International Journal of TROPICAL DISEASE & Health
12(3): 1-7, 2016, Article no.IJTDH.20380
ISSN: 2278–1005, NLM ID: 101632866

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Prevalence of Latent Tuberculosis Infection among Health Workers Resident in Akwa Ibom State, South-South Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author ANU wrote the study protocol and conducted the research. Author AEA conceptualized the study, wrote part of the manuscript and did literature search. Author LNAB did literature search, author AEM wrote part of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2016/20380
Editor(s):
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(2) Mochammad Hatta, Department of Molecular Biology & Immunology, Hasanuddin University, Indonesia.
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Complete Peer review History: http://sciencedomain.org/review-history/12337

Original Research Article

Received 25th July 2015
Accepted 14th September 2015
Published 18th November 2015

ABSTRACT

Background: Tuberculosis (TB) remains a Public health problem in Nigeria and Healthcare workers (HCWs) are at risk of Latent Tuberculosis Infections (LTBI) and TB disease. There has been no available information on the prevalence of LTBI in HCWs in Akwa Ibom State especially in hospitals for pulmonary diseases. With Interferon-gamma release assays (IGRA), a new method for diagnosis of LTBI, accurate data on prevalence of LTBI among HCWs could be obtained for infection control measures.

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Objectives: The study was designed to estimate prevalence of LTBI among 609 HCWs in hospitals for Pulmonary Diseases that routinely screen for TB infection.
Methods: LTBI was assessed by the QuantiFERON-Gold In-Tube (QFT-IT). Information on gender, age, workplace, job title, BCG vaccination and history of both for potential risk factors for LTBI were obtained from standard questionnaires and analysed using SPSS version 17 (SPSS Inc, Chicago, Illinois).
Results: The prevalence of LTBI was 24.8% and 45.8% as assessed by QFT-IT and TST respectively. In HCW younger than 30 years LTBI prevalence was 9.1% and in those older than 50 years, it was 51.3%. Ward Orderlies and Laboratory staff showed higher prevalence rate than other HCWs (31.4% to 33.8%). The putative risk factors for LTBI were age (>50 year OR 10.53, 95% CI 4.77–23.23), working for ≥ 11 years (OR 11.27% CI 3.5–36.34) and working as Ward Orderly and as Lab staff.
Conclusion: Prevalence of LTBI assessed by QFT-IT is high. This indicates a high infection risk especially in health care workers. Laboratory staff and ward orderlies as well as being in service for >10 years, were more significantly associated with LTBI. The higher LTBI prevalence rate in older HCWs might be due to the cohort effect or the longer time at risk. The difference in prevalence of LTBI between TST and QFT may be due to non-tuberculous mycobacterium (NTM). This may have grave implications of drug toxicity and development of resistance to anti-TB drug among individuals harbouring NTM, but receiving anti-TB medication.

Keywords: Prevalence, latent tuberculosis infection, QuantiFERON-TB gold, Akwa Ibom State.

1. INTRODUCTION

Mycobacterium tuberculosis is responsible for tuberculosis (TB), a disease that annually affects 8 to 9 million people worldwide, accounting for approximately 2 to 3 million deaths each year [1].

In most individuals, infection with *M. tuberculosis* is contained by host's immune defences making the infection to remain latent [2]. Healthcare workers are considered to be at high risk for this infection because infected persons eventually associate with them during hospitalization and treatment [3]. Currently, it is difficult to predict exactly which of the exposed individuals that will develop the disease. Unfortunately, the Tuberculin Skin Testing (TST) which until recently was the only practical way of detecting Latent Tuberculosis Infection (LTBI), does not meet all the diagnostic expectations because of being subjected to considerable variations and other limitations. Some of these include false-positive TST responses resulting from either exposure to environmental mycobacteria that share common antigens with *M. tuberculosis* or resulting from prior BCG vaccinations [4]. Technical errors such as placement of measuring apparatus and reading of the TST can also yield false-positive results.

