

# Tuberculosis Patients Who Are A Potential Source for Unprotected Exposure in Health Care Systems: A Multicenter Case Control Study

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**Setting.** Five health care systems in Texas.

**Objective.** To describe the epidemiology of inadequate isolation for pulmonary tuberculosis leading to tuberculosis (TB) exposures from confirmed TB patients and the patient factors that led to the exposures.

**Design.** A retrospective cohort and case-control study of adult patients with TB resulting in exposures (cases) vs those TB patients who did not result in exposures (controls) during January 2005 to December 2012.

**Results.** There were 335 patients with pulmonary TB disease, 199 cases and 136 controls. There was no difference between groups in age ( $46 \pm 14.6$  vs  $45 \pm 17$  years;  $P > .05$ ), race, or substance abuse. Cases were more likely to be transplant recipients (adjusted odds ratio [AOR], 18.90; 95% CI, 1.9–187.76), have typical TB chest radiograph (AOR, 2.23; 95% CI, 1.1–4.51), and have positive acid-fast bacilli stains (AOR, 2.36; 95% CI, 1.31–4.27). Cases were less likely to have extrapulmonary disease (AOR, 0.47; 95% CI, 0.24–0.95).

**Conclusions.** TB exposure resulting from inadequate isolation is frequent in health care settings. Extrapulmonary involvement resulted in earlier airborne isolation. Being a transplant recipient, having chest radiograph findings typical for TB, and sputum positivity acid-fast bacilli upon staining were associated with increased risk of inadequate isolation.

**Keywords.** exposure; infection control; pulmonary tuberculosis; safety.

Although tuberculosis (TB) cases have declined significantly (62%) from 1992 to 2013 in the United States, there were still 9563 cases reported to the Centers for Disease Control and Prevention (CDC) in 2015, and around 51% of those cases were reported in 4 states: California, Texas, New York, and Florida [1]. The relatively high prevalence of TB in Texas creates a concern for patients and health care professionals (HCP), making TB exposure a safety issue [2]. TB remains a challenge for health care systems in the United States. In the recent past, there were multiple reports of patients acquiring the infection while receiving medical care. This is partly due to the complexity of making a diagnosis, atypical nature of clinical presentation in many cases, and delay in identification of cases, perhaps due in part to the perception that TB is a problem of the past [1, 3, 4].

TB transmission in health care settings may go undetected and in some low-prevalence countries; it is only suspected by epidemiological links in about 25% of the cases [5]. Furthermore, if transmission occurs and subsequent infections are diagnosed, many patients and HCP choose not to receive or do not complete latent TB infection (LTBI) therapy [6]. Furthermore, multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB are endemic in some parts of the world, and globally about 20% of isolates are resistant to at least 1 firstline TB medication [7]. This is critical because about two-thirds of active TB cases occur among foreign-born individuals, and most of the reported TB cases were from individuals born in Asian countries or Mexico [1].

A deviation from CDC guidelines due to the delay in suspecting and diagnosing active TB or placing patients with suspected active TB under appropriate isolation precautions has been associated with an increased rate of LTBI among HCP. This has been described in multiple reports of health care-associated outbreaks [8–14]. In this study, we describe the magnitude of burden, clinical features, and risk factors associated with exposure to a patient with microbiologically confirmed active pulmonary TB.

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## MATERIALS AND METHODS

### Study Design and Population

This is a retrospective case-control study performed at 5 health care systems in Texas over an 8-year period, January 2005 to December 2012. The study sites included 3 VA health care systems: South Texas Veterans Health Care System (STVHCS), Central Texas Veterans Healthcare System, Temple (CTVHCS), Valley Coastal Bend Veterans Healthcare System (VCBVHCS), and 2 public safety-net health care systems, University Health System at San Antonio (UHS) and Parkland Health and Hospital System, Dallas (PHHS), located in Texas. The hospitals had both teaching services (including resident trainees) and nonteaching services. The study included inpatients and outpatients. We combined the data from STVHCS and VCBVHCS because they were 1 system during part of the study and had a unified infection control program.

The aim of the study is to evaluate clinical, demographic, epidemiological, and radiological features and clinical management of TB patients and to compare microbiologically confirmed pulmonary TB patients who were sources of unprotected exposure to TB in health care settings (cases) with those patients who did not result in TB exposure (controls). All patients included had active TB with positive acid-fast bacilli (AFB) in sputum or respiratory cultures, with or without extrapulmonary compromise.

