The large Worksite Tuberculosis exposure; devising a functional risk model

by

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CERTIFICATE OF APPROVAL

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ABSTRACT

Background: In March 2007, an employee at a large call center in Oregon was admitted to the hospital with active tuberculosis disease (TB). The Local Health Department initiated a contact investigation and determined that the patient had been symptomatic since October 2006. *Objective*: We conducted a worksite investigation to identify the number of coworkers who had TB infections resulting from exposure to the index case and to examine the risk of infection by proximity and duration of that exposure to an infectious person. *Setting*: The investigation took place at a call center with >1500 employees. Initial worksite testing of 18 co-workers who participated in new employment orientation with the index case in October revealed that 60% of those screened had new LTBI infection. *Methods*: We compiled a list of all employees who worked at the call center from October 2006 to March 2007. We encouraged current and former employees to be tested with mailings, phone calls, and on-site outreach in an effort to find as many employees infected with TB (latent and active disease) as possible. Information on proximity to the index case and duration of exposure was collected for everyone tested and used as predictors of risk for infection. *Data collection*: tuberculin skin tests (TST's) and/or Quantiferon-gold (QFT-G) blood tests were offered to all employees. We gave employees a self-administered questionnaire that solicited information about demographics, natality, medical history, past TB exposures, smoking history, location during the exposure period, and the duration of their exposure. *Outcome measure*: positive QFT-G or TST results were considered a definitive positive for TB infection. *Results*: During the study period, 1,641 people worked at the call center. Of these, 531 employees were fully evaluated for TB infection and associated risk factors 65 of which

tested positive for new infection (12%). In addition, three secondary cases were diagnosed among the index patient's co-workers. Proximity to the index case was classified as sitting within 1-25 feet of the index case or >25 feet while duration was classified as exposed to the index case for > or < 60 days. Employees who sat close to the index case had a new infection prevalence of 41% and had a relative risk of 3.1 (95%CI: 1.8-4.7); in addition, employees who had worked at the call center >60 days had a new infection prevalence of 17%, and the relative risk of those long-term employees was 2.5 (95%CI: 1.3-4.2). Combining proximity and duration of exposure into a single ordinal variable showed a dose response effect, with those sitting closest to the case for the longest having a new infection prevalence of 43% compared to those sitting elsewhere for a shorter period (new infection prevalence 6%). *Conclusions*: This large open workspace contact investigation showed that (excluding previously infected people) asymptomatic TB infection among employees was no less than 11%. Taken together, proximity and duration of exposure can be a useful dimension for prioritizing contacts to be evaluated in the course of contact investigations after large open workspace exposures.

INSTITUTIONS**:** Washington County Department of Health and Human Services, Hillsboro Oregon; Multnomah County Health Department, Portland Oregon; Tuberculosis Program, Oregon State Public Health Division: TB/HIV department; Oregon Health and Sciences University.

BACKGROUND

In March 2007 the Washington County Department of Health and Human Services investigated a cluster of tuberculosis cases at a local call center that occurred after a man with highly infectious pulmonary TB disease was admitted to a local hospital. The call center housed >1,500 employees in a large, open, single-room divided into cubicles housing multiple employees.

Descriptive Epidemiology of Tuberculosis

Despite advances in medical science over the past century, tuberculosis (TB) is a disease that persists in the United States. The annual incidence has been declining since 1953 when it was 44.0 per 100,000 among whites and 125.8 per 100,000 among people of color. [1] In 2006, the US experienced only 13, 676 reported cases (4.6 per 100,000), a historic low. A resurgence in reported TB occurred during the early 1990's, fueled by the HIV epidemic and decreased public spending on TB control, but a renewed commitment to combating TB by government and local health agencies counteracted the trend, and TB incidence has been declining since. [2] The rate of decline has slowed since 2000 attributed to increased incidence among foreign-born persons. [3, 4]

Tuberculosis Disease

Tuberculosis is primarily a disease of the lungs. The causative bacterium, *Mycobacterium tuberculosis* (MTB), is spread from person to person through the air carried on droplets expelled from individuals with symptomatic infection when they cough, talk, or sneeze. [5] If an exposed person is infected, that infection can evolve in different ways. Most commonly, the infected person's natural immunity sequesters the infection indefinitely, resulting in longstanding asymptomatic infection. People with established, asymptomatic

infection are often said to have latent tuberculosis infection (LTBI). People with LTBI cannot transmit tuberculosis. About 10% of people with asymptomatic TB infection will develop symptomatic disease, otherwise known as active TB disease, during their lifetime when their immune response is no-longer sufficient to sequester and contain the infection. Most people with asymptomatic infection who develop symptomatic disease do so within two years of the original exposure and infection. Occasionally, people exposed to and infected with MTB immediately develop symptomatic disease without passing through an asymptomatic period. This is sometimes called primary tuberculosis, though it is impossible to know definitively whether someone with symptomatic TB disease has primary disease or symptomatic disease that has evolved from asymptomatic infection or LTBI. One of the hallmark symptoms of active pulmonary tuberculosis disease is a productive cough. Depending on room-size and the atmospheric conditions, coughing can send droplet nuclei 2 meters away at 10 meters/second, and sneezing can expel large droplets up to 6 m away before evaporating. [6] With its lighter-than-air traveling capacity, MTB can spread throughout a room by riding on air currents generated by ventilation systems.

