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THE INCIDENCE OF LATENT TUBERCULOSIS (TB) AMONG HEALTH CARE WORKERS IN BAGHDAD/AL-RUSAFA'S LOCAL ANTI-TB PROGRAM

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1. INTRODUCTION

Tuberculosis (TB) poses a significant health risk in both developing and industrialized countries. According to the World Health Organization (WHO), tuberculosis (TB) affects around one-third of the global population.[1] The World Health Organization (WHO) has set a goal to significantly decrease the worldwide impact of tuberculosis (TB) by the year 2030. Tuberculosis (TB) ranks among the top 10 primary causes of mortality.[2] Tuberculosis control programs should include the capability to oversee individuals who are suspected of having the disease and offer evaluation and diagnostic services.[3]

The natural history of tuberculosis begins with the inhalation of dissemination, followed by immunologic containment of viable *Mycobacterium tuberculosis* organisms; a period of bacterial replication and colonization. The result of this process is asymptomatic latent tuberculosis infection, which is defined as a state of persistent bacterial viability, immune control, and no evidence of clinically manifested active tuberculosis.[4] Currently, it is not possible to directly diagnose *M. tuberculosis* infection in humans; therefore, latent tuberculosis infection is diagnosed by response to in vivo or in vitro stimulation by *M. tuberculosis* antigens with the use of the tuberculin skin test or interferon-γ release assays (IGRAs). Studies suggest that active tuberculosis will develop in 5 to 15% of persons with latent infection during their lifetimes[5] (and a higher percentage if the persons are immunocompromised); thus, persons with latent infection serve, according to Osler, as the "seedbeds" of tuberculosis in the community.[6] This article will review the pathogenesis, epidemiology, diagnosis of latent tuberculosis infection. It will address critical gaps in our understanding of this complex condition and propose the necessary research agenda.

Approximately one quarter of the world population is estimated to have latent tuberculosis infection (LTBI).[7] At this stage, infected subjects do not experience clinical symptoms and are not contagious. However they have a 5–10% life-time risk of developing active tuberculosis (TB),[8] which is most pronounced during the early stage of infection,[9] thereby also becoming an important source of TB contagion. LTBI screening in targeted populations is thus pivotal in order to prevent the spread of TB. Healthcare workers (HCWs) have a higher risk of contracting TB than the general population through occupational exposure.[10] Several studies have investigated the prevalence of and the risk factors for LTBI in HCWs in countries highly endemic for TB. Reported pooled prevalence ranged from 37 to 63% in these recent meta-analyses[10-13] with variability depending on important factors such as countries' income, Bacillus Calmette-Gue´rin (BCG) vaccination coverage, and LTBI status definition.

In order to diagnose a latent tuberculosis infection (LTBI), the response is assessed using either the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs). These diagnostic screening methods are particularly useful for identifying high-risk groups, such as individuals who come into contact with individuals with active TB disease, immune compromised and healthcare workers (HCWs) who work with populations at high risk of TB infection.[14]

The tuberculin skin test (TST) has been used to support the diagnosis of tuberculosis (TB) and latent *Mycobacterium tuberculosis* infection for almost a century. It assesses cell-mediated hypersensitivity to *M. tuberculosis* antigens after intradermal injection of tuberculin PPD, a complex mixture of proteins derived from *M. tuberculosis* cultures. A positive TST result indicates an increased risk of currently having or subsequently developing TB.[15,16] However, false-positive TST responses may occur after contact with

environmental mycobacteria that share common antigens with *M. tuberculosis* or after bacille Calmette-Gue´rin (BCG) vaccination.[15,17,18] False-negative TST results may occur in the presence of HIV infection or after recent vaccination with live-attenuated virus vaccines.[18] Errors in the placement and reading of the TST also adversely affect accuracy.[16]

