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Elizabeth N. Smith April 20, 2015

Change in Chest Radiography and Examination of Clinical Features to Identify Pulmonary Tuberculosis in a Haitian Prison

By

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Master of Public Health

Epidemiology

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Anne Spaulding, MD, MPH

Committee Chair

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B.S.

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in Epidemiology

2015

Abstract

Change in Chest Radiography and Examination of Clinical Features to Identify Pulmonary Tuberculosis in a Haitian Prison

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Introduction: TB is a major cause of morbidity and mortality among prisoners worldwide. Prison environments are often conducive to tuberculosis transmission due to overcrowding, poor ventilation, and limited access to medical care and tuberculosis treatment. This study aims to determine if there is active tuberculosis transmission in a Haitian prison and to identify features that are most indicative of progression to active TB disease.

Methods: Data was collected from chest radiograms and BMI measurements taken of 309 prisoners in a Haitian prison during routine health screenings. Univariate and multivariate logistic regression analyses were conducted to identify predictors of TB by chest X-ray (CXR) and GeneXpert analysis.

Results: Univariate predictors of TB positivity by CXR were decreasing length of incarceration; multivariate predictors were decreasing incarceration time and BMI ≤ 20 kg/m^2. Univariate predictors of TB positivity by GeneXpert analysis were age, increasing length of incarceration, and any positive CXR reading. BMI ≤ 20 kg/m^2 and length of incarceration over 2 years were examined in a multivariate model to determine their suitability as predictors of TB positivity by GeneXpert and both were found to be significant.

Conclusions: Length of incarceration may not be a suitable predictor of TB positivity by CXR but may be a suitable predictor of TB positivity by GeneXpert. Length of incarceration and BMI ≤ 20 kg/m^2 are easy covariates to obtain in the prison setting and can be used to improve selection of high risk persons for TB screening. Active transmission of TB cannot be determined from the available data. Therefore, improvement of health and nutritional status, implementation of infection control practices, and reduction of overcrowding should be all performed to reduce TB incidence in the absence of more targeted TB reduction approaches.

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Acknowledgements

I'd like to thank Dr. Anne Spaulding for her encouragement and support during my time at Rollins and Dr. John May and the Health through Walls staff for their logistical support and their hospitality during my visit to Haiti. Thanks also to Benjamin Ide for his love, friendship, and encouragement.

Contents

Introduction

Pulmonary tuberculosis (TB) is a major cause of morbidity and mortality among prisoners worldwide. TB incidence in prisons is on average 23 times higher than TB incidence in the general population and can be up to 81 times higher. This is partially due to prison populations being disproportionately drawn from populations that have a high risk of TB: the homeless, substance-abusers, and those of low socioeconomic status. Also, prison environments are conducive to tuberculosis transmission due to overcrowding, poor ventilation, close contact between prisoners, prison staff, and visitors, and limited access to medical care and tuberculosis treatment (1,2). Prison conditions can worsen the health status of inmates—causing, for example, malnutrition and stress—which increase likelihood of infection.

This analysis examines TB in the Bois Verna cell block of the Prison Civile in Port-au-Prince, Haiti. The discovery of an MDR-TB infected person prompted aggressive screening of the entire cell block and lead to the discovery of 5 additional cases of TB, including one with rifampin resistance. Through analysis of demographic, penal, and clinical characteristics of the prisoners, the investigator seeks to answer the following questions:

1. Is there active transmission of TB in Bois Verna?
2. What factors are predictive of high likelihood of TB diagnosis?
3. Is change in BMI predictive of abnormal chest X-ray (CXR) or positive GeneXpert results?

Background

Natural History of Tuberculosis

The *Mycobacterium tuberculosis* complex, consisting of *M. tuberculosis*, *M. bovis, M. africanum, M. canetti, M. caprae, M. microti,* and *M. pinnipedii,* cause disease in a variety of mammal hosts (3). Human infection is due mainly to *M. tuberculosis* and occurs when airborne droplet nuclei containing tubercle bacilli are inhaled. Bacilli are engulfed by alveolar macrophages upon entering the lungs. A protective outer mycolic acid layer allows the bacilli to survive and multiply, undetected and undamaged by host defenses (4). *M. tuberculosis* inhibits apoptosis, instead inducing necrosis of the macrophage by which bacilli are released and spread to other macrophages (5,6). Bacilli can also be released into the bloodstream where they travel to and infect the nervous system, bones, joints, or organs. Infections in these sites are forms of extrapulmonary tuberculosis (7).

Active infection ends with the initiation of the adaptive immune response wherein infected macrophages are walled off inside granuloma (8). Inside granuloma, bacilli persist in a dormant state known as latent tuberculosis infection (LTBI). Approximately 10% of immunocompetent persons undergo granuloma necrotization or caseation in which the bacilli are released and rapidly begin multiplying (9). This progression from LTBI to active disease can take months to years to occur. In immunocompromised persons, the immune system cannot stop the multiplication of the bacilli in the initial infection, leading to a more rapid progression to active disease (10). In some instances, progression to active disease may be caused by exogenous reinfection rather than reactivation of the original strain (11,12).

