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Evaluation Of The Ltbi Cascade Of Care At The Winchester Chest Clinic

Alyssa Manni Robinson
t_s_eliot890@yahoo.com

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Alyssa Manni Robinson

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Advisor/Committee Chair: Lucian Davis, MD

Committee Member: Sheela Shenoi, MD, MPH

Abstract

Background: Latent tuberculosis infections affect around two billion people world-wide. In order to effectively control and reduce TB incidence, latent TB cases must be identified and treated. The latent TB cascade of care involves screening, diagnosis, evaluation, prescription of a treatment regimen, and completion of treatment. Existing studies have identified low rates of LTBI treatment completion among patients in diverse settings.

Objective: The aim of this study was to assess certain steps in the cascade of care among the LTBI-positive patients referred to the Winchester Chest Clinic in order to determine where patients were lost to follow up and potential inequities in care between patient groups.

Methods: This was a retrospective cohort study performed through medical chart data review for LTBI-positive Winchester patients. The presence of a chest x-ray, medication prescription, at least one follow-up appointment and at least four follow-up appointments were used to assess patient completion of the evaluation and treatment stages of care. Multivariate models were created using demographic variables classifying gender, race, ethnicity and age as the independent variables, and the outcome variables as the dependent variable.

Results: Female patients had lower odds of being prescribed medications and completing at least one follow-up appointment than did their male counterparts (OR 0.4 and OR 0.3, respectively). Non-Hispanic or Latino patients were more likely than Hispanic or Latino patients to be prescribed TB medications or complete at least one follow-up appointment (OR 1.6 and OR 1.8, respectively). Black patients were also less likely to complete a follow-up appointment than non-black patients (OR 0.5), and Asian patients were less likely to be prescribed medications than non-Asian patients (OR 0.5).

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Introduction

Around two billion people worldwide are infected with latent tuberculosis. Latent tuberculosis occurs when an individual is infected with the tubercle bacillus but does not experience any symptoms of the disease, and is not infectious to others. The initial immune response effectively traps the bacteria and prevents it from spreading or multiplying. Nevertheless, the infected individual may still be at risk of developing active TB and spreading it to others, especially those with compromised immune systems. Treatment of latent tuberculosis is an important component of addressing the tuberculosis epidemic as a whole. When reflecting on his landmark latent tuberculosis study years later, George Comstock reflected that treatment "had reduced the incidence of TB by 60% overall and by better than 90% among those who regularly took their pills" (Selvam & Passannante, 2008). It was clear that latent TB must be treated in order to reduce active TB incidence. Subsequent worldwide tuberculosis elimination models have further shown the necessity combining screening and treatment of latent TB with active tuberculosis treatment and prevention in order to achieve elimination (Dye, Glaziou, Floyd, & Raviglione, 2013).

One of the great challenges of tackling this global epidemic is ensuring that infected patients successfully pass through every stage of the cascade of care, which starts with diagnosis and continues through the treatment process. Because the cascade of care contains so many steps and takes place over an extended period of time, it is often difficult for patients to successfully complete each step. Alsdurf, et al., completed a systemic review and meta-analysis of existing research on TB treatment outcomes, and determined that only 10% of the general population completed treatment. They identified certain steps where patient losses were the greatest: intended for screening, completed medical evaluation, recommended for treatment and completed treatment. Furthermore, they determined that those with certain medical indications, like HIV, completed treatment at a rate five times higher than that of the general population. Clearly there are certain identifiable factors that contribute to successful completion of treatment.

The primary aim of this study was to apply this cascade of care framework to the patient populations at one New Haven clinic in order to better understand the current successes of the treatment programs as well as opportunities to improve care and patient outcomes going forward. A retrospective cohort study was performed using routinely collected clinical data from individuals referred to the Winchester Chest Clinic for LTBI evaluation and treatment. Indicators signifying the completion of evaluation and treatment were identified in the patient data, and then these outcomes were tracked among different demographic groups. The end result was an analysis of the evaluation and treatment stages of care which highlighted treatment gaps and risk factors for loss to follow up.

Background Information

The first step in addressing a latent TB infection is screening. Only certain groups are targeted in general screening guidelines, generally based on risk factors for infections. In its guidelines for low-burden countries, the WHO lays out its screening recommendations as follows:

> The guidelines strongly recommend systematic testing and treatment of LTBI in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor treatment, patients receiving dialysis, patients preparing for organ or haematological transplantation, and patients with silicosis. In prisoners, healthcare workers, immigrants from high TB burden countries, homeless persons and illicit drug users, systematic testing and treatment of LTBI is conditionally recommended, according to TB epidemiology and resource availability. (Getahun et al., 2015)

It is important to note that one of the limiting factors mentioned here is resource availability and potential prioritization of other public health concerns over latent TB treatment, which does indeed impede larger-scale screening across populations. Treating latent TB infection is becoming a greater priority amongst US public health officials, resulting in greater resource allocation to these efforts (Blumberg & Ernst, 2016). Another limitation in screening "homeless persons and illicit drug users," as well as other marginalized groups, is access to the patients themselves. Logistically, it may be difficult to screen these patients in a systematic manner.

The next step in the process is that of actual diagnosis. PPD and IGRA are the standard, initial diagnostic tests, which work by responding to T cells that have been exposed to tuberculosis antigens. Since IGRA tests have been introduced, there has been some evidence that their usage may improve patient retention and completion of the cascade of care (Roth et al., 2017). Unfortunately, both tests have limitations. For instance, tuberculosis skin test results may read positive for those that have had the BCG vaccine, or any past exposure to non-TB mycobacteria that has been resolved (Getahun, Matteelli, Chaisson, & Raviglione, 2015). Beyond the limitations in specificity and sensitivity, which all diagnostic tests have to some extent, these tests are also limited in their ability to distinguish between latent and active TB (and the progression between the two) and to predict the likelihood of progression from latent to active TB (Trajman, Steffen, & Menzies, 2013). There is some evidence that IGRAs have better predictive capabilities than PPD tests, though the positive predictive value is still low at 2.7% (Diel, Loddenkemper, & Nienhaus, 2012). Understanding the patient's likelihood of progressing from latent to active TB is clearly important when determining the best course of action for the patient, and the diagnostic tests themselves provide only basic exposure information to the provider.