People with active disease are given treatment and those latently infected are given prophylactic treatment. Treatment protocols for cavitary pulmonary TB disease include a nine month regimen of multiple TB medications with the goal of curing the disease and reduce the risk of transmission. The recommended prophylactic regimen for TST positive patients is a 6-9 month course of TB medication to which the strain is susceptible. [7] Latently infected people are treated in order to prevent progression to symptomatic disease and subsequent transmission. Protection from progression to active disease is

conferred to approximately 70% of people with LTBI who complete at least six months of treatment [8].

Diagnosis of Tuberculosis

Pulmonary TB disease can be diagnosed by microscopic observation of tuberculosis bacilli within the smeared sputum of the patient after a special staining technique is applied. Although it has been replaced by a newer staining method, the original staining process capitalized on the color-fast properties of *Mycobacterim spp.* after application of a color stain followed by acid wash. Consequently, a sputum specimen consistent with active TB disease is said to contain acid-fast bacilli (AFB). People with pulmonary disease also often have abnormal chest X-rays. Clinical symptoms of TB disease include productive cough, night sweats, weight loss, fever, and fatigue. [9] An active case is defined as a person with a positive skin test and symptoms associated with TB disease, or a positive test with abnormal chest X-ray, or laboratory confirmed TB. Only people with active pulmonary disease can spread the infection to others [5]. Approximately 80% of reported US cases of active TB disease are pulmonary; the remainders affect other organs and are known as extra-pulmonary. [10]

Asymptomatic or latent TB infection (LTBI) can be diagnosed by tuberculin skin testing (TST) in which proteins derived from inactivated bacteria are injected intradermally. When asymptomatic infection is present, the immune system mounts a response resulting in a palpable induration within 48-72 hours. During a contact investigation, an induration of ≥5mm in width is considered a positive result in the US. [5] The Quantiferon Gold (QFT-G) blood test is an interferon-γ blood assay which contains synthetic peptides that simulate two proteins found in the TST. Due to the differences in the antigens between

the two methods TST results can be falsely positive in the presence of previous vaccination with Bacillus Calmette-Guerin (BCG) but QFT-G is not affected by prior vaccination. [11] A positive QFT-G test generally means the person has latent TB infection.

Tuberculosis control and limitations

Reporting cases of TB to the health department is compulsory in all 50 states. The response to cases of tuberculosis by the health department typically begins with evaluation and confirmation of disease. If TB is confirmed, treatment and a contact investigation follow. The contact investigation is a key component in the prevention of TB. The CDC has developed guidelines for contact investigations involving Tuberculosis. If an investigation is deemed necessary, the infectious period and possible sites of transmission and must be resolved. It is then possible to identify the total number of possible contacts. This is followed by assigning priority to the contacts. The priority scheme is used to direct resources to those with the greatest need: 1) secondary cases, 2) recent infections most likely to benefit from treatment, and 3) susceptible contacts who would likely suffer severe morbidity with TB disease. Characteristics used to determine susceptibility include age, immune status, medical conditions and exposure status. Exposure is commonly determined by assigning contacts to one of four exposure scenarios: sharing the space the size of a 1) car 2) bedroom 3) house 4) larger than house with an infectious case. [12] There is no real exposure classification associated with duration of exposure. [13] One author attempted to determine the prevalence and treatment of LTBI from workplace exposures, but found that inconsistent approaches to data collection precluded the ability to apportion the causes of direct infection rates. [14]

Current guidelines lack an empiric and practically applicable definition of a close contact that can be applied in open work areas with many employees like the one we encountered here.

Public health professionals urgently need evidence-based approaches to narrow the scope of some contact investigations, focusing limited resources on those at greatest risk of infections and subsequent transmission. A single person with infectious tuberculosis can expose many other people given the right circumstances. For example, in 1993, a Maryland student was diagnosed with laryngeal and cavitary tuberculosis and over 500 potential contacts were tested; 4% of these were found to have developed new asymptomatic TB infection. [15] Officials also tested an additional 1,400 students who were probably not directly exposed. In a small rural community during 1994 -- 1996 a single person with infectious tuberculosis infected 21 people, some after only a few hours of exposure during two days. All family members, over two-thirds of co-workers, and half of casual contacts were also infected. [16] After the delayed diagnosis of a TB patient in a small community in Maine during 1992--1998, public health officials chose to test nearly 10,000 co-workers and community members; 697 people were newly infected. [17]

Dangers particular to congregate settings

Outbreaks in large open spaces continue to confound public health officials. [2] Examples of such settings include prisons, homeless shelters, and workplaces with numerous employees. During an investigation of an outbreak in a New York prison of multidrug-resistant TB (MDR-TB) in 1991, 30% of 306 screened inmates had skin test conversions and were considered newly infected. [18] Officials investigated outbreaks of TB in two California prison's HIV wards in 1995 & 1996. Eight hundred sixty seven total inmates,

parolees, and prison staff were screened. TB was diagnosed in 29 inmates/parolees with seven secondary cases and 28 asymptomatic converters. [19] In 2002-2003 there were outbreaks in homeless shelters in both Portland, Maine and New York. The New York investigation turned up over 1000 contacts of which 223 among the homeless population and 16 among the shelter staff tested positive for LTBI (not including previous positives). Twenty-nine cases of active TB disease were found. [20] The investigation in Maine reported over 1000 contacts with 56 testing positive for LTBI (excluding previous positives) and 163 required chest radiographs. No other cases of active TB disease were found. [21] Workplace investigations included a meat processing plant in Hawke's Bay which experienced an outbreak in 2002. More than 300 employees were tested. Twenty-nine tested positive for LTBI (excluding previous positives) and 10 had TB disease. [22] An office furniture installation company in the District of Columbia in 2006 saw >500 employees exposed to TB. Over 250 employees were tested, forty-two of which were LTBI positive. There were no other cases of TB disease found. [23] Numerous TB outbreaks have also occurred in other congregate settings including bars, schools, and churches. TB investigations are often limited to a relatively few contacts (i.e. housemates and intimate friends) which health departments around the US deal with regularly. When the disease enters congregate settings, the problem can magnify beyond a point to which local health departments are equipped to handle. Finding better ways to implement targeted testing may serve to mitigate the burden placed on health department resources by the sheer volume of potential contacts.