Risk Factors

A person with active pulmonary or laryngeal TB can expel infectious droplet nuclei when coughing, sneezing, singing, and shouting. The droplet nuclei can remain suspended in the air for several hours. Transmission is dependent on 1) the susceptibility of the exposed person, 2) the infectiousness of the person expelling bacilli, 3) environmental factors, and 4) the proximity, frequency, and duration of exposure (10).

Lönnroth et al. (2010) describe downstream biological, genetic, physical, social, and economic risk factors that affect transmission and interrelate to form a causal web that determines likelihood of infection with and progression to active TB disease. These factors are ultimately affected by upstream international and national determinants such as globalization, urbanization, and inequitable economic, social, and health systems (13).

The integrity of the immune system plays a vital role in determining the susceptibility of a person to development of active TB. Advanced age, comorbidities such as HIV and diabetes, lung diseases, malnutrition, and alcoholism can weaken the immune system and increase the likelihood of developing active disease and severe consequences thereof. Tobacco smoking and indoor air pollution can impair the host's ability to clear bacilli from airways due to cilia damage. Stress and depression are also theoretical risk factors due to their potential to reduce immune function.

Concentration of infectious droplet nuclei, limited space, inadequate ventilation, and limited air circulation are among environmental factors related to TB transmission. These are especially relevant risk factors among the urban poor and in many prison settings. In overcrowded prison environments, at least 60% of contacts inhaling airborne bacilli could become infected—double the average in non-incarcerated populations (14).

Barriers to accessing, affording, and adhering to adequate TB treatment regimens are among social and economic risk factors. WHO enumerates four barriers to accessing health care among the poor: economic, geographic, sociocultural, and health system-related (15). Centralized TB centers can make it difficult for TB patients to obtain the care they need. Costs incurred by traveling, missing work, seeing a physician, and buying medicine can be as high as 70% of annual per capita income (13). Lack of health awareness, misunderstanding of the disease, or fear of social stigma can prevent people with TB from seeking treatment. Even when people do seek treatment, health systems may be inadequately staffed and unable to address their needs, especially in rural or isolated regions.

Because risk factors are more highly concentrated among the poor and the poor may have exposure to several risk factors at the same time, poverty is a major determinant of TB. Several studies have shown the inverse relationship between wealth and TB incidence at the individual and country levels (13,16,17). Oxlade and Murray (2012) found that Indian persons in the poorest quintile with low BMI and exposure to indoor air pollution had 5-fold increase in risk of TB over those with neither exposure, demonstrating a dramatic increase in risk when there are several exposures at once (18). These studies underscore the need to address poverty to overcome tuberculosis on a wide scale.

Tuberculosis in Prison Populations

TB is a major cause of morbidity and mortality among prisoners worldwide. TB incidence in prisons is on average 23 times higher than TB incidence in the general population and can be up to 81 times higher. This is partially due to prison populations

being disproportionately drawn from populations that have a high risk of TB: the homeless, substance-abusers, and those of low socioeconomic status. Also, prison environments are conducive to tuberculosis transmission due to overcrowding, poor ventilation, close contact between prisoners, prison staff, and visitors, and limited access to medical care and tuberculosis treatment (1,2). Prison conditions can worsen the health status of inmates—causing, for example, malnutrition and stress—which increase likelihood of infection.

In addition, prisons have unique challenges that increase risk of tuberculosis and infectious disease in general. Despite United Nations doctrines establishing the basic right to medical access for all prisoners, limited availability and access to these services poses a threat to health of prisoners and the wider community (19). Prison health is not usually a high ranking national policy priority, meaning few funds for healthcare (20). Prison staff may view prisoner health as secondary to the safety of the prison environment and dispensing of punishment and therefore attempt to limit access to existing medical services. Prisoners themselves may not seek care for several reasons: inability to recognize symptoms, trivialization of symptoms, prioritization of personal safety over health, fear of stigma, and fear of prison transfer or delay in release (14).

The health of incarcerated persons impacts the surrounding populace. Prisons act as reservoirs of tuberculosis and cause increases in tuberculosis transmission in the wider community (1,21,22). Circulation of prisoners, prison staff, and civilian visitors between prisons and the community facilitates the spread of disease. For the health of prison communities and the larger population, prisons must be included in national TB surveillance and control efforts.