Utilizing in vitro techniques to assess cell-mediated immune reactivity presents potential benefits and may circumvent certain constraints associated with the TST. The advancement of in vitro techniques is progressing rapidly due to the ability to assess several antigens and test parameters simultaneously. Efforts have been concentrated on IFN-g as a crucial cytokine for protecting the host against *M. tuberculosis.*[19,20] IFN-g release assays (IGRAs) detect IFN-g release from lymphocytes after incubation with *M. tuberculosis* antigens. The QuantiFERON-TB assay (QFT; Cellestis) was the first Interferon-Gamma Release Assay (IGRA) approved by the US Food and Drug Administration as a substitute for the Tuberculin Skin Test (TST). The assay quantifies the release of IFN-gamma when a whole blood sample is activated with PPD.[21,22] The process of identifying and describing M. tuberculosis proteins, such as early-secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10), has resulted in their utilization as antigens in interferon-gamma release assays (IGRAs).[23] The proteins mentioned are derived from a specific part of the genome called RD1. This region is found in M. TB and pathogenic M. bovis strains, but not in BCG or most non-tuberculous mycobacteria (NTM). IGRAs that assess the immune response to ESAT-6 and CFP-10, using either recombinant antigens or combinations of overlapping peptides, demonstrate a high level of specificity.[24,31] However, the sensitivity of IGRAs using these antigens has ranged from 70% to 97%.[28,31,35] Due to significant variations in IGRA methodologies, interpretation criteria, and study populations across published publications, the sensitivity of IGRA remains unknown. Due to the fact that ESAT-6 and CFP-10 induce a lower release of IFN-g compared to PPD, it is necessary to use IGRAs with higher analytic sensitivity.

In 2023, approximately 7,000 new cases of tuberculosis were recorded in Iraq, 1,319 of them in Baghdad/Al-Rusafa[36] alone, and therefore it was necessary to conduct this study for HCWs in the Tuberculosis Control Program in Baghdad/Al-Rusafa.

2. MATERIALS AND METHODS

This study included a total of 88 healthcare workers (HCWs) specializing in various fields such as physicians, pharmacists, technicians, nurses, and administrators. These HCWs were from the Baghdad/ Al-Rusafa local anti-TB program facilities in Baghdad, Iraq.

Study Design and Population

A cross-sectional study was conducted from January 2024 to May 2024 at Baghdad/Al-Rusafa local anti-TB program facilities in Baghdad, Iraq. HCWs were recruited from the local TB clinic and 9 district TB MUs, During the five months period of enrollment, the TB incidence in Baghdad/Al-Rusafa was around 27/100,000. (normal range is 24/100000 in IRAQ according to WHO recommendations)

We included in the study all adult HCWs with an age between 23 and 72 years who accepted to participate. Exclusion criteria were ongoing pregnancy, immunosuppressive treatment, history of clinical TB disease, known chronic HIV, hepatitis B or C infections, as well as known cancer or chronic renal failure. Information on the following variables was obtained using a questionnaire: sex, age, comorbidities such as diabetes or asthma (yes/no), smoking status (yes/no), history of TB in family members (yes/no), working area, and occupation. The working area variable consisted of three relevant categories: non-clinical departments (such as administrative sectors or laboratories, with indirect exposure to patients), clinical departments (direct exposure to patients) and the pulmonology unit (direct exposure to high-risk patients). The occupation variable was divided into three categories: the non-medical staff (such as administrative personnel, secretaries), the paramedical staff (lab technicians and auxiliaries), and the medical staff (physicians and nurses). All HCWs declared to have been vaccinated with BCG at birth. The sample size was determined by the number of HCWs who fulfilled the inclusion criteria and responded favorably to the questionnaire.

QuantiFERON-TB Gold In-Tube test (QFT-GIT) assays

QFT-GIT testing was performed on blood samples collected before the TST was carried out, in accordance with the kit manufacturer's instructions. Briefly, 5 ml of peripheral blood was drawn directly into each of three blood collection tubes under vacuum: the nil tube or negative control, the mitogen tube containing phytohaemagglutinin or positive control and the TB specific antigen tube containing specific antigens (early secretory antigenic target 6, culture filtrate protein 10 and TB 7.7 antigen) for *M. tuberculosis*. The contents of each tube were mixed and the tubes were incubated at 37˚C for 16 to 24 hours within 16 hours of collection. Then they were centrifuged at 2500 rpm for 15 minutes at room temperature. The supernatant was stored at -20˚C. The concentration of IFN-γ in each sample was determined by QFT-GIT ELISA (enzyme-linked immunosorbent assay) kit. QFT-GIT results, calculated as TB antigen minus nil value (IU/mL), were categorized as positive (≥0.35 IU/mL, QFT+), negative (<0.35 IU/mL, QFT-) or indeterminate following the software provided by the manufacturer.[37,38]

Statistical analysis: Data was entered into a database using the double data entry approach to ensure verification. The statistical analyses were conducted utilizing version 27.0 of the Statistical Package for the Social Sciences (SPSS). The sensitivity was calculated by dividing the number of positive test results by the number of individuals who had confirmed cases of tuberculosis through culture, or, if indicated, by the number of these subjects who had valid test results. A chi-square test was employed to examine the proportions of healthcare workers (HCWs) from various departments. A significance level of 0.05 and a confidence level of 95% were utilized. The healthcare workers were requested for verbal informed permission. The independent variables comprised age, sex, and department. Regression diagnostics were used to measure collinearity. Data pertaining to the characteristics of the population and the factors under investigation were gathered. Our intention was to provide services to healthcare workers who tested positive for IGRA after the screening process.

