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Daniel W. Mercer April 25, 2013

Tuberculosis Prevalence Among Entrants and Stock Population in a Haitian Prison: A Quality Assessment of Screening Procedures

By

Daniel W. Mercer
Master of Public Health

Global Epidemiology

Anne Spaulding, MD, MPH
Committee Chair

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By

Daniel W. Mercer

B.A., B.S.E.
University of Pennsylvania
2008

Thesis Committee Chair: Anne Spaulding, MD, MPH

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 Global Epidemiology
2013

Abstract

Tuberculosis Prevalence Among Entrants and Stock Population in a Haitian Prison: A Quality Assessment of Screening Procedures
By Daniel W. Mercer

Introduction: Tuberculosis among the most common causes of morbidity and mortality in correctional settings due to high prevalence among entrants and conditions that promote disease transmission among the stock population. This assessment seeks to evaluate the tuberculosis screening efforts at the Prison Civile in Port-au-Prince, Haiti by comparing prevalences among new entrants and stock prisoners and by identifying factors associated with prevalence among the stock population.
Methods: Prison and staff from a non-governmental organization at the Prison Civile collected tuberculosis-related data during and after a universal screening effort from March-June 2012. The investigator conducted logistic regression on the comparison between stock population and entrants and covariates including body mass index, age, and tuberculosis treatment history to determine prevalence odds ratios for the screened population. Logistic regression on covariates among stock prisoners determined prevalence-associated factors.
Results: The overall prison prevalence of tuberculosis was 1,540 cases per 100,000 persons, which is higher than the national prevalence (307/100,000). The odds of having tuberculosis among stock prisoners was 2.72 (95% CI: 1.65, 4.49) times the odds for new entrants after controlling for body mass index. Each month of time served in the Prison Civile since 2010 was associated with a 4% increase in the odds of having tuberculosis (OR: 1.04, 95% CI: 1.02, 1.06). Stock prisoners not included in the mass screening had odds twice those of assessed stock prisoners (OR: 2.15, 95% CI: 1.15, 4.03). Among stock prisoners, prevalence was associated with residence on a particular floor (OR: 3.31, 95% CI: 1.90, 5.75) and lower body mass index (OR: 0.76, 95% CI: 0.67, 0.85).
Conclusions: Tuberculosis prevalence in the Prison Civile is higher than in the general Haitian population, but the magnitude of the difference is less than that seen in many developing countries. Higher prevalence is significantly associated with length of time spent in the prison, though causal conclusions cannot be drawn from this cross-sectional study. The Prison Civile may be acting as a reservoir, with those incarcerated earlier experiencing different underlying tuberculosis exposure before incarceration. Given the differences in prevalence between stock and entrants, a future longitudinal study might be warranted.

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Acknowledgements:

The author thanks Dr. Anne Spaulding for her support and guidance over the often rocky course of this evaluation; Dr. John May and the Health through Walls staff in the Prison Civile for their logistical help and for allowing me to conduct this assessment; Elisa Ignatius for letting me hijack her trip to Haiti so I could get the data; and Aiden Varan and Sonia Harris for paving the way. Thanks also to Aashima Kapoor for constant emotional support and encouragement.

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Introduction

Tuberculosis disease (TB) is one of the most common causes of morbidity and mortality among prisoners in custody around the world (1). The high prevalence of this disease has impacts both within prison walls and in the wider communities in which these prisons are located. TB prevalence in prison has been documented as 3.5-20 times higher than in the general population (2-9) and incarceration has been associated with increases in TB rates among the non-incarcerated (1).

The largest prison in Haiti is the Prison Civile (PC) in the capital, Port-au-Prince. It shares with other prisons a number of characteristics that can lead to high levels of TB transmission. It is overcrowded, with poor ventilation in a number of areas, and access to high-quality nutrition and health care is limited (4, 8, 10-13). These factors, coupled with the fact that Haiti has a high endemic level of TB (14), indicate that prisoners in the PC are likely to have higher TB prevalence than the general population of Haiti. TB infection is a concern for both prison staff and Health through Walls (HtW), a non-governmental organization that has provided health care services to the PC for over ten years (15), though no assessment of prevalence has been conducted previously. From March to June of 2012, HtW conducted a mass screening effort of the stock prisoner population at the PC in order to identify and start treatment for all individuals with active TB disease.

This evaluation seeks to assess the effectiveness of that TB screening program. To do so, the prevalence of TB disease discovered during the universal screening will be compared the prevalence amongst new entrants to the prison from March 2012 to March 2013. The new entrants to the PC are assumed to represent the endemic conditions in the population of Port-au-Prince. A significantly higher prevalence among the stock population will indicate that TB control remains a major issue. In that case, the investigator will provide recommendations based

on the literature for improving the ongoing entry screening effort. Factors associated with increased prevalence within the prison will also be investigated to help guide future TB control policies at the PC.

Background

Tuberculosis

In the United States, the Centers for Disease Control and Prevention (CDC) publishes the Core Curriculum on Tuberculosis, which gives details for clinicians on TB transmission and risk factors for infection, symptoms, methods of testing and diagnosis, treatment, and infection control. Except where noted, all information in the following section comes from that source (16).

Tuberculosis Information and Pathogenesis

Tuberculosis is a disease caused by one of eight species of mycobacterium. The disease is spread through the air and infection with TB begins when a person inhales *Mycobacterium tuberculosis* bacilli into the lungs. There the bacilli enter alveoli and begin to reproduce as pulmonary TB. While the lungs are the primary location for bacilli growth, they can also spread throughout the body in what is known as extrapulmonary TB. Some of the more common sites of infection are: kidneys, spine, larynx, and meninges.

The immune system defends against TB infection by surrounding clumps of reproducing bacilli with cells known as macrophages. These cells wall off the tubercle bacilli and prevent them from spreading throughout the lungs and the rest of the body. The state when bacilli are all contained within shells of macrophages is known as latent tuberculosis infection (LTBI). LTBI is not infectious, but it can become so if the macrophage shells break and bacilli begin to reproduce rapidly. The state of such rapid reproduction is known as active TB, or TB disease, and is the subject of this quality assessment.

Transmission

Tubercle bacilli are transmitted from person to person in the nuclei of airborne droplets from the lungs of person infected with pulmonary TB or TB of the larynx. The bacilli are only infectious while in the air, not on surfaces. According to the CDC, there are four main factors associated with TB transmission: 1) the susceptibility of the exposed, which is higher among the immunosuppressed and those with poor nutrition, 2) the infectiousness of the infected person, where those with higher counts of TB bacilli are more likely to infect others, 3) environmental factors, and 4) the proximity, frequency, and duration of exposure. The final two are of particular interest when considering the prison environment.

There are six environmental factors related to TB transmission. Three of those are effectively inapplicable in the Prison Civile setting. The level of air circulation applies to indoor areas in which airflow is limited and controlled, with the possibility of recirculation. In the open-air facilities in the PC, there is no climate control and no recirculation. The potential for mishaps in specimen handling is another environmental factor for transmission that is not a major concern in this setting, in this case because there are few specimens taken in the facility, and analysis is primarily performed in external locations. The third inapplicable environmental factor is the use or misuse of air pressure. In high-resource settings, negative pressure environments are often used to house the infected while they undergo treatment. The PC does not have the capacity for such facilities, so constructed pressure environments are not an issue in infection.

Therefore, there are three environmental factors related to transmission of TB at play in the PC. The first is the concentration of droplet nuclei in the air, which is related to the infectiousness of each infected individual. The second in exposure to infected persons in small, enclosed spaces. The immediately obvious enclosed space in the prison setting is the cell, to which prisoners are confined for much of the time. In South Africa, prison cells have been identified as very conducive to TB transmission between prisoners (10). The third environmental

factor is insufficient ventilation. If droplet nuclei do not have adequate space or air flow in which to disperse and be removed from an area, the chances of infection are much higher. In the PC, nearly every cell is open to the outside air through windows that do not shut. This increases the amount of ventilation, at least on the upper floors of cell blocks. However, given how densely packed each cell is, and therefore how little air volume per person in each cell, open windows may not provide enough ventilation to clear any exhaled bacilli.

The risk of TB transmission increases with longer duration of exposure, more frequent exposures, and exposure at closer proximity. In a crowded setting such as the PC, it can be expected that many inmates may have long and frequent exposures at close proximity to those infected with TB, if they are not identified and isolated for treatment. The close quarters contact in the PC may also constitute a risk for transmission to health care workers in the prison if appropriate protections are not taken (17).

Symptoms

Both pulmonary and extrapulmonary TB share a number of the same symptoms, including: appetite loss, weight loss, night sweats, fever, and fatigue. Pulmonary TB in particular is characterized by: a cough lasting longer than three weeks with or without sputum, coughing up blood, and chest pain. The specific locations of extrapulmonary TB have their own symptoms: a symptom of kidney TB is blood in urine, a symptom of TB of the meninges is headache, TB of the spine is accompanied by back pain, and hoarseness is a symptom of laryngeal TB.

Testing and Diagnosis

There are several methods for testing and assessing whether an individual has TB. The first, the Mantoux Tuberculin Skin Test (TST), is recommended by the CDC in developed countries. This test involves an injection of tuberculin-derived purified protein derivative underneath the skin of the arm. After several days, the injection site is observed for the presence of any reaction. There are several disadvantages to this method in a low-resource setting, like the

PC, in a low-resource country, such as Haiti. The first is that the test requires two exactly-timed visits with a physician, which becomes difficult when medical resources are stretched thin. The second is that the results can be biased by previous exposure to the BCG vaccination for TB. Since Haiti is a country with an active BCG program, the Mantoux TST may not be an ideal diagnostic method, though the CDC does recommend TST use on inmates in American correctional facilities from countries with high levels of endemic TB and BCG programs (18).