Epidemiology of Tuberculosis

Globally

Recent WHO estimates of TB burden show 9.0 million new cases and 1.5 million deaths occurred in 2013 with a third of the world's population latently infected (23). A quarter of those deaths were in HIV-positive persons and about 14% of deaths were from MDR-TB. The mortality rate has fallen by 45% since 1990 but TB is still a leading cause of death due to an infectious agent and is the leading cause of death for HIV co-infected persons (234). Global declines also mask the limited progress that has been made in some areas of the world, as is the case with rising rates of MDR-TB in China and Eastern Europe. Twenty-two low and middle income countries account for more than 80% of cases worldwide.

In Haiti

Haiti has the highest burden of tuberculosis per capita in Latin America and the Caribbean (25). In 2012, TB incidence was estimated at 206 per 100,000 population and prevalence at 254 per 100,000 population (26). MDR-TB is also of concern, accounting for nearly 5% of all notified MDR-TB cases in the Americas with a prevalence of at least 2.9% among newly diagnosed cases and 20% among retreatment cases (27,28).

Role of Haiti's Health Systems in Tuberculosis Control

Haiti's national TB control program, Programme National de Lutte contre la Tuberculose (PNLT), is operated centrally from the Ministry of Health in Port-au-Prince in conjuction with each of Haiti's 10 departments. PNLT began implementing the DOTS strategy in 1997. The strategy relies on five components: political commitment with

increased and sustained funding; case detection through quality-assured bacteriology; standardized treatment with supervision and patient support; an effective drug supply and management system; and monitoring and systems evaluation and impact measurement (29).

The public health budget in Haiti is low—less than 6% of the 2011 GDP was dedicated to public health (30). Funding for the PNLT comes in part from USAID, PEPFAR, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria. A number of NGOs contribute funding, supplies, and personnel (31).

Following the 7.0 magnitude earthquake that struck Haiti in 2010, the public health infrastructure was dealt a serious blow. Over 200,000 people were killed and over 2 million people were displaced. Internally displaced persons camps quickly became crowded and living conditions within the camps declined. A cholera outbreak ten months after the earthquake exasperated health and recovery efforts. The U.S Centers for Disease Control and Prevention (CDC) developed the Health Systems Reconstruction Program (HSRP) to combat this and other health issues. Among the goals of the HSRP was to improve TB diagnostic capabilities at the National Public Health Laboratory. As of 2013 the National Lab was able to culture TB and perform drug susceptibility testing (32). Diagnostic testing is also performed in 2 regional labs and 232 diagnostic and treatment centers.

TB case detection across the country is limited by lack of active case finding and screening activities. Most cases are identified through self-referral, which detects approximately 65% of cases (27). This falls below the WHO recommended 75% case detection rate which, in combination with 85% treatment success, is modeled to reduce

annual TB incidence. Cultural beliefs and fear of stigma may hamper case detection as well as varying levels of perceived disease severity and ability of biomedicine to treat the disease (33). In addition, the inadequate health force—consisting of 2 doctors and 1 nurse for every 10,000 Haitians—and low retention rates exacerbate detection efforts (30,34).

Infection Control and Prevention

WHO describes 4 levels of TB infection control for congregate settings: managerial, administrative, environmental, and personal protective equipment (35).

Managerial-Level Infection Control Practices

At the national-level, managerial activities start with strengthening and ensuring funding for a national TB infection control agency. TB surveillance should be conducted nationally and should include prison settings. In prisons, a TB infection control plan should be developed and should be routinely monitored and evaluated for effectiveness (35). Advocacy and education is necessary to reduce stigma, allow self-identification of symptoms, and encourage utilization of medical services.

Facility-Level Infection Control Practices

Facility-level administrative measures are often the least expensive measures to implement (14). These include the prompt identification of persons with TB. An entry medical screening which looks for TB is widely recommended (14,36). Those with active TB should be separated from the general population. All inmates and prison staff should be educated about and encouraged to practice cough etiquette to reduce airborne pathogens. Finally, facilities should make attempts to reduce overcrowding and ensure proper ventilation.

Environmental Infection Control Practices

Environmental infection control measures include ensuring proper ventilation, maximization of natural light (or use of UV lights), and reduction of crowding. WHO recommends at least 12 air changes per hour in prison cells. This can be achieved by having large open windows. If infrastructure or weather does not permit this, exhaust fans should be installed. Windows also allow for natural light to enter—allowing for some air disinfection. Where adequate ventilation and natural light are not possible, ultraviolet germicidal irradiation (UVGI) should be considered. When properly installed at the top of a room UVGI can disinfect the air with the equivalence of 10-20 air changes per hour.

A study conducted by Sanchez et al. (2012) found that in a highly crowded Brazilian prison, the majority of cases were clustered and due to 2 genotypes (37). There was exogenous infection of persons with LTBI which contributed to rapid progression to active disease. This highlights the importance of crowding reduction as an aspect of environmental infection control.

