QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

LATENT TUBERCULOSIS INFECTION AMONG HEALTH CARE WORKERS AT THE COMMUNICABLE DISEASE CENTER IN QATAR: PREVALENCE AND DETERMINANTS

BY

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ABSTRACT

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Title: Latent Tuberculosis Infection among Health Care Workers at the Communicable Disease Center in Qatar: Prevalence and Determinants

Supervisor of Thesis: Mohammed, Fasihul, Alam.

Background: To estimate the prevalence of latent Pulmonary Tuberculosis infection among healthcare workers in Communicable Disease Center (CDC) in Qatar and explore the factors associated with latent tuberculosis infection LTBI.

Methods: A retrospective cohort study was carried out from Sep 2018 up to March 2019, among CDC healthcare workers. Univariate and multivariate logistic regression models were used to identify the potential predictors of LTBI.

Results: Out of the 415 staff, 27% [95% CI: 22.7%; 31.3%] were diagnosed with LTBI. This is considerably higher than the prevalence reported from high-income countries but lower than most low and middle-income countries including sub-Saharan Africa, India, and China. Being born in high tuberculosis (TB) burden country was found to be the main predictor for LTBI (OR:2.0 95% CI 1.2, 3.4). We also found that diabetes mellitus (DM) (OR: 2.24 95% CI 0.98, 5.1) was a predictor at univariate levels.

Conclusion: Prevalence of LTBI is relatively higher among healthcare workers in CDC in Qatar when compared to countries with similar TB profile. Public health actions are warranted to identify and treat LTBI in healthcare workers in Qatar and to enhance compliance with the global WHO –end TB strategy.

DEDICATION

I dedicate this work to all healthcare workers in the world especially for the Communicable disease center who dedicate their carrier to help fight against Tuberculosis and infectious diseases for a better health

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To my mother and father the most precious in the world who I own them to what I am.

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Abbreviations:

Admin: Administration

AIDS: Acquired immunodeficiency syndrome

BCG: bacilli Calmette-Guerin

CDC: Communicable Disease Center

CI: Confidence interval

DM: Diabetes Mellitus

EMR: Electronic medical records

FEM: fixed effect model

HC: Health Card

HCW: Health care worker

HCWs: Health care workers

HICs: High-income Countries

HIPAA: Individually Identifiable Health Information

HIV: Human immune deficiency virus

HMC: Hamad Medical Corporation

IGRAs: Interferon–Gamma Release Assays

IRB: Institutional review board

LTB: latent tuberculosis

LTBI: latent tuberculosis infection

MRC: Medical research center

PTB: pulmonary tuberculosis

REM: Random effect model

RR: Relative risk

SD: Standard deviation

TB: Tuberculosis.

TST: Tuberculin Skin Test

WHO: World Health Organization

Chapter 1: Introduction:

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* that usually infects the lungs and other parts of the body, such as brain, kidney, and bone [1, 2]. TB infection, in particular, that of the lungs and throat, is considered infectious and contagious. People who are in close contact and share the same airspace with an affected individual are at high risk for infection. Air droplets that are expelled from an infected individual during sneezing, coughing and talking are the main source of transmission [1].

TB is a treatable infection once properly identified but can be fatal when not properly treated [1, 2]. As such, the 2018 report of World Health Organization (WHO) ranked the deaths associated with TB to be the ninth leading cause of mortality worldwide, with an estimated 1.3 million deaths in 2017[1]. Although, WHO aimed to eradicate the TB by 2035, it does not appear to be disappearing so soon form the global scene. In 2017 alone, there were 6.3 million new cases of TB which was, in fact, up from 6.1 million cases detected in 2015[1, 2].

More importantly, one of the major concerns with TB is the alarmingly higher latent TB prevalence in the general population. According to the WHO report that was published in 2018, almost 25% of the global population is infected with latent TB [3]. Although latent TB is not contagious and infected individuals do not manifest any signs or symptoms, studies have shown that 5 to 10% of those individuals will develop active TB during their life [11]. Studies have also shown that health care workers (HCW) are twice as likely to be infected with latent TB, compared to the general public[4].

Due to stringent measures imposed on infectious disease control in Qatar, the incidence and prevalence of TB have been relatively lower. According to the latest WHO report, the incidence of TB in the state of Qatar was 26 per 100,000 populations in 2017[3]. As such, WHO classifies Qatar to be one of the low TB burden countries [3]. Nonetheless, there is a paucity of data on latent TB in Qatar, apart from a single study in a much selected Cuban worker population, with limited external validity [5].

1.1 Aim of the Study

In this study, we aim to estimate the prevalence of latent TB infection among healthcare workers, who are one of the high-risk populations for such infection. In Qatar, as the communicable disease center (CDC) is the main facility that handles almost TB patients identified through various health care facilities we aimed to assess the prevalence of latent TB among CDC workers. We made use of the data collected from electronic medical records of all CDC workers during the period of Sep 2018 to March 2019 to identify the prevalence of latent TB.

In addition, this study will also evaluate the potential predictors of latent TB among HCW in Qatar. Our electronic database has data on predictors such as age, gender, nationality, months of experience, Diabetes Mellitus and type of HCWs, but do not have information other well-known predictors such smoking, other comorbidities, and BCG vaccination. However, one novel addition in this study that has not been investigated before by the previous researchers is the inclusion of N95 mask fittest as a potential predictor in our study population. N95 mask fit test is a qualitative measure used to check the most fitted, secured and comfortable size and type of masks to be used by the health care workers to provide the optimum protection against patient's droplets or airborne particles [6]. N95 fit test shall be done initially upon selecting the proper size and yearly or in the instant that the healthcare worker underwent facial surgery, change in weight or any physical condition that might affect the fitness of the N95 mask [6].