Another testing method is through use of an interferon-gamma release assay (IGRA). IGRAs require only a single visit to a health care provider, at which time blood may be drawn for the test. This test is not confounded by previous vaccination history, which is an advantage over the TST.

A third method of TB exposure assessment is a chest radiograph. Abnormalities in such a radiograph consistent with TB infection are only considered suggestive by the CDC and not diagnostic of TB, but CXR programs in highly endemic prisons can have significant benefits in TB discovery (13). In its guidelines for TB control in correctional settings, the CDC does refer to CXR as "an effective means of detecting new cases of unsuspected TB disease at intake to a correctional facility", though it does caution that CXR cannot identify inmates with LTBI (18). This is the testing technique used most frequently in the PC (12). Abnormalities are usually found in the apical or posterior segments of the upper lobe, or the superior segments of the lower lobe. If nodular or fibrotic lesions are detected, than TB disease can be ruled out, and treatment for LTBI can be considered. Calcified, discrete, and/or nodular lesions indicate a low risk of progression from LTBI to TB disease. Care must be taken when examining radiographs from HIV-positive patients, as their results may not be typical and may not show any lesions. It is generally accepted that a chest x-ray can exclude a diagnosis of pulmonary TB if the patient has a positive TST, no symptoms, and is HIV-negative.

Treatment

Treatment for TB disease can take anywhere from six to nine months, depending on illness severity, susceptibility to medications, and overall health of the infected person. For several reasons, including the possibility of encouraging drug resistance and potential side effects, patient adherence can become a major concern in treatment protocols. To address this issue, directly observed therapy (DOT) is recommended by CDC and has been demonstrated to be effective in low-resource setting such as rural Haiti and modeled to be very effective in prison settings (13, 19). DOT is when someone is responsible for observing a patient take each and every pill in their regimen. This observation has been linked with greater protocol adherence and better treatment outcomes.

Multiple antibiotics can be effective against tuberculosis, depending on the susceptibility of the particular strain. The first-line drugs used in treating TB disease are: isoniazid, rifampin, ethambutol, pyrazinamide, and rifapentine. Of these, the first four are considered to be "core" by the CDC. These are also the drugs used for most treatment of TB disease in the PC (Personal communication with Elisa Ignatius). The second-line drugs, used in case of resistance to the first-line are: streptomycin, cycloserine, ρ-aminosalicyclic acid, levofloxacin, moxifloxacin, gatifloxacin, amikacin/kanamycin, and ethionamide. Because few individuals with resistant TB have been identified and because susceptibility testing is difficult to obtain, Health through Walls (HtW) and PC health staff empirically add streptomycin to the four core drugs in the case of a patient with previous exposure to TB treatment (Personal communication with Elisa Ignatius).

The CDC has laid out specific regimens for drug combinations to deliver effective treatment. While these regimens may be effective for a low-endemicity, high-resource country, they are not necessarily applicable to the PC setting. The CDC protocol calls for the four core drugs to be taken for two months in the "initial phase". Next is the continuation phase, four to seven months of additional treatment depending on any complications that arise during the initial

phase or early parts of continuation. In the end, treatment completion depends on drug regimen. In the PC, HtW uses an empirical treatment regimen. After two months on the four core drugs, or five for those with previous exposure, the patient is tested again via sputum sample. If he has converted from testing positive to negative, the treatment continues for another four months, for a total of six months of treatment. If the patient has not converted as of two months, sputum is sent for additional testing at three months and the treatment is extended by between two and eight months. All retreatments, for anyone with a possibility of previous TB treatment, are set at 8 months (Personal communication with Elisa Ignatius).

There are two forms of resistance to TB medication regimens. If the initial infection is a resistant strain, it is considered primary resistance. If the resistance is acquired over the course of therapy due to an insufficient or inappropriate regimen, lack of adherence in completing the course of medication, or interactions with other drugs, it is considered secondary resistance. HtW has not identified a case of resistant TB in the PC since they began testing again after the 2010 earthquake. However there is little resistance testing performed at the PC, so it is possible that this could be due to lack of detection of resistant TB.

Infection Control

According to the CDC, infection control programs need to have several characteristics in order to be effective. TB must be detected promptly so that action can be taken to isolate infected individuals and prevent person-to-person spread of disease. Airborne precautions, with a preference for the use of airborne infection isolation (AII) rooms, are recommended to limit the potential for interpersonal transmission. The last recommended characteristic is treatment of suspected and/or confirmed cases. The PC treatment program has adapted criteria similar to the above to meet the resources available to HtW and prison health staff.

The CDC notes that correctional facilities have unique needs when it comes to infection control. Transmission in prisons is a major concern, because overcrowded and poorly ventilated

facilities can facilitate outbreaks that can then spread to the community at large as inmates are released or visitors are infected. In prisons where the risk of new entrants having TB is non-minimal, the CDC recommends that all inmates be screened for TB at entry and should be placed in isolation if they demonstrate symptoms of TB and should stay there until they are demonstrated to be non-infectious (18). Healthcare workers are indicated to be at medium or high risk of infection with TB disease, and the CDC recommends annual screening. It also recommends that prisons have at least one AII room, and practice isolation for known or suspected cases of TB. In countries with tropical climates, an AII room may not be necessary, as construction of isolation wards can take advantage of the natural ventilation afforded by continually open windows.

In addition to the above recommendations, an important part of the practice of infection control has been contact tracing. Contact tracing is the systematic investigation of those people who have been in close contact with known TB cases in order to discover additional cases of both TB disease and LTBI (20). Unfortunately, there are no set standards for what constitutes a close contact, and multiple definitions have been used in the literature: anyone with known exposure to a case, anyone with intimate contact, and anyone having shared air with a case for a prolonged period are among the definitions employed. Even the duration of exposure can change between studies (20). Additionally, though it is recommended by the CDC (18), contact tracing may not be very helpful in the prison environment, where nearly the entire population can be considered to be in close contact (21). This is especially true in the PC due to overcrowding. Clustered strains of TB have been found to spread throughout prisons, beyond the confines of cell walls, indicating the extent of close contacts in the populations (11). Furthermore, it can be difficult to estimate the degree to which individual index patients contributed to transmission to and infection of other cases (20).

Haiti and the 2010 Earthquake

On January 12, 2010 a 7.35-magnitude earthquake centered near Port-au-Prince struck Haiti, leveling much of the capital city, killing 230,000, and injuring 300,000 people. More than 600,000 individuals moved away from damaged or ruined locations and 2,000,000 moved into internally-displaced person (IDP) camps (22).

Beyond the damage done directly by the earthquake, a massive cholera outbreak was a major impact of the international relief effort. In October 2010, cases of cholera were reported in two departments: Plateau Centrale and Artibonite. Cholera had not been a serious concern in Haiti for many years, so its reemergence was an unwelcome and unexpected surprise. A large effort was launched to prevent deaths and the spread of disease, determine the risk factors for infection, and establish national capabilities for surveillance. People in IDP camps were largely spared the impact of the outbreak due to supplies of clean water from the earthquake relief effort. The response to cholera led to improved diagnostic laboratory capacity that could theoretically help in TB infection control efforts (22).

Health in Haiti

Haiti has low life expectancy at birth (61 years) and a high infant mortality ratio (64 per 1,000 live births) (23). There is a high rate of BCG vaccination coverage (75% in 2011) (24) but also high rates of infection with HIV (1.8% of the population aged 15-49) (25) and TB (307 cases per 100,000 population) (14). These two diseases commonly go together as HIV-positive status is a risk factor for opportunistic TB infection. One half of the population of Haiti lacked access to healthcare, 36% could not obtain treated drinking water, and over three-quarters of the population did not have access to a latrine in 2011 (22). These conditions were exacerbated by the destruction of the national health infrastructure during the earthquake.

Tuberculosis in Haiti

Even before the earthquake and the aforementioned damage to Haiti's healthcare system, TB was a major health concern throughout the country. TB treatment and control operates at multiple levels: national, departmental, and NGO. Each of the eleven departments has its own operations and three NGOs provide management and technical support (26). Treatment services have been integrated into primary health care provision at 243 healthcare facilities throughout the country. Five NGOs provide training, supervision, and monitoring support for these facilities, while another seven organizations assist in community outreach and service delivery. All of these NGOs are coordinated by Medecins Sans Frontiers at meetings held every quarter. Haiti has a Country Coordinating Mechanism to facilitate treatment efforts and has had a National Tuberculosis Protocol (NTP) since 2001. However, the nation has struggled with funding its program and needed USAID to guarantee support after restrictions were imposed by the World Bank around 2000. Security for TB programs is provided by the NTP, the Pan-American Health Organization, and the NGOs themselves (26). These organizations have had some success in their control efforts. The Hopital Albert Schweitzer demonstrated that DOT could improve treatment outcomes even in very rural areas, areas of extreme poverty, and among HIV-positive patients (19).

Despite this network of governmental and non-governmental groups working on TB prevention, the disease is highly endemic. In developing countries overall, between five and ten percent of those patients who show up for at testing centers concerned about HIV have active pulmonary TB disease (27). In Haiti, these co-infected individuals tend to have high rates (8%) of multi-drug resistant (MDR) TB (27). At a TB center in Port-au-Prince in 2012, prevalence of MDR-TB among the newly diagnosed was 2.9% (28). This high prevalence raises fears that drug resistance may be on the rise in Haiti after the earthquake caused major interruptions in medication supply and delivery mechanisms, leading to treatment default. The movement of

massive populations into IDP camps has also been a concern as people share closer quarters and more contact with others, including those infected with TB (28).

