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Risk factors for tuberculosis among health care workers in South India: a nested case–control study

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Abstract

Objective: The epidemiology of tuberculosis (TB) among health care workers (HCWs) in India remains under-researched. This study is a nested case–control design assessing the risk factors for acquiring TB among HCWs in India.

Study Design and Settings: It is a nested case–control study conducted at a tertiary teaching hospital in India. Cases (n = 101) were HCWs with active TB. Controls (n = 101) were HCWs who did not have TB, randomly selected from the 6,003 subjects employed at the facility. Cases and controls were compared with respect to clinical and demographic variables.

Results: The cases and controls were of similar age. Logistic regression analysis showed that body mass index (BMI) <19 kg/m^2 (odds ratio [OR]: 2.96, 95% confidence interval [CI]: 1.49–5.87), having frequent contact with patients (OR: 2.83, 95% CI: 1.47–5.45) and being employed in medical wards (OR: 12.37, 95% CI: 1.38–110.17) or microbiology laboratories (OR: 5.65, 95% CI: 1.74–18.36) were independently associated with increased risk of acquiring TB.

Conclusion: HCWs with frequent patient contact and those with BMI <19 kg/m^2 were at high risk of acquiring active TB. Nosocomial transmission of TB was pronounced in locations, such as medical wards and microbiology laboratories. Surveillance of high-risk HCWs and appropriate infrastructure modifications may be important to prevent interpersonal TB transmission in health care facilities.

Keywords: Tuberculosis; Health care workers; Infectious disease transmission, patient-to-professional; Risk factors; Nested case–control study; Low body mass index; Nosocomial tuberculosis transmission

1. Introduction

TB continues to be an important public health problem in India, with an annual two million new cases of TB from India accounting for a fifth of the new TB cases occurring globally [1]. Two of every five Indians are infected with the TB bacillus [2]. With an increase in the number of people living with HIV and AIDS in India, the incidence of HIV/TB coinfection is expected to be on the rise. The high incidence of multidrug-resistant TB (MDR TB) in India is yet another issue that poses a challenge to infection control measures [3,4].

The Revised National TB Control Program (RNTCP) in India has been successful in providing access to Directly Observed Treatment Short Course (DOTS) for the whole population [2]. However, control of nosocomial transmission of TB is still neglected in Indian hospitals [5]. Delay in the diagnosis and treatment of TB in hospitalized patients [6,7], underutilization of rapid diagnostic techniques, failure to isolate infectious TB cases routinely, unrecognized drug resistance among the mycobacterial strains, lack of recommended engineering and environmental standards [8–10], large number of TB patients being handled in crowded and poorly ventilated wards [11] and waiting rooms, lack of recommended personal protection equipment [12], financial and logistic constraints in implementing infection control measures, and absence of national guidelines for screening and treatment of latent TB infection (LTBI) among health care workers (HCWs) all contribute to high rates of nosocomial TB, particularly among HCWs. Poor knowledge and attitude, with perceived lack

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What is new?

Key findings:

- Health care workers (HCWs) with frequent direct patient contact were at high risk of acquiring tuberculosis (TB).
- Nosocomial transmission of TB may be pronounced in locations, such as medical wards and microbiology laboratories.
- The risk was higher for HCWs with BMI <19 kg/m^2.
- In this study, we have documented a modestly increased rate of active TB (314 per 100,000 HCWs) and a markedly increased rate of extrapulmonary TB (EPTB; 148 per 100,000 HCWs) among HCWs at a tertiary care center in India.

What this adds to what is known?

- To the best of our knowledge, low body mass index has not been earlier shown to be an independent risk factor for acquiring TB.
- Our institutional data clearly show that the EPTB rates are much higher in HCWs as compared with the general population

What is the implication, what should be changed now?

- Surveillance of high-risk HCWs and appropriate infrastructure modifications should be implemented to prevent interpersonal TB transmission in health care facilities.

of vulnerability to TB among HCWs [13] and poor compliance with routine screening for TB among HCWs [14] need to be addressed. Infection control practices recommended by international agencies [8,9,12] have limited practical feasibility in most of the health care centers in India because they are not cost-effective. The World Health Organization (WHO) guidelines for hospitals in resource-limited settings [15] have also not been strictly adhered to.