In order to determine that the patient does have a latent infection, the provider must confirm that there is no active TB infection. This is done by taking a chest x-ray, which should

appear normal in patients with a LTBI, and checking for other signs and symptoms of active infection, as well as a sputum examination ("Diagnosis of Latent TB Infection | LTBI," 2018).

After determining that the patient does indeed have LTBI, then the next question is whether to treat the infection. Again, there are certain risk factors that make a latent infection more likely to progress to an active infection. Many of those risk factors are the same as those that prompt screening in the first place: compromised immune function due to HIV or immunosuppressant drugs, contact with others patients with active TB, a history of active TB (Grzybowski, Fishaut, Rowe, & Brown, 1971), silicosis. The US Preventative Services Task Force (USPSTF) also highlights a few other risk factors that can affect progression or are associated with higher rates of active TB. Foreign-borne people living in the US have much higher rates of active TB than those born in America, especially those from India, Mexico, China, the Philippines and Vietnam. The USPSTF also suggests that prisoners and homeless people, especially those living in cramped quarters like homeless shelters, are at higher risk for developing and spreading active TB, and thus should be treated (Bibbins-Domingo et al., 2016). Other factors can also play a lesser role in the severity of eventual active infection or likelihood of progression to active disease, like diabetes, tobacco use or corticosteroid usage (Ai, Ruan, Liu, & Zhang, 2016). Certain risk factors, like HIV status, carry more weight for treatment decisions, but even those with only a moderate effect must be considered, especially if multiple risk factors are present.

Other considerations for providers at this point are the benefits and detriments of treatment for the patient. Isoniazid is one of the most well-established drugs for treating LTBIs, but can have serious side-effects like neuropathy and, occasionally, severe hepatotoxicity (Chee, Reves, Zhang, & Belknap, 2018). The less severe side-effects can still be extremely uncomfortable for the patient and compromise treatment completion. Rifampin and Rifapentine can also have negative side-effects on the patients. Furthermore, the CDC estimates that only around 5-10% of latent infections progress to active disease, and the risk of reactivation decreases generally decreases over time. As mentioned previously, the currently available diagnostic tests do not reliable identify which patients are more likely to progress to active disease. Providers therefore must consider carefully the patient's risk factors for progression and overall health and wellbeing before deciding on the best course of action. While this paper treats treatment as a necessary step in the cascade of care, in reality, there may be cases where not treating the patient is the best choice, and not a failure on the part of the health system.

Once patients are diagnosed and referred for treatment, then the provider must determine what type of treatment regimen is most appropriate. The available treatment options are three months of Isoniazid and Rifapentine, four months of Rifampin, and six to nine months of Isoniazid. Within those options, providers must decide on dosage and frequency of that dosage. ("Treatment Regimens for Latent TB Infection | Treatment | TB | CDC," 2019) Of these, the once weekly, three-month Isoniazid and Rifapentine regimen is clearly the most attractive, as it requires the patient to take the smallest number of doses over the least amount of time. It is easier for patients to adhere to this regimen, especially as new guidelines allow for

the 12 doses to be self-administered ("Latent TB," n.d.). Furthermore, this regimen is now considered to be compatible with some types of HIV antiretrovirals; specifically, Efavirenz and Raltegravir, which do not have negative interactions with Rifapentine (Borisov, 2018). This means that HIV-positive patients that are either not on ART or are taking these specific antiretrovirals can also be prescribed this shortened regimen. The updated guidelines also allow for children as young as two years old to undergo this 12-dose regimen (Borisov, 2018). Furthermore, many studies have shows that the shorter regimen is not inferior to the longer ones in terms of treating LTBIs, and indeed often causes fewer negative side effects in patients (Belknap R, Holland D, Feng PJ, Millet JP, Cayla JA, Martinson NA, Wright A, Chen MP, Moro RN, Scott NA et a, 2017; Sterling et al., 2011).

Diagnosing and treating latent TB infections is clearly a long process, which involves a number of steps in which both the provider and patient must participate. There are many opportunities for loss to follow up or inefficiencies. Patients may also face practical barriers to pursuing or completing their treatment, such poor public transportation or medical insurance. In their meta-analysis of studies on TB treatment completion, Alsdurf, et al., found that "only 50% of people with medical indications completed latent tuberculosis infection treatment, compared with 14% of migrants, and 10% of the general population cohorts"(Alsdurf, Hill, Matteelli, Getahun, & Menzies, 2016). That means that completion levels were low even among high-risk groups, and that this process can likely be improved in many cases to better treatment adherence and lower loss to follow up.

Research Design

In order to better understand how patients progress through the cascade of care and complete their LTBI treatments within the Yale New Haven Health System, a retrospective cohort study of patients with positive LTBI diagnoses was performed. The LTBI cascade of care consists of multiple steps that signify treatment progress, from initial diagnostic testing to completion of the assigned treatment regimen. By matching cascade steps to variables present in the medical chart data, each patent's progress through the cascade could be tracked. This study then noted where patients were being lost-to-follow-up and identified common risk-factors among those who dropped out of treatment.

Setting

This study used data extracted from electronic medical records by a research team at Yale (JDAT). The specific inclusion criteria given to the JDAT team were patients 18 years or older that attended the Winchester Chest Clinic Friday afternoon LTBI clinic anytime during the period from 2012 to 2018. The Winchester Chest Clinic holds a weekly clinic devoted to LTBI patient intake and assessment; this provides an easy way to track patients referred to the clinic specifically for LTBI. After those patients were identified, their charts were tracked and analyzed until the patient stopped attending the clinic, or until February 2019.