After having dealt with difficulties caused by the earthquake, Mauch et al. offer the following suggestions to continue effective TB prevention work in Haiti. First, the example of Haiti shows that TB control can be effective even in fragile states, so well-considered investments have value. Second, national and local involvement in leadership and stewardship are needed to ensure cultural appropriateness and obtain buy-in from participants. Third, effective coordination and partnerships are required, as poor communication can make a bad situation worse. Finally, consistent monetary support from donor organizations is critical to ensure that programs can be maintained on an ongoing basis (26). If these points are at the heart of Haiti's national program, it can be expected to have a greater level of success in TB control.

Health and Tuberculosis in Prisons

As TB is among the most common causes of death among prisoners in custody around the world (1), its wide prevalence impacts prisoners and civilians alike. In Central Asia and Eastern Europe, mass incarceration has been connected with increases in TB rates in the general population (1). In developed nations, the rates of TB within prisons have been found to be several times higher than outside. In a study in Israel, the prevalence of TB among prisoners was 3.5 times the national prevalence (25 cases per 100,000 prisoners compared to 7.9 cases per 100,000 general population) (2). Studies in the United Kingdom and Spain also reported higher prison prevalences, and a systematic review of studies on correctional TB found an average developed nation prison TB prevalence of 237.6 cases per 100,000 prisoners (3, 4). In developing nations the comparison is even starker. In Eastern Ethiopia, prison TB prevalence was seven times that of the general population while it was 20 times higher in a Bangladeshi jail than in the nation as a whole (5, 6). Additional studies in Malawi, Cameroon, and Brazil confirm a consistent pattern of considerably higher TB prevalence in prison communities (7-9). Prisons become reservoirs for

disease, while TB prevention, control, and treatment tend to be among the lowest priorities of correctional authorities as they allocate their limited budgets (29, 30). International agreements on the rights of prisoners and medical ethics require that prisoners receive the same level of health care to which they would be entitled outside of detainment. As Dara et al. write, there are three main points to consider when looking at the problem of TB in prisons:

1. The health of prisoners and inmates is an integral part of the health of the wider community;
2. The diagnosis of TB and resistant forms of TB is not often readily available in penitentiary settings;
3. And poor medical management of patients in penitentiary settings and/or inadequate follow-up of released prisoners with TB can undermine TB prevention and control efforts in society at large (31)

The risks posed by TB in correctional settings are apparent, as is the need for cost-effective infection control and prevention.

Globally, prisoners tend to have worse health status and outcomes than those in the community overall. There are a number of reasons for this characteristic. Prisons throughout the world tend to be overcrowded as there are more people being incarcerated than beds, cells, and space overall (8, 11). The PC is no exception to this, holding over 4,000 inmates though it was designed for only 800 (12). Overcrowding leads to extensive close contact between many detainees, allowing for a single infection to spread rapidly to many others. In a study of TB genotypes in a Brazilian prison with high rates of infection, 84% were found to belong to one of two strains (11). In addition to overcrowding, simply being exposed to many other people on an extended basis has been found to be a risk factor (8, 32). In a study in Eastern Ethiopia, overcrowding was not found to be a risk factor, though sharing a cell with someone infected with

TB was (5). Extensive contacts, whether due to overcrowding or the general prison environment, can lead to increased disease transmission and greater risks of contracting TB.

Prisons also tend to have poor ventilation as large windows are seen as apertures for escape rather than good sources of airflow (5, 11, 33). In some prisons, windows do not open at all and all ventilation must come via mechanical means. As mentioned above, ventilation may not be as serious a concern in the PC due to the permanently open windows in its cell blocks. However, overcrowding within cells may reduce the benefit of greater airflow. More broadly than just ventilation, poor construction is common in prisons throughout the world, as efforts are made to make facilities difficult to escape rather than conducive to respiratory and other types of health (34). Lack of quality construction can contribute to the environmental factors that help the spread of TB disease.

Apart from the physical infrastructure that accompanies prisons, another cause of poor health among the incarcerated is limited access to and poor utilization of health services (11, 29, 30). Prisons may lack adequate number of health care workers, from physicians to lab technicians. These positions often have low retention and high turnover due to bad pay and benefits (35) and those who remain on correctional health staffs may not be qualified to find positions elsewhere. Even when health care workers are present, detainees may not be able to access their services. Prison guards have been noted to view prisoner health as a privilege to be taken away to punish infractions, rather than an inalienable human right (29). From the perspective of the prisoners, there is a tendency to prioritize survival over health. That is, being labeled as “sick” could result in physical danger, as the individual is seen as weak, or the loss of livelihood within the prison. Being sick could limit family visits or other freedoms (29).

Other characteristics of detainees may result in their poor health. Those at highest risk for detention in jails or prisons are often from high-risk and low health attainment communities in the general population (13). Those entering prisons are more likely to have immunosuppression due

to HIV co-infection (4). In Haiti, the prevalence of both HIV and TB is high, at 1,900 per 100,000 population ages 15-49 and 307 per 100,000 population (all ages), respectively (14, 25). Both prisoners and their visiting family members are likely to have low health education, especially when it comes to the risks for transmitting or being infected with TB disease (30). Without that education, disease transmission into and out from the prison setting becomes more likely.

Recommendations from the Literature

One of the most common areas the literature highlights for improvement related to TB has to do with screening for the disease. Appropriate and effective screening will improve the health of those infected, by allowing them to get the treatment they need, and those uninfected, by isolating those at risk of transmitting the disease to others. Screening on arrival at the prison system is the preferred time (7, 32), and periodic subsequent screenings could act as a supplement to detect any in-prison transmission. A common, though not recommended, method of conducting screening is to screen only those with symptoms of TB or a history of risk factors of TB. Very few studies recommend symptomatic screening as an effective method of case discovery. A study by Banu et al. posits that it can serve when chest x-rays are not available (6). Other studies note that symptomatic screening can miss many cases: 40% would have been missed in a Cameroonian prison (8), and similar results were observed in a Brazilian prison (9). More studies indicate that universal screening on entry is the preferred detection method (2, 4, 34) and one indicates that using chest x-rays to conduct this screening, as is done in the PC, is a good solution (9). Regardless of the method, rapid diagnostic testing followed by the implementation of treatment and institutional controls is the recommended way to reduce transmission (33).

Active case-finding is also recommended in the literature on correctional TB control (10, 32, 34, 35). Rather than waiting for prisoners to come forward with symptoms of TB, as mentioned above this is ineffective as prisoners often make their health a lower priority (29), active case-finding involves the ongoing assessment of prisoners regarding their infection status.

This would allow for a more methodological evaluation of in-prison prevalence, and ongoing active case-finding would allow for the estimation of transmission and incidence. Once persons with TB disease have been identified, they should all be put on therapy (33). This would be obvious in other settings, but in prisons, with limited resources and the perception of detainee health as less than a right, it can represent a definite change in policy. In addition to just TB treatment, prisons are recommended to conduct HIV and TB prevention efforts in concert due to the serious risk of co-infection (34). This process would include counseling and testing at entry to and exit from the prison, as well as during health care visits. Condom provision and male circumcision are two additional HIV prevention options that could limit the spread of TB disease in the prison environment (34).

Policy changes are another area with many recommendations in the literature. Moller et al. advocate what they call a "whole prison" approach to reduce transmission (36). This approach includes political and management support of policies that have been proven effective in controlling TB and have been specifically targeted to the needs of the prison environment. Inclusion of input from prison staff is a critical aspect of such policies. Changing the metrics by which prison management is evaluated to include health measures in addition to security objectives is another aspect. Health staff would be encouraged to treat prisoners as patients, and would themselves receive support and protection to prevent their infection with TB. These staff member would also receive ongoing training and benefits would be restructured to improve retention. From the prisoner side, health literacy is an important part of the "whole prison" approach if it can provide information to meet prisoner needs and abilities (36). Rutz et al. focus on ensuring that screening policies are followed, as failure to perform the appropriate tasks can undermine the best-crafted TB infection control policy. This is of particular concern with respect to timing, as delays in testing and isolation could result in additional transmission (21). Participatory communication is recommended as a way to increase prisoner utilization of health

services by correcting misunderstandings, reducing the stigma surrounding TB, and strengthening community ties within the prison environment (30).

At a physical level, improvements to prison architecture and infrastructure could help to reduce the transmission of TB (33). These improvements would address the environmental factors leading to TB infections. A greater number of smaller cells would reduce the impact of overcrowding and cell sharing as risk factors, and designs that allow for better natural airflow would decrease droplet nuclei density without needing to rely on mechanical circulation. However, this sort of change may be beyond the capacity of many countries, including Haiti. Furthermore, Reid et al. demonstrate that improvements in infrastructure alone will not resolve TB transmission within prison environments and must be couple with other changes (34).

The broadest recommendations in the correctional TB literature come at the structural or systemic level. These more political efforts involve health authorities, prison staff, families of prisoners, NGOs, and donor organizations (30). Such diverse groups would work together to raise awareness in the community about conditions within prisons and how they impact the overall health of the population. Improving the coordination of care delivery could be a focus of such work. Better collaboration between the ministry for prison administration and the health ministry is another high-level improvement that could noticeably improve prisoner health and reduce the spread of TB (36). The principles of Restorative Justice would remove much of the punitive aspects of incarceration and would be expected to improve inmate health by improving the entire correctional culture. This sort of change may be beyond Haiti's ability to effect, and may not be desirable to the Haitian people. It is certainly beyond the scope of this assessment project.

Mongolia represents an example of how a prison system can be changed to substantially reduce in-system transmission of TB. Yanjindulam et al. describe the implementation of a standardized double entry screening process between 2002 and 2005 (32). All detainees are held in one of 16 detention centers while awaiting trial. Each is screened upon arrival to the center and

then again after sentencing when they are moved to the single allocation center before being assigned to one of the prisons throughout the country. The centralized testing location consolidates laboratory facilities and functions as the referral hospital for the prison system. TB positive prisoners are housed in the prison TB hospital. Passive detection is used to discover incident cases among those determined to be without TB at the time of allocation. This process has resulted in a 60% reduction in TB case notification. Mongolia's example shows that large-scale transformations are possible and can have strong positive results.