Predicting Risk

Quantitative models to predict infection risk for large open workspace environments have

been developed but remain of limited practical use in applied settings. The first attempt at modeling transmission of airborne infection, the Wells-Riley model, calculates the relative infectiousness of contagion. [24] This model is based on assumptions such as the presence of a steady-state environment and is therefore limited in its practical application. The Gammaitoni-Nucci model builds on the Wells-Riley model and allows for more variability in exposure conditions and is regarded as a better method for simulating TB outbreaks in enclosed space environments. However, it requires information that may not be readily available (if ever) until well into an investigation [25, 26]. Even with the improvements made to models over time such as the non-steady state Wells-Riley model which accounts for ventilation schemes common to modern office buildings, the model does not incorporate more personal factors like proximity to the disseminator and individual susceptibility. [27] More general, practical methods for *a priori* prediction of infection risk among contacts based on typically available attributes of the case and contacts is still needed.

No practical evidence-based protocols are available for assessing the risk of individuals or groups relative to an index case in large open workspaces housing many employees. Duration and proximity have each been found to be significant predictors of risk in separate situations, but only one study has found significance with both variables together, however that was for much shorter exposures within smaller rooms. [12, 28, 29] More information is needed to better understand the effect of proximity *and* duration of exposure on disease distribution patterns.

Large open, workspaces present a unique prevention challenge to combating outbreaks of tuberculosis. In these types of work areas an employee with infectious tuberculosis

can expose many people while talking with coworkers or clients, continuously expelling infectious particles into common airspace. We hypothesized that that the closer someone worked to an index case and the longer they did so, the greater the likelihood of TB infection, after controlling for other factors.

Study Objectives

The purpose of this study was to measure the relationship between proximity of workstation to an infectious TB case in a large, common workspace and duration of employment and acquisition of new TB infection. Large, common work spaces housing many employees will probably increase with globalization, outsourcing, functional modulization, and increasing need for highly specific technological support. Cases of infectious tuberculosis occurring in situations such as this might become more common as these low-paying jobs fall to foreign-born workers with higher incidence of TB.

METHODS

Population/Setting

The Index Case

A US-born male, aged 41 years, presented to his primary care physician in February of 2007 with a chronic cough, night sweats, fever, and weight loss. The patient also reported having recently received azithromycin for presumed community acquired pneumonia, which did little to relieve his symptoms. A chest x-ray showed a cavity in the right upper lobe of the lung. The patient's symptoms worsened, and he presented to a local hospital following what would be his last day of work in early March 2007 and was admitted for suspected tuberculosis disease for further evaluation and treatment. Acid-fast bacilli (AFB) were observed in his sputum, and the sputum cultures grew *Mycobacterium tuberculosis* that was sensitive to all standard TB drugs. The hospital reported the

case to the local health department for case-management. The Washington County Health Department began a contact investigation in mid-March. The index patient had five household contacts all of whom were tested by TST. Applying CDC guidelines the public health staff determined that the presumptive exposure period coincided with the commencement of the patient's employment at the call center (October 2006). [10]

Case definition

New LTBI cases were defined as those who tested positive either by TST or QFT-G and had no history of past positive TST or indications of active disease. A person was considered to be infected if a TST resulted in an induration ≥5 mm or had a QFT-G result ≥1.5 IU. [5, 30] If a negative or equivocal TST were contraindicated by QFT-G, the positive QFT-G was considered a definitive positive. People with a previous positive TST were evaluated for TB disease by symptom review and chest radiograph, but were not included in the analysis. Secondary active cases were defined as anyone with a positive TST/QFT-G and symptoms associated with TB disease, or a positive test with abnormal chest X-ray, or laboratory confirmed TB.

Study population

Initially, we offered testing to all employees we could contact who worked at the call center any time during the period October 2006 through March 2007. TST's were offered to most while QFT-G's were offered to those who received the BCG vaccine (to address possibility of false positives) or reported a history of positive testing. If an individual had an equivocal TST or was highly symptomatic and tested negative by TST, a QFT-G was drawn for confirmation. QFT-G was also used later in the investigation as an incentive to get people in for testing; the incentive being a person would only need to come in once for a blood draw rather than twice as for a TST (once for planting the antigen and

once for reading the results). We identified employees by the workgroups to which they had been assigned and by time periods they had worked with each group. After results were available from the first few rounds of testing, we identified workgroups which surpassed an arbitrary minimum threshold of positive TST or QFT-G rates and made members of those groups who had yet to be tested the highest priority for subsequent efforts. This was decided in the interest of time and resources with the understanding that testing would still be available to all other workgroups should they seek it out. Workgroups not meeting the threshold were designated "low priority."

This high/low priority classification affected how diligently we sought contacts who were no longer working at the call center. We sent a letter to high priority contacts describing the exposure, called them at least three times, and searched for them on Social Networking Sites before we abandoned efforts to contact. In addition, we asked high priority contacts who were current employees and declined testing to sign waivers stating that they understood the risk that they were taking. We sent letters to low priority contacts describing the exposure and offered screening services should they require it, but made no additional efforts to screen them.