3. RESULTS AND DISCUSSION

A total of 88 healthy HCWs were recruited from the anti TB program in Baghdad/Al-Rusafa (n = 88); we excluded 2 participants because of an indeterminate QFT-GIT result.

The Baseline characteristics of the 86 HCWs with reliable QFT-GIT results are displayed in Table 1. Overall, 81.4% of HCWs were male (n = 70) (figure 1), 31.4% were between 46 and 55 years old (n = 27) (figure 2), and 31.4% of them worked in the administration department (n = 27) (figure 3). When considering the LTBI status among individuals with concordant positive (QFT+) and concordant negative (QFT-) results, the prevalence of QFT+ was 45.2% (95% CI 40.7–49.5%).

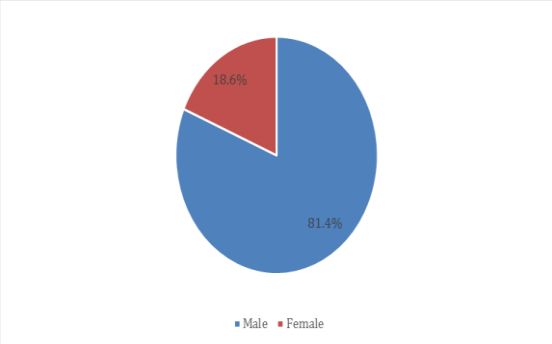

Figure 1: Sex of participants.

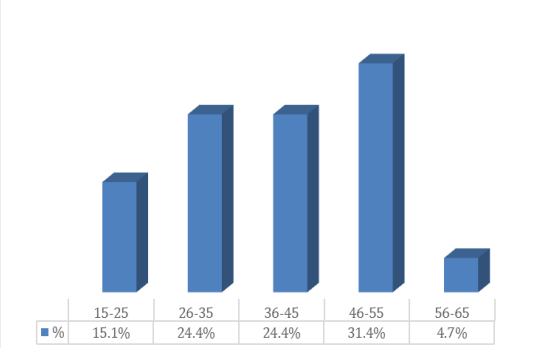

Figure 2: Age groups of participants.

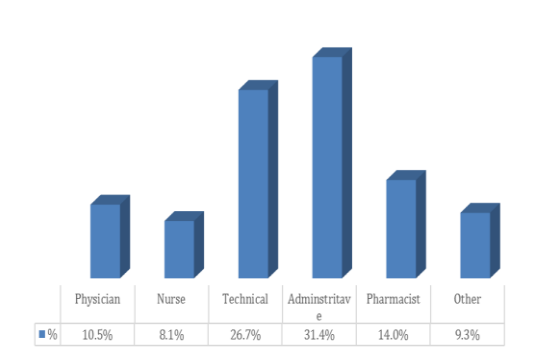

Figure 3: Job's departments participants.

Table 1: Baseline characteristics of participants (n=86).

Characteristics	n	%
Sex		
Male	70	81.4%
Female	16	18.6%
Age group		
15-25	13	15.1%
26-35	21	24.4%
36-45	21	24.4%
46-55	27	31.4%
56-65	4	4.7%
Jobs departments		
Physician	9	10.5%
Nurse	7	8.1%
Technician	23	26.7%
Administrative	27	31.4%
Pharmacist	12	14.0%
Other	8	9.3%
QFT-GIT		
Positive	21	24.4%
Negative	65	75.6%

Table 1: baseline characteristics of participants: The table provides baseline characteristics of 86 participants in the study. It includes information on sex, age group, job departments, and the number of participants who underwent QuantiFERON-TB Gold In-Tube (QFT-GIT) testing. Males made up the majority of participants (81.4%), while females made up 18.6%. The age distribution reveals a fairly even distribution across age groups, with the 46–55 age group having the largest number (31.4%). The largest representation of workers across job departments was found in administrative personnel (31.4%), followed by technicians (26.7%). When tested with QFT-GIT, 75.6% of the individuals had negative results. The participants exhibit a notable gender imbalance, with a greater proportion of males. A wide range of participants is indicated by the age distribution, with a substantial number in the middle age groups. The distribution of job departments highlights the varied roles of healthcare workers involved in the study.