Data were collected using a standardized database in Excel. Each investigator completed a case report form and transferred it to the shared secure database. Case reports were validated by the study coordinator and the principal investigator as they were entered to ensure data quality. Adult patients meeting the definition of active TB (TB with pulmonary involvement by positive respiratory tract cultures consistent with *M. tuberculosis*)

during January 2005 to December 2012 were included in the analysis.

The study was divided in 2 parts. In the first part, TB patients who led to an exposure were identified based on review of the medical records at each site. These data included the number of exposed contacts detected by the infection control teams at each institution (Table 1). We defined a TB exposure to have occurred when a patient with active TB was not isolated after the first evaluation by a licensed independent practitioner or the patient did not have a surgical mask put on after first contact with the health care system, usually at the registration, resulting in potential TB exposure to other patients or health care workers.

In the second part, we evaluated documentation in the charts of all TB patients, those who led to potential TB exposures (cases) as well as those who were isolated at presentation and did not lead to further exposures (controls). All patients with positive respiratory cultures for *M. tuberculosis*, age 18 years or older, whose clinical data were available were included in the analysis and were further classified as cases and controls.

### Statistical Methods

Statistical analysis was performed using SAS software (version 3.4, 2012, Windows SAS Institute, Cary, North Carolina). Means and proportions were determined. To compare groups, we used Fisher's exact for categorical variables and the Wilcoxon rank-sum test for continuous variables. A stepwise logistic regression model with the default keep and stay criteria was used for assessing the significance of explanatory variables based on the case status. All statistical testing was 2-sided, with a significance level of 5% [15].

**Table 1. Characteristics of Each Health Care System (January 2005–December 2012)**

Location	PHHS	UHS	CTVHCS	STVHCS/VCBVHCS
TB exposure	No documentation of mask application on the patient at the time of arrival in the emergency department and/or no documentation of airborne isolation placement in the hospital	Health care workers and patients who are identified as having had interactions with a patient diagnosed with active transmissible tuberculosis prior to the patient being placed in an appropriate room and N95 masks being utilized are considered potential exposures	Infection Prevention considers an exposure to TB to be one that occurs prior to the initiation of any control measures (i.e., N95 respirator usage, negative pressure rooms).	Respiratory etiquette not initiated in the clinic setting at the first opportunity to do so (patient was not given a barrier mask), and the staff members did not use appropriate N95 respirator while examining or treating the patient
Services	900-bed tertiary care medical care that treats medical, surgical, transplant, burn care trauma, and high-risk obstetrics	500-bed tertiary care medical care that treats medical, surgical, and trauma	520-bed tertiary care medical care that treats medical, surgical, trauma, and outpatient clinics	1450-bed tertiary care medical care that treats medical, surgical, transplant patients, and outpatient clinics
Dates of data collection	01/01/2009 to 12/31/2011	01/01/2008 to 12/31/2012	01/01/2008 to 12/31/2010	01/01/2005 to 12/31/2012

Abbreviations: CTVHCS, Central Texas Veterans Healthcare System; PHHS, Parkland Health and Hospital System; STVHCS, Dallas South Texas Veterans Health Care System; UHS, University Health System at San Antonio; VCBVHCS, Valley Coastal Bend Veterans Healthcare System.

**Table 2. Number of Patients by Health Care Facility**

Location	PHHS	UHS	CTVHCS	STVHCS/VCBVHCS
Total number of TB patients	n = 171	n = 133	n = 9	n = 22
Cases	n = 122 (71.3%)	n = 62 (46.6%)	n = 8 (88.8%)	n = 7 (31.8%)
Controls	n = 49 (28.7%)	n = 71 (53.4%)	n = 1 (11.2%)	n = 15 (68.2%)

Abbreviations: CTVHCS, Central Texas Veterans Healthcare System; PHHS, Parkland Health and Hospital System; STVHCS, Dallas South Texas Veterans Health Care System; UHS, University Health System at San Antonio; VCBVHCS, Valley Coastal Bend Veterans Healthcare System.

## RESULTS

A total of 342 patients with active TB meeting inclusion criteria were identified. Seven patients were excluded due to lack of documentation. Table 1 summarizes the specific definitions of TB exposure, characteristics, and timeline of data collection employed at the various study sites. Of the 342 patients with TB, 199 were recognized as sources of unprotected exposure in the health care facility (cases) and 136 were not sources of TB exposure (controls). Table 2 compares the number of patients by care facility. Contact tracing for unprotected exposure to these 199 TB patients in the health care systems where they were cared for was performed on at least 2302 individuals including health care professionals and patients. Contact tracing data were not available at 1 of the health care systems in the study.