Barriers to Health Improvement

There are barriers to improving the health of prisoners at higher, policy levels and at more immediate, interpersonal levels. With respect to national organization and budgeting, prison health care is often provided by the Ministry of Justice, or other group in charge of prisons overall, and can be isolated from the funds and goals of Ministries of Health (36). This isolation results in poorer health conditions for prisoners as well as the community at large, which is harmed by the spread of health conditions that result from time in prions. Moller argues that health issues in prisons cannot be the sole responsibility of prison health care staff and should be connected with the overall goals of the Ministry responsible for Health in each country (36).

Prisons in Haiti – Prison Civile

The Prison Civile is the primary prison in the capital and largest city of Haiti, Port-au-Prince. It was overcrowded in 2004, when 1028 prisoners escaped during a coup d'état. At the start of 2010, it held over 4,000 people in a space built for 800 (12). The growth in prison population was largely due to the slow pace of the judicial system, with only a small fraction of those detained having been convicted of a crime. The vast majority were being held while awaiting trial. During the earthquake, the cell blocks remained largely intact, but there were collapses in administration buildings. As guards and prison staff left their posts to search for their families or find new housing, the prisoners also fled. Within a month though, it started to fill

again, and as of September 2012, held over 3000 detainees again. Pre-trial detainees still make up a large percentage of the prison population (12). These people, who have not yet been convicted of any crime, are being directly exposed to the health risks that prisons represent.

The PC is located in downtown Port-au-Prince. The dome of the collapsed presidential palace was visible from the facility in 2012, prior to the razing of that building. The prison is composed of multiple buildings of cell blocks. The largest is known as Titanic, and contains several floors with over ten cells per floor. These cells will hold up to 30 detainees in spaces designed for far fewer. There are not enough beds for all those housed in each room, so most sleep in hammocks made of bed sheets hung from the bars on the windows and the doorframes. International agencies recommend a minimum of 5.4 m^2 for each inmate in a solitary cell and 3.4 m^2 for each inmate in a dormitory-style, multiple-occupancy cell (37), but the PC overall has much less space per person than this and conditions are much more crowded. The detainees spend much of their days and nights in these cells, with limited time available to move about the exterior areas within the walls.

Nutrition in the prison is limited, as the cooking facility prepares two meals a day with the resources they have. There were systematic outbreaks of beriberi during periods in which the budget did not allow for the purchase of nutritional food (12). Many detainees have their nutrition supplemented by family member or friends who will bring food in to them directly. Figure 1, from Google Earth, shows the layout of the prison with different areas labeled for reference purposes.

Health through Walls in Haiti

Since its formation in 2001, Health through Walls (HtW) has provided multiple services, including training, technical assistance, direct patient care, and resources such as supplies and medicine to prisons in several developing countries. Prior to the 2010 earthquake, HtW was engaged with multiple projects. The organization spearheaded efforts to control the spread of

infectious diseases such as TB and HIV within the prison walls, and had also developed programs aimed at helping prisoners improve their own living space and sanitation. The ongoing infectious disease control project is called the Control and Prevention of the Spread of Contagious Disease project (CPSCD). This project is an attempt to build the capacity for both treating victims of these diseases in the prison and preventing new cases from occurring. Before the earthquake, HtW was in the process of establishing a TB detection program using a digital chest x-ray machine for diagnostic purposes. While many TB prevention efforts in low-resource settings have not focused on newer technologies in the same way, HtW believes that digital technology allows for more effective diagnoses. The digital radiographs could be sent via email for evaluation in other parts of the world with greater capacity to make a diagnosis quickly. The digital machine would be more portable than traditional x-ray machines, so if it proved to be effective in the PC it could be moved to other prisons for screening efforts there without requiring the expense of additional machines. Unfortunately, in the aftermath of the earthquake the x-ray machine was lost to HtW and it has only recently been replaced. This replacement has led to the first-ever mass screening of prison stock population for TB, coupled with ongoing screening of all new entrants. It is the effectiveness of this screening program that this evaluation has been conducted to assess (15).

Methods

A presentation at Emory University in March 2012 by Dr. John May of Health through Walls sparked this assessment. Dr. May discussed the plans to conduct this mass screening effort and mentioned an interest in having the process evaluated for effectiveness. In September 2012 the investigator visited the Prison Civile in order to discuss in person the planned assessment with prison and HtW staff. This visit allowed the investigator a sense of the facility, the work that HtW does there, and what data and records would be available for use in such an assessment.

Data Sources

The data for this evaluation has come primarily from a database maintained by HtW staff. In March 2012, two students from Emory University visited the PC and assisted with the establishment of an EpiInfo (CDC, Atlanta) database which would be used to organize and compile data collected during the mass screening already underway. This database contains information on all prisoners screened, both new entrants and stock population. Furthermore, these data include the necessary date fields to determine to which group (entrant or stock) each screened prisoner belongs, allowing the exposure of interest to be assessed. This database also includes information on such potential confounders as: body mass index (BMI), cell block housing, results of HIV testing (if any), and prisoner age at time of screening.

The EpiInfo screening database has been supplemented with two additional data files. The first is a prison roster maintained by United Nations and Ministry of Justice staff working with the PC. The roster contains records for each prisoner entering the PC since its reopening in 2010 after the earthquake. The demographic fields of interest for this study included: residence location prior to incarceration, as well as fields allowing for the verification of prisoner age, cell block assignment, and date of entry to the prison. Residence prior to incarceration was used in an attempt to determine whether prisoners from areas with higher endemic levels of TB would be more likely to be infected. Date of entry information helped in the assignment to the stock or entry group.

Additional prisoner data comes from the database maintained by HtW doctors for the purpose of managing the care of those being treated for active TB disease. From this data set the investigator has obtained information on the outcome variable of interest: the case status of each screened inmate. All identified individuals with TB disease have been included in this listing, so all other screened inmates are considered non-cases. Additionally, this database has provided information on the dates of: entry into the prison, screening for TB, and commencement of

treatment for TB. The investigator has also been able to verify the ages of prisoners at the time of screening using this dataset.

The versions of these data used in the final evaluation were gathered by Elisa Ignatius, a medical student at Emory University, on a trip to Haiti in March-April 2013.

Data Security

The Emory Institutional Review Board reviewed this assessment before any data gathering or research took place and determined that it did not meet the standards of research and therefore would be exempt from review. Experts on HIPAA requirements at Emory University reviewed the evaluation methodology and advised on avoiding any violations regarding personally identifiable information.

All data were de-identified before being passed to the investigator for analysis. Names of inmates and family members were removed from the files as they were directly identifiable. Prisoner ID numbers were kept in the data sets temporarily, as these numbers were the only unique field in common to each of the three datasets. Once the data had been joined together, the prisoner ID numbers were removed and replaced with randomly assigned unique identifiers.

Data Cleaning and Analysis

Starting with the prison roster dataset, as it had the largest number of prisoner records, the EpiInfo database was joined based on matching prisoner ID numbers. The case record dataset was then joined to the combined file also based on prisoner ID numbers. The data were then reviewed and corrected where possible. There were a number of individuals for which the ID number had been mis-keyed during data entry into one of the datasets, so in those cases records were matched manually using other available information including birthdate or date of entry into the prison. There were also coding errors in dates, particularly due to different practices in date formats between the French and American systems (day/month/year compared to

month/day/year, respectively). Categorical variables were also cleaned to remove redundant labels. Figure 2 depicts the data cleaning process graphically. Data cleaning and joining were performed using Microsoft Excel 2010.

Outcome classification came directly from the case database. Each prisoner in that database was considered a case of TB disease, and all other screened prisoners were considered non-cases. The exposure of interest was time spent in the prison, so prisoners were divided into new entrants or stock population. New entrants were any prisoners screened within one month of arrival at the PC. Stock prisoners were categorized in two different ways. In the first, they were all prisoners screened more than one month after arrival. In the second, stock prisoners screened between the beginning of March and the end of June 2012 were considered part of the mass screening effort, while those screened either before or after were considered other stock. In order to estimate a linear relationship between time in the prison and prevalence of TB disease, exposure was also considered on a continuous monthly scale, with new entrants as zero months, and stock prisoners as the difference between their arrival and screening would indicate.

Potential covariates and confounders were identified based on a review of the literature on correctional TB. HIV and TB are common co-infections as HIV lowers the body's ability to fight TB infections and prevent LTBI from becoming active TB disease. Since HIV testing was performed for some of those ever screened for TB by HtW, the results of HIV testing could be related to likelihood of being a TB case (16). In order to assess transmission based on the close interpersonal contact provided by living quarters (10), cell block has been added as a covariate. The two stories of the Brick cell block have been collapsed into one in order to avoid a zero value for combinations of case status and cell block. The seven prisoners in isolation have been excluded from the cell block analysis, both to avoid another zero-value cell and to reflect that isolation likely inhibits transmission of TB bacilli. Increased age may be connected to increased likelihood for contracting TB or having LTBI convert to TB disease, so prisoner age at screening

has been included as a potential covariate. Location is not only a transmission concern within the prison, so inmate residence prior to incarceration has been considered as another covariate. A history of previous treatment for TB indicates prior infection, and if treatment was interrupted due to the earthquake or other cause, it could lead to transmission of resistant strains (12). Low BMI can be connected to poor health and decreased ability to fight infection (16), but can also be a symptom of TB so it will be considered a potential risk factor and confounder.