Advances in genomics and immunology have led to a promising alternative, the *in vitro* interferon-gamma (IFN-**γ**) assays [5-7] which are based on the concept that T cells of infected individuals released IFN-**γ** in a significant detectable level. These assays utilise antigens such as the early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These proteins are significantly more specific to *M. tuberculosis* than the purified protein derivative (PPD) used in TST, as they are not shared antigens with BCG sub-strains and non-tuberculous mycobacteria species that might cause non-specific sensitization. Also, they are unaffected by previous bacillus Calmette-Guerin (BCG) vaccination [7]. A limited number of studies evaluating the performance of interferon-gamma release assays (IGRAs) have been conducted in TB endemic settings. Some studies outside Nigeria have examined the use of these tests in healthcare workers (HCWs) [8-11] but there is dearth of data from Nigerian studies in this regard.

This study evaluated the prevalence and risk factors of Latent TB Infection among healthcare workers in Akwa Ibom State, Nigeria using the TST and an enhanced Interferon-gamma assay (QuantiFERON-TB Gold).

2. MATERIALS AND METHODS

2.1 Study Design

This study was conducted among 609 HCWs in the two major tuberculosis referral hospitals in Akwa Ibom State, the Infectious Diseases

Hospital (IDH) and the QIC TB/Leprosy Hospital, and also other TB treatment centres located within the state between December, 2009 and December, 2010.

2.2 Collection of Data

Information on the following variables was collected using a standardized questionnaire: Age, gender, educational level, job title, occupational exposure to TB, years of service in health care sector, BCG vaccination, and prior TST. BCG vaccination was verified by confirmation of the presence of scar.

The study protocol was approved by the ethics review committee of the Akwa Ibom State Ministry of Health. All the participants gave written informed consent prior to their inclusion in the study.

3. DIAGNOSTIC METHODS

Tuberculin Skin Testing (TST) was performed using 5TU of the purified protein derivative (PPD). Basically, 0.1 ml volume of the antigen was injected intra-dermally into the dorsal surface of the forearm of each participant with the aid of a disposable tuberculin syringe. The results were read after 48-72 hours and the size of the indurations was recorded in millimetres after measuring with the aid of a transparent meter rule. Based on published guidelines, indurations ≥ 10 mm was considered a positive TST in HCWs (American Thoracic Society, 2000).

For the interferon-gamma assay, the QuantiFERON-TB Gold In-Tube test was used (Cellestis Limited, Carnegie, Australia). This whole blood assay uses overlapping peptides corresponding to ESAT-6, CFP-10, and a portion of tuberculosis antigen TB7.7 (Rv2654). Briefly, a total of 3 ml of blood was drawn from each subject and 1ml delivered into each of the three tubes labelled as nil control, positive control and *M. tuberculosis* specific antigens (ESAT-6, CFP-10 and TB7.7). Tubes were incubated at 37℃ overnight before centrifugation, and IFN-**γ** release was measured by enzyme-linked immunosorbent assay (ELISA) following the protocol of the kit manufacturer (Stimulation of the antigenic mixture occurs within the tubes used in collecting the blood). All the assays performed met the manufacturer's quality control standards. Interpretation of test result was done as recommended by the manufacturer and based on previous study by Pai et al. [11]. A positive QFT-3G was defined as IFN-**γ** ≥ 0.35 IU/ml if the response to TB antigens minus the negative control was ≥ 0.35 IU/ml and >25% of the negative control, negative if these criteria were not met, and indeterminate if either the negative control had a result >8 IU/ml or if the positive control had a result <0.5 IU/ml. Data analysis was performed using SPSS version 17 (SPSS Inc, Chicago, Illinois). Correlation between continuous TST and QFT values were calculated and a logistic regression analysis was performed in order to adjust for multiple covariates for variable selection. The results of the final model are presented as adjusted Odds ratios for QFT at 95% confidence interval. A p-value ≤ 0.05 is defined as statistically significant.

4. RESULTS

Results for both TST and IFN-**γ** assays were available for the 609 subjects which comprised 199(32.5%) males and 410(67.5%) females. Participation rates were higher among the Nursing officers (58.1%) and low among the Physicians (5.25%).