Participants

The main selection criteria for patients included in this study was that the patient had attended the Friday afternoon LTBI clinic at the Westchester Chest Clinic. Patients under 18 years of age were excluded. A consecutive sampling method was used, wherein any patients that met these broad, easy to verify, criteria were selected, regardless of that patient's diagnosis, eventual progress through the cascade of care, demographic features, or other health concerns.

From this initial data, only patients with a latent TB infection diagnosis were included in the final sample. Patients that do not have latent tuberculosis do not need to undergo treatment for LTBI, and thus were not included in this evaluation of the cascade of care. LTBI diagnosis was determined by the values in the "Diagnosis" field in the dataset provided by JDAT. A number of patients included in the data set did not have a LTBI diagnosis, and did not undergo any sort of diagnostic testing or treatment for TB. Only patients with diagnoses listed as the following were included: TB lung, latent; LTBI; Positive PPD; Tuberculosis; Latent Tuberculosis; (QFT) QuantiFERON-TB test reaction without active tuberculosis; History of positive PPD; TB (pulmonary tuberculosis); Positive QuantiFERON-TB Gold test; Latent tuberculosis by skin test; Positive purified protein derivative (PPD) skin test with negative chest x-ray; Latent tuberculosis by blood test; Pneumonia of right upper lobe due to infectious organism; Latent tuberculosis infection. Patients without explicit LTBI diagnoses but with positive PPD or IGRA test results were also included in the sample.

A similar process of filtering out non-LTBI related tests and medications also occurred. Only variants of IGRA lab tests and TSTs were kept. The medications of interest were Isoniazid, Rifampin and Rifapentine of various dosages; all other medications were filtered out.

Variables

The initial step in defining variables for this study was identifying the steps of the cascade of care in the available patient data. The steps laid out by Alsdurf, et al., were used as a starting point. The initial step in the cascade is that patients with probable LTBI are intended for screening. However, all patients that attend the Friday clinic at the Winchester Chest Clinic were already intended for screening; they were referred to this clinic to be screened or to receive treatment for LTBI. Therefore, all patients included in this sample already successfully passed the first step of the cascade. This step was thus not included in any analyses.

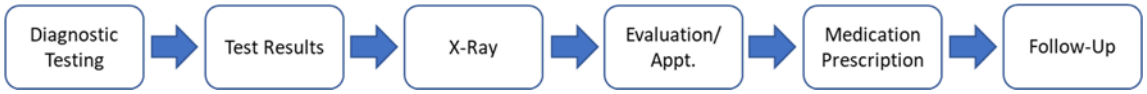
The first step of the cascade that was assessed in this analysis was the initial TB diagnostic test. This may have been a PPD or IGRA test, and it may have occurred prior to the patient's referral to the Winchester Clinic. The occurrence of a diagnostic test was verified by the presence of IGRA or TST test results. For the purposes of this study, a tuberculin skin test resulting in an induration of at least five millimeters was considered positive ("Fact Sheets | Testing & Diagnosis | Fact Sheet - Tuberculin Skin Testing | TB | CDC," 2018).

The next step of the cascade was a patient evaluation following positive test results. This step was verified by checking for the presence of a chest x-ray and a follow-up appointment. Following a positive diagnosis and chest x-ray, the provider determined if treatment is appropriate. Then, a course of treatment was recommended for the patient, usually a six- or nine-month regimen of Isoniazid (INH) or four-month course of Rifampin (RIF), or a three-month regimen of Isoniazid and Rifapentine. Completion of this step was evidenced by prescription of one or more of these medications.

The final step in the cascade is completion of treatment. This step could not be verified directly, but the completion of follow-up appointments indicated the continuance of treatment. Up to four follow-up appointments were tracked to evaluate the patient completion of this step.

In order to track patient process through all of these steps in the cascade, a completion variable was also created. This variable was the sum of all steps completed, with a maximum of eight. Test results were not included as a separate step here, as all who underwent diagnostic testing had test results on file. Separate variables were created and analyzed for the completion of eight steps, at least seven steps, and at least 4 steps.

Figure 1: Steps in the Cascade of Care Evaluated



JDAT also provided some demographic data on patients, which was utilized to identify trends among the those that completed or did not complete steps in the cascade. The demographic data included primary race, ethnicity, age and gender. Demographic traits were transformed into discrete variables. Age was divided into four groups: 18-30 (reference group), 31-45, 46-65 and 65+. Race was divided into five groups: Black, Caucasian, Asian, Native Hawaiian and Pacific Islander, and Other (reference group). Male and Hispanic or Latino were designated reference groups for the gender and ethnicity variables, respectively.

Outcomes

Two LTBI outcomes were analyzed during the course of this study: evaluation and preventative therapy completion. The evaluation outcome was measured as the proportion of patients who underwent a chest x-ray, one of the final steps of LTBI diagnosis. The therapy completion outcome was evaluated through a few different indicators: prescription of tuberculosis medications, attendance of at least one follow-up appointment and attendance of at least four follow-up appointments. The proportion of patients that fulfilled each of these indicators was defined as the proportion to successfully complete preventative therapy.

Statistical Analysis

For each cascade and demographic variable, a simple univariate analysis was performed to determine what proportion of the patient sample completed each step of the process, and the demographic breakdown of the overall sample. Subsequently, the values for each patient were summed up, and an average calculated to indicate the percentage of steps completed for each patient. This also provided an overall average completion rate for the sample as a whole.

Next, I performed a bivariate analysis of each demographic variable paired with indicator variables and completion variables. For instance, relationships between gender and completion of x-rays, medication prescriptions, appointments and follow-up appointments, and all steps of the cascade were analyzed. This was repeated with the race, ethnicity and age demographic variables in order to produce odds ratios for all indicators.