For purposes of studying the relationship between proximity and duration of exposure and new TB infection, we included all employees who had a positive or negative QFT-G result or TST result after May 8, 2007 (8 weeks after last possible exposure).[13] We excluded those employed who reported having had a previous positive (size of induration not specified or verified) TST, and foreign-born persons who tested positive with no history of prior testing and who emigrated from countries with high TB prevalence. The remaining subjects who tested positive we considered to have new TB infection, that

is, they contracted TB infection as a result of the call center exposure.

Data Collection

From March through June of 2007 we conducted TST and/or QFT-G testing and collected questionnaires at five clinics at the call center to test employees for TB infection; in addition, we tested some employees in field locations and at the health department.

We gave each screened employee a self-administered questionnaire just prior to testing [See appendix B]. Variables gathered from the questionnaire included race, age, country of origin, medical risks, smoking history, date of hire/termination (duration of exposure), workgroup (proximity), gender, and symptoms.

A person was considered eligible for the study only if tested after May 8, 2007 and the accompanying questionnaire was completely filled out in regards to the risk factors under review. The health department, anticipating problems related to self-reporting, obtained a complete list of hire and termination dates for all employees from the human resources department of the call center. These records were cross-referenced to the exposure period thus serving as a proxy for duration of exposure.

Statistical Analysis

Exposure classification

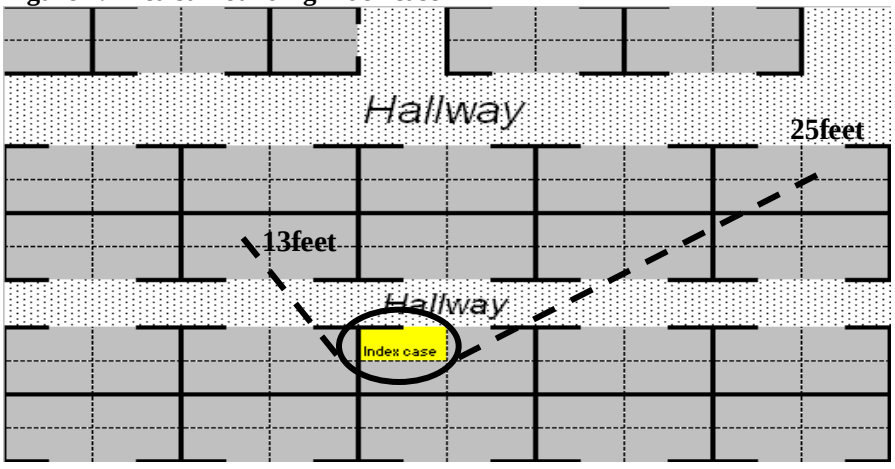
The unit of measure for duration of exposure was days. We decided *a priori* to examine the duration variable in intervals of 7 days (week), 30 days (month), 60 days (2 months), and as a continuous variable. We will examine the distribution characteristics of duration as a continuous variable to evaluate whether it is appropriate as a measure of duration in this outbreak. The intervals were chosen because they would make intuitive sense to health department officials dealing with an outbreak. We conflated the concepts of

race and ethnicity into a single dichotomous variable defined as white (non-Hispanic) and other, and recorded age as a continuous variable. Country of origin was also conflated into US-born and foreign born (dichotomous).

We assigned employees working within one cubicle (1-13 feet) of the index patient to the first proximity level, employees working within two cubicles (14-25 feet) were assigned to the second proximity level, and everyone else we assigned to a third, 'distant' proximity level. These parameters will be examined as a 3-level stratified variable. The Human resources department provided us with and exact seating chart in the area surrounding the index case (see figure 1) allowing for the concentric ring analysis. People who attended the new employment orientation group spent multiple weeks within 14-25 feet of the index case, and therefore, were included in second proximity level.

We also explored the possibility that when analyzed together and compared to a referent group duration and proximity will show risk increases an absolute amount when either duration increases or an individual moves closer to the index case. We did this by creating "dummy" variables and including them in the multivariate model and also tested the resulting strata for trend using a chi-square test.

Figure 1. Area surrounding index case



Regression Analysis

We examined categorical risks factor using frequencies, proportions and univariate logistic regression. We explored continuous variables using histograms, descriptive statistics, and univariate logistic regression. Non-significant variables were eliminated from the model by setting the univariate regression p-value at <.15 for statistical significance, and we looked for possible interactions between age, gender, race, and natality. We calculated strength of independent risk of TST conversion for proximity and duration of exposure adjusted for potential confounders and covariates using multivariable logistic regression. We used $p<0.05$ thresholds for backwards selection of independent variables. Since the incidence in the study population was >10% and the odds ratios' were greater than 2.5, OR was not the better measure of "true risk" and so were corrected using the Zhang approach [31]:

$$RR = \frac{OR}{(1 - P_0) + (P_o \times OR)}.$$

All analyses were performed using SPSS statistical software (16.0 Version, SPSS Inc., Chicago, USA).

RESULTS

Population/Setting

Study Population

A total of 93 (15%) tested individuals were excluded from the study pursuant to the exclusion criteria. These included eleven employees with a history of previous infection, twelve people from countries with high TB prevalence and no testing history, and seventy individuals with incomplete questionnaires (see figure 2).