Table 2: Risk factors associated with a positive QFT-GIT result in 86 healthcare workers.

Variables	Total n=86	QFT- n=65	QFT+ n=21	OR (95% CI)	P
Sex					
Male	70	54	16	3.375 (1.932-5.896)	**< .001**
Female	16	11	5	2.200 (0.764-6.332)	0.144
Age group (years)					
15-25	13	13	0	Ref	0.992
26-35	21	10	11	0.909 (0.386-2.141)	0.827
36-45	21	18	3	6.000 (1.767-20.369)	0.004
46-55	27	20	7	2.857 (1.208-6.757)	**0.017**
56-65	4	4	0	Ref	0.995
Department					
Physician	9	5	4	1.250 (0.336-4.655)	0.739
Nurse	7	5	2	2.500 (0.485-12.886)	0.273
Technician	23	15	8	1.875 (0.795-4.422)	0.151
Administrative	27	20	7	2.857 (1.208-6.757)	**0.017**
Pharmacist	12	12	0	Ref	0.992
Other	8	8	0	Ref	0.994

CI: confidence interval; QFT-GIT: QuantiFERON-TB Gold In-Tube.
OR: odds ratio obtained in a multivariable regression including all the variables explored in univariable analyses
p: p-value corresponding to the coefficient obtained in a multivariable regression including all the variables explored in univariable analyses
Bold text indicates a statistically significant result

Table 2: Risk factors associated with a positive QFT-GIT result in 86 healthcare workers: When considering the LTBI status defined only by QFT results, univariable analyses showed that QFT+ was significantly associated

with male sex (OR = 3.375; 95%CI 1.932-5.896, p = < .001), older age between 46–55 years (OR = 2.857; 95%CI 1.208-6.757; p = 0.017) and administrative department workers of TB (OR = 2.857; 95%CI 1.208-6.757; p = 0.017). All these variables remained significant in multivariable analysis

4. CONCLUSION

In conclusion, we observed certain risk factors for LTBI among HCWs in the TB center. Evidence-based TB control programs that focus on the protection of HCWs might be the priority in TB centers. In addition, replacing the TST with QFT assays might provide more objective data. Future studies may focus on evaluating the conversion and reversion rates in these groups. Cost-benefit analyses and analyses to determine the factors affecting the acceptance of LTBI screening and treatment may also be useful to further identify what would be the best approach for the control of health care-related TB.

To ensure a safe working environment, TB controllers should ensure that employees who are likely to be exposed to M. TB do not have LTBI, as it is the source of new TB cases in health care institutions. The target for TB controllers should be to have no new TB cases among employees providing care for persons with TB who have been LTBI-negative as a baseline. In cases were starting anti-LTBI treatment for employees with a negative TST is strongly indicated, QFT is more specific and can prevent unnecessary anti-LTBI treatment. Using QFT as an initial screening method in TB centers would reduce the number of inadequate LTBI treatments.

Worldwide, the prevalence of LTBI among HCWs ranges from less than 5% to 38%, with trends to be higher in low- and middle-income countries than in high-income countries. The contributors to LTBI among HCWs include inadequate controls of TB transmission, close proximity to persons with infectious TB, the presence of host factors or facilitator factors such as overcrowding, exposure duration, working unit, working hours, job title, age, sex, and having a smoking habit. Moreover, the TB screening policies of HCWs may also impact the epidemiology of LTBI, as does the use of BCG vaccination for HCWs at risk for M. TB infection.

Our findings indicate that among HCWs working in the TB center, the prevalence of latent TB infection (LTBI) was 24.4%, with several risk variables, such as longer employment length. The highest percentage among administrators (receptionists) and technicians (in laboratories and radiology units) was expected, as these departments have a high risk of infection due to their direct contact with patients visiting the clinics. This percentage resulted from overcrowding in Baghdad's Rusafa areas, where the population's percentage of infections is high.

5. Recommendation

1. All employees in specialized facilities for chest and respiratory disorders as well as TB centers should undergo latent TB screening by (IGRA) in order to identify latent tuberculosis infection (LTBI).
2. More protective measures must be taken to prevent TBinfection to medical and non medical staff

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