Regression analysis was performed using proc logistic in SAS. The independent variables were all of the demographic variables. Multiple regressions were run using each indicator and completion variable. After each initial regression was run, variables with a p-value of greater than 0.3 were removed from the model, and the regression was run again. If any remaining variables had a p-value of greater than 0.2, they were removed and the model run again. The odds ratios and p-values of the remaining variables was recorded.

Ethics Approval

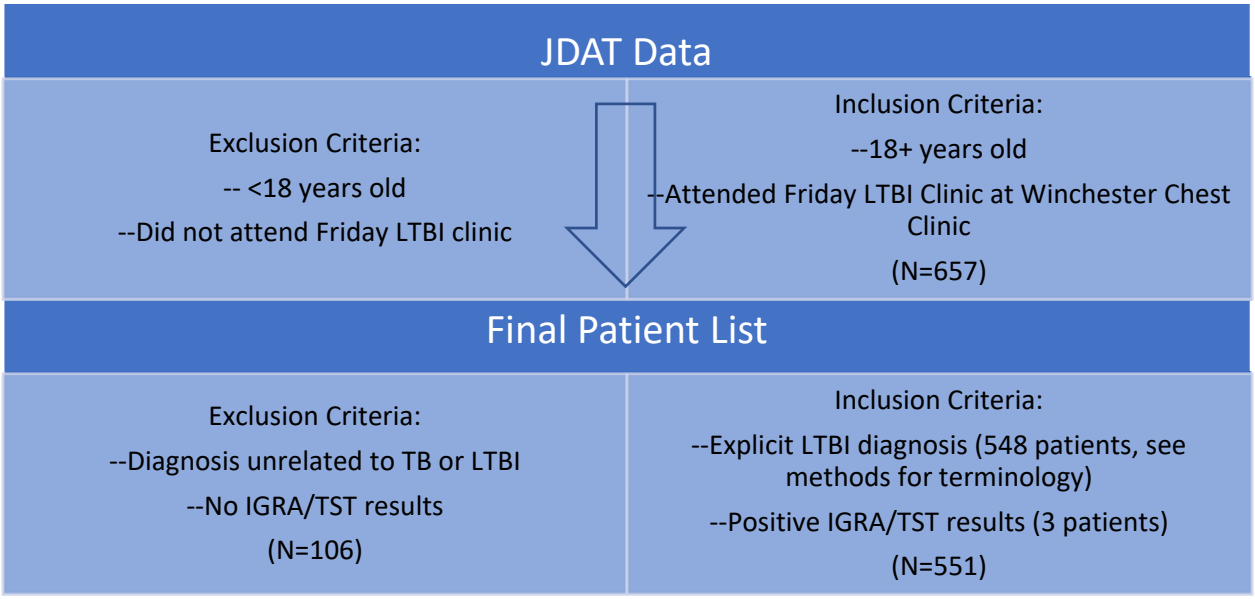
This study received IRB approval from Yale University Internal Review Board on January 31, 2019. Due to minimal risk to the included patents, the requirement for written consent was waived.

Results

Sample Description

JDAT initially pulled the records of 658 patients that had attended the Friday LTBI clinic at the Winchester Chest Clinic between January 2013 and February 2019. From this initial sample, a review of the “Diagnosis” column indicated that 548 of these patients had an explicit latent tuberculosis diagnosis (see methods section for exact terminologies) and three had positive IGRA and/or TST test results. Therefore, the final sample consisted of 551 patients that had attended the Winchester Chest Clinic and were diagnosed with latent tuberculosis and/or had a positive diagnostic test on file.

Figure 2: Patient Selection



Of these patients, 68% were women and the average age was 42 years old (SD=13.73), with ages spanning from 19 to 93 years old. The racial breakdown was 19% Black or African American, 11% Asian, 11% White or Caucasian, and 0.2% Native Hawaiian or Other Pacific Islander (with only one participant identifying this way). The remaining 60% (329 patients) were listed as other, other/not listed, patient refused or unknown. The ethnic breakdown of the sample was 58% non-Hispanic, 41% Hispanic or Latino and 1.1% unknown or patient refused. (See Table 1 in Appendix for all demographic information.) The number of appointments that patients had scheduled ranged from one single appointment to 26 appointments.

Patients can fit into multiple demographic groups, so a correlation analysis was run on the demographic variables. The only two variables with a correlation factor higher than 0.1 were gender and ethnicity, with a correlation coefficient of 0.21. 48% of the female patients also identified as Hispanic or Latina, and 79% of the Hispanic or Latino patients were women (with 178 patients who were both female and Hispanic/ Latina).

Indicators

Diagnostic Testing

Of the 551 patients included in the sample 127 received some sort diagnostic test (seven received both TST and IGRA tests). Therefore, only 23% of the sample completed the diagnostic testing step in the cascade of care. 43 were tested via TST, and 91 via IGRA lab tests. Of those that were tested by TST, 32 (74%) received positive results. Of those that received IGRA lab tests, 80 (88%) received positive results. These patients that tested positive for TB should have then continued in the cascade, and undergone a chest x-ray as the the next step in their evaluation.

X-Ray

485 (88%) of the patients underwent a chest x-ray at some point during their care. Multivariate analysis showed that the odds of white or Caucasian patients receiving a chest x-ray was twice that of non-white or Caucasian patients, with an odds ratio of 2.1 (95% CI 0.86, 5.1). This result had a p-value of 0.1044, and thus was not strongly significant. Asian patients also had higher odds of undergoing a chest x-ray than non-Asian patients, with an odds ratio of 2 (95% CI 0.8, 4.8). This result was also weakly significant with a p-value of 0.133. There were no significant differences in x-ray rates between genders, ethnicities or ages. (See Table 3 in Appendix.)