Chapter 2: Literature Review

2.1 Epidemiology of Latent TB

Latent TB is defined as "a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB" [1]. The issue of latent TB has become a major health issue for the public health community due to the fact that almost one in four of the global population is infected with latent TB [1]. Although individuals with latent TB do not manifest any signs or symptoms and are considered non-contagious, studies have shown that 5 to 10% of them will develop active TB during their life [1]. This usually occurs within the initial 5 years after the first infection [1].

Several factors could determine the risk of developing active TB in those who are infected with latent TB. The main determinant has been the immunity status of the infected individual and those immuno-compromised individuals are at high risk of progressing to active disease from latent status. Populations such as HIV patients, young and older population are particularly vulnerable for such progression [7, 8].

TB is generally transmitted via airborne droplets transferring TB bacilli from active TB patient to those who share the same air space [9]. Not all patients who are exposed to TB bacilli will develop active TB, however, most of them are likely to harbor latent TB [7, 9]. Those at higher risk of developing latent TB are health care workers who are in constant touch with TB patients, children and older adults, immigrants from countries with high tuberculosis prevalence, homeless and people using illicit drugs, prisoners, tobacco smokers, underweight, people with harmful alcohol use as well certain patient populations such as diabetic, those undergoing organ or hematological transplants, patients receiving anti-tumor necrosis factor (TNF) therapy and patients with silicosis

[4].

Although there is no gold standard method to detect latent TB, two methods that are often used includes the TB skin test (TST) and TB blood test. The skin test that is administered intradermal using the Mantoux technique by injecting 0.1 ml of 5 TU purified protein derivative (PPD) solution is tested positive if there were an induration within 48 to 72 hours [10]. On the other hand, TB blood test uses interferon-gamma release assay (IGRA) to screens for exposure to TB by indirectly measuring the body's immune response to antigens derived from these bacteria [10]. These tests will be utilized along with the chest radiography, physical examination, and sputum test to diagnose latent TB infection. Physicians' decision to initiate the proper treatment is based on the ability to differentiate between active TB and Latent TB based on the findings from the above investigations [8].

2.2 Prevalence of latent TB among HCW

Health care workers have been shown to have a much higher risk of having latent TB than the general population. Data from countries such as Colombia, Zimbabwe, Brunei, Paraguay, Dominican Republic, and Honduras have shown the risk among HCW is more than double that of the general population [4]. Further, a recent meta-analysis has shown that odds of having latent TB infection among HCW is little more than double compared to the general population as indicated by the pooled odd ratio of 2.27 (95%CI: 1.61 to 3.20) [28].

In terms of the actual prevalence of latent TB among HCW appear to vary widely based on the geographic region. Those countries that have higher TB burden, in general, appear to have higher rates of latent TB infection and the vice versa. A recent systematic review with a meta-analysis revealed that the pooled prevalence of latent TBI among HCW was as high as 47% with 95% CI of (34% to 60%) [21]. Further subgroup analysis showed that the prevalence was highest in South Africa with 64% and lowest in Brazil with 37 %. Another very recent systematic review published in July 2017, showed that health care workers continue to be at higher risk of LTBI. They estimated the pooled prevalence of latent TB among HCW to be 37% with a 95 % CI of (28%-47%). This systematic review included data for 30,961 HCW from 16 different countries from Asia, Europe, Africa, and South America. The studies included were mainly observational studies such as cross-sectional, cohort and case-control studies.

Studies have shown that low and middle-income countries have higher latent TB prevalence compared to high-income countries, most likely to due higher TB burden in these countries. This was demonstrated by a systematic review that included a sample of 32,630 HCW from 85 different studies from 26 low and middle-income countries. The pooled prevalence of latent TB ranged from 14% to 98% with an average of 49%. The authors have also shown even when the TB were tested using more stringent IGRA test the prevalence of latent TB infection did not alter much with a range of 9% to 86% and the average of 39%. [29].

Among the low and middle-income countries, China and India have been reported to have a very high prevalence of latent TB among their HCW. According to the latest WHO estimates, there were 9299 diagnosed cases of pulmonary tuberculosis from 65 different countries of which 35% of them were from China and 11% from Brazil [4]. Moreover, a cross-sectional study done in China investigated late TB using TSTs among HCWs in two types of public hospitals in China and reported that 58% of the HCWs in the infectious disease hospital were positive for latent tuberculosis infection while about 34% of the HCWs in the non-TB hospital were positive [15]. Such a high prevalence among HCW is more likely is linked to the fact that China is considered the second highest TB burden country in the globe. This is evident by the fact that almost

9% of all globally reported TB cases in 2017 were from China. This is the second most TB burden country after India which accounted for 27% of all global TB cases in the same year [(14)].

On the other hand, countries like Malaysia had reported a much lower prevalence of latent TB. A cross-sectional study estimated the prevalence of latent TB among HCWs in four hospitals in Malaysia from December 2008 to May 2009. They reported a prevalence of latent TB to be 10. 6% (95% CI: 8.6; 12.6%) among HCWs. An Italian study has reported an even lower prevalence of about 5% based on a survey among 3, 374 health care students [(23)]. However, there appears to be substantial variability within and between countries. For instance, another Italian study that included 628 healthcare workers during the period of Jan 2014 to Jan 2015 estimated the prevalence of latent TB to be 20.9%, which almost four times higher than those among health care students [(25)]. Likewise a similar cohort study from Portugal among 2, 889 healthcare workers estimated the prevalence of latent TB infection to be 29.5% during the same time period that is slightly higher than that of Italy.

Some other countries reported substantially higher prevalence and demonstrated the huge variability between countries and regions. A good example is a South African study that involving seven health care facilities with 505 staff and they reported a very high latent TB prevalence of 84% [(21)] Likewise, a Rwandan study showed the latent TB in among health care workers to be 62% [(27)].

There is very little data on the prevalence of latent TB in our region. A study in Saudi Arabia investigated 2650 participants from four major tertiary care hospitals in Riyadh showed the prevalence of latent TB among health care workers to 11 %, which is much lower than China, India, and reports from Africa [(31)]. A descriptive observational study from Cuban hospital which is one of Hamad Medical corporation community hospitals revealed the latent TB infection was only about 7% among healthcare workers in Qatar. However, this study was focused mainly on Cuban health care workers with limited external validity [32].

