) followed by pleural effusion (28%). The most affected professional category were medical residents (38%) with the emergency service (48%) being the work place with the highest risk.

Some of the limitations of this study include that it is not compulsory for HCWs to attend a health examination, therefore there could be selection bias, and the data we obtained may not be representative of the population of HCWs in our hospital. A differential characteristic between HCWs included in the study and the HCWs registered and not included was analysed, in order to detect differences among the variables of the study. The only statistically significant differences found were age at the moment of the last TST and the duration of employment at the beginning of the follow-up. Both mean of age or mean of the duration of employment were higher in cases included in the study than in not included cases (31.9 vs. 39.7 years, and 9.5 vs. 7.4 respectively). This could be due to staff turnover, which is especially high in younger workers and those with shorter duration of employment. This makes it difficult to periodically perform TST.

No data were collected on socioeconomic status of HCW, but this lack of information is not likely to have significantly biased the conclusion of this study. There are no extreme differences of socioeconomic status and lifestyle among HCW, as reported in others studies(27). Finally, we must take into account the

limitations of the TST interpretation. In this sense we must mention that both, the administration and reading TST throughout the period of 20 years was conducted by the same trained nurse.

To conclude, this study describes the decline in annual incidence of LTBI among HCWs in a hospital in Spain over a 20 years period. This incidence has been significantly higher in those who work in high-risk areas for TB. There is indirecte evidence of the effectiveness of the implementation in control measures of nosocomial tuberculosis in reduction the LTBI among HCW. However another important factor that can also explain this decrease is the decline of the incidence of TB among the general population during the same period. It is crucial to create training programs for HCWs, which should include specific training for an early detection of TB, promote the use of personal high-efficiency particulate air masks, and fulfil isolation measures and surveillance programs for TB in HCWs.

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CONFLICT OF INTEREST

The authors do not have any financial or personal relationships with other people or organizations that could inappropriately influence their work in the present article.

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Table

Table 1. Characteristics of employees included in the follow-up of TST[1] conversion (n= 614)		
	N	**%**
Gender		
Male	156	25.4
Female	458	74.6
Mean age (SD) years (range 20 to 58 years)	31.6 (7.7)	
Mean of working time at the beginning of follow-up, years (SD) (range 1 to 35 years)	9.4 (6.9)	
BCG vaccination		
No	563	91.7
Yes	51	8.3
Risk group		
Low risk	448	73.0
High risk	166	27.0
Profession		
Physician	64	10.4
Residents	82	13.4
Nursing	358	58.3
Technician	73	11.9
Orderly	37	6.0

SD: Standard deviation

[1]TST: Tuberculin skin test

Table 2. Incidence of TST[1] conversion (CI 95%) at 4 years follow-up according to different variables.

	Cumulative incidence	CI 95%	*P* value*
Cumulative probability of TST[1] conversion	**15 %**	**12.6-18.5**	
Gender			.06
Male	11.4	5.1-16.8	
Female	17.2	13.0-20.9	
Age (years)			.774
<26	14.2	8.12-19.8	
26-35	16.1	12.1-19.9	
>35	15.2	9.12-20.8	
BCG vaccination			.888
No	16.1	12.08-19.9	
Yes	15.2	5.2-24.8	
Risk group			**.004**
Low risk	12.3	8.1-15.9	
High risk	21.2	15.1-26.8	
Profession			.395
Physician	11.2	3.16-28.8	
Residents	19.3	9.2-28.8	
Nursing	17.2	13.1-20.9	
Others	11.4	6.1-17.8	
Time period			**<.0001**
1991-1995	57.3	39.4-74.6	
1996-2001	20.4	16.0-23.9	
2002-2007	6.1	4.0-7.9	

- *Log-rank test
- [1]TST: Tuberculin skin test

Table 3. Hazard ratio (HR) (IC95%) of TST[1] conversion. Multivariant analysis.