Follow-up Appointments

Because attendance at the Winchester Chest Clinic was one of the criteria for patient inclusion given to JDAT, almost all of the patients had at least one appointment there: 550 of the 551 total patients. 385 (70%) had at least one follow-up appointment, 314 (57%) had at least two follow-up appointments, 252 (46%) had at least three follow-up appointments, and 165 (30%) had at least four follow-up appointments. That is a 30% drop from the initial appointment to the follow-up appointment, and a 57% drop in patients from the initial follow-up to the fourth follow-up appointment. On average, each patient completed around four appointments at the Winchester Chest Clinic.

The multivariate analysis showed that the odds of women completing an initial follow-up appointment was much lower than that of men, with an adjusted odds ratio of 0.4 (95% CI 0.2, 0.6; p-value <.0001). Race also affected the odds of patients completing a follow-up appointment, with black patients half as likely as non-black patients to complete a follow-up appointment (Adj. OR 0.5; 95% CI 0.3, 0.9; p-value 0.0196). The odds of non-Hispanic patients completing a follow-up appointment were significantly higher than those of Hispanic or Latino patients (Adj. OR 1.82; 95% CI 1.1, 3.0; p-value 0.0204). There also seemed to be some evidence to suggest that the odds of older patients completing at least four follow-up appointments is higher than that of the youngest group, though that evidence was not conclusive. In the multivariate analysis, the 46-65 age group had an adjusted odds ratio of 2.15 (95% CI 1.13, 4.09; p-value 0.0202) and the 31-45 age group had an adjusted odds ratio of 1.75 (95% CI 0.97, 3.14; p-value 0.0614) for completion of at least four follow-up visits. (See Table 4 in Appendix.)

Medication Prescriptions

380 (69%) patients were prescribed some sort of TB medication, either a single type of some combination of medications. Both the bivariate and multivariate analyses showed that the odds of medications prescriptions being written for women were significantly lower than they were for men (Adj. OR 0.3; 95% CI 0.2, 0.5; p-value <.0001). Asian patients also had lower odds of being prescribed medications than non-Asian patients (Adj. OR 0.5; 95% CI 0.3, 0.9; p-value 0.0209), while non-Hispanic patients were more likely to be prescribed medications than

were Hispanic or Latino patients (Adj. OR 1.6; 95% CI 1.1, 2.4; p-value = 0.0277). There was some weak evidence in the bivariate analyses to suggest that older patients might have higher odds of being prescribed medications than younger patients, but this distinction was less clear in multivariate analysis, indicating that this effect may be due to other factors. (See Table 5 in Appendix.)

Completion of Cascade

On average, patients completed 50.27% of the steps in the cascade, including follow-up appointments. 13 (2.4%) patients completed all of the treatment steps included in this study, 62 (11%) completed at least seven steps, and 321 (58%) completed at least half of the steps. As the number of patients that completed all steps was small, statistical analyses of this group were not useful. Regarding patients that completed at least seven of the eight steps, the odds of completion were higher for whites than for non-whites (Adj. OR 2.1; 95% CI 0.98, 4.5; p-value 0.0567), though this result is only borderline statistically significant. The odds of completing at least four steps in the cascade was lower for women compared to men (Adj. OR 0.4; 95% CI 0.3, 0.6; p-value <.0001), as well as for black patients compared to non-black patients (Adj. OR 0.6; 95% CI 0.4, 0.98; p-value 0.0411). See Table 6 in the Appendix for more details.

Discussion and Conclusions

Key Findings

Theses analyses produced identified gaps in care affecting certain groups. At several points in the cascade, there appeared to be gender disparities. The odds for female patients completing at least one follow-up appointment, being prescribed TB medications and completing at least four steps out of the eight evaluated were significantly lower than they were male patients. This means that women were, proportionally, less likely to start or complete preventative therapy regimens, one of the primary outcomes evaluated in this study. This represents a clear gender inequity in care.

There were also seeming disparities between non-Hispanic and Hispanic patients. Non-Hispanic patients had much higher odds of being prescribed medications and completing at least one follow-up appointment than did Hispanic or Latino patients. There was a relatively large number of female Latina/Hispanic patients in the sample, and it could be that much of the disparity in preventative treatment affected primarily this smaller group, though more analysis is needed in this area.

Racial differences were also associated with differences in outcomes. Black or African American patients had lower odds of completing at least one follow-up appointment and of completing at least four steps in the overall cascade than did non-black patients. Asian patients had lower odds of being prescribed medications, but perhaps higher chances of undergoing a chest x-ray. White patients were potentially more likely to have chest x-rays or complete at

least seven steps in the cascade, though these results were only borderline significant. White and Asian patients each made up 11% of the total patient sample (with 58 and 61 patients, respectively), so perhaps a larger sample was needed to produce significant results. Another issue affecting the race variable and classification was that 52% of the sample identified as "Other Race." It would be helpful to better understand the racial identities of these patient as well as why so many patients marked this option, in order to better elucidate the relationship between race and LTBI care outcomes.

Beyond the potential inequities in care relating to gender, race and ethnicity, there were certain steps in the cascade were large numbers of patients were lost to follow up. Follow-up appointments are important, especially to ensure medication compliance and completion of treatment. However, less than half of the LTBI-positive patients in the sample completed at least three follow-up appointments, and less than a third four follow-up appointments. This may indicate a weakness in the care process, buts needs to be further investigated to determine its extent and causality.

Limitations

The study may have suffered from selection bias, as data was not available for the underlying population from which this sample was pulled. Incorporating information on outcomes for patients that were referred to the clinic but either never scheduled an appointment or were no-shows, along with those for patients that may have been eligible for but did not receive referrals to Winchester, would have provided a useful baseline. The patients included in this data set may have already been those more willing to seek medical care and referrals to other providers than the general population. Without understanding the larger LTBI patient pool, it is not possible to control for any bias resulting from the referral process or patient engagement with the medical system.