Cases and control patients had no statistically significant differences with respect to mean age ( $46 \pm 14.6$  vs  $45 \pm 17$  years), gender (80% vs 77% were males), race (most common, Hispanic  $n = 89$ , 47.9%, vs  $n = 66$ , 55.0%; African American  $n = 46$ , 24.3%,

vs 16, 13.3%; white  $n = 33$ , 17.5%, vs  $n = 21$ , 17.5%; Asian 11, 5.8%, vs  $n = 10$ , 8.3%;  $P = .09$ ), comorbid conditions, substance abuse history, or demographic characteristics (Table 3).

On univariate analysis, patients admitted to a teaching service were less likely to be cases than those admitted to a non-teaching service ( $n = 157$ , 78.89% vs 119, 88.15%;  $P = .02$ ).

There was a significant difference in the proportion of cases vs controls per managing specialty: medicine 96% ( $n = 199$ ) vs 86% ( $n = 117$ ), followed by surgical specialties 2% ( $n = 4$ ) vs 8% ( $n = 11$ ), family medicine 1.5% ( $n = 3$ ) vs 2.2% ( $n = 3$ ), pediatrics 0.5% ( $n = 1$ ) vs 2.9% ( $n = 4$ ), or surgical subspecialties 0% vs 0.7% ( $P = .01$ ). Data were not available for 1 patient.

There was no difference in location at the time of diagnosis (inpatient 96% vs 93.4%;  $P = .32$ ).

### Clinical Features of TB Disease

There was no significant difference in symptom duration between cases and controls prior to the clinical TB diagnosis (mean  $3 \pm 4.9$  months vs  $3.2 \pm 4$  months;  $P = .54$ ).

**Table 3. Distribution of Potential Clinical Risk Factors in the Study Population and the Differences Between Those Who Were Inadequately Isolated (Cases) and Those Who Were Adequately Isolated (Controls) Upon Univariate Analysis**

Clinical Factor	Patients With Clinical Factor (n = 335), n (%)	Control (n = 136), n (%)	Case (n = 199), n (%)	PValue
Admitted to Teaching services	276 (82.63)	119 (88.15)	157 (78.89)	.02
DM	67 (20.06)	22 (16.18)	45 (22.73)	.16
COPD	10 (2.99)	3 (2.21)	7 (3.54)	.75
ILD	6 (1.8)	2 (1.47)	4 (2.02)	1
Cirrhosis	13 (3.89)	6 (4.41)	7 (3.54)	.78
CKD	23 (6.89)	11 (8.09)	12 (6.06)	.51
CKD_HD	3 (0.9)	0 (0)	3 (1.52)	.27
CHF	10 (2.99)	7 (5.15)	3 (1.52)	.1
HIV	56 (16.77)	18 (13.24)	38 (19.19)	.18
Infections	55 (16.47)	20 (14.71)	35 (17.68)	.55
Rheumatologic diseases	6 (1.8)	4 (2.94)	2 (1.01)	.23
Immunosuppressive	16 (4.79)	7 (5.15)	9 (4.55)	.8
Malignancy	15 (4.49)	6 (4.41)	9 (4.55)	1
Transplant	6 (1.8)	1 (0.74)	5 (2.53)	.41
Classical TB findings on CxR	248 (74.03)	82 (60.29)	166 (83.42)	<.001
Extra pulmonary TB involvement	81 (24.18)	51 (37.5)	30 (15.08)	<.001
Previous Active TB	34 (10.21)	17 (12.5)	17 (8.63)	.27
History of treated TB	30 (9.06)	17 (12.5)	13 (6.67)	.08
History of latent TB	27 (8.11)	14 (10.29)	13 (6.6)	.23
AFB sputum positive	177 (56.01)	52 (40.31)	125 (66.84)	<.001

Abbreviations: AFB, sputum positivity acid-fast bacilli; Infections, clinical syndromes or diagnosis of other infection (non mycobacterial) at the time of the TB diagnosis; CKD, chronic kidney disease; CKD HD, chronic kidney disease in hemodialysis; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; ILD, interstitial lung disease; Immunosuppressive (agents), use of medications that cause systemic immunosuppression such as systemic steroids; Malignancy, active systemic malignancy of any kind; TB, tuberculosis; TNF-alpha blockers, excluding chemotherapeutic agents.