2.3 Risk factors of latent TB in HCW

Several risk factors have been shown to be related to latent TB infection among HCW. One of the major factors is the prevalence of active TB in the country as well as the infection prevention and control measures implemented in the health care facilities. Moreover, a number of personal characteristics of HCW have also been shown to be significantly related to infection transmission risks. The key variable is the immunity status of HCW. Those immune-compromised due to comorbidities, such as HIV infection, Diabetes mellitus, organ transplantation, cancer and taking immunosuppressive medications are at higher risk [8, 16, 17, 18].

Additionally, years of work experience, work location, history of contact with active pulmonary TB patients and the nature of healthcare workers have been shown to be statistically associated with latent TB infection [30]. Years of experience, in particular, has been shown to be an important factor in many studies including studies from South Africa, Rwanda, Portugal, Singapore and Italy [22]. For instance, a study from Italy that included 3, 374 health care students have shown a significant association between latent TB infection and age and being non-Italian born. A similar study carried out in Portugal also showed that years of experience and age are significantly linked to latent TB infection [26]. They also showed, however, that gender was not associated with latent TB infection [26].

Some researchers attempted to quantify the risk associated with the increasing year of experience. A Rwandan study has shown that a 4% increase in the risk of latent TB infection with every year increase of work exposure in a health care setting [27]. These authors showed that the increase of infection along with the years of experience is consistent across the facility type, work setting, or the nature of occupation [27].

Like of years of experience, age was also shown to be linked to risk of infection. Many studies have shown that as the HCW get older the risk of latent TB also increases [8]. A Malaysian study has shown that those older than 35 years have almost 9.5 times risk of having latent TB compared to those younger than 35 [OR= 9.49; 95% CI: 2.22; 40.50] [8].

Other factors that significantly increased the risk of infection were history of living with someone who was diagnosed with active TB (OR= 8.69 95% CI: 3.00; 25.18), being a nurse compared to other health care workers (OR = 4.65 with 95% CI:1.10; 19.65). Most studies have failed to find a gender association with latent TB infection, except one study, showed being a male was significantly associated with late TB with an OR of 3.70 (95% CI: 1,36; 10.02) (16).

2.4 Risk of latent TB in relation to Health Care Setting

Pulmonary tuberculosis cannot be transmitted by touching patients, or patient's equipment, food or environment. It can only be transmitted via breathing in the Mycobacterium bacilli from an infected patient. Mycobacterium bacilli are small in size (less than 5 micrometers) and when expelled from the patients it will be floating in the air and suspend for longer distance. As such it is crucial to select an appropriate mask or respirator to be used by the healthcare workers. Additionally, it is also vital to perform a risk assessment for the need of the negative pressure room or what is called airborne isolation infection rooms (AII) in the healthcare settings to reduce the risk of transmission [12, 13, 14].

In this context, the mechanical ventilation system plays an important role in infection prevention and control of TB transmission. The availability of a well maintained heating ventilation air conditioning (HVAC) system, with a built-in high efficiency particulate air (HEPA) filters, along with the proper air change per hour (total volume of air of a given space being change within one hour) and the existence of negative pressure rooms, reduces the risk of TB transmission among healthcare workers, patients and visitors [12, 13, 14].

The important of the air change per hours come from the principle of reducing the number of the TB bacilli and its concentration in the patient's room by changing the total air of the room itself as active PTB patient is supposed to be shedding the tuberculosis bacilli in the room as he or she cough, sneeze and speak [12, 13, 14].In addition, it is very important that the air flow will be from outside the room into the room to prevent any leak or escape of the bacilli from the patient's room to the corridor.

Other factors are the implementation of infection prevention and control measure within the healthcare facilities mainly in emergency departments or in an area with a triage center. The higher the sensitivity of a triage tool in identifying active pulmonary TB patients and rapidly isolate them before being exposed to other healthcare workers, visitors and patients, less the risk of TB transmission is [12, 13, 15].

Availability of proper personal protective equipment like respirators for health care workers and fit test of the masks used to play a vital role in protecting the HCWs from being exposed to active pulmonary tuberculosis [8, 16, 17, 18].

Availability of a proper triaging tool that enables the health care workers to early detect and rapidly isolate suspected active pulmonary TB patients before being exposed to other staff, patients and visitors [8, 16, 17, 18].

Other variables are related to the healthcare workers immunity status which will be similar risk for non-healthcare workers, in which the immune system is compromised due to comorbidities, Diabetes mellitus, or risky behaviors such as HIV infection, substance use, organ transplantation, cancer, taking immunosuppression medication, substance abuse and other risk factors [8, 16, 17, 18].

Chapter 3: Methods:

3.1 Study Design: Setting and study population

A retrospective cohort study was carried out from Sep 2018 up to March 2019, at communicable disease center (CDC) which is one of Hamad Medical Corporation (HMC) facilities in Qatar. As per the rules and regulation of HMC, all healthcare workers are screened for communicable diseases like measles, chicken pox, Hepatitis B and C and other diseases including Latent TB infection at the stage of recruitment.

TST and IGRA test are used to screen the CDC staff for latent TB infection. If a staff tested positive for either of these tests, further diagnostic tests would be carried to rule out active TB infection. These tests include chest X-Ray, sputum for smear, Polymerase Chain Reaction (PCR) and Mycobacterium culture. Then the staff shall receive proper treatment indicated by the infectious disease physicians in CDC. As per the clinical guideline, a worker is diagnosed to have latent TB if he/she has either a positive TST (induration of 10 millimeters or more) or positive IGRA test along with normal chest X-Ray and negative sputum tests (smear, PCR and culture).

3.2 Sample Size:

For this study, we have collected data on all individuals who are currently employed at CDC. There are 415 individuals currently working and we collected data on all of them.