After cleaning, the data were transferred to SAS 9.3 (Cary, NC) for analysis. Univariate logistic regression was conducted between the different classifications of exposure (entry/stock, entry/mass screening/other stock, number of months between arrival and screening) and the other covariates to assess which are associated with being a case. Multivariate regression was conducted for each of the categorizations of exposure using backwards elimination to develop a final model indicating the risk factors for TB disease in the PC. Looking specifically at the broad group of prisons considered in the stock population, covariates will be assessed using univariate logistic regression to see which are associated with increased prevalence in the PC.

Results

General Results

New entrants to the PC represent just over half (54.3%) of the evaluation population, with the balance belonging to one of the two types of stock population (Table 1). The mean length (in months) between admission and screening is: 6.02 [8.52]. Average prisoner age at time of screening is: 29.73 [9.36] and the average BMI is: 22.30 [8.52]. The majority of prisoners screened for TB did not have an accompanying HIV test (79.30%). Of those who did 1,053 (20.28%) were negative and 22 (0.42%) were positive. The majority of prisoners (50.84%) come from Ouest Department, which contains Port-au-Prince. Admission is the cell block housing the

largest concentration of screened inmates (45.73%). A vast majority of prisoners have not had prior treatment for TB (96.12%).

The overall prevalence of TB in all screened inmates is: 1,540 cases per 100,000 persons (Table 2). This value is several times the WHO-estimated national prevalence of 307 cases per 100,000 persons (14). The prevalence among new entrants is 780 cases per 100,000 persons and among stock prisoners it is 2,444 cases per 100,000 persons.

Before starting the modeling process to predict differences in TB prevalence based on prison arrival classifications, the covariates identified from the literature were tested against case outcome in univariate logistic regressions. As can be seen in Table 3, regardless of classification, the time between arrival at the prison and TB screening was significant at the 5% level. Of the different levels of cell blocks, Dispensaire, Titanic 1, and Titanic 2 had significantly different odds of prevalent cases (ORs and 95% CIs: 6.57 [1.44, 29.91], 8.10 [2.39, 27.52], 4.88 [1.15, 20.67], respectively). The other cell locations were not significantly different from the referent group, Titanic 3. BMI, coded as a continuous variable, was the only other covariate significantly associated with case status (OR: 0.78 [0.70, 0.86]), with higher BMI associated with lower prevalence of TB. History of previous treatment for TB was nearly significant at the 5% level (OR: 2.19 [0.94, 5.11]) but age at screening was not associated with increased prevalence (OR: 0.99 [0.97, 1.02]). HIV status was not significantly associated with increased prevalence (OR: 4.13 [0.51, 33.24]) but given the small subset of prisoners tested and recorded, this estimate may not be stable. Previous location could not be plotted against the outcome due to the high number of cells with zero associated individuals, but Fisher's exact test (P=0.0002, Prob<P: 0.002) suggests there may be some relationship between location and prevalent cases.

Stock Population / Entrant Classification

The unadjusted odds ratio between new entrants to the PC and all stock prisoners is: 3.185 [1.944, 5.219] (Table 4). In this case, new entrants are the referent group as they have not

been exposed to conditions within the prison. The unadjusted odds of being a prevalent case are more than three times higher for stock prisoners than for entrants to the prison. After conducting backwards elimination starting from a model with stock/entry classification, BMI, age at screening, previous treatment, and interaction terms between exposure and the covariates, only BMI remained significant along with stock/entry. Cell block location was excluded from this analysis due to concerns about the relationship between exposure and location. A chi-square test indicated that the interaction terms were not significant (χ^2, 3 df: 3.13). The odds ratio comparing stock prisoners to new entrants adjusted for BMI is: 2.72 [1.65, 4.49]. Adjusted for BMI, the odds of being a prevalent case are significantly different between entrants and stock prisoners.

Entrant / Mass Screening Stock / Other Stock Population Classification

Stock prisoners not included as part of the mass screening were either missed during the effort or diagnosed prior to its commencement. For this categorization, the stock prisoners screened during the mass screening are considered the referent group so that differences between them and other stock prisoners could be highlighted. The unadjusted OR for new entrants compared to mass screening stock is: 0.35 [1.72, 4.25] while the unadjusted OR for other stock prisoners compared to the mass screening is: 2.15 [1.14, 4.03]. Prisoners in the mass screening have odds of being a prevalent case significantly different from both new entrants and other stock prisoners. Modeling started from a similar model to the above, with indicators for the levels of exposure along with BMI, age, treatment history, and interaction terms between exposure and covariates. Again, a chi-square test indicated that there was no significant interaction in this model (χ^2, 6 df: 5.57). As with the above dichotomous exposure classification, backwards elimination resulted in a model with only BMI significantly associated with case outcome. The adjusted OR for new entrants is: 0.38 [0.23, 0.64], while the adjusted OR for other stock prisoners is: 2.15 [1.15, 4.03]. Both new entrants and other stock prisoners have significantly different odds than those prisoners accounted for in the mass screening after adjusting for BMI.

Continuous Time from Entry to Screening

The unadjusted OR for time (in months) between entry to the PC and screening is: 1.05 [1.02, 1.07]. For each additional month in the PC for screening, the odds of being a prevalent case increase by 5%. Backwards elimination was conducted starting with the same type model as in the previous two classifications (covariates and exposure/covariate interaction terms). A chi-square test indicated a lack of significant interaction (χ^2, 3 df: 3.39). Again, after the process of backwards elimination, only BMI remained a significant predictor. The adjusted OR for time in the prison as a continuous exposure is: 1.04 [1.02, 1.06]. After adjusting for BMI, each month spent in the PC before screening increases the odds of being a prevalent case.

Stock Population Prevalence Factors

To investigate which covariates are associated with increased prevalence among the stock population, restricted univariate logistic regression was conducted (Table 5). From cross-tabulation of cases and cell block locations, it was estimated that Titanic 1 has higher prevalence than other locations. The difference in prevalence was significant (OR: 7.90 [2.33, 26.81]), indicating that more cases came from this floor than would be expected by chance. BMI was also significantly associated with prevalence in the stock population (OR: 0.76 [0.67, 0.85]), though HIV (OR: 2.97 [0.35, 25.12]), history of previous treatment (OR: 1.40 [0.43, 4.58]), and age (OR: 0.99 [0.96, 1.02]) were not significant factors.

Discussion

Tuberculosis prevalence in the Prison Civile (1540 cases per 100,000 persons) is higher than the national prevalence estimate (307 cases per 100,000 persons) (14). Stock prisoners have a prevalence (2,444 cases per 100,000 persons) nearly eight times the general population and the prevalence among new entrants (780 cases per 100,000 persons) is more than double the national level. While these levels of TB disease seem high, they actually suggest that the situation in the

PC is more controlled than in the correctional systems of other developing countries. A jail survey in Bangladesh found a prevalence 20 times higher than the national level, and a survey of prisons in Eastern Ethiopia found a correctional prevalence seven times that of the general population (5, 6). The situation in the PC and Haiti is better than in the United States, which has a correctional TB prevalence (81 cases per 100,000 persons) nearly eight times as high as the non-incarcerated prevalence (11.9 cases per 100,000 persons) (38). These estimates indicate that the TB control and treatment strategies are working and the higher prevalence in the PC could be due to the prison acting as a reservoir for TB cases by importing individuals who are at higher risk for TB infection and come from vulnerable populations (13).

There are multiple possible explanations for the different levels of prevalence among those exposed and unexposed to the PC environment. First, ongoing importation of TB cases in entrants and differential patterns of release by infection could result in result in higher numbers of infected persons among the stock population. Second, the stock population is made up of the prisoners incarcerated first after the PC reopened following the earthquake. If these prisoners were different from those incarcerated later in terms of TB exposure prior to prison, the time of incarceration would be impacted by a kind of selection bias. If, for example, those incarcerated earlier were the hardened criminals or the poorest of the poor, their risk for prior TB exposure could be higher and their prevalence would therefore be expected to be higher. This cross-sectional study cannot distinguish between these possibilities, but a follow-up longitudinal analysis of these individuals could answer the question of why prevalence is so much higher among prisoners, and especially among stock prisoners.

Regardless of how exposure is characterized, more time spent in the environment at the PC is associated with higher odds of being a prevalent case of TB disease. This relationship is visible in both unadjusted odds ratios and odds ratios adjusted for confounding by BMI. Taken as a group, the odds of being a prevalent case among the stock population are more than twice the

odds among new entrants (OR: 2.72, [1.65, 4.49]). Each month spent in the PC environment increase the odds of being a case by four percent (OR: 1.04 [1.02, 1.06]). When the stock population is broken out by those screened as part of the universal effort and those screened at another time, the latter group has significantly higher prevalence odds (OR: 2.15 [1.14, 4.03]).

These estimates of the prevalence odds ratios represent a baseline in the evaluation of TB control strategies in the PC. Higher prevalence among stock populations does not necessarily indicate that there is ongoing transmission of TB between prisoners, but it does demonstrate that TB should continue to be a priority for HtW and prison health staff. Higher stock prevalence may be the result of an ongoing influx of TB cases. If these cases are not detected at arrival, they move into the stock population and add to the prevalence even without transmission. A follow-up study to compare this estimate of 2012 prevalence with future prevalence would allow for better assessment of the trend in cases and determination of risk factors.

The association between increasing time in the PC and increasing odds of TB prevalence indicates the need for screening and treatment of all new entrants soon after arrival at the prison. Those prisoners not included or missed in the universal screening had higher prevalence odds (OR: 2.15 [1.14, 4.03]) than both new entrants and stock prisoners screened during the mass effort. This difference may be due to passive case finding based on symptoms and the higher prevalence of TB among those having spent considerable time in the PC reinforces the importance of continuing TB screening and control efforts.