The description of the study population and responses from the participants are indicated in Table 1. Among the clinical staff, 5.25% were physicians, 58.46% were nurses while laboratory staff and ward orderlies constituted 13.14% and 8.37% respectively. Non-clinical staffs were 14.78%. History of BCG vaccination was recorded for 73.89% of the participants. Table 2 shows the factors associated with QFT positivity while Table 3 shows the factors associated with TST positivity. A positive QFT and TST results were observed in 151(24.8%) and 279(45.8%) of the participants respectively. However, 384(63.05%) were positive for both QFT and TST. In univariate analysis, the prevalence of LTBI assessed by QFT correlated with age, years of service and job category while education was not significant using the multivariate analysis.

5. DISCUSSION

The increased risk of healthcare workers for tuberculosis is well established. Therefore, screening of HCWs for LTBI and active tuberculosis is fundamental in infection control programs [12]. To the best of our knowledge, this is the first study that compared the performance of TST and QFT among HCWs in Nigeria.

This study has shown the prevalence of latent TB infection by TST to be 45.8%. On the other hand,

the prevalence as assessed by IGRA is 24.8%, about 2-fold lower than TST's result. However, the high prevalence of LTBI in healthcare workers as demonstrated in this study is not surprising as Nigeria is among the high TB burden nations. Currently, Nigeria ranks 11th among the high burden nations but the results obtained here is consistent with estimates from other developing countries [13-15].

Table 1. Description of the study population

Variable	N (%)
Gender	
Female	410(67.32)
Male	199(32.68)
Age(years)	
21 - 30	88(14.45)
31 – 40	58(9.52)
41 – 50	307(50.41)
51 – 60	156(25.62)
Educational qualification	
B. Sc/HND	58(9.52)
College	337(50.41)
GCE/SSC	156(25.62)
FLSC	58(9.52)
Job category	
Physician	32(5.25)
Nursing Officer	356(58.46)
Lab Staff	80(13.14)
Ward Orderly	51(8.37)
Admin Staff	90(14.78)
Years of service	
1 – 10	111(18.23)
11 – 20	390(64.04)
21 & above	108(17.73)
History of TST	
No	287(47.13)
Yes	322(57.87)
BCG vaccination	
No	13(26.11)
Yes	596(73.89)

B. Sc = Bachelor of Science, HND=Higher National Diploma, GCE/SSC=General Certificate of Education/Senior School Certificate, FSLC= First School Leaving Certificate

From similar studies, higher differences in infection rates of LTBI among HCWS as assayed by these two methods have been documented. Nienhaus et al. [16] investigated 261 healthcare workers from different hospitals for pulmonary infections in Germany and found a prevalence of 9.6% with IGRA compared to 24.1% with TST. Schblon et al. [9] also tested 270 healthcare workers in a hospital for pulmonary diseases but in the northern part of Germany and had a prevalence rate of 7.2% with IGRA and 30.7% with TST. The relatively low positivity rates of IGRA compared with TST in this study further confirms the low specificity of TST especially in BCG vaccinated individuals and those infected with non-tuberculous mycobacteria (NTM) as earlier reported. It therefore suggests the extent of over-diagnosis of LBTI in studies that solely rely on TST results. In IGRA, the level of IFN-ɣ produced by lymphocyte cells sensitized with antigens such as ESAT-6 and CFP-10, so measured, are significantly more specific to *M. tuberculosis* infection than PPD, and are not shared with BCG sub-strains or several non-tubercular mycobacteria species that might cause non-specific sensitization (Anderson et al. 2000). Stebler et al. [17] studied the prevalence of latent TB infection among 777 hospital employees at the University hospital of Barne using the IGRA and found a prevalence rate of 7.6%. Also Haradu et al. [10] investigated the prevalence of latent TB infection among 322 workers in a Japanese general hospital and had a rate of 9.9%. Again, these reports are consistent with others having relatively low LTBI rates when measured with IGRA. The over-diagnosis of LBTI as observed with TST in this and other studies may be due to infection with the non-tuberculous mycobacterium (NTM) since TST is non-specific [15]. Where routine diagnosis and treatment of TB relies only on TST, it may implicitly have grave implications of drug toxicity and development of resistance to anti-TB drug in individuals harbouring NTM, but receiving anti-TB medication. Studies conducted on disease progression and probability of developing TB disease have shown higher rates of individuals with LTBI progressing to TB disease among those with positive IGRA (14.6%) compared to TST (2.3%). This implies that the 5-10% progression rate estimated by WHO (Stop TB partnership) using TST is lower than the actual rate if analysed by IGRA [9]. This further indicates the need for treatment of LTBI among healthcare workers in developing countries. If HCWs develop active TB, they are at risk of transmitting the infection to their patients, including those who are immuno-compromised.