**Table 4. Multivariate Logistic Regression of Case Status (Inadequate Isolation of Tuberculosis) in Terms of Clinical and Demographic Characteristics Based on Stepwise Selection<sup>a</sup>**

Characteristic	OR	95% CI	PValue	Log Odds	Std_Err
Extra pulmonary TB involvement (yes)	0.47	(0.24–0.95)	.03 <sup>a</sup>	−0.75	0.35
Previous Active TB treatment (yes)	0.52	(0.2–1.31)	.16	−0.66	0.48
HIV (yes)	2.14	(0.98–4.65)	.06	0.76	0.40
Transplant (yes)	18.90	(1.9–187.76)	.01 <sup>a</sup>	2.94	1.17
Classical TB findings on CxR (yes)	2.23	(1.1–4.51)	.03 <sup>a</sup>	0.80	0.36
Admitted to teaching services (yes)	0.52	(0.24–1.15)	.11	−0.65	0.40
Acid-fast bacilli sputum positive	2.36	(1.31–4.27)	.004 <sup>a</sup>	0.86	0.30
Location <sup>b</sup> (STVHCS/VCBVHCS)	0.35	(0.12–1.03)	.06	−1.05	0.55
Location <sup>b</sup> (CTVHCS)	11.16	(1.19–104.64)	.03 <sup>a</sup>	2.41	1.14
Location <sup>b</sup> (PHHS)	3.05	(1.71–5.41)	<.001 <sup>a</sup>	1.11	0.29

Stepwise selection from extrapulmonary TB involvement, previous active TB treatment, DM, HIV, transplant, classical TB findings on CxR, admitted to teaching services, gender, age, location, immunosuppressive, acid-fast bacilli sputum positive, CKD\_HD.

Abbreviations: CTVHCS, Central Texas Veterans Healthcare System; OR, odds ratio; PHHS, Parkland Health and Hospital System; STVHCS, Dallas South Texas Veterans Health Care System; TB, tuberculosis; UHS, University Health System at San Antonio; VCBVHCS, Valley Coastal Bend Veterans Healthcare System.

<sup>a</sup>P value < .05.

<sup>b</sup>University Hospital is the reference group.

Cases were more likely to have exclusive pulmonary disease (no evidence of concomitant extrapulmonary disease;  $n = 169$ , 84.92%, vs  $n = 85$ , 62.5%;  $P < .001$ ), meningeal involvement ( $n = 4$ , 2%, vs  $n = 2$ , 1.5%), and miliary TB ( $n = 8$ , 4%, vs  $n = 4$ , 2.9%). On the other hand, cases were less likely to have bone involvement ( $n = 1$ , 0.5%, vs  $n = 15$ , 11%), gastrointestinal/genitourinary involvement ( $n = 3$ , 3%, vs  $n = 8$ , 7.0%), or lymph node involvement ( $n = 12$ , 11.7%, vs  $n = 17$ , 12.4%).

With regard to sputum samples, more samples were collected in the cases vs controls ( $3.2 \pm 2$  vs  $2.5 \pm 2$ ;  $P < .001$ ), and AFB stain positivity was higher among cases (1+ positive: 11.3% vs 11.5%; 2+ positive: 17.7% vs 3.9%; 3+ positive: 16.1% vs 8.5%; and 4+ positive: 21.5% vs 16.9%;  $P < .001$ ). Cases were more likely to receive sputum induction as well ( $n = 82$ , 41%, vs  $n = 27$ , 20.3%;  $P \leq .001$ ).

Cases were also more likely to have chest radiographs consistent with classic active pulmonary TB (upper segment of the lower lobe infiltrates, upper lobes infiltrates, pulmonary cavities, or a miliary pattern;  $n = 166$ , 83.42%, vs  $n = 82$ , 60.2%;  $P < .001$ ).

Table 4 summarizes a multivariate Stepwise Logistic Regression model of case status.

## DISCUSSION

Tuberculosis continues to cause significant morbidity in the United States, particularly in Texas and other border states [1]. Although the incidence of TB cases declined overall during 2009–2014, the number of cases increased by 1.6% in 2015 [16]. We found in our study that despite implementation of the CDC guidelines to prevent tuberculosis in health care settings [17], inadequate isolation resulting in potential exposure to health care professionals and patients is common ( $n = 199$ , 59%). Failure to isolate patients with active TB is not uncommon in

North America [18]. A study performed in Canada including 429 patients admitted with active pulmonary TB to 17 hospitals over a 3-year period found that TB diagnoses were initially missed in 45% of cases, and even after 1 week, 30% of the patients were still not properly treated [18]. The treatment costs for patients with TB range from \$28 000 per patient [19] for a patient with drug-susceptible tuberculosis to \$134 000 for MDR TB and \$430 000 for XDR TB [20]. In addition, the cost of TB contact tracing is significant, including the time of frontline staff to compile the list of potentially exposed individuals, the infection preventionist time to coordinate the exposure evaluation and send notification letters to patients and HCP, the time and direct cost to screen HCP for LTBI with tuberculin skin testing or interferon gamma release assays, the costs in time of work lost for HCP and patients during LTBI testing, and the cost of therapy for LTBI infection among those found to be infected among others [21, 22].