The demographic characteristics of the population eligible for the study are presented in

Table 1. Seventy-one (13.4%) were newly infected. Mean age was 33±11.7 years old. The population was predominantly white non-Hispanic (79.9%). and 65% was male. TST

Table 1. Demographics and LTBI in Screened Population

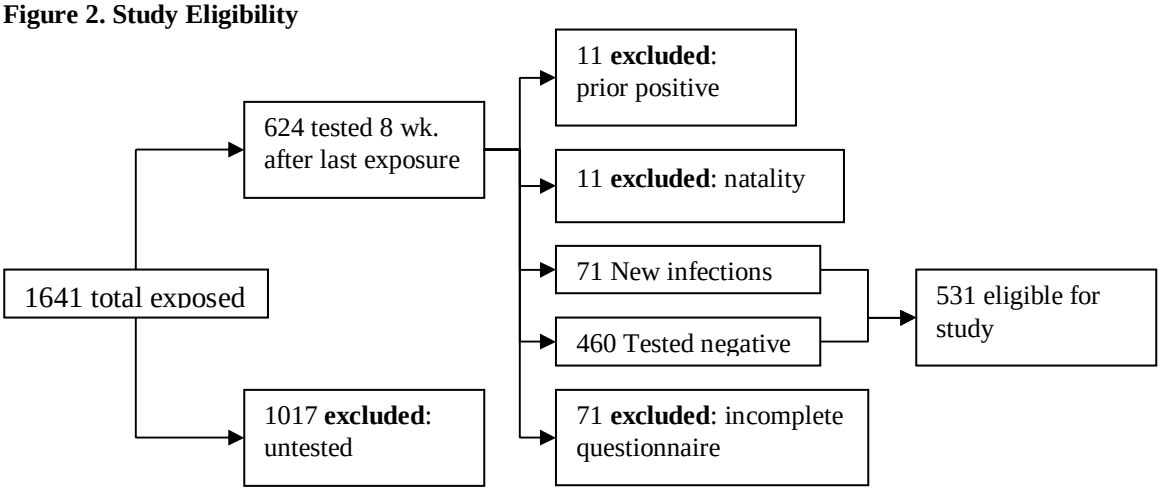
		PPD/QFT-G results			
	Total (n=531)	Positive (n=71)	Negative (n=460)	OR (95%CI)	P-Value
Age (years)					
Mean ± SD	33.2± 11.7	32.79±9.2	33.21±9.2	1.0 (0.98-1.0)	0.78
Range	17-75				
Gender, n (%)					
Male	347 (89.6)	57 (16.4)	290 (83.6)	Referent	0.006
Female	184 (34.7)	14 (7.6)	170 (92.4)	0.42 (0.23-0.78)	
Race, n (%)					
Caucasian (non-Hispanic)	476 (89.6)	55 (11.3)	421 (86.8)	Referent	0.001
Other	55 (10.4)	16 (29.1)	39 (70.9)	3.1 (1.6-6.0)	
***Foreign Born, n (%)**					
No	487 (91.7)	60 (12.3)	427 (87.7)	Referent	0.003
Yes	33 (6.2)	†10 (30.3)	23 (69.7)	3.1 (1.4-6.8)	
Proximity 1, n (%)					
>25 feet	487 (91.7)	53 (10.9)	434 (89.1)	Referent	>.0001
<25 feet	44 (8.3)	18 (40.9)	26 (59.1)	5.7 (2.9-11.0)	
Proximity 2, n (%)					
>25 feet	487 (91.7)	53 (10.9)	434 (89.1)	Referent	**>.0001
14-25 feet	26 (4.9)	8 (30.8)	18 (69.2)	3.7 (1.5-8.8)	.004
1-13 feet	18 (3.4)	10 (55.6)	8 (44.4)	10.2 (3.9-27.1)	>.0001
Duration 1 (%)					
1-30 days	85 (16.0)	6 (7.1)	79 (92.9)	Referent	**.016
31-60 days	94 (17.7)	6 (6.4)	88 (93.6)	0.9 (0.3-2.9)	0.86
61-90 days	43 (8.1)	9 (20.9)	34 (79.1)	3.5 (1.2-10.6)	0.03
>90 days	309 (58.2)	50 (16.2)	259 (83.8)	2.5 (1.1-6.1)	0.04
Duration 2 (%)					
1-60 days	179 (33.7)	12 (6.7)	167 (93.3)	Referent	
>60 days	352 (66.3)	59 (16.7)	293 (83.2)	2.8 (1.5-5.4)	0.002
Duration 3 (%)					
† 7 days					0.6

*Country of origin unknown for 2.1% of respondents
† overall significance of 15 stratified weeks
**overall significance of univariate analysis

positivity was higher among males (16%) than females (7.6%). Ninety-two percent of the screened population was born in the United States twelve percent of which were positive for TB infection.

We gathered test results from 592 employees after the first few rounds of testing (before the 8 week cutoff date). Three of the twenty-nine workgroups had positivity rates that surpassed the minimum threshold and were subsequently designated “high priority”. All other workgroups were designated “low priority”. As the investigation continued the numbers which resulted in each workgroup’s priority designation was revisited, but the minor fluctuations in positiviy rates did not call for redesignation of any workgroup’s priority rating. This meant that of the 1,641 people employed during October 2006 – March 2007, 589 (36%) were high priority and 1,052 (64%) were low priority. Six-hundred-twenty-four had valid test results: 56% (330) of high priority employees and 9% (294) of low priority employees. Of these, 531 were considered eligible for the study; 273 from the screened high-priority employees and 258 from the screened low-priority employees [see figure 2].

Figure 2. Study Eligibility



Data Collection

Ninety percent of the testing and questionnaire data for the study was collected during the four months following the initiation of the investigation. The remaining 10% was collected through follow-up effort by the local health department.