Data obtained in this study could not be compared to the general population since there are no base-line epidemiologic data available for LTBI in the general population.

Table 2. Frequency, adjusted Odd Ratios (OR) and 95% Confidence Interval (CI) for covariates associated with QFT results

Covariates	No. positive/Total tested (%)	Adjusted Odd Ratio	95%
Age			
21-30	8/88 (9.1)	1.00	
31-40	16/58 (27.6)	2.10	0.80-5.56
41-50	47/307 (15.3)	0.76	0.31-1.88
51 & above	80/156 (51.3)	2.67	0.99-7.20
Sex			
Male	53/199(26.6)	1.00	
Female	98/410 (23.9)	0.75	0.49-1.14
Educational attainment			
University	8/58 (13.8)	1.00	
College	93/337 (27.6	1.89	0.85-4.19
Secondary	20/156 (12.8)	1.70	0.67-4.34
Primary	30/58 (51.7	3.47	1.33-9.00
Years of service			
1-10	3/111 (2.7)	1.00	
11-20	93/390 (23.8)	10.92	3.06-39.05
21 & above	55/108 (50.9)	26.23	6.47-106.28
Job category			
Physician	3/32 (9.4)	1.00	
Nurses	82/356 (23.8)	3.32	0.90-12.31
Lab. staff	27/80 (83.8)	16.53	3.41-80.20
Ward orderly	16/51 (31.4)	13.07	2.00-85.24
Admin. Staff	23/90 (25.6)	6.75	1.23-36.94
History of TST			
No	66/28 (23.0)	1.00	
Yes	85/322(26.4)	0.88	0.53-1.49
BCG Scar			
No	3/13 (23.1)	1.00	
Yes	146/596 (24.5)	0.42	0.12-1.54

Table 3. Frequency, adjusted Odd Ratios (OR) and 95% confidence interval for covariates associated with TST results at 10 mm indurations

Covariate	No. positive/Total tested (%)	Adjusted
Age		
21-30	19/88 (21.6)	1.00
31-40	25/58 (43.1)	1.75 (0.79-3.85)
41-50	116/307 (37.8)	0.68 (0.32-1.43)
>51	119/156 (76.3)	2.47 (1.02-5.97)
Sex		
Male	75/199 (37.7)	1.00
Female	204/410 (49.8)	1.51 (1.04-2.20)
Educational qualification		
BSc/HND	20/58 (34.5)	1.00
College	191/337 (56.7)	2.38 (1.27-4.46)
SSCE	36/156 (23.1)	1.12 (0.54-2.32)
FLSC	32/58 (45.8)	1.19 (0.52-2.73)
Years of service		
1-10	18/111 (16.2)	1.00
11-20	179/390 (45.9)	2.20 (1.07-4.53)
>21	82/108 (75.9)	6.80 (2.70-17.11)

Covariate	No. positive/Total tested (%)	Adjusted
Job category		
Med. Officer	8/32 (25.0)	1.00
Nurses	178/356 (50.0)	2.01 (0.78-5.18)
Lab staff	41/80 (51.3)	0.31 (4.06-31.46)
Ward orderly	19/51 (37.3)	2.92 (0.98-8.70)
Admin Staff	33/90 (36.7)	3.00 (1.14-7.89
History of TST		
No	99/287 (34.5)	1.00
Yes	180/322 (55.9)	1.38 (0.95-2.01)
BCG scar		
No	6/13(46.15)	1.00
Yes	266/596 (44.6)	0.000

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6. CONCLUSION

In conclusion, the results obtained in this study have been validated by other reports claiming superiority of IGRA to TST methods in LBTI diagnosis and provided a base-line information regarding LTBI prevalence and infection risk among healthcare workers involved in TB control in Akwa Ibom State. Obtaining base-line and valid information on LTBI among healthcare worker population is important given that one of the priorities of TB control is the implementation of effective TB infection control measures.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
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