There is the potential for uncontrolled confounding in these models due to HIV and prior location. With respect to HIV, only 20% of the inmates screened for TB had a recorded result for an HIV test. That proportion included very few cases of TB, so the estimates generated by logistic regression with HIV status as a covariate were not stable. The investigator elected to remove HIV as a potential covariate from the models and accept potential confounding in favor of stable odds ratio estimates. With respect to prior location, the vast majority (95.94%) of prisoners comes to

the PC from Ouest department generally and Port-au-Prince specifically (76.44%), which makes sense given the prison's location. There were only three locations that gave rise to cases of TB (Port-au-Prince, Croix des Bouquets, and Petit Goave), and the number of zero-value cells resulted in quasi-complete separation of values in logistic regression. As with HIV, the investigator preferred to accept potential uncontrolled confounding over unstable estimates.

The cell block was excluded from the list of potential covariates in the modeling strategy because it was determined to be, in part, caused by exposure. The proportion of new entrants assigned to the Admission block (75.21%) is noticeably different from the proportion of stock prisoners in the same building (10.56%). This difference, coupled with the name of the building, suggests that new entrants are often assigned to Admission temporarily before being given a permanent housing location. Therefore, cell block could not be considered a determinant of exposure, but was rather a result of it. Controlling for housing location in the prison may block an indirect association between exposure and outcome.

In addition to comparing TB prevalence among entrants and stock prisoners, this assessment identified two factors significantly associated with higher prevalence among the stock population. The first floor of the Titanic building (Titanic 1) had a higher prevalence of stock population cases (6.23%) than the other cell block categories (average: 1.88%). This difference turned out to be a significant predictor of case status among stock prisoners (OR: 3.31 [1.90, 5.75]). This result suggests the first floor of Titanic, which is lower to the ground and has poorer ventilation than the upper floors of Titanic, would be a good site to investigate for ongoing interpersonal transmission of TB. More granular data, including the specific cell each prisoner is assigned to and the overlap of groups in the prison yard at the same time, would allow for more precise estimates and models of transmission. Lower BMI, as with the models above, was the other factor significantly associated with case status among stock prisoners (OR: 0.76 [0.67,

0.85]). Weight loss is a known symptom of TB (16), so this result is not surprising, but it may be used as a criterion for re-screening in attempts to discover evidence for transmission.

Limitations

There are several limitations to the conclusions that can be drawn from this assessment. The first is that due to the cross-sectional nature of the data, no inferences can be drawn as to the rate of infection occurring within the PC. The analysis in this evaluation cannot determine whether the higher prevalence observed among stock prisoners is due to an ongoing influx of previously-infected prisoners or to interpersonal transmission between prisoners. Another potential assessment limitation based on the study design is the use of different periods to define prevalence for the different exposure groups. The different time periods raises a concern about exchangeability between the stock and entrant populations.

In addition to limitations from the study design, the available data also restrict the conclusions that can be drawn from this evaluation. There is potential for misclassification of exposure, outcome, and/or covariates due to improper data entry or combination and inconsistent recordkeeping. Several hundred records in the EpiInfo screening database could not be matched to the roster due to unusable prison ID numbers. These IDs are seven-digit numbers designed to reflect the year, month, and order of an individual's incarceration. The unusable ID numbers often had fewer than seven digits or did not reflect a possible date of entry. Therefore the time between entry and screening could not be calculated for many of these inmates, and without an exposure they had to be excluded. As all identified cases of TB disease were matched, this exclusion may have resulted in overestimation of the prevalence. Dates were also inconsistently recorded, and the investigator often had to change the dates in the data based on a decision as to whether a French (day/month/year) or American (month/day/year) coding was intended. This may have led to misclassification of exposure. Misclassification of outcome may have arisen as the case listing may have been incomplete and missing cases discovered early in the screening

process (Personal communication with Elisa Ignatius). Misdiagnosis of active TB could also come from a lack of analyzed sputum cultures. The testing laboratory is notably inconsistent, but HtW staff attempt to mitigate through the use of empirical treatment among individuals with suspected TB (Personal communication with Elisa Ignatius).

Selection bias is another potential concern and limitation on the evaluation results. The mass screening effort was not fully universal, and bias may have occurred if those who were missed in the screening were significantly different from those who were included. The odds ratios for the three-level classification of exposure indicate that this may be the case. Among the covariates, HIV testing represents potential selection bias. The decision for having an HIV test was left to the individual, resulting in tests for only 20% of those screened. This low percentage made it difficult to analyze the role of HIV-TB co-infection, which is an important factor in transmission based on the literature. While the above limitations do raise questions about the magnitude of the observed relationships between TB disease, exposure to the prison environment, and covariates, the strength of association is such that the investigator feels confident in the overall conclusion that TB prevalence is higher among the stock prisoners than new entrants.

Recommendations

While higher TB disease prevalence in the PC population than in the general Haitian population indicates that this is a good place to focus screening efforts, the fact that the difference between these prevalences is smaller than in many countries suggests that the control efforts of HtW have had success in preventing rampant transmission. Based on the results above, the investigator recommends that HtW maintain the broad strokes of the current procedures. HtW and prison health staff should continue to screen inmates upon their entry to the prison. This screening should be conducted soon after arrival - preferably within a month to avoid the monthly increase in odds of being a prevalent case. Any missed individual represents a risk for infection, so HtW should continue to be rigorous about working to screen all new entrants and work on screening

any backlog of overlooked inmates. Late screening is better than no screening, though if HtW can acquire the capacity to conduct on-site GeneXpert testing, the time needed to detect acid-fast bacilli in sputum would be reduced and infectious persons could be isolated more quickly. Guidelines for data collection and entry should be standardized to allow for tracking of individuals over time and comparison between data sets.

One of the weaknesses of this evaluation is its cross-sectional nature, so the investigator would recommend that HtW continue to monitor the number of TB cases and the overall population level so that the estimate of prevalence among the stock population may be updated in several years and any trend may be assessed. Once a trend has been established, causal factors associated with prevalence can begin to be investigated and addressed.

In the meantime, the data suggests that Titanic 1 should be made a priority for environmental improvements. If ultraviolet germicidal irradiation fixtures are available, installation in Titanic 1 could have the most impact on preventing transmission if there is any occurring. Designating space in the new cell block, New York, to some of the prisoners currently housed in Titanic 1 would reduce overcrowding on that floor and could help ameliorate some of the close contact that is correlated with transmission in the literature (8, 11, 12, 16, 32).

Public Health Impact

This assessment of TB disease in the Prison Civile adds another demonstration of how prevalence in correctional facilities is frequently higher than in the general population (1, 5-9). While the results of this evaluation are not necessarily generalizable to other prisons, they can serve, as mentioned above, as a baseline for follow-up analyses. In several years, such studies could compare these results to updated prevalences to assess any trends in prevalence and identify causal factors associated with it. Follow-up studies could also apply these data to investigations of transmission.

Beyond the walls of the Prison Civile, the data used in this study could be applied to a follow-up assessment of the digital x-rays used to diagnose cases. If that procedure is determined to be an effective substitute to sputum culture in low-resource settings, the techniques developed at the PC could be applied to prisons throughout Haiti and the developing world. The focus on TB diagnosis in such locations could shift to portable digital machines, decreasing the need for sophisticated laboratory analysis.

Tables and Figures

Table 1: Descriptive Statistics of Covariates of Active TB Disease among Screened Inmates in the Prison Civile, Haiti from March 2012-13

Covariate	n	(%)
Time in Prison		
Entrant	2,819	(54.30)
Total Stock	2,373	(45.70)
Entrant	2,819	(54.30)
Mass Screening	2,331	(44.90)
Other Stock	42	(0.81)
Months to Screening μ [sd]	6.02	[8.52]
HIV Status		
HIV Status Unknown	4,117	(79.30)
HIV Negative	1,053	(20.28)
HIV Positive	22	(0.42)
Cell Block		
Admission	2,364	(45.73)
Bois Verna	268	(5.18)
Brick	956	(18.49)
Dispensaire	83	(1.61)
Greffe	651	(12.59)
Isulement	7	(0.14)
Titanic 1	340	(6.58)
Titanic 2	138	(2.67)
Titanic 3 (referent)	363	(7.02)
Previous Location		
Artibonité	7	(0.13)
Centre	9	(0.17)
Grand'Anse	6	(0.12)
Nippes	4	(0.08)
Nord	28	(0.54)
Nord-Est	1	(0.02)
Nord-Ouest	3	(0.06)
Ouest	3,159	(60.84)
Sud-Est	27	(0.52)
Sud	1,958	(37.52)
Previous Treatment for TB		
No	4,882	(96.12)
Yes	197	(3.88)
Age at Screening μ [sd]	29.73	[9.36]
BMI μ [sd]	22.30	[3.83]

Table 2: Prevalence of TB Disease among Screened Inmates at the Prison Civile, Haiti from March 2012-13

Stock / Entry Breakdown	**Cases**	**Total Population**	**TB Prevalence** (cases/100,000 persons)
Prison Civile Overall	80	5,192	1,540
Entrants	22	2,819	780
Stock	58	2,373	2,444
Mass Screening Stock	52	2.331	2,231
Other Stock	6	42	14,286

Table 3: Univariate Analysis of the Association of Active TB Disease and Covariates among Screened Inmates in the Prison Civile, Haiti from March 2012-13