The Workplace

The workplace was a two-story corporate building with the call center occupying the entire second floor. The call center occupied 100,000 sq. ft and housed 1,641 employees comprised of contract employees, environmental and cafeteria staff, and a small subset of off-site service providers (e.g. people who serviced vending machines) who spent time at the site during the exposure period [See Appendix A for call-center layout]. In December of 2006 (halfway through the exposure period) there was a generalized relocation of some of the workgroups including the one to which the index case belonged. This reorganization had minimal effects on the investigation.

The great majority of cubicles measured either 10 x 10 or 8 x 12 ft. and was high paneled. The large cubicles housed four workstations while the row end-caps contained one or two workstations. Occupational and Safety and Health Administration (OSHA) inspected the ventilation system. Airflow was not shared between the call center and other parts of the building. A preliminary assessment found the HVAC systems serving the building did no appear to present an unusual risk of dispersion of TB organisms.

Statistical Analysis

Exposure Classification

Duration was measured as a discrete rather than continuous variable as frequency statistics showed a disproportionate number of employees were present during the entire exposure period. Univariate analysis of the one week stratification of duration was shown to be non-significant overall (p=0.6). The thirty day intervals were found to be significant overall (p=.016). On further examination however, we found that there was no significant change in risk between an exposure of 1-30 days and 31-60 days (RR=1.1; CI: 0.4-2.9), similarly there was no significant change in risk between 61-90 days and >90

days (RR=1.3; CI: 0.7-2.1). As a result we collapsed the first two terms into a single duration length of 1-60 days We also collapsed the last two terms into a single duration of >60 days. When proximity was examined as a three-level stratified variable, there was an overall increase in risk for level-one and level-two when compared to those further away (p>.0001) [see table 1]. It was also found, however, that there was no significant change in risk when comparing the people in level-one to the people in level-two (RR=0.4; CI: 0.1-1.1). Level 1 and 2 were thus collapsed creating a dichotomous variable with strata classified as within 1-25 feet and >25 feet. The final proximity measures were then combined with the final duration measures into: >60 days/1-25 feet, 1-60 days/1-25 feet, >60 days/>25 feet, 1-60 days/>25 feet which were then conflated into a single dummy variable for analysis.

Regression Analysis

The variables were examined for possible interactions between risk factors; none were found. After the exclusionary criteria (P<0.15) was applied to the variables from univariate regression gender, race, proximity, and duration achieved significance and were added to a multivariate model. When included in the final model, country of origin was not a significant predictive factor at the p<.05 level however clinical and public health judgment tells us that country of origin is important in predicting risk for TB so the variable was returned to the model. Table 2 lists results of multivariate LTBI by proximity and duration of exposure, controlling for race, and gender, and country of origin, the variables which comprised the final model. We found no significant association between risk and age. Those who were in close proximity had three times the risk of acquiring infection than those located elsewhere in the room (RR= 3.1; CI: 1.8-

4.7). Employees who were present for greater than 60 days also had a significantly increased risk in acquiring infection (RR= 2.5; CI: 1.3-4.2).

Table 2. LTBI by Proximity and Duration Controlling for Gender, Race, and County of Origin

	OR (95% CI)	p-value
Proximity		
>25 feet	Referent	<0.0001
1-25 feet	4.2 (2.1-8.5)	
Duration		
1-60 days	Referent	.005
>60 days	2.8 (1.4-5.6)	
Gender		
Male	Referent	.005
Female	0.4 (0.2-0.8)	
Race		
White	Referent	.044
Other	2.3 (1.0-5.1)	
Foreign Born		
No	Referent	.161
Yes	2.0 (0.8-5.3)	

A strong positive trend was observed in the paired exposure parameters of duration and proximity (chi-square p-value <.0001). An increase in risk was observed for those who were within 1-25 feet of the index case for >60 days (OR: 11.1; CI: 4.5-27.5) compared to someone who was seated far away and was present for less than 60 days.

Combining duration and proximity variables showed a dose response effect with each progressive exposure (see table 3) showing an increase in risk. For “short term” exposures adding proximity increased risk 19%, and when a “long term” exposure is added to proximity risk is increased by 17%.

Within the group considered to be at highest risk, the positivity rate was approximately 40% while the group used as a referent group representing “background” rates had a positivity rate of 6.0%.

Table 3. Trends for proximity and duration		
	OR (95%CI)	% positive
>25 feet & 1-60 days	referent	6.3
>25 feet & >60 days	2.9 (1.4-6.0)	13.5
1-25 feet & 1-60 days	8.0 (0.66-96.9)	25.0
1-25 feet & >60 days	11.5 (4.6-29.1)	42.5
X^2 for trend: p-value <.001		

DISCUSSION

The results of the analysis support our hypothesis that there is a physical and temporal demarcation where risk for TB infection increases significantly in a large room, long term exposure. Proximity appeared to have the greatest influence over risk of contracting TB; contacts within twenty five feet of the index case had three times the risk of infection than others in the room. Prior studies have shown proximity is a valid predictor in a large single-room workplace, but only as a function of a room assessed in quarters where contacts designated as most at risk were in the same quarter an infectious individual. Our study shows a more defined "zone of risk" would be a plausible measure of risk in similar situations. [29] Duration of exposure was also a significant predictive factor in the acquisition of new LTBI. Employees who were present during at least half of the exposure period had twice the odds of acquiring LTBI than employees who were present for less than half of the exposure period. When proximity and duration were taken together a clear trend of increasing risk was observed as relative distance from the index case decreased and duration of exposure increased, suggesting that both must be taken into account if targeted testing is implemented in a TB outbreak investigation.