Few studies, including one from our institution, have reported a high incidence of active TB among HCWs in India [13,16]. However, these observational studies have had many limitations. Lack of controls have particularly limited their validity. Interpersonal transmission of TB is of concern in hospitals in India [17]. In low- and middle-income countries, the median prevalence of LTBI was 63% (range: 33–79% across studies), with one Indian study reporting 50% prevalence in 2005 [18]. The very-high prevalence of LTBI coupled with concerns about emergence of drug-resistant TB strains have led to controversy over the feasibility of treating LTBI in such settings. Even in 2010, LTBI prevalence rates as high as 50.2% continue to be reported from India [19]. Hence, a strategy of identification of hotspots of interpersonal TB transmission in the health care setting may lead to implementation of cost-effective infrastructure modifications to contain such transmission. The surveillance of high-risk subpopulations among HCWs is vital to achieve early diagnosis of active TB and rapid initiation of effective anti-TB drugs. Hence, data collected from 2003–2004 was critically analyzed to identify potential risk factors for transmission of disease so that cost-effective interventions may be initiated to reduce the nosocomial spread of TB. The present study is a nested case–control design assessing the risk factors for acquiring active TB among HCWs in a tertiary teaching hospital in India.

2. Methods

2.1. Setting

The study was conducted at the Christian Medical College Hospital (CMCH), Vellore between March 2003 and December 2004 using a nested case–control design by enrolling cases and controls from an established larger cohort of HCWs. Subjects who developed TB were recruited as cases and the control group was sampled from unaffected members of the cohort. Covariate information was collected only for established cases and sampled controls. Certain exposure data were available for the whole cohort of HCWs, thereby limiting the recall bias. CMCH is a 2,100-bedded tertiary care referral hospital located at Tamil Nadu, South India with a cohort of more than 6,000 HCWs who have long-time employment in the institution. All HCWs are offered preventive and curative health care services through the Staff Students Health Services. Medical records of all services are maintained at the medical records department.

All employees are given a thorough medical examination, including investigations and chest X-rays. Those with active TB are not selected for employment till completion of anti-TB therapy. Thereafter, all employees undergo a voluntary annual or biannual medical examination that includes history and physical examination, blood tests, and imaging as deemed appropriate by the physician-in-charge. All these details are recorded in the employees' medical chart in a standardized format; the chart is retained in the hospital medical records division permanently. The hospital has implemented RNTCP standard procedures for recording its employees diagnosed with TB since the start of the cohort in 1994.

CMCH has more than 1,300 TB hospitalizations each year. DOTS is provided by the hospital through the RNTCP. TB patients requiring admission are provided initial inpatient care in all the medical wards and if found to be sputum smear positive, they are subsequently shifted to the isolation ward, where known MDR TB cases are also admitted.

HCWs attending patients in the isolation ward are mandated to use surgical masks for personal protection. Nearly 100 sputum microscopy specimens are processed each day in the laboratory and information is generated on mycobacterial culture and sensitivity. The estimated annual risk of TB infection in South India is 1.0% [20]. Studies from Tamil Nadu estimated the incidence and prevalence of smear-positive TB to be 82 and 210 per 100,000 populations, respectively [21].

3. Definitions

3.1. Cases

Cases were HCWs employed at CMCH who were diagnosed with active TB. HCW was defined as any person registered as a staff member in the hospital either on a permanent or temporary basis, with duration of employment more than 6 months and working in the hospital at the time of diagnosis of TB. Cases were identified by screening of hospital medical records, microbiology mycobacterial smear and culture specimen register, and pharmacy records. All medical diagnoses are coded; and using these codes, the employees with TB were identified from medical records. HCWs diagnosed to have TB during the pre-employment screening or those who had active TB before joining the institute were excluded. HCWs who were having a relapse of TB during the study period with the initial episode occurring before November 1994 were also excluded. WHO definitions were used to define a case of TB, extrapulmonary TB (EPTB), and pulmonary TB (PTB): sputum smear positive/sputum smear negative [22]. Cases were enrolled retrospectively (from November 1994 to March 2003) and prospectively (from March 2003 to December 2004), over a 10-year period. Incidence was calculated from cases reported among the prospectively followed-up cohort of all HCWs (from March 2003 to December 2004). At the end of the study, the incidence of active TB among the HCWs and the risk factors for developing TB were described.