Covariate	Active TB cases		Non-cases of TB			
	n	(%)	n	(%)	OR (95% CI)	P value
Time in Prison						
Entrant	22	(0.78)	2,797	(99.22)	1	
Total Stock	58	(2.44)	2,315	(97.56)	3.19 (1.94, 5.22)	<0.0001*
Entrant	22	(0.78)	2,797	(99.22)	0.35 (0.21, 0.60)	<0.0001*
Mass Screening	52	(2.23)	2,279	(97.77)	1	
Other Stock	6	(14.29)	36	(85.71)	2.70 (1.72, 4.25)	<0.0001*
Months to Screening [μ (sd)]	10.64	(9.31)	5.95	(8.49)	1.05 (1.02, 1.07)	<0.0001*
HIV Status						
HIV Negative	12	(1.41)	1,041	(98.86)	1	
HIV Positive	1	(4.55)	21	(95.45)	4.13 (0.51, 33.24)	0.1824
Cell Block^						
Admission	16	(0.68)	2,348	(99.32)	0.88 (0.26, 3.05)	0.8446
Bois Verna	5	(1.87)	263	(98.13)	2.47 (0.58, 10.40)	0.2194
Brick	19	(1.99)	937	(98.01)	2.63 (0.77, 8.94)	0.1214
Dispensaire	4	(4.82)	79	(95.18)	6.57 (1.44, 29.91)	0.0150*
Greffe	8	(1.23)	643	(98.77)	1.61 (0.43, 6.12)	0.4819
Titanic 1	20	(5.88)	320	(94.12)	8.10 (2.39, 27.52)	0.0008*
Titanic 2	5	(3.62)	133	(96.38)	4.88 (1.15, 20.67)	0.0316*
Titanic 3 (referent)	3	(0.83)	360	(99.17)	1	
Previous Location						
Artibonité	0	(0.00)	7	(100.00)	1	
Centre	0	(0.00)	9	(100.00)	-	-
Grand'Anse	0	(0.00)	6	(100.00)	-	-
Nippes	0	(0.00)	4	(100.00)	-	-
Nord	0	(0.00)	28	(100.00)	-	-
Nord-Est	0	(0.00)	6	(100.00)	-	-
Nord-Ouest	0	(0.00)	3	(100.00)	-	-
Ouest	66	(2.09)	3,093	(97.91)	-	-
Sud-Est	0	(0.00)	27	(100.00)	-	-
Sud	0	(0.00)	52	(100.00)	-	-
Previous Treatment for TB						
No	69	(1.41)	4813	(98.59)	1	
Yes	6	(3.05)	191	(96.95)	2.19 (0.94, 5.11)	0.0694
Age at Screening μ [sd]	29.19	[8.38]	29.74	[9.38]	0.99 (0.97, 1.02)	0.6152
BMI μ [sd]^	20.40	[2.59]	22.33	[3.84]	0.78 (0.70, 0.86)	<0.0001*

* Significant at α = 0.05 level

^ Significantly associated with stock/entry categorizations

Table 4: Unadjusted and Adjusted Multivariate Models for Impact of Stock/Entrant Population Categorization on TB Case Prevalence in the Prison Civile, Haiti from March 2012-13

Exposure Classification	Estimate	P Value	OR	(95% CI)
Entrant/Stock				
Unadjusted:				
Stock v. Entrant	1.16	<0.0001	3.19	(1.94, 5.22)
Adjusted:				
Stock v. Entrant	1.00	<0.0001	2.72	(1.65, 4.49)
BMI	-0.24	<0.0001	0.79	(0.71, 0.87)
Entrant/Mass Screening/Other				
Unadjusted:				
Entrant v. Mass Screening	-1.07	<0.0001	0.35	(0.21, 0.57)
Other Stock v. Mass Screening	0.99	<0.0001	2.70	(1.72, 4.25)
Adjusted:				
Entrant v. Mass Screening	-0.96	0.0002	0.38	(0.23, 0.64)
Other Stock v. Mass Screening	0.77	0.0167	2.15	(1.15, 4.03)
BMI	-0.24	<0.0001	0.79	(0.72, 0.87)
Linear Time in Prison				
Unadjusted:				
Time in Prison	0.04	<0.0001	1.05	(1.02, 1.07)
Adjusted:				
Time in Prison	0.04	0.0001	1.04	(1.02, 1.06)
BMI	-0.25	<0.0001	0.78	(0.71, 0.86)

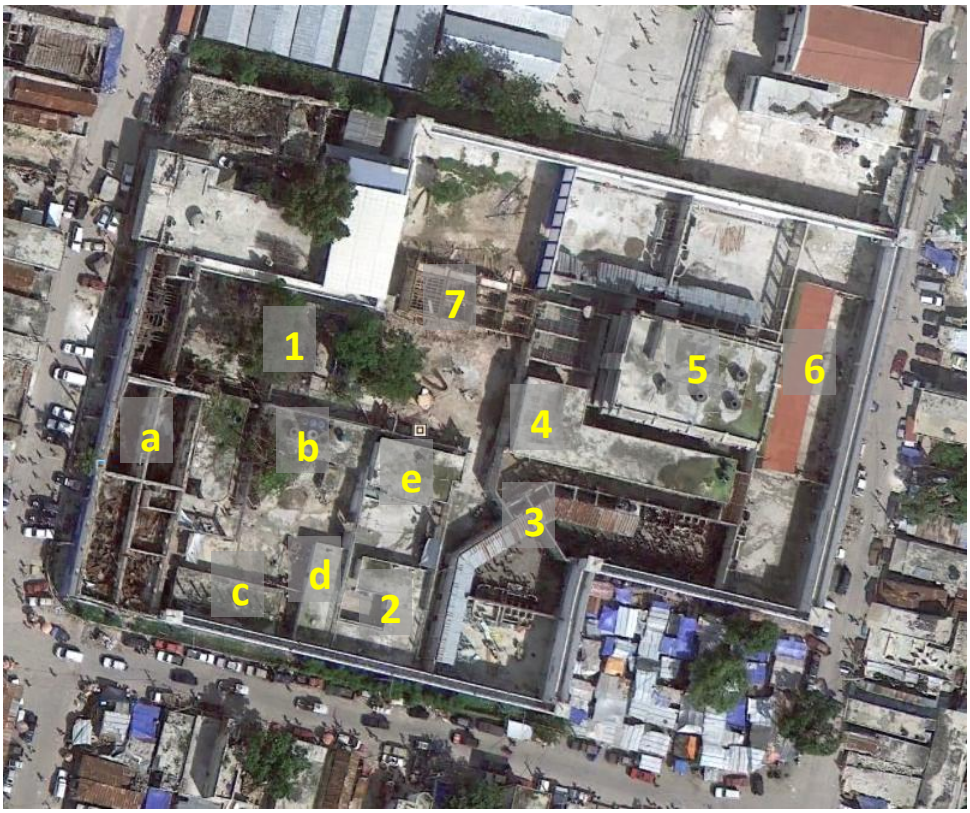
* Significant at α = 0.05 level

Table 5: Testing of Factors Associated with Prevalence of TB Disease among Stock Population in the Prison Civile, Haiti from March 2012-13

Factor	OR	(95% CI)
Cell Block (Titanic 1 v. all others)	3.31	(1.90, 5.75)
BMI	0.76	(0.67, 0.85)
HIV Status	2.97	(0.35, 25.12)
Previous Treatment	1.40	(0.43, 4.58)
Age at Screening	0.99	(0.96, 1.02)

* Significant at α = 0.05 level

Figure 1: Aerial View of the Prison Civile with Labeled Structures (Google Earth, 2010)



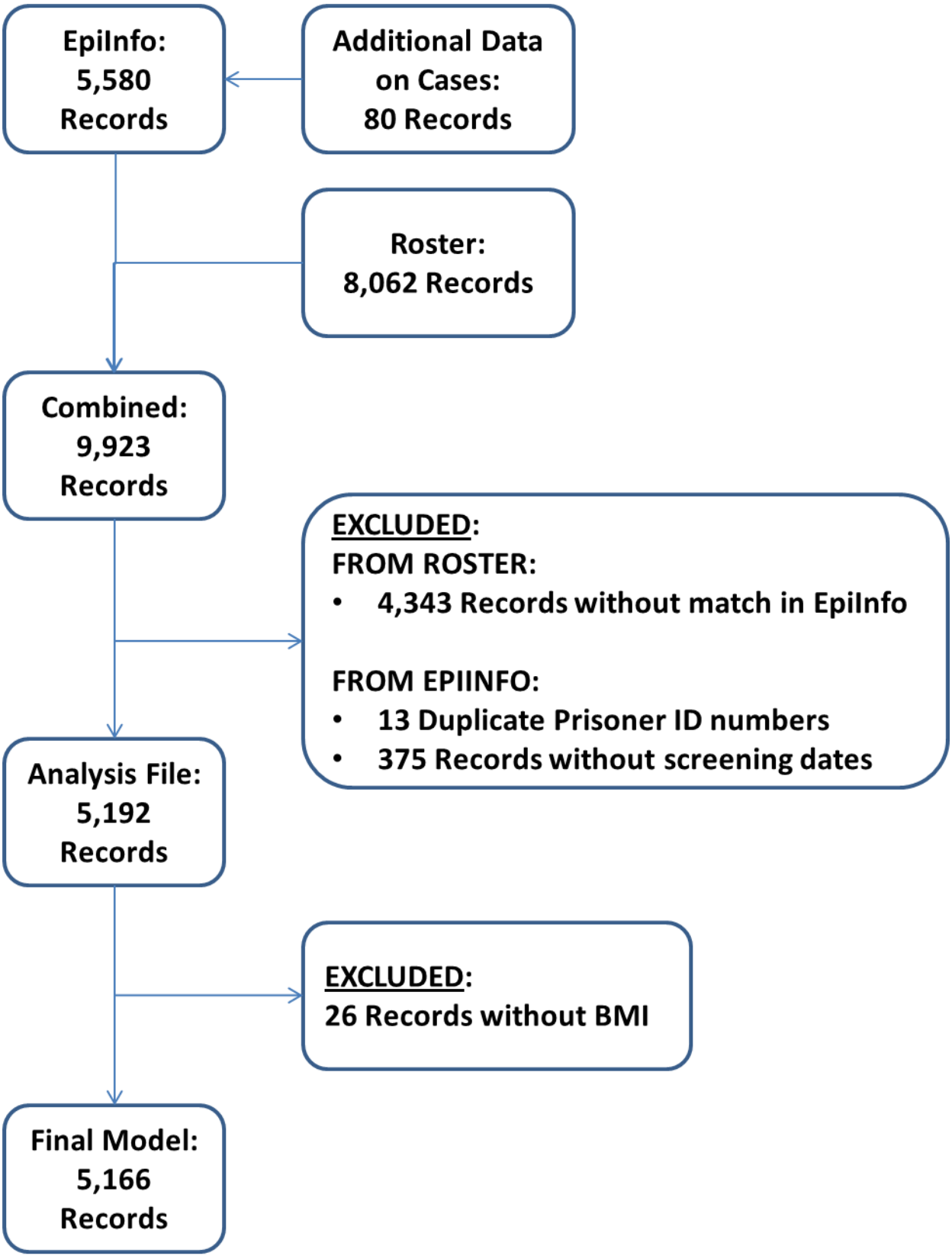
Cell Blocks:

1) Admission
2) Dispensaire
3) Greffe
4) Brick
5) Titanic
6) Bois Verna
7) New York (Under construction)

Other Buildings:

a) Entrance
b) Administration
c) Kitchen
d) Medical Buildings
e) TB treatment ward

Figure 2: Data Consolidation, Cleaning, and Analysis Process Flow



References

1. Baussano I, Williams BG, Nunn P, et al. Tuberculosis Incidence in Prisons: A Systematic Review. *PLos Med* 2010;7(12).
2. Mor Z, Adler A, Leventhal A, et al. Tuberculosis behind bars in Israel: Policy making within a dynamic situation. *Isr Med Assoc J* 2008;10(3):202-6.
3. Anderson C, Story A, Brown T, et al. Tuberculosis in UK prisoners: a challenge for control. *J Epidemiol Community Health* 2010;64(4):373-6.
4. Marco A, Sole N, Orcau A, et al. Prevalence of latent tuberculosis infection in inmates recently incarcerated in a men's prison in Barcelona. *Int J Tuberc Lung Dis* 2012;16(1):60-4.
5. Abebe DS, Bjune G, Ameni G, et al. Prevalence of pulmonary tuberculosis and associated risk factors in Eastern Ethiopian prisons. *Int J Tuberc Lung Dis* 2011;15(5):668-73.
6. Banu S, Hossain A, Uddin MKM, et al. Pulmonary Tuberculosis and Drug Resistance in Dhaka Central Jail, the Largest Prison in Bangladesh. *PLoS One* 2010;5(5).
7. Banda HT, Gausi F, Harries AD, et al. Prevalence of smear-positive pulmonary tuberculosis among prisoners in Malawi: a national survey. *Int J Tuberc Lung Dis* 2009;13(12):1557-9.
8. Noeske J, Ndi N, Mbondi S. Controlling tuberculosis in prisons against confinement conditions: a lost case? Experience from Cameroon. *Int J Tuberc Lung Dis* 2011;15(2):223-7.
9. Sanchez A, Larouze B, Espinola AB, et al. Screening for tuberculosis on admission to highly endemic prisons? The case of Rio de Janeiro State prisons. *Int J Tuberc Lung Dis* 2009;13(10):1247-52.
10. Johnstone-Robertson S, Lawn SD, Welte A, et al. Tuberculosis in a South African prison - a transmission modelling analysis. *SAMJ S Afr Med J* 2011;101(11):809-13.
11. Sanchez A, Huber FD, Massari V, et al. Extensive Mycobacterium tuberculosis circulation in a highly endemic prison and the need for urgent environmental interventions. *Epidemiol Infect* 2012;140(10):1853-61.
12. May JP, Joseph P, Pape JW, et al. Health Care for Prisoners in Haiti. *Ann Intern Med* 2010;153(6):407-U103.
13. Legrand J, Sanchez A, Le Pont F, et al. Modeling the Impact of Tuberculosis Control Strategies in Highly Endemic Overcrowded Prisons. *PLoS One* 2008;3(5).
14. WHO. Tuberculosis Profile: Haiti. 2013. (https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=HT&LAN=EN&outtype=html). (Accessed April 14 2013).
15. Health_through_Walls. Health through Walls: Sustainable prison healthcare in developing countries. 2012. (http://www.healththroughwalls.org/). (Accessed 4/14/2013 2013).
16. CDC. Core Curriculum on Tuberculosis: What the Clinician Should Know. Atlanta: Centers for Disease Control and Prevention, 2011, (no. Fifth Edition)(Services DoHaH
17. Chai SJ, Mattingly DC, Varma JK. Protecting health care workers from tuberculosis in China: a review of policy and practice in China and the United States. *Health Policy Plan* 2013;28(1):100-9.

18. CDC. Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC. *Morbidity and Mortality Weekly Report* 2006;55(RR09):1-44.
19. Olle-Goig JE, Alvarez J. Treatment of tuberculosis in a rural area of Haiti: directly observed and non-observed regimens. The experience of Hopital Albert Schweitzer. *Int J Tuberc Lung Dis* 2001;5(2):137-41.
20. Fox GJ, Barry SE, Britton WJ, et al. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Resp J* 2013;41(1):140-56.
21. Rutz HJ, Bur S, Lobato MN, et al. Tuberculosis control in a large urban jail: Discordance between policy and reality. *J Public Health Manag Pract* 2008;14(5):442-7.
22. Tappero JW, Tauxe RV. Lessons Learned during Public Health Response to Cholera Epidemic in Haiti and the Dominican Republic. *Emerg Infect Dis* 2011;17(11):2087-93.
23. Fund UNCs. State of the world's children. 2011. (http://www.unicef.org/sowc2011/index.php). (Accessed April 25, 2013 2013).
24. WHO. Immunization Profile. 2012. (http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileresult.cfm?C=hti). (Accessed).
25. UNAIDS. Epidemiological Fact Sheet: Haiti. UNAIDS; 2013. (http://www.unaids.org/en/regionscountries/countries/haiti/). (Accessed April 14 2013).
26. Mauch V, Weil D, Munim A, et al. Structure and management of tuberculosis control programs in fragile states-Afghanistan, DR Congo, Haiti, Somalia. *Health Policy* 2010;96(2):118-27.
27. Joseph P, Severe P, Ferdinand S, et al. Multidrug-resistant tuberculosis at an HIV testing center in Haiti. *Aids* 2006;20(3):415-8.
28. Ocheretina O, Morose W, Gauthier M, et al. Multidrug-resistant tuberculosis in Port-au-Prince, Haiti. *Rev Panam Salud Publica* 2012;31(3):221-4.
29. Larouze B, Sanchez A, Diuana V. Tuberculosis behind bars in developing countries: a hidden shame to public health. *Trans Roy Soc Trop Med Hyg* 2008;102(9):841-2.
30. Waisbord S. Participatory communication for tuberculosis control in prisons in Bolivia, Ecuador, and Paraguay. *Rev Panam Salud Publica* 2010;27(3):168-74.
31. Dara M, Chadha SS, Melchers NV, et al. Time to act to prevent and control tuberculosis among inmates. *Int J Tuberc Lung Dis* 2013;17(1):4-5.
32. Yanjindulam P, Oyuntsetseg P, Sarantsetseg B, et al. Reduction of tuberculosis burden among prisoners in Mongolia: review of case notification, 2001-2010. *Int J Tuberc Lung Dis* 2012;16(3):327-9.
33. Nardell E, Dharmadhikari A. Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings. *Int J Tuberc Lung Dis* 2010;14(10):1233-43.
34. Reid SE, Topp SM, Turnbull ER, et al. Tuberculosis and HIV Control in Sub-Saharan African Prisons: "Thinking Outside the Prison Cell". *J Infect Dis* 2012;205:S265-S73.
35. Sanchez AR, Diuana V, Larouze B. Tuberculosis control in Brazilian prisons: new approaches to an old problem. *Cad Saude Publica* 2010;26(5):851-.
36. Moller L, Gatherer A, Dara M. Barriers to implementation of effective tuberculosis control in prisons. *Public Health* 2009;123(6):419-21.
37. Hight I, et al.,. Water, Sanitation, Hygeine and Habitat in Prisons: Supplementary Guide. Geneva: International Committee of the Red Cross, 2012:1-79.

38. Hammett TM, Harmon P, Rhodes W. The burden of infectious disease among inmates of and releasees from US correctional facilities, 1997. *Am J Public Health* 2002;92(11):1789-94.

Appendix: IRB Determination

EMORY UNIVERSITY

Institutional Review Board

DATE: March 29, 2013

Daniel Mercer
Public Health

RE: Determination: No IRB Review Required
eIRB#: IRB00064280
Title: *Tuberculosis Prevalence in a Haitian Prison: A quality assessment of screening and treatment procedures*
PI: Daniel Mercer

Dear Mr. Mercer:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" or "clinical investigation" involving "human subjects" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will conduct a program evaluation to specifically investigate the effectiveness of the TB screening and treatment program at Prison Nationale in Port-au-Prince, Haiti. This is not research requiring IRB review but a quality improvement project to improve the local system of care. The findings from the analysis will be used to generate recommendations to improve the TB screening and treatment program and Prison Nationale. It is the understanding of the IRB that dataset that will be brought to the U.S. to complete the analysis will be completely stripped of all identifiers.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Carol Corkran, MPH, CIP
Senior Research Protocol Analyst
This letter has been digitally signed

Emory University
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu
An equal opportunity, affirmative action university