The rearrangement of workgroups midway through the exposure period likely had a limited effect on the proximity exposure classification. Movement outside the 25

foot radius surrounding the index case would be irrelevant as their ">25 feet" classification would not change. The locations of positives were recorded pre and post move and everyone within the 25 foot radius was in the same workgroup and thus would have moved in tandem with the index case. This one-time rearrangement of workgroups, however, undermined the chances for more accurate proximity measurements within the lower risk group and for greater precision of duration categorization.

Employees who were considered low risk (1-60 days/>25 feet) had rates of LTBI which were slightly higher than expected among the background population in the US. Potential explanations include undetected contact with the index case, environmental conditions within the building that provided the opportunity for unusually widespread infection, or baseline prevalence of LTBI in this group that was higher than the local general population. In similar settings, brief exposure to infectious cases in similar workplaces resulted in conversion [25, 32] suggesting that casual undetected exposure is one explanation for unexpectedly high TST/QFT-G positive test rates among the employees at lowest risk. We believe that *extensive* undetected contact with the index case in this setting is unlikely, but intermittent brief contact cannot be excluded. The habits of the index case could have introduced differential bias. In interviews, the index case reported repeated use of the pool table in the recreational area. He also reported being a smoker and the smokers at the call center generally used a single dedicated area outside the building for smoke breaks. If anyone shared in these activities with the index case on a regular basis it could result in a systematic under-estimation of risk among those people as informed by proximity. The index case had difficulty in recalling anyone specifically who may have participated in these activities with him outside people's whose

exposure had already been accounted for. This recall difficulty suggests that repeated exposures may not have occurred. Ventilation systems in the call center were well maintained and functioning properly, but sheer size of the room could have been a contributing factor in spreading the contagion. The existence of eddies in air flow and/or areas where there is little or no circulation of air within the room are possible were not investigated. In addition, people of lower socioeconomic status, like most of those employed at this call center have been shown to have higher prevalence of LTBI [33]. Age is also a known risk factor for TB conversion but when accounted for in the analysis, it was not a significant contributing factor to the risk of developing TB infection. [34] There were some indications during the contact investigation that a number of individuals who worked at the call center have experienced either homelessness or incarceration, both of which are circumstances which increase risk of acquiring LTBI. [18, 19, 20] This is another possible source of increased background LTBI infection. Since screening was voluntary and all persons with completed screening forms were used for the study it is unlikely selection bias on the part of investigators played a part in inflating background rates.

The information gathered in this investigation could be useful to Public Health officials. In this outbreak, prioritizing screening to those at moderate and high risk (excluding those not in close proximity and who were present for <60 days) would have measurably lessened the expenditure. This must be weighed against the possibility of missing cases; in the case of this investigation, three cases of new LTBI would have been missed had the low risk group not been included in screening.

There is a potential for problems with external validity as not all space-specific

outbreaks will have the same physical characteristics, however many modern office buildings share similar ventilation schemes [27]. There is strong evidence of an association between ventilation and air movement and the spread of infectious disease, though nothing substantial specifying what a minimum safe air exchange rate may be has been demonstrated [35]. In the case of the call center, Occupational and Safety Health Administration (OSHA) confirmed the ventilation system met industry/performance standards.

We were disappointed in the proportion of employees that we successfully screened and that completed the questionnaire. In the future, better approaches to motivating people to cooperate with contact investigations would be very helpful.

SUMMARY/CONCLUSION

Proximity is strongest predictor of risk in this type of single-room exposure situation. A person within 25 feet is at 3 times the risk of acquiring TB than those further away after accounting for gender, race, and natality. Duration is also a significant predictor of risk. Someone exposed for >60 days has 2 ½ times the risk of acquiring infection than someone exposed for less. Also, a person within 25 ft. of an infectious person for >60 days has a 19% greater chance of acquiring infection than if they were so for <60 days. Someone seated further away from an infectious person has a 17% greater chance for infection if they are exposed for >60 days. Using these measures will allow public health officials to more effectively target people who need testing in a long term single room Tuberculosis exposure, saving time and resources while simultaneously sparing more people from inconvenience and needless testing.

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APPENDIX A: FLOOR-PLAN OF THE CALL CENTER

Appendix B: Survey Tools

TB Screening for Worksite

Employee Name:		**Date of Birth:**	
Mailing address:			
Home phone		**Cell phone:**	
Do you have medical insurance?	Yes		No
What is the name of your primary health care provider? (Doctor)			
Race/Ethnicity:			
Place of birth:			
If you were born outside the United States, what year did you first move to the U.S.?			
Have you ever received Tuberculosis (TB) vaccine - BCG?	Yes	No	
What is your contract workgroup:			
What date did you start working for Stream in Beaverton:			
What is your <u>main</u> reason for being tested today: ☐ **I am a member of the client team in which the person with TB worked.** ☐ **I was informed that I spent time in the workstation area where transmission is suspected to have occurred.** ☐ **I am concerned that I may have been exposed.** ☐ **Other:_____**			

Have you ever had a TB skin test before? **If "YES",** **<u>Where</u> was this test done? And <u>When</u> was this test done?**	**Yes**	**No**
What were the results of your TB skin test?	Negative test	Positive Test
Have you ever been treated for inactive (latent) TB infection?	Yes	No
Have you ever been treated for active TB disease in the past.	Yes	No

Are you having any of the following symptoms that have <u>lasted for more than 3 weeks?</u>	**Yes**	**No**	**Comments** **(When did it start? How long has it lasted?)**
Fever			
Coughing phlegm			
Coughing blood			
Unexplained fatigue			
Unexplained weight loss			
Drenching night sweats			

Do you have any of the following medical conditions:		
Are you a smoker	**YES**	**NO**
• Diabetes	**YES**	**NO**
• HIV/AIDS, other serious immune system problems or immunosuppressive therapy	**YES**	**NO**
• Organ transplant		

I have received, read & had questions answered about the TB skin test. I request that this TB test be given to me.