3.3 Data Collection:

Electronic medical records were used to collect data on the following variables: TST or IGRA test results, age, gender, work experience, nationality and country of origin, and diabetes mellitus diagnosis and N95 fit test status (pass or fail). Exact age was collected as a continuous variable. Work experience at CDC was measured in months and computed using the joining date of the staff that was taken from the departmental records. N95 mask fit test results were taken from the infection prevention and control department, where the test is being repeated annually for all CDC staff.

3.4 Case definitions:

3.4.1 Latent Tuberculosis infection:

As per Communicable Disease Center clinical guideline, an individual is diagnosed with latent TB if he/she has either a positive TST (induration of 10 millimeters or more) or positive IGRA test **and** has a Normal chest X-Ray.

3.4.2 N95 fit test:

A qualitative test is a pass/fail test that relies on the individual's sensory detection of a test agent, mainly their taste or smell.

The healthcare workers were asked to wear their N95 mask then put on a secure hood in their heads and a saccharine solution was puffed into the hood in different predetermined exercises during sitting, standing position, moving the head left, right, pending forward, during walking, and reading a 2 paragraph statements. The health care worker is considered failed if he or she tastes saccharine at any stage of the test and pass the test if the staff did not taste the saccharine solution at the end of the test. However, the administrator shall assess the staff ability to taste the saccharine solution prior to the test

3.5 Data Analysis:

3.5.1 Data cleaning

A rigorous process was used to detect and correct inaccurate records and randomly validate its accuracy by comparing it with the original source like electronic medical records. We used various auditing procedures to double check the records. Data were individually extracted from electronic medical records. Once compiled the range (upper and lower values) were checked to see if all values were within the plausible ranges. When implausible values were detected for any variables the electronic medical records were double checked and corrected accordingly.

3.5.2 Data coding and recoding:

Healthcare workers from different occupational categories were divided into high and low-risk groups depending on whether they are working with pulmonary tuberculosis patients or share the same air space with the patients. Those whose daily job activity does not include sharing the same air space with an active pulmonary TB patient are classified to be lower risk category which is aligned with the CDC guidelines [(9)].

The nationalities and country of origin of the healthcare workers were also divided into two categories depending on whether they were born in a high or low TB burden country according to the WHO global tuberculosis report published in 2018. If an HCW was born in one of the 30 top high TB burden countries the worker is classified to come from a high TB burden country and otherwise considered to originate from a low TB burden country. Table 2 shows the classification of countries as per the latest WHO report [(4)].

3.5.3 Descriptive statistics:

Percentages and mean were calculated for categorical (qualitative) and continuous (quantitative) variables, respectively as presented in table 1.

3.5.4 Computation of Prevalence:

Prevalence of latent TB was calculated and reported along with the 95% Confidence interval. There was no CDC staff were diagnosed with active TB, no analysis was carried out active TB.

3.5.5 Modeling to identify the predictors:

Univariate logistic regression models were used to identify the potential predictors at a crude level. Multiple regression models were then employed to identify the independent predictors. Age, gender, high or low TB burden country, months of experience, diabetes mellitus status (positive or negative), type of healthcare work (high risk or low risk) and N95 mask fit test were evaluated for their predictive ability for latent TB.

Purposeful selection method was used to build the multiple logistic regressions to assess the association of latent TB with the set of variables identified above. Those factors that were identified to have some direction of association at a p-value less than 0.25 in univariate analysis were selected to be included in the initial multivariate model.

The multivariable logistic regression models were used to identify the independent predictors of latent TB. All non-significant variables were dropped from the initial model to include variables with either a p-value less than 0.05 or those showed clinically significant effect measures. Comprehensive methods were used to test the goodness of fit of the model, that include Hosmer-Lemeshow test, Pearson chi2, classification tables, and receiver operating characteristics (ROC) curve. Specification error test was done to test if the model has all the relevant predictors and the linear combination of these predictors is sufficient.

Multi-collinearity was assessed using tolerance and variance inflation factor. Tolerance test used to assess how much collinearity can be tolerated during the regression analysis. Variance inflation factor (VIF) test was used to detect how much of the inflation of the standard error could be caused by collinearity. 0.1 or less and 10 or more were selected as a threshold for Tolerance test and VIF test respectively.

3.4.6 Statistical software

All statistical analysis including descriptive statistics, computation of the prevalence as well as the statistical modeling were carried out using Stata version 15 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP)

3.5.7. Ethical clearance:

Ethical clearance for this study was obtained from the HMC ethics committee.

Chapter 4: Results

4.1 Socio-demographic characteristics of the study population

From the 415 total CDC staff, 164 (39.52%) were nurses, 53 staff (12%) were admin staff, 49 staff (11%) were housekeeping staff, 35 (8.43%) were physicians, 30 (7.23%) were engineering, 24 (5.78%) were security, 22 staff (5.30%) were from radiology, 19 staff (4.85%) were from pharmacy, 16 staff (3.86%) from laboratory, 3 staff (0.72%) were from infection control. From the above-mentioned staff, 299 staffs (72.05%) were classified as a high-risk group and 116 staffs (27.95%) were classified as a low-risk group depending on if their daily work includes sharing the same air space with active PTB patients table 3.

The mean age for the 415 staff in CDC was 34.33 (sd: 8.7) years old. Males accounted for 57.83% of the total CDC population and females were 42.17%. Average months of experience in were 59.93 months. 270 staffs (65.06%) were born in high TB burden countries and 145 staffs (34.94%) were born in low TB burden countries Table 4.

25 staff (6.02%) were known to have Diabetes mellitus type II and 390 staff (93.98%) were negative for DM. N95 mask test was performed to all 415 staff and 396 staff (95.42%) pass the test and 19 (4.58) staff failed with the N95 mask fit test.