In our study, we found that the presence of extrapulmonary TB involvement was associated with significantly lower risk for inadequate isolation and, consequently, less unprotected exposure of health care professionals and patients to TB. Patients with extrapulmonary involvement such as involvement of spine, meninges, and other organs were probably more likely to be appropriately isolated because they tend to be more ill and they may additionally have multi-organ involvement that allows earlier diagnosis upon admission. A previous study in a low-prevalence setting found that patients with pulmonary and extrapulmonary TB involvement had a higher 6-month mortality when compared with pulmonary TB [23].

Being a transplant recipient, having chest radiograph findings considered to be typical for TB such as upper lobe consolidation or cavitary lesions, and sputum positivity for AFB upon staining (graded +1 to +4) were associated with increased risk



of inadequate isolation, and therefore potentially greater likelihood of unprotected exposure of TB bacilli to health care professionals and other patients.

We evaluated whether there was a significant correlation between HIV and TB coinfection and delays in isolation, and we did not find a significant association. In a previously published study, about 28% of chest radiographs performed on HIV-positive patients with culture-positive TB are read as normal [24].

Transplant recipients are at increased risk of developing active TB (especially solid organ transplant patients), and we found that they are more likely to have inadequate isolation in our study. TB diagnosis may be challenging due to the presence of immunosuppression, low sensitivity and reproducibility of tests used to diagnose latent TB infection before transplant, and the potential for atypical presentation [25].

We also found that chest radiograph findings typical for TB (defined as upper segment of lower lobe infiltrates or middle lobe/upper lobe infiltrates, presence of cavitory disease, miliary disease) were associated with increased risk of exposures. Chest radiographs with classic TB findings are not specific (with many non-TB pathologies sharing radiological features) and may be inaccurately interpreted in low-prevalence settings [26, 27]. It is not possible to ascertain why this correlation occurred, but we hypothesize that health care providers are not as familiar with TB given the declining prevalence of this disease, and TB was lower on their differential [18].

Positive sputum staining for AFB was associated with increased risk of unprotected exposure to TB in our study. This could be due to a delay in ordering sputum AFB testing in a patient not initially suspected to have TB. The CDC recommends that patients undergoing testing for TB are placed in respiratory isolation during the evaluation [17].

The main limitation of our study is its retrospective nature. The study was performed at 5 health care systems in a state with a relatively high rate of TB. Because of its retrospective nature, we were not able to standardize criteria for what constituted inadequate isolation at each health care system leading to a contact tracing investigation. We observed that risk of having cases was significantly different depending on the health care system where the patients were enrolled. Different infection control personnel and practices at the various health care systems could result in variability in evaluation. The actual risk of TB transmission is dependent on numerous variables that include patient factors (ie, cavitation on chest radiographs, degree of sputum positivity on the AFB smear), the setting where the potential TB exposure occurred (ie, higher risk in small closed spaces and during prolonged periods of time), and the procedures performed on the patient (ie, respiratory tract manipulation, including intubation). However, this variation between facilities and the different clinical factors that determine actual risk of TB transmission in health care settings is reflective of “real world” issues in tuberculosis control.

Early clinical suspicion and prompt placement in airborne isolation, as well as maintaining the isolation for an appropriate duration warranted by the clinical presentation, are critical for employee safety and to save unnecessary time and effort expended by infection control and employee health staff in tracing contacts and doing follow-up exposure testing.

TB exposure due to inadequate isolation is relatively frequent in health care settings. Our review has shown that HIV infection, transplant recipient status, and classic TB findings on chest radiographs were significantly associated with a TB patient being a source of exposure, whereas extrapulmonary involvement, history of previously treated TB, and admission to a teaching service resulted in earlier clinical suspicion and better timeliness and duration of isolation, leading to fewer potential exposures. Infection control departments in the United States can utilize the results of this study to further refine TB and infection control risk assessments. Because of the substantial costs and resources needed for contact tracing, investigation, and management of exposed individuals in health care systems, the results of this study highlight the importance of TB prevention training and maintaining appropriate clinical suspicion to aid in early diagnosis and appropriate isolation.

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