Personal Protective Equipment

Healthcare workers are advised to wear particulate respirators when treating prisoners suspected of and known to be infected with TB—especially those with MDR-TB. It is also recommended that visitors wear particulate respirators when in enclosed areas with infected prisoners. Prisoners with active TB should wear surgical masks as part of cough etiquette practices.

Preventive Therapies for LTBI

In the prison setting, preventive therapies have been used with some success. Regimens are 4 to 9 months long with completion rates ranging from 3 to 87% due to

negative side-effects or transfer or release. Preventive therapies with isoniazid alone reduce the risk of LTBI progression to active TB disease by up to 90%, depending on length of treatment. With a completion rate of about 50%, preventive therapies are more cost effective than treatment due to reactivation and prevent transmission to other prisoners (38). Due to concerns of the development of resistance alternatives to monotherapy have been developed, however many present an increased risk of hepatoxicity (39). Additionally, the effects of isoniazid preventive therapy in individuals latently infected with MDR or XDR-TB is unclear (2,40).

With high LTBI prevalence in Haiti, it is worth considering implementation of preventive therapies for those at highest risk of progression to or reactivation of TB. National policy, however, requires laboratory confirmation of TB prior to distribution of medication.

Diagnostic and Screening Methodologies

Active disease is identified through a combination of clinical and microbiological methods. When clinical symptoms are indicative of possible pulmonary TB disease further diagnostic and microbiological testing is performed.

Diagnosis

The symptoms of TB in any location include anorexia, weight loss, fever, night sweats, weakness, and malaise. Extrapulmonary TB has symptoms dependent upon the site of infection. Pulmonary TB is characterized by a cough lasting for at least three weeks and occasionally hemoptysis (41).

Chest radiography is used to detect abnormalities in the lungs that are useful in determining presence and stage of TB infection. In immunocompetent adults, primary TB

infection results in the appearance of infiltrates in the middle and lower lung and is often accompanied by hilar adenopathy. Reactivation causes upper lobe abnormalities such as cavitation. Healed TB is identified by scarring, hardening of old nodules and lesions, and loss of lung volume. Normal chest radiographs are common in the HIV co-infected.

The ease and speed with which sputum smear analysis can be done usually makes it the first diagnostic test performed in high resource settings. An acid-fast staining procedure is used to identify and count bacilli in a clinical sputum specimen. Several thousand bacilli per milliliter are required for detection with higher numbers of bacilli indicative of greater infectiousness. Smear analysis can be a fairly unreliable diagnostic measure of TB disease with as many as 50% of pulmonary tuberculosis patients having negative smears. This technique also requires laboratory personnel and equipment which are unavailable in most prison settings.

Specimen culture is the gold standard confirmatory methodology. It is conducted using solid media and, in some cases, liquid broth to detect organisms that may have been missed in the smear and to identify exact mycobacterial species. Drug susceptibility testing is also done using cultured bacteria. Mycobacterium takes up to 8 weeks to grow on solid media and up to 3 weeks in broth.

While waiting for organisms to grow, NAAT can be used to aid clinical diagnosis. NAAT is highly sensitive, highly specific, and has rapid turnaround time. Its main benefit lies in ruling out TB infection rather than in confirming diagnosis (42). Microbiological diagnosis via culture and NAAT is hindered in Haiti by lack of laboratory capacity, lack of trained staff, and high cost of reagents, necessitating the need for alternative diagnostic measures.

GeneXpert is a cartridge-based desktop machine that detects *M. tuberculosis* and rifampicin resistance in sputum samples using NAAT. Its benefits include 2 hour diagnostic time and operational simplicity. It was found to be highly specific and sensitive when compared to sputum smear analysis (43). For low resource settings GeneXpert has a number of limitations, including need for reliable electricity, restrictions on operating temperature and humidity, and cost (44). If the operating requirements can be met, however, Meyer-Rath et al. predicted an annual 30%-37% increase in TB case detection and a 69%-71% increase in MDR-TB case detection in South Africa.

Screening

Tuberculin skin testing (TST) and interferon-gamma release assay (IGRA) are used to identify infection but cannot be used to distinguish active disease from latent infection. Tuberculin is an antigen that causes the formation of an induration at the injection site if there is cell mediated immunity from current or previous infection. A small amount of tuberculin purified protein derivative is injected under the skin and results are interpreted one to three days later. Accurate interpretation of the results relies on measurement of the induration with respect to risk of TB infection. There is a decreased threshold of positive interpretation for higher risk populations, such as laboratory personnel, contacts of TB-infected, and the HIV-infected. BCG vaccination can cause false-positive results.

With the high BCG coverage in Haiti, TST has limited usage in identifying the latently infected. IGRA is the preferred screening method among BCG vaccinated persons. Infected persons' white blood cells release interferon-gamma when mixed with

tuberculosis antigens—which are distinct from those found in the BCG vaccine. IGRA can have results within a day and do not necessitate patient follow-up visits (45).