3.2. Controls

Controls were randomly, prospectively selected HCWs who were free of active TB disease as assessed clinically. Controls were prospectively selected from a master list of all the employees in the hospital, ordered alphabetically. From this list, unmatched controls were chosen by systematic random sampling, one for each case. All the members of the control group were subjected to a clinical examination. Exclusion criterion for this group of controls was the presence of active TB in the past based on history and physical examination along with sputum tests and chest X-rays when indicated.

3.3. Other parameters

Cases and controls were further classified according to the type of work and the degree of exposure to the patients (Table 1). Frequent direct contact was defined as HCWs involved in regular clinical care of patients. Limited direct contact was defined as HCWs not involved in day-to-day clinical care of patients, but interacted with patients and their relatives for a limited period of time during their work schedule. Area of employment was defined as the actual location or the ward where the HCW was posted during most of the months in the previous year. Department was defined as the department where the HCW was posted during most of the months in the previous year. HCWs in a particular department may be assigned to different locations in the hospital and hence classified accordingly. The presence of Bacille Calmette–Guérin (BCG) vaccination was documented by identifying the vaccine scar on the shoulder of the subject. Smoking was defined as having ever smoked for at least 1 year. Body mass index (BMI) was calculated using the weight and height documented in the medical records 1 year before acquiring TB for cases and recordings 1 year before the enrollment for controls. This value was taken as the baseline BMI. The HCWs were distributed into two different groups based on their residence: those who have their residence in the hospital campus and those residing away from the hospital campus in the community. High-risk procedure was defined as any diagnostic or therapeutic procedure that induced cough. Delay in diagnosis of TB was calculated as the number of days between onset of symptoms and diagnosis. These data were obtained both from medical records as well as interviews.

3.4. Data collection and analysis

HCWs, both cases and controls, were administered a questionnaire by one of the investigators regarding demographic information, education, work, residence, presence of comorbid illnesses, use of personal respiratory protection devices, knowledge regarding TB, previous recognized episodes of exposure to TB, nonoccupational exposure to TB, BCG

Table 1. Classification of health care workers according to extent of patient contact

Contact with patients	Categories of staff
Frequent direct contact with patients	Physicians, nurses, nursing assistants, technicians, and respiratory therapists
Limited direct contact with patients	Medical records personnel, ward clerical staff, ward attendants, social workers, dietitians, cleaning staff, enquiry office workers, phlebotomists, social workers, transporters, and pharmacists. Includes staff in the above group with only limited direct patient contact.
No direct contact with patients	Accountants, administrators, cashiers, laboratory personnel, and laundry workers. Also includes staff in above two occupational groups with no direct patient contact.

vaccination, smoking, and use of immunosuppressive therapy. Hospital medical records and pharmacy records were reviewed for all cases and controls. The research committee of the hospital approved the study. Informed consent was taken from all individuals. The identities of the cases were protected.

3.5. Analysis

We calculated a sample size of 100 patients with 100 in-hospital controls. The power calculation showed that the study (100 in each group) had 86% power at 5% level of significance to detect an odds ratio (OR) of 2.5 or more, assuming the percentage of HCWs in the control group exposed by work in laboratory areas and medical wards to be 25% [23]. Association between each of the factors and the risk of TB was evaluated using chi-square or fisher exact tests (if the expected frequency in any cell was <5), as appropriate. Crude ORs and 95% confidence intervals (CIs) were obtained. All risk factors that showed a P-value <0.05 on univariate analysis were included in the multivariate logistic regression analysis. Backward stepwise logistic regression analysis was carried out using TB as dependent variable and the variables that were identified ($P < 0.05$) in the univariate analysis as independent variables. Adjusted ORs with 95% CIs were presented from this model. All analyses were performed using STATA (Version 10, Stata Corporation, College Station, TX).