	HR	CI 95%	*P* value
Gender			.73
Male	1	-	
Female	0.92	0.59-1.45	
Age (years)			.68
<26	1	-	
26-35	1.22	0.77-1.94	
>35	1.20	0.72-2.00	
Risk group			**.02**
Low risk	1	-	
High risk	1.55	1.05-2.27	
Profession			.889
Physicians	1.10	0.57-2.15	
Residents	1.27	0.68-2.60	
Nursing	1.20	0.69-2.07	
Others	1	-	

[1] TST : Tuberculin Skin Test

Figure

Figure 1. HGTP workers baseline tuberculin screening.

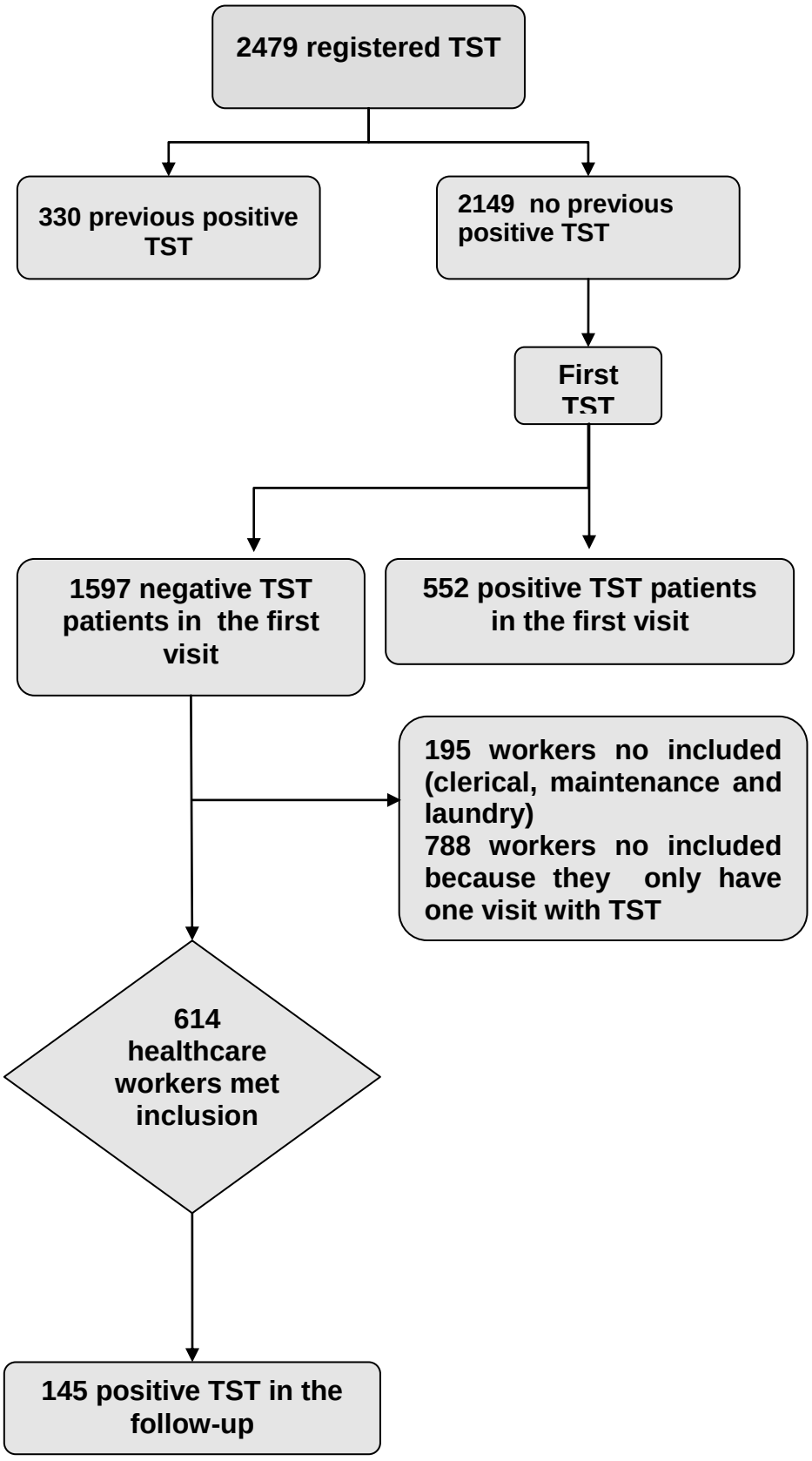
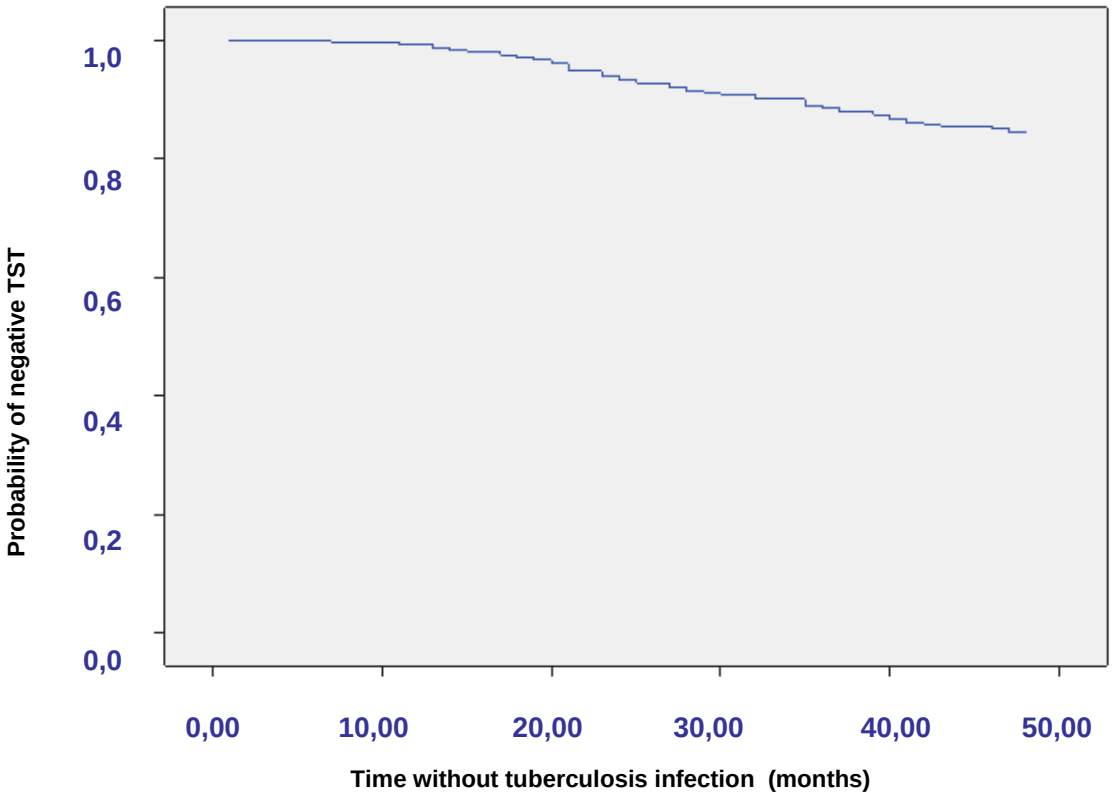
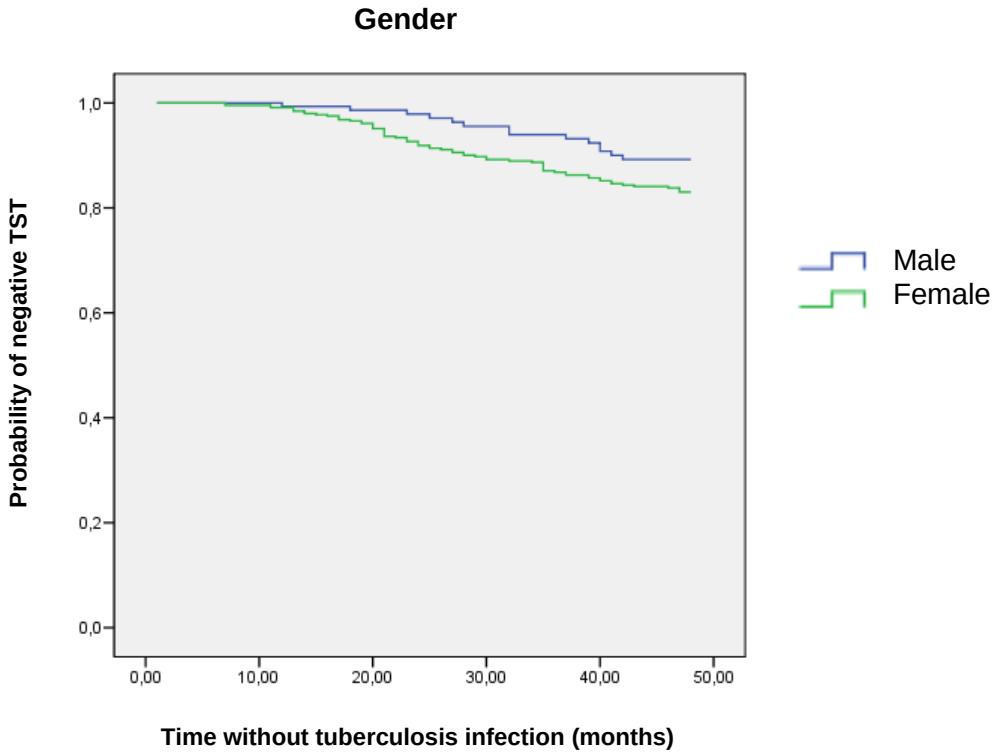
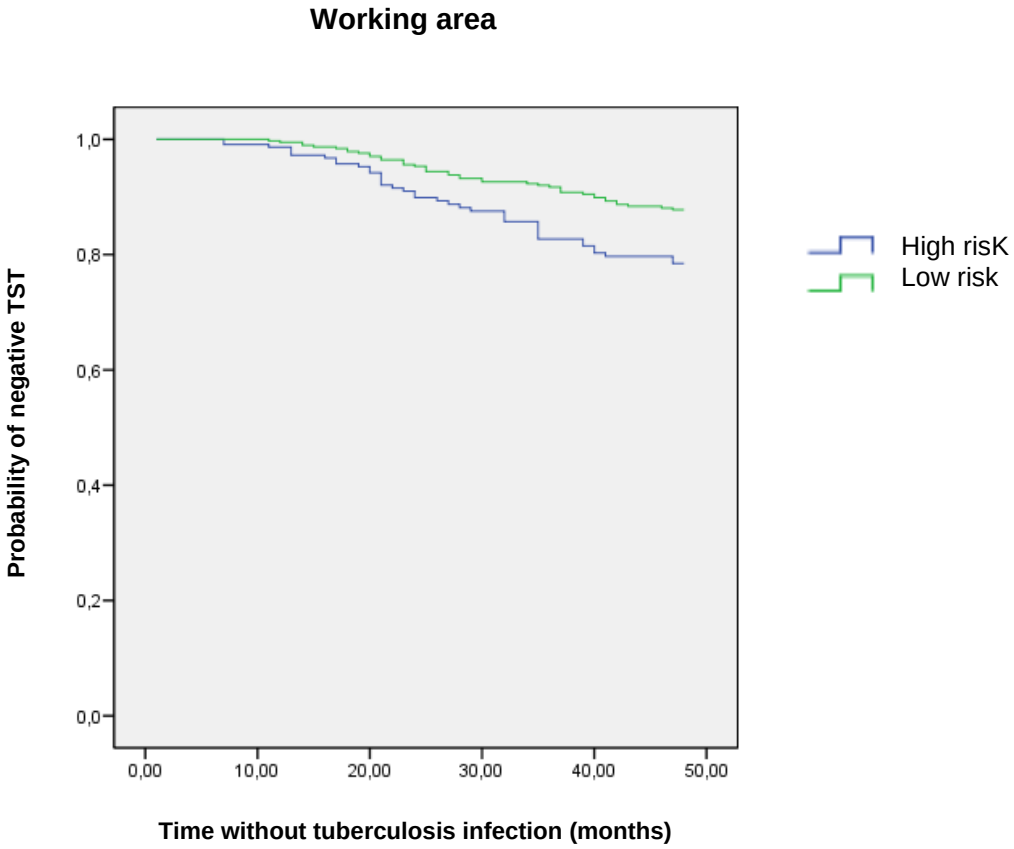