An issue affecting one of the primary outcomes tracked in this study was that it could not be verified patients prescribed medications actually completed their treatment regimen successfully. Patients who appeared to successfully complete all steps examined in this study, may have actually failed to complete their treatment regimen or have been lost-to-follow-up then. There is also no information on medication adherence, or side effects, which varies depending on the medications prescribed and would also likely affect the treatment outcomes. For example, patients prescribed the nine-month INH regimen may have been lost to follow up at higher rates.

The diagnostic testing data is also limited, in that only the raw results were provided by JDAT. In reality, the interpretation of these test results would generally require an understanding of the patient's overall health. The size of a TST induration will be interpreted differently for those that are HIV positive, for example. For this study, however, a threshold of five millimeters was set for all patients to signify a positive result. This was potentially a source of misclassification bias that resulted in more positive test results than there really were. The

IGRA test results were also difficult to interpret, because the nil value was often missing. IGRA test results must be compared to the nil value in order determine the presence of infection, and a nil value of greater than 8.0 indicates that the test results are faulty. Without that information, many test results could only be marked indeterminate.

Furthermore, many more patients were diagnosed with latent tuberculosis (551 patients) than underwent diagnostic testing (127 patients), according to these records. Therefore, it is likely that every patient in this sample did have some sort of diagnostic test at one point, and many more patients completed that step in the cascade of care. Those records are missing from the medical chart data analyzed for this study. That is why medication prescription was evaluated as a marker for completion of treatment, as physicians would not prescribe tuberculosis antibiotics without first determining TB infection through diagnostic testing.

In addition, because many steps in the cascade could not be evaluated through this data, and the steps present occurred in various temporal configurations, it was impossible to map out a clear progression of patients through the steps in the cascade and thus to identify where patients were being lost to follow-up. As mentioned above, data was missing on diagnostic tests, so the number lost-to-follow-up during that test could not be clearly evaluated. Also, while medication prescription indicates that patients began treatment, the lack of a prescription does not necessarily indicate that a patient did not receive adequate care. As discussed in the background section, there are many considerations when providers decide if treatment is appropriate for patients. Some LTBI-positive patients in this sample may not have been suitable for treatment, for one reason or another. The fact that they were not prescribed medication does not necessarily indicate a failure in their treatment. This may be another form of misclassification bias, wherein the lack of prescribed treatment may be incorrectly labeled as a failure of care.

Generalizability of Findings

Because this study focused on a small patient sample at one specific clinic, its results may not be generalizable to LTBI care in other settings. More information is also needed about the Winchester patients in order to better understand where else these results may be applicable (e.g. socioeconomic status, access to care, country of origin, etc.). Regardless, these finding may be useful for other specialty clinics treating LTBIS that are fed a diverse group of patients via referrals from other providers in the United States. These would likely be clinics set in urban or semi-urban areas with sizable immigrant and foreign-born populations. While this dataset does not include any information on patient country of origin, there is a large foreign-born population in the greater New Haven area which is likely reflected in the Winchester patient population (“Understanding the Impact of Immigration in Greater New Haven | DataHaven,” n.d.).

Recommendations and Next Steps

A number of other studies have evaluated portions of the LTBI cascade of care in different settings. One recent study evaluated completion of diagnosis and treatment through chart review and interviews in Sao Paulo, Brazil, and recorded high levels of loss to follow up, as well as reluctance among patients to undergo preventative therapy (Wysocki et al., 2016). Another study in Brazil identified a similar lack of knowledge about the necessity for preventative therapy via a KAP survey (Salame et al., 2017). Though the setting of a clinic in Brazil, a high-burden, middle-income country, is different than that of our study, the underlying issue of poor patient understanding of the importance of preventative therapy may be a similar issue.

Many of the studies on this topic in low-burden countries focus on marginalized or high-risk populations. For instance, one study evaluated the cascade of care at a Canadian refugee clinic, and founds high rates of completion (Rennert-May et al., 2016). While information on refugee status among patients in our sample was not available, it is highly likely that a number of the patients were refugees or immigrants. Comparing refugee and immigrant patients to American-born patients would have added an extra dimension to this study; perhaps future investigations into the cascade of care at the Winchester Chest Clinic can explore this further. A meta-analysis examined the testing and referral to care steps in among homeless populations in the United States, and concluded that homeless patients were completing these steps at a high rate (Parriott et al., 2018). The Winchester study did not evaluate the referral system feeding patients into the clinic, only the care patients received after referral and attendance at the clinic; referrals should be further investigated in the future. This data set also did not include any information on homelessness or socioeconomic status. According to the USPSTF, homelessness is a risk factor LTBI, so that population should be targeted for screening and referrals to the clinic. Potentially identifying a relationship between socioeconomic status, or living situation, and treatment outcomes would shed more light on risk factors and barriers to completion.

With this in mind, a useful next step to continue exploring the findings of this study would be to perform qualitative research at the Winchester Chest Clinic. This study focused solely on analyzing medical chart data, and thus could not provide any patient or provider perspectives on the experience, or hypotheses on causality. I would recommend structured interviews with patients and providers, followed by the distribution of surveys for both groups. If possible, it would be helpful to reach out to patients included in the original study population, in order to better understand that populations reasons for continuing or not continuing care. A widescale survey such as this, targeting both current and former patients, could also gather information on other risk factors not available in the patients' medical charts. For instance, questions on homelessness/living situation, income, and immigration date and country of origin (for patients born outside of the United States) could be included on such a survey. Information learned from the structured interviews with providers and patients could also be incorporated in the drafting of the survey.