4. Results

During the period from November 1994 to December 2004, 141 HCWs developed TB. Of these, 101 workers were still continuing to serve at the health facility. The incidence of TB was noted to be 314 cases per 100,000 HCWs (95% CI: 190–493 per 100,000 HCWs). During this period, the incidence of smear-positive PTB and EPTB cases were 111 per 100,000 HCWs (95% CI: 36–217 per 100,000 HCWs) and 148 per 100,000 HCWs (95% CI: 68–284 per 100,000 HCWs), respectively. Among the 101 cases, the main subtype of TB was PTB ($n = 38$). Twenty-four (23.8%) cases were smear-negative PTB and 39 (38.6%) were EPTB cases. EPTB cases included TB lymphadenitis ($n = 17$), genitourinary TB ($n = 5$), disseminated TB ($n = 6$), spine/bone TB ($n = 5$), abdominal TB ($n = 3$), and TB meningitis ($n = 3$).

Of the 101 cases, mycobacterial cultures were performed in 80 cases. The major source of specimen was sputum (43 cases); this was followed by pleural biopsy cultures (12 cases), lymph node biopsy cultures (9 cases), and cerebrospinal fluid cultures (4 cases). Culture growth was present in 45 cases. There were three patients with MDR TB. Of these, one was employed in the microbiology department as an attendant, another patient was a respiratory medicine technician, and yet another was a nursing staff. Biopsy for obtaining histopathology was performed in 46 cases, of which 43 revealed granulomatous inflammations consistent with a diagnosis of TB. The delay in diagnosis of TB was 37.9 days.

The cases were similar to the controls in age (mean: 34 years and 36 years, $P = 0.149$) and proportion of females (57.4% and 52.5%). Baseline BMI was noted to be significantly different between cases and controls (mean [standard deviation (SD)]: 20.4 (3.95) and 22.4 (3.84) kg/m^2, respectively; $P < 0.0003$). The duration of work at the institute before onset of the disease was noted to be lower in cases as against controls (mean [SD]: 7.3 (7.65) and 10.8 (9.92) years, respectively; $P = 0.008$). The factors associated with increased risk of acquiring TB, which emerged significant on univariate analysis, included occupational subgroups, such as doctors (OR: 4.31, 95% CI: 1.34–13.81) and nurses (OR: 3.64, 95% CI: 1.27–10.41), being employed in medical wards (OR: 6.40, 95% CI: 2.08–19.71) or microbiology laboratories (OR: 9.43, 95% CI: 1.13–78.58) in the previous 1 year, being affiliated to the medicine department (OR: 9.3, 95% CI: 1.07–81.1) or microbiology department (OR: 10.9, 95% CI: 1.28–92.7), having frequent direct patient contact (OR: 2.83, 95% CI: 1.32–4.12), being in the initial 4 years of employment (OR: 2.23, 95% CI: 1.01–4.91), having a baseline BMI <19 kg/m^2 (OR: 2.60, 95% CI: 1.39–4.85), and residing in the hospital campus (OR: 2.88, 95% CI: 1.56–5.33; Table 2).

Using logistic regression model, independent risk of the above-mentioned factors were assessed. It showed that only four factors were independently associated with the risk of acquiring TB after adjusting for all the intervariable interactions. They were: being employed in the microbiology laboratories (OR: 5.65, 95% CI: 1.74–18.36), being employed in medical wards (OR: 12.37, 95% CI: 1.38–110.17), having frequent direct patient contact (OR: 2.83, 95% CI: 1.47–5.45), and having baseline BMI <19 kg/m^2 (OR: 2.96, 95% CI: 1.49–5.87; Table 3).

5. Discussion

We have documented a modestly increased rate of active TB and a markedly increased rate of EPTB cases among HCWs at a tertiary care center in India. The high incidence of active TB was similar to the rates from other developing countries [24,25]. During 2003–2004, at 314 per 100,000 person-years, the rate of all cases of active TB among HCWs was 1.86 times higher than that estimated for the country (168 per 100,000 population) [1]. During the same period, the incidence of EPTB among HCWs was 148 per 100,000 compared with the national notification rate (DOTS + non-DOTS) of 14 per 100,000 populations, at a relative risk of 10.57. With an estimated 62% total case detection rate for the country [1], this study still revealed a very high incidence of EPTB among HCWs. EPTB constituted 38.6% of the total 101 cases studied as compared with 13% of the total number of cases reported nationally [1]. DOTS program and RNTCP are more sensitive toward the detection of smear-positive TB

Table 2. Risk factors associated with tuberculosis among health care workers on univariate analysis