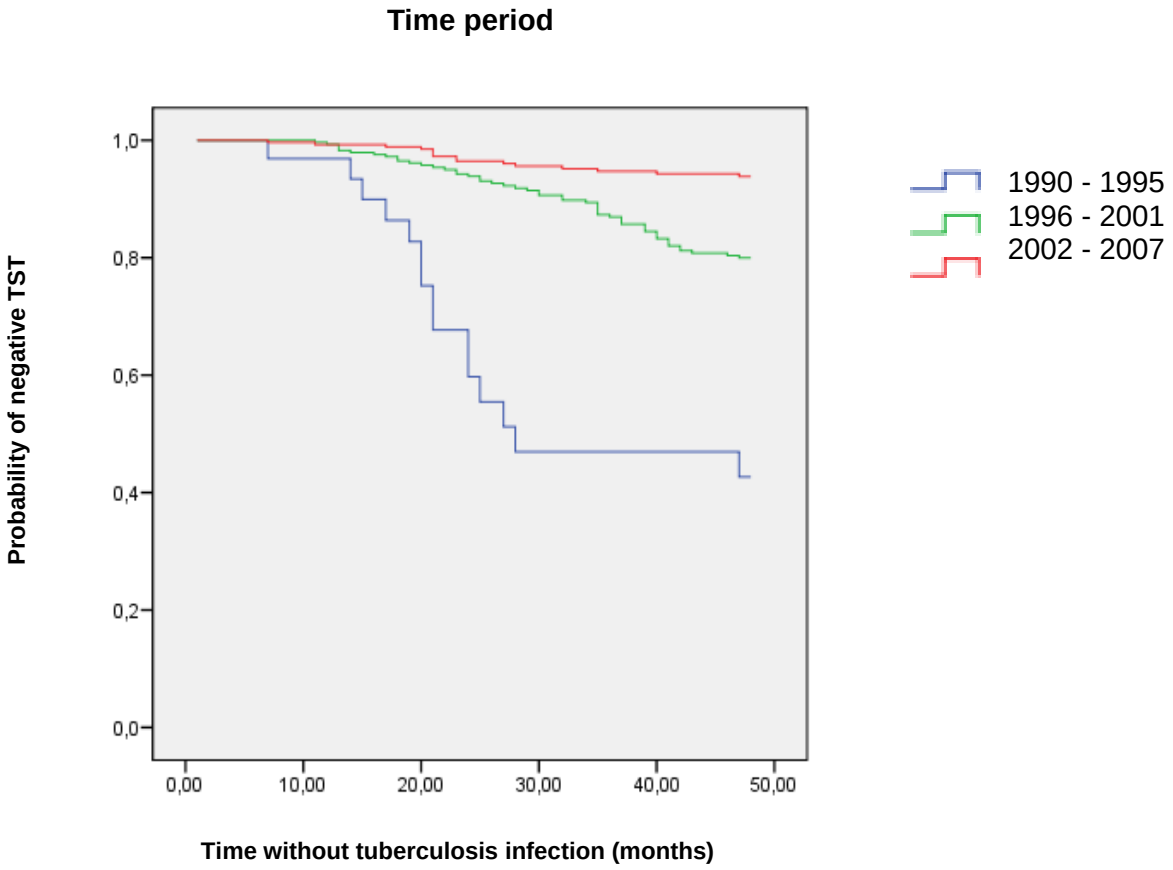
Figure 2. Kaplan-Meier survival curve of the probability of maintaining a negative TST in HCWs at 4 years follow-up.



Figures 3-5. Kaplan-Meier survival curve of the probability of maintaining a negative TST in HCWs at 4 years follow-up according to gender, working area and time period.






Time period
Probability of negative TST
1,0
0,8
0,6
0,4
0,2
0,0
0,00
10,00
20,00
30,00
40,00
50,00
Time without tuberculosis infection (months)
1990 - 1995
1996 - 2001
2002 - 2007