Symptom screening and scoring algorithms can be used to determine likelihood of tuberculosis infection. While inexpensive, symptom screening methodologies have low sensitivity and specificity (46). Comparison of three symptom screening methodologies (cough lasting at least 3 weeks, WHO score of at least 5, and presence of any potential TB symptom) in a prison in Rio de Janeiro, Brazil showed that none of the methodologies were reliable. All three missed at least 50% of TB suspects and radiography-based screening was recommended (47).

In a prison setting, chest radiography is cost effective, rapid, and detects more cases of active pulmonary TB than TST or symptom screening alone. WHO recommends screening upon entry and two mass screenings per year, given adequate resources and in combination with other case finding strategies (14). Studies conducted in a variety of prison settings have found regular chest radiography to be effective in identifying active cases. In prisons of the former Soviet Union, annual mass miniature radiography was found to be both more effective and more cost-effective than symptom screening or self-referral alone; however, annual sputum PCR was found to be the most effective of the screening strategies investigated in reducing TB and MDR-TB prevalence (48). In an overcrowded prison with 4.6% prevalence of active TB and 2.1% seroprevalence of HIV in Rio de Janeiro, Brazil, active case detection based on chest radiography was deemed more effective than DOTS strategy alone in reducing prevalence. Mass radiography screening at entry in combination with DOTS performed best after TB prevalence was first reduced by three annual mass radiography screenings (49).

Treatment

The first-line anti-TB drugs are: isoniazid (H), rifampin (R), pyrazinamide (Z), streptomycin (S), and ethambutol (E). Standard first line treatment for people who have no prior treatment history is 2HRZS/4HR (50). DOTS is the method in which treatment is administered and supervised by a healthcare worker to ensure adherence and prevent development of drug-resistance. Treatment is successful 85% of the time, and within as little as two weeks of starting the standard treatment regimen, an infected person becomes non-infectious (23).

For those who have previously been treated, a drug susceptibility test (DST) should be performed to identify effective treatment regimens. Because this requires culture of the bacilli, results can take several months. In the interim the standard retreatment regimen (2HRZES/1HRZE/5HRE) can be given, however care must be taken to ensure that only those with a low risk of MDR-TB receive this regimen. Success rates are lower than standard first-line treatment (60%-80%) and inappropriate use of this regimen can contribute to amplification of drug resistance (51,52). If individual DST cannot be obtained, national drug resistance patterns can be used to determine the best empiric treatment regimen (14).

Multi-Drug Resistant Tuberculosis

Resistance to streptomycin—the first anti-tuberculosis drug discovered—was identified shortly after the start of its clinical use (53). To combat this, multi-drug regimens were instituted to lower the chance of selecting for drug-resistant strains. In the U.S., prevalence of drug resistance to at least one drug rose steadily from 2% in the

1970s to 33% in the 1990s as TB patients defaulted treatment, leading to the development and implementation of DOTS.

Multi-drug resistant tuberculosis (MDR-TB) is defined as TB that is resistant to at least isoniazid and rifampin (50). The three factors leading to development of MDR-TB are: 1) inadequate treatment regimens, 2) inadequate drug supply, and 3) inadequate drug intake (14). Second line treatment regimens involve the use of five or more drugs for up to 24 months. These drugs are more expensive and more toxic, if available at all**.** It is therefore imperative to protect the efficacy of anti-TB drugs by rapidly detecting drug resistance and by administering appropriate treatment for the full recommended duration.

Methods

Data Source

The data for this analysis come from custody records, chest radiograph readings, *M. tuberculosis* test results, and BMI measurements for 322 male prisoners in the Bois Verna cell block of the Prison Civile. The data were collected through routine health screenings carried out by the non-governmental organization Health through Walls.

Data Security

The Emory University Institutional Review Board reviewed the research proposal and granted approval before data analysis began. Names were removed from the dataset by Dr. Spaulding prior to analysis by the investigator. Dr. Spaulding had been granted access to this information through the course of her evaluation of Health through Walls. Data were kept on a password-protected computer.

Confidentiality agreements were signed by the investigator and by Dr. Spaulding.

Data Cleaning and Analysis

Data were provided to the investigator in several Microsoft Excel spreadsheets containing prisoner ID number, age, new and old cell numbers, HIV seropositivity, BMI measurement dates and results, CXR dates and results, and Gene Xpert screening dates and results. Prior to receipt by the investigator, Dr. Spaulding matched prison ID numbers to prisoner names to create one complete dataset. Names were then removed and data cleaning was performed in Microsoft Excel 2007 and in SAS 9.4 (Cary, NC).

Data cleaning involved removal of released prisoners as they did not have complete data. Prison ID numbers were updated to the standard 7 digit format (2 digit intake year-2 digit intake month-3 digit indicator of entry order) to facilitate determination of intake date and calculation of time incarcerated. All CXR abnormalities were indicated in the excel spreadsheet regardless of TB suspect status, necessitating the determination of suspect TB CXR by Dr. Spaulding.