Variables	Case, *n* (%)	Control, *n* (%)	OR	*P*-value	95% CI
Sex					
Female	58 (57.4)	53 (52.5)	1.22	0.489	0.70–2.12
Male	43 (42.6)	48 (47.5)	(Reference)		
Education					
Higher secondary	16 (15.8)	25 (24.8)	0.59	0.305	0.21–1.61
Graduate	72 (71.3)	64 (63.4)	1.03	0.931	0.44–2.43
Postgraduation	13 (12.9)	12 (11.9)	(Reference)		
BCG vaccination					
Yes	84 (83.2)	89 (88.1)	1.50	0.318	0.67–3.33
No	17 (16.9)	12 (11.9)	(Reference)		
Occupation					
Attendants	13 (12.9)	22 (21.8)	1.57	0.44	0.49–5.03
Doctors	21 (20.8)	13 (12.9)	4.31	0.01	1.34–13.81
Nurses	41 (40.6)	30 (29.7)	3.64	0.02	1.27–10.41
Engineers and technicians	15 (14.9)	14 (13.9)	2.85	0.08	0.87–9.37
Laboratory staffs	3 (2.9)	4 (3.9)	2.0	0.44	0.34–11.70
Social workers	2 (1.9)	2 (1.9)	2.67	0.38	0.31–23.42
Administrative staffs	6 (5.9)	16 (15.8)	1 (Reference)		
Area of employment					
Medical wards	19 (18.8)	4 (3.9)	6.40	0.001	2.08–19.71
Microbiology laboratories	7 (6.9)	1 (0.9)	9.43	0.04	1.13–78.58
Radiology	5 (4.9)	3 (2.9)	2.24	0.28	0.51–9.73
Medical stores	4 (3.9)	4 (3.9)	1.35	0.68	0.32–5.59
Others	66 (65.4)	89 (88)	1 (Reference)		
Frequent direct contact with patients					
Yes	65 (64.4)	44 (43.5)	2.83	0.003	1.32–4.12
No	36 (35.6)	57 (56.4)	1 (Reference)		
Department of employment					
Microbiology	7 (6.9)	1 (0.9)	10.9	0.03	1.28–92.7
Medicine	6 (5.9)	1 (0.9)	9.3	0.04	1.07–81.1
Radiology	5 (4.9)	2 (1.9)	3.9	0.11	0.71–21.2
Nursing	42 (41.6)	30 (29.7)	2.1	0.01	1.15–4.12
Personal office	6 (5.9)	11 (10.9)	0.85	0.77	0.29–2.51
Others	34 (33.7)	53 (52. 5)	1 (Reference)		
Location of residence					
Hospital campus	45 (44.5)	22 (21.8)	2.88	0.001	1.56–5.33
Other areas	56 (55.5)	79 (78.2)	1 (Reference)		
Diabetes					
Yes	4 (3.9)	2 (1.9)	2.04	0.42	0.37–11.40
No	97 (96.1)	99 (98.1)	1 (Reference)		
Connective tissue disease					
Yes	2 (2.0)	2 (2.0)	1.00	—	—
No	99 (98.0)	99 (98.0)			
Respiratory protection					
Yes	14 (13.9)	6 (5.9)	2.54	0.06	0.94–6.92
No	87 (86.1)	95 (94.1)	1 (Reference)		
Exposure to high risk procedures					
Yes	38 (37.6)	27 (26.7)	1.65	0.09	0.91–3.00
No	63 (62.4)	74 (73.3)	1 (Reference)		
Knowledge about respiratory protection					
Inadequate	17 (16.8)	23 (22.8)	0.68	0.29	0.34–1.38
Adequate	84 (83.2)	78 (77.2)	1 (Reference)		
Family contact with TB					
Yes	4 (3.9)	6 (5.9)	0.65	0.52	0.18–2.38
No	97 (96.1)	95 (94.1)	1 (Reference)		

(*Continued*)