Table 1 shows the prevalence and the distribution of age, gender and country of origin as to whether a staff was born in a high or low TB burden and month of work experience. As can be seen, latent TB infections were diagnosed among 112 staff (26.9% with 95% CI, 22.7%; 31.3%) out of 415 CDC staff in Qatar. Males and staff from high TB burden countries are more likely to be infected. Healthcare workers born in high TB burden countries were more likely to have latent TB and accounted for almost 73% of all cases in CDC, Qatar. Males accounted for about 59% of the total positive cases. The mean age of those infected was approximately 3 years higher than those who were not infected. The average age of those tested positive was 36.4 years whilst that tested negative was 33.5 years. Likewise, those tested positive had longer work experience compared those who did not have latent TB. Mean months of CDC work experience of those tested positive and negative were 80 and 52 months, respectively. On the other hand gender of the HCWs appears to be not associated with latent TB status.

Table 1. Distribution of Socio-demographic Characteristics of the Study Population (n=415)

	Total positive for LTBI, N (%)	Total Negative for LTBI, N (%)	Total
Total CDC staff, n (%)	112 (26.9)	303 (73.1)	415 (100)
Gender, n (%)			
Male	66 (27.5)	174 (72.5)	240 (57.9)
Female	46 (26.3)	129 (73.7)	175 (42.1)
Nationality			
High TB burden country	82 (30.4)	188 (69.6)	270 (65.1)
Low TB burden country	30 (20.7)	115 (79.3)	145 (34.9)
Age (years)			
Mean	36.4	33.5	34.3

4.2 Occupational characteristics of the study population:

Table 2 illustrates the distribution of high-risk occupational exposure, diabetes status, and N95 mask fit test findings for those with and without latent TB. As expected those classified as a high-risk occupational category are more likely to be infected with LTBI than those with a low-risk occupational category. Majority of the CDC were free from diabetes with only about 6% and this prevalence among those with latent TB were slightly higher (10%). N95 mask fit test, contrary to the expectation was found to be not appear related to latent TB status. Most CDC staff passed the N95 test and there was little variability to be linked to the latent TB status.

Table 2. Prevalence of LTBI among HCW and its Possible Predictors.

	Total positive for LTBI, N (%)	Total Negative for LTBI, N (%)	Total
Mean months of experience (sd)	80.8(8.9)	52.2(3.7)	59.9
Diabetes mellitus			
Positive	11 (44)	14 (56)	25 (6.0)
Negative	101 (25.9)	289 (74.1)	390 (93.9)
Healthcare workers Risk group, n (%)			
High risk	81 (27.1)	218 (72.9)	299 (72.1)
Low risk	31 (26.7)	85 (73.3)	116 (27.9)
N95 mask fit test			
Pass	109 (27.5)	287 (72.5)	396 (95.4)
Fail	3 (15.8)	16 (84.2)	19 (4.6)

Table 3. Classifications of HCWs Risk Group Whether They Share The Same Airspace with Active TB Patients

	Low risk	**High risk**	Total
Admin, n (%)	53 (94.6%)	3 (5.36%)	56 (100%)
Engineering, n (%)	26 (86.6%)	4 (13.33%)	30 (100%)
Housekeeping staff, n (%)	0 (0%)	49 (100%)	49 (100%)
Laboratory, n (%)	0 (0%)	16 (100%)	16 (100%)
Nursing, n (%)	0 (0%)	164 (100%)	164 (100%)
Pharmacy, n (%)	12 (63.1%)	7 (36.8%)	19 (100%)
Physician n (%)	0 (0%)	35 (100%)	35 (100)
Radiology, n (%)	0 (0%)	22 (100%)	22 (100%)
Security, n (%)	24 (100%)	0 (0%)	24 (100%)
Total, n (%)	115 (27.7%)	300 (72.2%)	415 (100%)

4.3 Occupational and socio-demographic characteristics of CDC staff

From the 415 total CDC staff, 164 (39.52%) were nurses, 53 staff (12%) were admin staff, 49 staff (11%) were housekeeping staff, 35 (8.43%) were physicians, 30 (7.23%) were engineering, 24 (5.78%) were security, 22 staff (5.30%) were from radiology, 19 staff (4.85%) were from pharmacy, 16 staff (3.86%) from laboratory, 3 staff (0.72%) were from infection control. From the above-mentioned staff, 299 staffs (72.05%) were classified as a high-risk group and 116 staffs (27.95%) were classified as a low-risk group depending on if their daily work includes sharing the same air space with active PTB patients table 3.

The mean age for the 415 staff in CDC was 34.33 (sd: 8.7) years old. Males accounted for 57.83% of the total CDC population and females were 42.17%. Average months of experience in were 59.93 months. 270 staffs (65.06%) were born in high TB burden countries and 145 staffs (34.94%) were born in low TB burden countries Table 4.

25 staff (6.02%) were known to have Diabetes mellitus type II and 390 staff (93.98%) were negative for DM. N95 mask test was performed to all 415 staff and 396 staff (95.42%) pass the test and 19 (4.58) staff failed with the N95 mask fit test.

Table 4. Classification of Nationalities Based on TB Burden and its Distribution Among CDC Staff

Nationality	TB burden Country classification	Number of staff (%) Total, (%N)
Bangladesh	High	32 (7.7%)
Filipino	High	65 (15.6%)
Indian	High	155 (37.3%)
Kenyan	High	9 (2.1%)
Nigerian	High	1 (0.2%)
Pakistani	High	8 (1.9%)
British	Low	4 (0.9%)
Cameroonian	Low	3 (0.7%)
Canadian	Low	3 (0.7%)
Egyptian	Low	19 (4.5%)
Eritrean	Low	1 (0.2%)
French	Low	1 (0.2%)
Ghanaian	Low	1 (0.2%)
Iranian	Low	2 (0.4%)
Iraqi	Low	1 (0.2%)
Jordanian	Low	11 (2.6%)
Libyan	Low	2 (0.4%)
Nepalese	Low	22 (5.3%)
Palestinian	Low	8 (1.9%)
Qatari	Low	23 (5.5%)
Saudi	Low	3 (0.7%)
Sudanese	Low	23 (5.5%)
Syrian	Low	3 (0.7%)
Tunisian	Low	5 (1.2)
Ugandan	Low	7 (1.6%)
Yemeni	Low	1 (0.2%)
Lebanese	Low	2 (0.4%)

4.4 Logistic Regression Model

4.4.1 Univariate analysis

The univariate analysis has shown a significant association of the following predictors with latent TB (Table 5). Age, months of experience, Diabetes mellitus, and originating from a TB burden country. From the crude odd ratio, staff with Diabetes mellitus were at higher risk of getting LTBI with OR= 2.24. Likewise, staff born in a high TB burden country has a higher risk with an OR= 1.67. Other predictors such as age and months of experience also showed statistically important predictive ability.