The ultimate outcome of interest was development of TB while incarcerated. Outcome was defined as having a CXR indicative of TB or having *M. tuberculosis* identified in the sputum by GeneXpert. Two sets of univariate logistic analyses were carried out—one for each TB determination method. For both CXR and GeneXpert determination, age, time incarcerated, BMI ≤ 20, and change in BMI were examined. For GeneXpert presence of any positive CXR and newly positive CXR were also examined.

Based on the existing literature and available data, several covariates were chosen to be tested against the outcome. Increased age and low BMI are associated with depressed immune functioning which can increase risk of developing TB. Change in BMI

was chosen as a predictor of TB positivity as weight loss is a symptom of TB. Increased incarceration time was examined since incarceration can lead to poor health outcomes and increase duration of exposure to those with active TB.

Two multivariate logistic regressions were conducted to identify prognostic factors of positive TB determination by CXR and by GeneXpert. Stepwise selection was used to identify statistically significant models. A significance level of 0.3 was required for covariate entry into the model and a significance of 0.35 to remain. The first model examined age, BMI $\leq$ 20, change in BMI, incarceration time over 2 years, and incarceration time as predictors of positive CXR. The second model contained an indicator for BMI ≤ 20 and an indicator for incarceration time over 2 years as predictor of positive GeneXpert results.

Since screening via GeneXpert can be costly, it is worth identifying only those inmates at highest risk for TB for additional screening. BMI and time incarcerated are easy data to obtain in the Prison Civile. Identification of these covariates as significant predictors of TB would allow for more efficient utilization of GeneXpert screening.

Results

Descriptive Statistics

There were 309 inmates from the Bois Verna cell block who received a baseline CXR [Table 1]. Mean age was 39 years and ranged from 16 to 75 years. Average baseline BMI was 21.36 kg/m^2 with follow-up BMI measurements taken on average of 22 months later. Average change in BMI was -0.68 kg/m^2. Five (1.62%) of inmates were HIV positive; none of those positive for TB were co-infected with HIV.

The baseline CXR screening found 29 with abnormal readings indicative of TB. Two hundred seventy inmates received a second CXR and 30 received a third CXR. Sixteen (5.97%) developed abnormal CXR readings between baseline and most recent CXR. Six (1.96%) of the 306 screened via GeneXpert were positive for TB. Average time incarcerated from entry to TB determination by CXR was 29 months; and 30 months from entry to TB determination by GeneXpert.

Further descriptive statistics were gathered on inmates by method of TB determination [Table 2]. For TB determination via newly positive CXR, prevalent TB cases were removed from examination. Sixteen inmates were positive for TB via CXR. Mean age was higher among those positive for TB (40 years vs. 38 years); BMI decreased by less (0.48 kg/m^2 vs. 0.52 kg/m^2); and incarceration time was shorter (21 months vs. 29 months). A higher proportion of TB positive inmates had BMI $\leq$ 20 (50% vs. 40%) and a lower proportion of TB positive inmates were incarcerated for more than 2 years (31% vs. 59%).

Six inmates were positive for TB via GeneXpert [Table 2]. Mean age was higher among those positive for TB (48 years vs. 38 years); BMI decreased more (1.32 kg/m^2 vs. 0.65 kg/m^2); and incarceration time was longer (42 months vs. 30 months). A higher proportion of TB positive inmates had BMI $\leq$ 20 (67% vs 42%) and a higher proportion were incarcerated from more than 2 years (83% vs. 59%).

Regression Analyses

In the univariate models, decreasing time incarcerated (coded as both continuous and bivariate) was the only covariate significantly associated with positive CXR at α=0.05 [Table 3]. Increased incarceration time in months was protective among this

group (OR: 0.96 [0.93, 0.99]) as well as incarceration time greater than 2 years (OR: 0.32 [0.13, 0.79]). Age, time incarcerated (coded as continuous), and presence of any positive CXR were significantly associated with positive GeneXpert results at α=0.1. Increased age in years (OR: 1.05 [1.00, 1.11]) and increased time incarcerated in months (OR: 1.07 [1.01, 1.13]) were associated with TB incidence. Any positive CXR was associated (OR: 32.49 [3.70, 285.28]) but newly positive CXR was not (OR: 3.29 [0.51, 21.03]).

Stepwise analysis of the covariates for newly positive CXR resulted in a model containing the indicator for BMI $\leq$ 20 and continuous incarceration time [Table 4]. Stepwise analysis of the covariates of positive GeneXpert resulted in a model containing both the indicator for BMI $\leq$ 20 and an indicator for incarceration time over 2 years.