The original design for this study also included two other clinics were LTBIs are treated: the Nathan Smith and Haelen HIV clinics. Because the IRB Approval included collecting data from these clinics as well, it would be easy to submit another JDAT request for similar chart data for these two patient populations, and conduct similar analyses as were completed in this study. Those results could also then be expanded through qualitative research via patient and provider interviews and surveys. This would expand the patient sample and allow for a more nuanced understanding of the LBTI Cascade of Care in the Yale New Haven Health System.

Furthermore, collecting data on the underlying patient populations from which these patients were referred for LTBI treatment would allow for an evaluation of the initial screening and diagnosis steps in the cascade. Some of that data would be difficult to collect, such as the number of LTBI-positive patients that were not ever targeted for screening. However, a possible starting point would be to collect more information on referrals and the referral process in order to determine which patients were referred for further care but did not follow through, as well as which patients might have been referred based on guidelines or best practices for referrals, but were not. These analyses would enhance the findings of this study and by targeting earlier points in the cascade as well as provide valuable information on potential selection biases in the original patient sample.

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Appendix

Table 1. Sample Demographics

	Patients (N=551)	P-Value
Mean (SD) Age	41.91 (13.73)	<.0001
Female Sex (%)	372 (67.51%)	<.0001
Male Sex (%)	179 (46.87%)	<.0001
Black or African American Race (%)	102 (18.51%)	<.0001
White or Caucasian Race (%)	58 (10.53%)	<.0001
Asian Race (%)	61 (11.07%)	<.0001
Native Hawaiian or Pacific Islander (%)	1 (0.018%)	0.3178
Other Race (%)	287 (52.09%)	<.0001
Hispanic or Latino Ethnicity (%)	225 (40.83%)	<.0001
Non-Hispanic Ethnicity (%)	320 (58.72%)	<.0001
Ages 18-30 (%)	94 (17.06%)	<.0001
Ages 31-45 (%)	283 (51.36%)	<.0001
Ages 46-65 (%)	130 (23.59%	<.0001
Over 65 Years of Age (%)	44 (7.99%)	<.0001

Table 2: Proportions of Patients Completing Each Step in the Cascade

Step in the Cascade of Care	Patients (N=551)	P-Value
Diagnostic Testing (%)	127 (23.05%)	<.0001
TST (%)	43 (7.8%)	<.0001
IGRA (%)	91 (16.52%)	<.0001
X-Ray (%)	485 (88.02%)	<.0001
Appointment (%)	550 (99.82%)	<.0001
First Follow-Up Appointment (%)	385 (69.87%)	<.0001
Second Follow-Up Appointment (%)	314 (56.99%)	<.0001
Third Follow-Up Appointment (%)	252 (45.73%)	<.0001
Forth Follow-Up Appointment (%)	165 (29.95%)	<.0001
Medication Prescription (%)	380 (68.97%)	<.0001
Average Number of Steps Completed (SD)	4.02 (2.09)	<.0001
Average Completion Rate of All Steps (SD)	50.27% (26.11%)	<.0001

Table 3: X-Ray Odds Ratios for Demographic Variables

	Unadjusted		Adjusted	
Demographic Characteristic	X-Ray Odds Ratio (95% CI)	P-Value	X-Ray Odds Ratio (95% CI)	P-Value
Female vs. Male Sex	1.12 (0.57, 2.2)	0.7425		
Black vs. Non-Black	0.56 (0.21, 1.45)	0.2321		
Asian vs. Non-Asian	1.64 (0.69, 3.85)	0.2612	1.98 (0.81, 4.81)	0.133
Caucasian vs. Non-Caucasian	1.74 (0.74, 4.12)	0.2056	2.09 (0.86, 5.1)	0.1044
Other Race vs. Black/Asian/Caucasian/ NHPI	0.71 (0.38, 1.33)	0.2819		
Non-Hispanic vs. Hispanic	0.79 (0.43, 1.48)	0.4689		
Ages 18-30 vs. Ages 30 plus	1.32 (0.61, 2.85)	0.4831		
Ages 31-45 vs. Ages 18-30 and 45 plus	0.9 (0.48, 1.67)	0.7303		
Ages 46-65 vs Ages 18-45 and 65 Plus	0.72 (0.33, 1.6)	0.4244		
Ages 65 Plus vs. Ages 18-65	1.58 (0.59, 4.25)	0.3626		

Table 4: Odds Ratios for at Least One and at Least Four Follow-up Appointments for Demographic Variables

	Unadjusted		Adjusted		Unadjusted		Adjusted	
Demographic Characteristic	1st Follow-Up Appointment Odds Ratio (95% CI)	P-Value	1st Follow-Up Appointment Odds Ratio (95% CI)	P-Value	4th Follow-Up Appointment Odds Ratio (95% CI)	P-Value	4th Follow-Up Appointment Odds Ratio (95% CI)	P-Value
Female vs. Male Sex	0.33 (0.21, 0.52)	<.0001*	0.37 (0.23, 0.59)	<.0001*	0.88 (0.6, 1.2)	0.5		
Black vs. Non-Black	0.75 (0.47, 1.18)	0.2086	0.5 (0.28, 0.9)	0.0196**	0.76 (0.47, 1.24)	0.2775	0.59 (0.34, 1.04)	.0702***
Asian vs. Non-Asian	1.03 (0.58, 1.85)	0.9115	0.68 (0.34, 1.37)	0.2757	0.74 (0.4, 1.37)	0.3344	0.58 (0.29, 1.14)	0.1121
Caucasian vs. Non-Caucasian	1.27 (0.68, 2.35)	0.4551			1.06 (0.59, 1.91)	0.8482		
Other Race vs. Black/Asian/ Caucasian/ NHPI	0.98 (0.68, 1.41)	0.9027			1.23 (0.86, 1.78)	0.2958		
Non-Hispanic vs. Hispanic	1.64 (1.13, 2.37)	0.0088*	1.82 (1.1, 3.02)	0.0204**	1 (0.69, 1.45)	0.9819	1.29 (0.82, 2.04)	0.2734
Ages 18-30 vs. Ages 30 plus	0.61 (0.38, 0.96)	0.0332**			0.58 (0.34, 0.99)	0.0457**		
Ages 31-45 vs. Ages 18-30 and 45 plus	1.12 (0.78, 1.61)	0.5449	1.59 (0.95, 2.68)	0.0808***	1.04 (0.73, 1.5)	0.8155	1.75 (0.97, 3.14)	.0614***
Ages 46-65 vs Ages 18-45 and 65 Plus	1.11 (0.72, 1.71)	0.6359	1.61 (0.88, 2.94)	0.1235	1.27 (0.83, 1.93)	0.2672	2.15 (1.13, 4.09)	.0202**
Ages 65 Plus vs. Ages 18-65	1.51 (0.73, 3.13)	0.2678	1.61 (0.66, 3.94)	0.2989	1.23 (0.64, 2.36)	0.532	1.7 (0.71, 4.1)	0.2364