Table 5 Univariate Analysis with Crud Odd Ratio of LTBI, at a Significant Level of P-Value of 0.25

Predictor	OR	95 % CI	P value
Gender (Ref = Female)	1.06	[0.6,1.6]	0.783
Age in years	1.03	[1.01,1.06]	0.004
Months of experience	1.00	[1.00,1.00]	0.001
Diabetes Mellitus (Ref = no DM)	2.2	[0.98,5.11]	0.053
High TB burden country (Ref= low TB burden)	1.67	[1.03,2.69]	0.035
High-risk healthcare work, (Ref =low risk)	1.01	[0.62,1.65]	0.94
Use of N95 mask fit test (Ref = Pass)	0.49	[0.14,1.72]	0.269

4.4.2 Multivariate Analysis:

The initial full model for the multivariable assessment included age, TB burden country, DM and month of experience with their adjusted OR.

Table 6. Initial Full Model of LTBI at a Significance Level of P Value= 0.05

Predictor	OR	95 % CI	P value
Age in years	1.01	[0.97,1.04]	0.57
Months of experience	1.004	[1.23,3.42]	0.02
TB burden country (Ref= low TB burden)	2.055	[1.23,3.42]	0.00
DM (Ref = no DM)	1.38	[0.55,3.45]	0.48

Model P value= 0.0005

Psudo R2= 0.0417

The full model had statistically significant with a P value of less than 0.001 however; the only two statistically significant predictors were identified: month of experience and born in a TB burden country. The crude OR of diabetes mellitus declined from 2.24 to 1.38 meanwhile the OR of having latent TB from high TB burden country has increased from 1.67 to 2.05.

Table 7 Smaller Model of LTBI at a Significance Level of P-value = 0.05

Predictor	OR	96 % CI	P value
Months of experience	1.005	[1.002,1.008]	<0.001
High TB burden country (Ref= low TB burden)	2.089	[1.254,3.481]	0.005

Model P value= 0.0001

Pseudo R^2= 0.039

The simpler model was fitted with only month of experience and TB burden country then perform Likelihood –ratio Chi2 test was performed and LR chi2 = 1.02 with Prob>chi = 0.599 which mean that the smaller model with the two predictors fit the data better than the initial model. However, as age and DM status is clinically significant so we decided to select a bigger model. No confounding effect or interactions were assessed due to smaller sample size and lack of theoretical basis among the independent predictors selected.

4.4.3 Linearity assessment

The Lowes smoother test was employed to assess the linear relationship between LTBI status and the age of the staff member (Fig 1). It appears to show a linearly increasing trend that may require larger data to confirm.

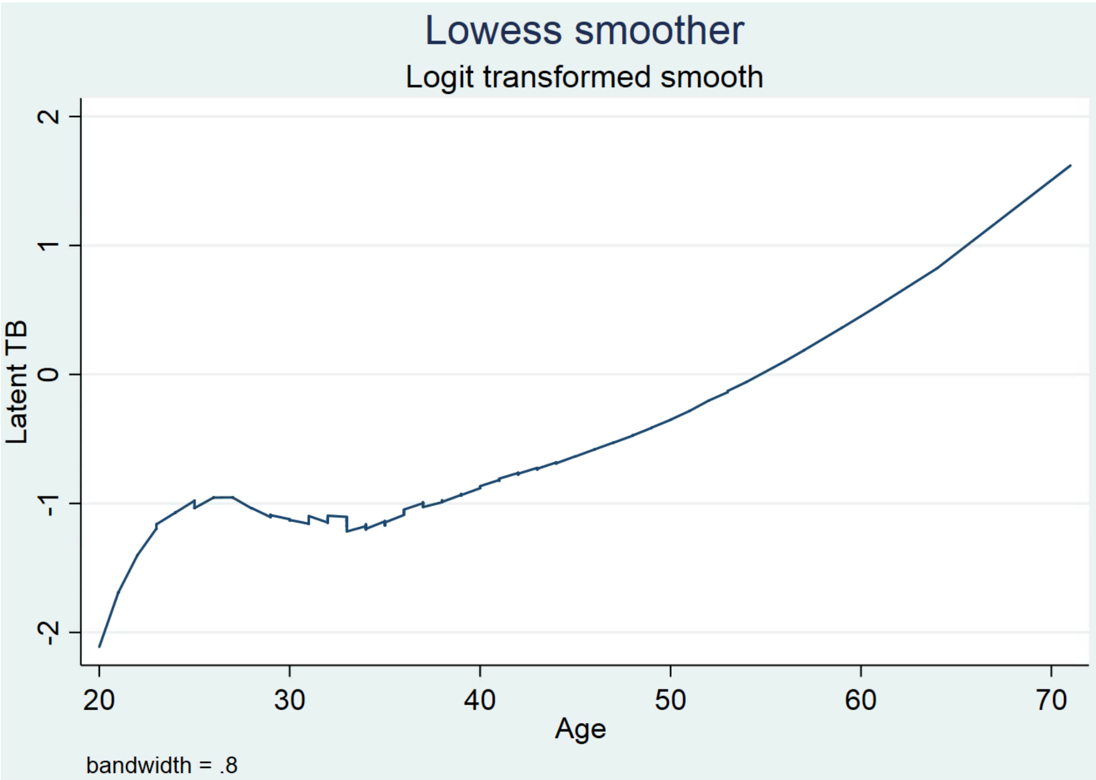

Figure 1 Lowess Curve Fitting of LTBI and Age

4.4.4 Assessment of the Goodness of Fit:

After selecting the model which contains age, months of experience, TB burden country and DM status table 6, comprehensive goodness of fit tests were performed, Hosmer-Lemeshow chi2 = 9.04 with a Prob>chi^2 =0.33 which means that the model fits the data well.