_____

_____

Employee Signature **Date**

Name:_____

**********FOR HEALTH DEPARTMENT USE ONLY**********

□ **TST is not applied. Employee gives a credible history of past + TST:** *(Describe):*		
TST Applied:		
Date TST administered:		
MFG: Aventis Pasteur	**Lot #:**	
Site of TST:	**LFA**	**RFA**
Test applied by ***(signature):***		
Return Visit for Test Results		
Date Read:	**Skin Test Results in mm:** **mm**	
Test read by ***(signature):***		
Refer for chest x-ray:	**YES**	**NO**
Radiology Facility:	**Body Imaging**	**Tuality Hospital** **St. Vincent's**
Other comments:		

STREAM (2007) First Name_____ Last Name_____

date of birth___/____/___ race/ethnicity_____ sex ❑ M ❑ F

phone (work)_____ phone (cell) _____

phone(home)_____

address_____ city_____ state_____

zip_____ county_____ email_____

country of birth_____ year moved to US (if not born in US)_____

	Y	**PREVIOUS EXPOSURE...**
A	❒	Do you have medical insurance?
B	❒	Do you have a primary care physician *If yes*, name of physician?_____
C	❒	**Have you ever been tested for tuberculosis**? *If yes*, In approximately which year were you last tested?_____
G	❒	Result of last TB test? D ❒ Pos E ❒ Neg F ❒ Don't Know
		Ever treated for tuberculosis disease (usually a prolonged physical illness and treatment with at least 4 medicines for (6 – 12 months)
h	❒	*If yes*, when (year)?_____ *Where?*_____
		Ever treated for tuberculosis exposure (infection) (usually no symptoms of illness physical illness; treatment with a single medicine for 6 – 9 months)
		If yes, when (year)?_____ W*here?*_____ *Where?*_____
i	❒	Have you been a smoker while working at Stream

	Y	**MAIN REASON FOR BEING TESTED…**
A	❒	Member of client team in which a person with TB worked.
B	❒	Informed that I spent time in the workstation area where transmission is suspected to have occurred.
C	❒	
D	❒	Concerned that I may have been exposed.
		Other (explain)_____ _____

Have you had any of the following signs and symptoms for more than 3 weeks during the past 6 months?

	Y	
A	❒	productive cough
B	❒	fever
C	❒	unexplained weight loss
D	❒	unexplained fatigue
E	❒	drenching night sweats
		explain_____

Have you ever been diagnosed with any of the following diseases or conditions?

	Y	?	N	
A	❒	❒	❒	diabetes
B	❒	❒	❒	cancer
C	❒	❒	❒	HIV/AIDS, other immune disease
D	❒	❒	❒	
E	❒	❒	❒	organ transplant
				other chronic disease explain_____ _____

WORK GROUPS

What is/was your contract workgroup_____

Date of Hire_____ Last Day of Work_____

Consent for Testing

(No previous skin test or previous negative skin test)

I have received and read information, and had questions answered about the TB skin test. I request that the TB skin test be given to me.

_____

_____

(Signature) (Date)

(Previous positive skin test)

I have received and read and had questions answered about the Quantiferon-Gold Blood Test for TB. I request that blood be collected from me for the Quantiferon-Gold test. Washington County Health Department will give me the results of my blood test when I phone for my results in 2 weeks.

_____

(Signature) (Date)

(If either of these tests show signs of tuberculosis infection, Washington County Health Department will notify me of the next steps necessary to make sure that I don't have tuberculosis disease. If I am discovered to have tuberculosis infection or disease, Washington County Health Department will make a recommendation about treatment.)

Health Department Use Only) First Name_____ Last Name_____

SKIN TEST#1 Lot #_____Site *A* ❒ LFA *B* ❒ RFA Applied (signature)_____ Date Placed ____/____/____ Date Read ____/____/____ Size _____(mm) Read(signature)_____	**SKIN TEST#2** Lot #_____Site *A* ❒ LFA *B* ❒ RFA Applied(signature)_____ Date Placed ____/____/____ Date Read ____/____/____ Size_____(mm) Read(signature)_____
QUANTIFERON TEST #1 Date Collected ____/____/____ Result *A* ❒ Neg *B* ❒ Indet (high nil) *C* ❒ Indet (low control) *D* ❒ Insufficient or not run *E* ❒ Pos _____(IU/m	**CHEST X-RAY #1** Date Collected ____/____/____ Facility *A*❒ Body Imaging *B*❒ Tuality Hosp *C*❒ St. Vincent Result *D* ❒ Normal *E* ❒ Abnormal (explain)
PREVENTIVE TREATMENT FOR LATENT TUBERCULOSIS *A* ❒ Not indicated *B* ❒ Declined *C* ❒ Contraindicated (exp)_____ *D* ❒ Started (date) ____/____/____ Medication *E* ❒ INH *F* ❒ Rifampin *G* ❒ Other *H* ❒ other Dose *I* ❒ 300mg *J* ❒ 600mg *K* ❒ other Other Med_____Other dose_____ Stop Date ____/____/____ (notes)	Reason for Stopping *L* ❒ Completed 6 mos *M* ❒ Completed 9 mos *N* ❒ Adverse Reaction (exp)_____ *O* ❒ Patient decision *P* ❒ Active disease