Table 2. Continued

Variables	Case, *n* (%)	Control, *n* (%)	OR	*P*-value	95% CI
BMI (kg/m^{2})					
<19	41 (40.6)	21 (20.8)	2.60	0.003	1.39–4.85
≥19	60 (59.4)	80 (79.2)	1 (Reference)		
Duration of employment (yr)					
<4	45 (45.0)	29 (29.3)	2.23	0.04	1.01–4.91
4–8	28 (28.0)	23 (23.2)	1.75	0.19	0.75–4.07
8–12	9 (9.0)	13 (13.1)	0.99	0.99	0.34–2.88
12–16	2 (2.0)	11 (11.1)	0.23	0.11	0.05–1.34
≥16	16 (16.0)	23 (23.2)	1 (Reference)		
Smoking					
Current smoker	13 (12.9)	7 (6.9)	1.92	1.92	0.73–5.04
Ex-smoker	2 (1.9)	5 (4.9)	0.42	0.42	0.07–2.19
Nonsmoker	86 (85.2)	89 (88.2)	1 (Reference)		

Abbreviations: OR, odds ratio; CI, confidence interval; BCG, Bacille Calmette–Guérin; TB, tuberculosis; BMI, body mass index.

Regarding department of employment, ''Others'' include the departments in the hospital excluding the five departments with the maximum reported incidence of TB. Similarly, for area of employment ''Others'' refer to areas in the hospital, excluding the four areas, which accounted for the maximum number of TB cases.

cases because of the reliance on sputum microscopy and chest X-ray as the main diagnostic tools. However, this alone or associated referral bias is unlikely to account for this increased rate of EPTB. Impact of referral bias was reduced through a nested case–control design selecting the cases from the whole population of HCWs. Young age, ethnicity, female sex, and HIV infection are known independent risk factors for nonrespiratory TB [26–28]. This study did not evaluate HIV infection as a risk factor. It has been noted that patients infected with the phospholipase-C gene D mutant *Mycobacterium tuberculosis* strains are more likely to have extrathoracic disease than those infected by a strain without this mutation [29]. The relative contribution of the above-mentioned patient and pathogen factors to the higher incidence of EPTB among HCWs need to be studied.

Identification of persons at high risk for active TB would allow us to direct TB-control efforts to those most in need of preventive therapy and most likely to become a source for further spread of the disease. There are risk factors for each of the four distinct steps in the pathogenesis of TB namely exposure, infection, disease, and death [30]. This study looked at the combined risk factors for the initial 3 steps of TB pathogenesis. We identified baseline BMI <19 kg/m^2, frequent direct patient contact, and being employed in medical wards or microbiology laboratories to be independent risk factors associated with the increased risk of acquiring active TB. Of these, frequent direct patient contact and being employed in medical wards probably indicates the increased exposure to active TB cases. High-risk work settings [11], including department of medicine, have been shown to be associated with a positive tuberculin skin test result in studies from developed countries [31]. As there are HCWs belonging to different departments working in the same area, we classified HCWs based both on the department and the site of employment. Site of employment may more accurately classify the risk of exposure. The institute has a protocol for isolating sputum smear-positive TB cases and MDR TB cases to an isolation ward. However, the large number of TB patients being handled causes logistic problems in using recommended personal protection equipment (e.g., N95 respirator masks). The increasing number of patients being admitted with HIV/TB coinfection and atypical chest X-ray findings often causes delay in the diagnosis and initiation of anti-TB therapy. Underutilization of rapid diagnostic techniques and increasing use of mechanical ventilation and intensive care for PTB cases without recommended engineering and environmental standards [8–10] might also contribute to the nosocomial transmission in medical wards. Noscocomial spread of TB in microbiology laboratories may be because of the exposure to infective TB specimens.

Some studies have shown that age is an independent risk factor for TB disease [24]. A recent study from India noted that increasing age and years in the health profession are significant risk factors for LTBI [18]. Although our study only looked at comparisons within health professionals in a hospital setting, we were able to show that duration of employment was significantly lower among cases as compared with

Table 3. Multivariate logistic regression analyses of risk factors for tuberculosis (stepwise)

Variables	OR	95% CI	*P*-value
Occupation			
Nurses	2.25	0.93–5.44	0.07
Area of employment			
Medical wards	12.37	1.38–110.17	0.004
Microbiology laboratories	5.65	1.74–18.36	0.02
Frequent direct contact			
With patients	2.83	1.47–5.45	0.002
BMI <19 kg/m^2	2.96	1.49–5.87	0.002

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index.