Discussion

The significant univariate predictors of having newly positive CXR were decreasing incarceration times (continuous and bivariate coding). This is contrary to findings from the literature. Length of incarceration may therefore be an unreliable predictor of newly positive CXR results.

The significant univariate predictors of a positive GeneXpert result were increasing age, increasing time incarcerated, and presence of any positive CXR. Increased age and increased incarceration time are established risk factors in the literature. Previous cross-sectional analysis in Prison Civile identified increased incarceration time as being associated with increased TB prevalence (Mercer, 2013). Because CXR was shown to be a predictor of positive GeneXpert results, CXR can be

considered an important diagnostic tool as well as a potential substitute for GeneXpert in some situations.

Low BMI may be a better diagnostic tool than change in BMI in the prison setting since there is no need for a comparison BMI reading. Association between length of incarceration and TB positivity by either diagnostic methodology points to need for regular TB screening to identify cases that may have developed since intake.

Early identification of TB is an essential part of infection control practices. Identifying factors that are easy to examine allows for recognition of inmates who should be the focus of more advanced screening.

Limitations

The data were spread across several datasets and were originally recorded by several people. Prison ID number was not universally used to record the results of health screenings. Inconsistent record keeping may have introduced these errors. Other issues arose with prison ID number where some numbers were duplicated and where the standard 7 digit formatting was not used. While unique prison ID numbers were not essential to this analysis, properly formatted prison ID numbers were needed to determine intake date.

There was no standard format for recording CXR interpretations. All abnormal CXR, regardless of significance in TB diagnostics, were highlighted in the original spreadsheet. This necessitated the identification of abnormal, TB suggestive CXR by Dr. Spaulding.

Recommendations

Prison Civile should conduct annual CXR screening for prisoners. Taking BMI measurements and conducting CXR at entry is also recommended to identify those who are at high risk of TB. Those suspected of having active TB should be isolated and treatment started promptly. Given the overcrowded setting, isolation this may be difficult. Temporary outdoor shelter may be an option for housing the TB diseased while initiating treatment.

Since it is impossible to differentiate active TB transmission from activation of LTBI from this data, general improvement of the health and nutritional status of inmates is recommended, as well as implementation of infection control procedures and crowding reduction. These interventions would likely impact rates of TB as well as other infections diseases.

Public Health Impact

While the results from Bois Verna may not be generalizable to other cell blocks within Prison Civile or to other prisons, they can be used to inform TB infection control practices. This also adds to the body of research that shows increasing length of incarceration puts inmates at increased risk of developing TB.

A follow-up study examining DNA fingerprints of TB strains in the prison would allow for differentiation of TB reactivation and exogenous TB reinfection. Reactivation of TB may be attributable to individual level factors such as low BMI that can be addressed by improved prison conditions. Exogenous reinfection points towards active

transmission within the prison and indicates need for prompt identification of TB positive inmates, initiation of treatment, and implementation of infection control practices.

Tables and Figures

Table 1. Overall Descriptive Statistics

Variables	
Demographic	**N=309**
Mean age, years (range)	38.59 (16-75)
Penal	
Mean incarceration time prior to CXR TB determination, months ± std	28.71± 4.57
Incarcerated > 2 years prior to CXR TB determination, n (%)	155 (58.27)
Mean incarceration time prior to sputum TB determination, months ± std	29.70 ±14.9
Incarcerated > 2 years prior to sputum TB determination, n (%)	182 (59.48)
Cell 1, n (%)	22 (7.41)
Cell 2, n (%)	150 (50.51)
Cell 3, n (%)	125 (42.09)
Clinical	
Mean baseline BMI (range)	21.36 (15.43-35.76)
Mean change in BMI, kg/m^2 (std)	-0.678 (2.49)
BMI ≤ 20 kg/m^2, n (%)	132 (42.72)
HIV-seropositive, n (%)	5 (1.62)
Baseline positive CXR, n (%)	29 (9.39)
Newly positive CXR, n (%)	16 (5.97)
Sputum positive, n (%)	6 (1.96)