Pearson chi2=348.5 with a Prob> chi^2= 0.334 which confirm the Hosmer-Lemeshow test that the model fit the data well.

Classification table showed that the model correctly classified with 73.49% with a PPV OF 58.33% NPV= 73.95%, specificity = 98.35% and sensitivity of 6.25%. Receiver operating characteristics (ROC) curve fig 3, Area under the ROC was 61.84% which is justified due to unavailability of all risk factors and proctor. Sample size can be one of the reasons as well for the low area covered under the curve.

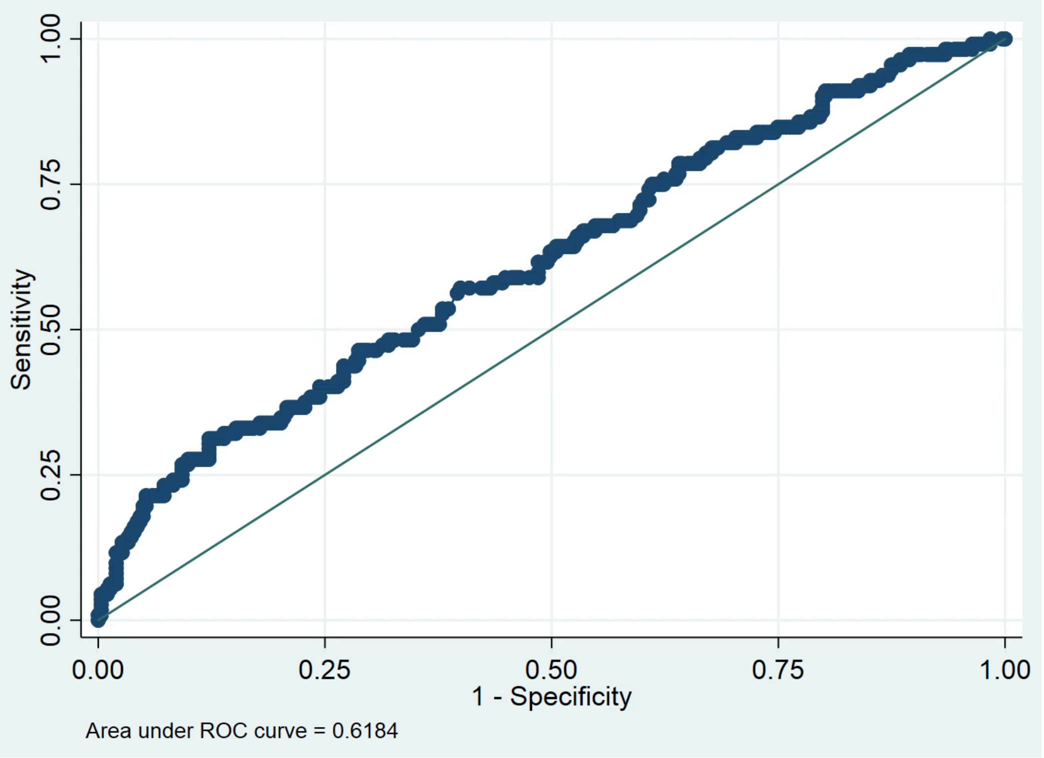

Figure 2. Receiver Operating Characteristic (ROC) of the Model

4.4.5 Specification Error

Specification error was the hatsq p value= 0.68 mean that the model has the sufficient predictor variable, however clinically there shall be more relevant predictor variable to be included as the current model sensitivity is only 6%.

4.4.6 Variance Inflation Factor (VIF)

The VIF and 1/VIF teat show there is no collinearity it was less than 10 and more than

0.1 respectively.

Table 8 Variance of Inflation Factors

Model predictors	VIF	1/VIF
High TB burden country	2.7	0.36
Months of experience	2.5	0.39
Age	4.9	0.2
Diabetes mellitus	1.1	0.8

Significance:

WHO target worldwide TB elimination by 2035, however, decline rate still below the expected decline rate in TB incidence. Many studies were consistent in that 5 to 10% of latent TB case will have active TB during their live mainly after 5 years from the initial LTBI (34).

CDC healthcare workers are in need to be tested for latent tuberculosis annually to detect any latent TB infection and provide them with the proper treatment to prevent further progression of the disease.

Chapter 5: Discussion

5.1 Prevalence of LTBI Qatar

This is the first study to quantify the prevalence of LTBI among HCW in the only TB facility in Qatar and to determine its predictors. Almost one in four staff at CDC is affected by LTBI. The LTBI prevalence in CDC way less than the prevalence of other infectious disease hospitals in China [(4)], and even less than the pooled prevalence estimated by the most systematic reviews done recently [(15, 29).] However, countries like Singapore [(22)], Malaysia [(14)] and KSA [(11)] have a lower prevalence of LTBI among HCWs. While all other studies from China, Oman, and South Africa showed a higher prevalence of LTBI among HCWs. This might be due to the vigorous screening for LTBI in CDC. However, this study is for only one facility of HMC, a similar study done in Cuban hospital which is also one of HMC healthcare facilities in Qatar, estimated a much lower prevalence with 6.9% of LTBI among 202 healthcare workers [(32)]. This might be related to the differences of the nationalities of the HCWs between the two facilities, in which staff in CDC are more likely to be coming from high TB burden country (65%), meanwhile the majority Cuban hospital staff are from Cuba which is not considered to be one of the highest 30 TB burden countries. Added to that the difference in the scope of service, for instance, CDC HCWs has daily contacts with TB patients for the fact that majority of the CDC patients are active PTB, CDC has assessed and triaged more than 11, 500 patients for PTB in 2018 only, meanwhile the Cuban hospital HCWs come in contact with TB patients occasionally.