*P-value of less than 0.01 **P-value of less than 0.05 ***P-value of less than 0.1

Table 5: Medication Prescription Odds Ratios for Demographic Variables

	Unadjusted		Adjusted	
Demographic Characteristic	Medication Prescription Odds Ratio (95% CI)	P-Value	Medication Prescription Odds Ratio (95% CI)	P-Value
Female vs. Male Sex	0.31 (0.2, 0.49)	<.0001*	0.33 (0.21, 0.52)	<.0001*
Black vs. Non-Black	1.29 (0.79, 2.1)	0.3069		
Asian vs. Non-Asian	0.6 (0.34, 1.03)	0.0640***	0.49 (0.27, 0.9)	0.0209**
Caucasian vs. Non-Caucasian	1.3 (0.7, 2.43)	0.402		
Other Race vs. Black/ Asian/ Caucasian/ NHPI	1 (0.7, 1.44)	0.9899		
Non-Hispanic vs. Hispanic	1.62 (1.12, 2.34)	0.0097*	1.58 (1.05, 2.38)	0.0277**
Ages 18-30 vs. Ages 30 plus	0.76 (0.47, 1.2)	0.2382		
Ages 31-45 vs. Ages 18-30 and 45 plus	0.84 (0.58, 1.2)	0.3408		
Ages 46-65 vs Ages 18-45 and 65 Plus	1.43 (0.92, 2.24)	0.1123		
Ages 65 Plus vs. Ages 18-65	1.38 (0.68, 2.81)	0.3689		

*P-value of less than 0.01 **P-value of less than 0.05 ***P-value of less than 0.1

Table 6: Odds Ratios for Completion of Cascade Steps for Demographic Variables

	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
Demographic Characteristic	Completion of Cascade (8 steps) Odds Ratio (95% CI)	P-Value	Completion of Cascade (8 steps) Odds Ratio (95% CI)	P-Value	Completion of Cascade (7+ steps) Odds Ratio (95% CI)	P-Value	Completion of Cascade (7+ steps) Odds Ratio (95% CI)	P-Value	Completion of Cascade (4+ steps) Odds Ratio (95% CI)	P-Value	Completion of Cascade (4+ steps) Odds Ratio (95% CI)	P-Value
Female vs. Male Sex	1.62 (0.44, 5.96)	0.4676			1.1 (0.62, 1.95)	0.7425			0.38 (0.26, 0.56)	<.0001*	0.4 (0.26, 0.6)	<.0001*
Black vs. Non-Black	0.8 (0.17, 3.65)	0.7595			0.83 (0.41, 1.69)	0.6086			0.7 (0.45, 1.07)	.0997***	0.6 (0.37, 0.98)	.0411**
Asian vs. Non-Asian	0.66 (0.09, 5.2)	0.6964			1.03 (0.45, 2.37)	0.953			1.04 (0.6, 1.78)	0.8988		
Caucasian vs. Non-Caucasian	3.98 (1.19, 13.37)	0.0252**	4.74 (1.34, 16.74)	.0156**	1.77 (0.84, 3.7)	0.1314	2.09 (0.98, 4.46)	.0567***	1.1 (0.63, 1.92)	0.7334		
Other Race vs. Black/Asian/Caucasian/NHPI	0.57 (0.18, 1.76)	0.3257			0.91 (0.54, 1.54)	0.727			1.09 (0.78, 1.53)	0.6282		
Non-Hispanic vs. Hispanic	1.13 (0.36, 3.5)	0.8344			0.65 (0.38, 1.1)	0.1103	0.65 (0.38, 1.11)	0.1168	1.3 (0.92, 1.84)	0.1363	1.32 (0.88, 1.99)	0.1792
Ages 18-30 vs. Ages 30 plus	3.15 (1.01, 9.86)	.0484**			1.34 (0.69, 2.58)	0.3862			0.6 (0.39, 0.94)	0.0259**		
Ages 31-45 vs. Ages 18-30 and 45 plus	0.59 (0.19, 1.81)	0.3517	0.45 (0.13, 1.59)	0.2138	1.09 (0.64, 1.85)	0.7552			1.24 (0.88, 1.74)	0.218	1.33 (0.91, 1.94)	0.1484
Ages 46-65 vs Ages 18-45 and 65 Plus	0.58 (0.13, 2.66)	0.4856	0.31 (0.06, 1.7)	0.1782	0.59 (0.29, 1.2)	0.1455	0.58 (0.28, 1.2)	0.1442	0.89 (0.6, 1.33)	0.578		
Ages 65 Plus vs. Ages 18-65	0.96 (0.12, 7.56)	0.969			1.27 (0.52, 3.14)	0.6024			1.78 (0.91, 3.49)	.0909***	1.75 (0.81, 3.81)	0.1562

*P-value of less than 0.01

**P-value of less than 0.05

***P-value of less than 0.1