Table 2: Descriptive Statistics by TB Determination Method

Variables	Newly Positive via CXR (n=16)	Negative or Not Newly Positive via CXR (n=225)	Positive via Sputum (n=6)	Negative via Sputum (n=297)
Demographic				
Mean age, years (range)	40.31 (22-57)	38.31 (16-75)	48.00 (24-75)	38.42 (16-75)
Penal				
Mean duration of incarceration prior to TB determination, months ± std	21.17 ± 15.17	28.81 ± 14.41	41.80 ± 10.21	29.82 ± 16.61
Incarceration > 2 years, n (%)	5 (31.25)	133 (58.85)	5 (83.33)	177 (59.00)
Cell 1, n (%)	1 (6.25)	20 (9.05)	0	22 (7.56)
Cell 2, n (%)	10 (62.50)	107 (48.42)	3 (75.00)	146 (50.17)
Cell 3, n (%)	5 (31.25)	94 (42.53)	1 (25.00)	123 (42.27)
Clinical				
Mean baseline BMI (range)	20.96 (17.78-24.34)	21.40 (15.43-35.76)	20.75 (18.94-22.66)	21.34 (15.43-35.76)
Mean change in BMI, kg/m^2 (std)	-0.48 (2.58)	-0.52 (2.31)	-1.32 (3.06)	-0.65 (2.45)
BMI ≤ 20 kg/m^2, n (%)	8 (50.00)	102 (40.48)	4 (66.67)	127 (42.33)
Baseline Abnormal CXR	N/A	N/A	4 (66.67)	24 (8.08)
Newly Positive CXR	N/A	N/A	1 (16.67)	15 (5.73)
HIV-Seropositive, n (%)	0	5 (2.19)	0	5 (1.63)

Table 3: Univariate Logistic Regression Analysis

TB Determination via CXR			
Covariate	**OR (90% CI)**	**Estimate**	**P-Value**
Age	1.012 (0.980, 1.045)	0.0116	0.5532
Change in BMI	1.009 (0.835, 1.219)	0.00878	0.9392
Time Between Entry and TB Determination	0.963 (0.932, 0.994)	-0.0382	0.0475*
	OR (90% CI)	**Estimate**	**P-Value**
BMI ≤ 20	1.533 (0.654, 3.595)	0.4274	0.4093
Incarcerated > 2 years	0.318 (0.127, 0.793)	-1.1462	0.0393*
TB Determination via Sputum			
Covariate	**OR (90% CI)**	**Estimate**	**P-Value**
Age	1.054 (1.002, 1.109)	0.0527	0.0886*
Change in BMI	0.898 (0.611, 1.321)	-0.1073	0.5859
Time Between Entry and TB Determination	1.068 (1.008, 1.131)	0.0654	0.0623*
	OR (90% CI)	**Estimate**	**P-Value**
BMI ≤ 20	2.724 (0.647, 11.469)	1.0022	0.2514
Incarcerated > 2 years	3.475 (0.567, 21.277)	1.2455	0.2583
Any Positive CXR	32.492 (3.701, 285.280)	3.4810	0.0017*
Newly Positive CXR	3.294 (0.516, 21.033)	1.1920	0.2903

Table 4: Multivariate Logistic Regression Analysis

TB Determination via CXR			
Covariates	**OR (95% CI)**	**Estimate**	**P-Value**
BMI $\leq$ 20 kg/m^2	1.791 (0.615, 5.219)	0.5828	0.2855
Time Between Entry and TB Determination	0.951 (0.913, 0.991)	-0.0498	0.0173*
TB Determination via Sputum			
Covariates	**OR (95% CI)**	**Estimate**	**P-Value**
BMI $\leq$ 20 kg/m^2	2.594 (0.466, 14.444)	0.9531	0.23767
Time Between Entry and TB Determination	3.309 (0.380, 28.792)	1.1968	0.2782

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Appendix I: IRB Approval

TO: Elizabeth Smith
Principal Investigator
Public Health

DATE: March 13, 2015

RE: **Expedited Approval**
IRB00078657
WHAT ARE THE PREDICTORS OF NEW CASES OF DEFINITE AND LIKELY PULMONARY TUBERCULOSIS?

Thank you for submitting a new application for this protocol. This research is eligible for expedited review under 45 CFR.46.110 and/or 21 CFR 56.110 because it poses minimal risk and fits the regulatory category[ies] F[1-9] as set forth in the Federal Register. The Emory IRB reviewed it by expedited process on 3/9/2015 and granted approval effective from **3/9/2015** through **3/8/2016**. Thereafter, continuation of human subjects research activities requires the submission of a renewal application, which must be reviewed and approved by the IRB prior to the expiration date noted above.

- The IRB grants the following waivers:
  - Complete waiver of HIPAA Authorization
  - Waiver of all elements of Informed Consent
- The following documents are approved for use or otherwise acknowledged:
  - Study Protocol, undated

Any reportable events (e.g., unanticipated problems involving risk to subjects or others, noncompliance, breaches of confidentiality, HIPAA violations, protocol deviations) must be reported to the IRB according to our Policies & Procedures at www.irb.emory.edu, immediately, promptly, or periodically. Be sure to check the reporting guidance and contact us if you have questions. Terms and conditions of sponsors, if any, also apply to reporting.

Before implementing any change to this protocol (including but not limited to sample size, informed consent, study design), you must submit an amendment request and secure IRB approval.

In future correspondence about this matter, please refer to the IRB file ID, name of the Principal Investigator, and study title. Thank you

Samuel Roberts, CIP
Senior Research Protocol Analyst
This letter has been digitally signed

CC: Spaulding Anne Epidemiology