Almost 73% of the positive cases (LTBI) were from high TB burden countries like India, Philippine, Bangladesh, Kenya, and others. This is perhaps the most important reason for the high prevalence (26.9%) of LTBI among CDC despite that Qatar is known to be a low TB burden country.

Lack of published data about LTBI from other HMC facilities, primary health centers, and private health sector make it difficult to generalize the CDC data for all healthcare workers in Qatar.

Table 9. Summary of Countries, Year of Reporting and Prevalence of LTBI.

Country (ref)	Year	Sample size	Prevalence (%)
South Africa [28]	2014-2015	505	84
Rwanda [27]	2010	1131	62
China (Infectious Disease Hospital) [4]	2017	Not reported	58
Systematic review study [29]	2005-2017	32630	49
Systematic review study [21]	2016	10078	47
Systematic review study [29]	2017	30961	37
China (non-infectious Disease Hospital) [4]	2017		33.9
Oman [17]	2012	371	33.2
Portugal [26]	2007-2010	2889	29.5
Qatar CDC	**2018-2019**	**415**	**26.9**
Italy (HCWs) [25]	2014-2015	628	20.9
Singapore [22]	2014-2019	1690	12.7
KSA [31]	2008-2009	2650	11
Malaysia [16]	2008-2009	954	10.6
Qatar Cuban Hospital [32]	2013	202	6.9
Italy (student population) [23]	2014-2015	3374	4.86
Italy (student population) [24]	2012	733	1.4

5.2 Predictors of LTBI in Qatar

We found the independent predators are, being born in high TB burden country is consistent with other findings from the systematic reviews and articles from Italy [15].

We also found that DM was predictors at univariate levels and since our sample size is relatively small there was not enough predictor power as a significant predictor, given in hands that none of the CDC staff has DM type I and the average years of age for the total staff is 34.3 years old who are at lower risk of developing DM at this age.

Reports from overseas have identified a number of factors that were related to LTBI in CDC settings. The most important factors were found to be; coming from a high TB burden country, then older age in which is assumed that those who are older have more exposure and likely to have LTBI, similarly for those who have longer experience and DM were also reported to be important predictors. A study from South Africa found that daily contact of TB patients is one of the main predictors for LTBI in addition to staff who have been involved in sputum collection from TB patients [(28)]. Other infection prevention and control measures were not evaluated in the study like usage of N95 mask early isolation of TB patients, ventilation system and cough etiquette. Such data were not quantified in this study otherwise it would have reflected the LTBI in CDC as it is a new facility. However further studies on the incidence of LTBI among CDC HCWs would give a better image about the effect of the infection prevention and control program on LTBI. Our expectation that the incidence will be much lower than any other places on the world due to the following; availability of TB infection prevention and control program, availability 65 negative pressure room, well designed and maintained ventilation system with HEPA filters built in and UV germicidal light, availability of N95 mask as PPE. Powered air purified respirator is already ordered for staff who failed with the N95 mask.

Another highlighted factor is the category of healthcare workers, in our study we found that those staff who are classified as a high risk of exposure based sharing the same air space with a TB patients are at a higher risk of getting LTBI 72% 84/112 and majority of the CDC staff are considered as high risk based on this definition in which 299/415 are classified as higher risk. Table 10 shows the list of factors that were found to be significant in each of the recent studies.

Table 10. Other LTBI Predictors From Different Countries.

Country	Years of Publication	Sample size	Predictors
South Africa (28)	2014-2015	505	Daily contact with TB patients HIV status collecting of sputum Infection control policy Ventilation measures Cough antiquate Early triage Early Isolation N95 Mask
Systematic review study (29)	2005-2017	32630	Years of experience Work location TB contact Job category
Systematic review study (21)	2016	10078	Infection control measures TB control measures at the health-care setting High TB burden country
Systematic review study (28)	2017	30961	Screening Method, increase with TST. Employment and socioeconomic status Being an HCW
Portugal (26)	2007-2010	2889	Age Number of years of experience
Italy (HCWs) (25)	2014-2015	628	Being a Nurse Workplace
Qatar			High TB burden country Month of experience Diabetes mellitus Age

Chapter 6: Limitation and Recommendation

6.1 Limitations

The main limitation of our study is the absence of data in regard to other risk factors, like other comorbidities, smoking, socioeconomic status, BCG vaccination and history of travel for a better prediction model of LTBI.

Due to the limited time frame of the study we were not able to collect data on other comorbidities. History of the BCG vaccination was not available on the staff electronic medical records, neither staff can remember whether they took the vaccine during their childhood nor they were able to provide any document about their BCG vaccination. The only option was to check the scare of the vaccine for the total CDC staff which was not a choice due to the limited time frame of the study and due to the fact that many staff will be on evening and night shifts. To avoid ending up with many missing data and to avoid data imputation we were not able to consider the BCG vaccination as a predictor in our study. Majority of the CDC healthcare workers were recently transferred to CDC from other HMC facilities, that is why attribution of the risk of LTBI to the Communicable Disease Center cannot be concluded. Infection prevention and control practices for the previous hospitals were not quantified in this study which would have added a better prediction for LTBI among the healthcare workers.

6.2 Recommendation

Further studies need to be done for the incidence of LTBI among CDC staff, the data of this study shall be considered as a baseline to detect the incidence next years.

With the 5 to 10% risk of progression from LTBI to active PTB reinforcement in regard to complying with HMC rules and regulation in the matter of TB screening for healthcare workers initially at the recruitment time and on yearly bases shall be a priority to prevent further TB transmission among healthcare workers and general community.

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