Residence, respiratory protection, exposure to risk, and duration of employment were the other variables in the model, which were sequentially excluded.

controls. This could be a chance finding as the factor did not emerge significant in the logistic model. Most HCWs employed in high-risk areas, such as medical wards, are young resident nurses and doctors, putting them at increased risk of exposure and disease. Residents and students often perform detailed clinical examination even for suspected PTB cases without adequate respiratory protection. The younger age of the new recruits and interpersonnel transmission because of accommodation in hostels during the initial years of service may also account for this finding.

The baseline BMI was found to be significantly associated with TB. Baseline BMI <19 kg/m^2 may be a risk factor for acquiring infection as well as for infection progressing to active disease. It is difficult in a case–control design to assign temporal association. It could be interpreted that low BMI is the result of TB, rather than risk factor for TB because low BMI is a known association of active TB [32]. However, in our case–control design, we believe that this is unlikely to be the reason because we took the baseline BMI rather than BMI at time of disease presentation as the risk factor in the analysis. The percentage of low-income persons within the employee's residential postal zone is known to be independently associated with tuberculin skin test conversion [33]. Our study was not able to accurately classify HCWs based on community TB exposure. However, we did not find an increase in TB cases among those HCWs residing in the community as opposed to the hospital campus. Finally, there was a significant delay in the diagnosis of TB in HCWs even when dedicated consultation and diagnostic facilities were available. If this delay in diagnosis contributed to nosocomial transmission of TB needs to be evaluated.

The following were the main limitations of the study. Forty patients (28.36%) could not be enrolled in the study. HIV status, which could have influenced the conclusion, was not checked because of ethical considerations. This study looked at the combined risk factors for the initial 3 steps of TB pathogenesis. Risk factors for active disease rather than infection were evaluated; hence, patient factors may have been emphasized more than environmental/exposure factors. However, this being a nested case–control study within a cohort of initially TB-free employees, BMI could be concluded with reasonable certainty to be a risk factor for acquiring TB disease. The role of malnutrition in pathogenesis of TB has been questioned by some researchers [34]. The extensive transmission of TB might have been because of the increased virulence of the strain rather than environmental factors or patient characteristics [35]. Potential virulence factors of the isolated strains were not studied. Because DNA fingerprinting of the mycobacterial strains could not be performed, it is difficult to differentiate between recent transmission of disease and reactivation of previous infection. We did not match the cases and controls because many of the conventional variables [32] used for matching, including gender [36,37] and age [24], are known associations of TB. Matching may have lead to greater study precision in terms of less OR variance.

This study highlights the benefits of doing nested case–control studies, especially in resource-limited situations, such as in India. We are unaware of any other similar studies from resource-limited countries evaluating these risk factors. A systematic review in 2006 has shown similar risk factors [38]. The study has lead to a hospital policy of careful review of HCWs in these high-risk areas for TB, although no further policy changes have been implemented based on these findings.

The study also highlights the benefit of the method used for selecting controls. The hospital has more than 6,000 employees. The easiest, most efficient, and cost-effective method of probability sampling was considered to be systematic random sampling. This method requires knowledge of the total number of employees in the hospital (their sampling frame) during the same time period and the number of controls required for study. We recommend that this simple but effective method be used in any situation with a large sampling frame from which controls need to be selected for a case–control study. This study also highlights the usefulness of this nested case–control design to identify hotspots in the hospital for other nosocomial infections, both to the HCWs and to the patients. However, such studies seem to be few and far between, possibly because of the lack of proper record keeping, something vital to a nested case–control study, inadequate laboratory support, and documentation, as well as rapid turnover of HCWs.

6. Conclusions

HCWs with frequent direct patient contact were at an increased risk of acquiring TB, especially in settings where patients with active TB are treated, as in the medical wards of a tertiary care center. Focal spread may also have occurred in microbiology laboratories where a high volume of infective TB specimens are handled. The risk was higher for those with baseline BMI <19 kg/m^2. In the absence of recommended infection control measures, it may be important that HCWs with low BMI be kept under surveillance to achieve early diagnosis of active TB. Our findings call for elimination of delay in the diagnosis of TB, intensification of appropriate TB control activities in the hospital setting, and education of high-risk groups about personal TB control measures to reduce the interpersonal transmission of TB in the hospital setting.

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