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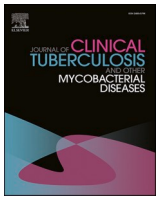

Cascade of care for the diagnosis and treatment of latent tuberculosis infection in an inner-city hospital prenatal clinic

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ABSTRACT

Treating latent tuberculosis infection (LTBI) is a core intervention in reducing the burden of tuberculosis. Treatment for LTBI is challenging due to the many steps in the process, collectively termed the cascade of care. In pregnant patients with LTBI, these challenges are heightened due to the medical and social intricacies introduced by pregnancy. In this study, we evaluate the effectiveness of a screening intervention for LTBI in the prenatal clinic of an inner-city hospital in the United States, and analyze the cascade of care to identify areas for improvement. Of the n = 99 patients who had a positive QuantiFERON Gold Test (QFN), 96.7 % had a chest x-ray (CXR) ordered by their provider, 95.6 % completed the CXR, 82.8 % were referred to the TB clinic, 44.4 % scheduled an appointment with the TB clinic, 23.2 % attended an appointment at the TB clinic, 21.2 % started medical treatment of LTBI, and 17.2 % completed LTBI treatment. Together this data shows that majority of patients in the prenatal clinic with a positive QFN do not complete LTBI treatment. Most patients are lost during the steps that transition them from obstetric care to the care of the TB clinic. Improving the cascade of care for LTBI will require increased education of patients on the importance of treating LTBI, and improving the process that transitions patients from obstetric care to the care of the TB clinic.

1. Introduction

Tuberculosis (TB) is still a major global health problem. An estimated 10.1 million people became ill with, and 1.6 million people died from tuberculosis in 2021 [1]. Cases of active TB are most often due to reactivation of latent tuberculosis infection (LTBI), therefore making it prudent to screen for and treat patients with LTBI before active infection can occur [2]. In the United States, the prevalence of LTBI is relatively low, estimated to be around 2.7 % [3]. Although the prevalence of TB is relatively low in high-income countries such as the United States, there are sub-populations within these countries that do have a high prevalence [4]. In the United States, TB rates are the highest in those of low socioeconomic status and foreign-born persons [5]. It is estimated that the prevalence of LTBI in US-born persons is 1.0 %, whereas it is 13.9 % in foreign born persons in the US [3].

In pregnant patients, there is a blunting of T-cell responses which begins to occur in the third trimester [6]. This decrease in immune function is believed to mediate the observed increase in rates of TB reactivation during pregnancy and in the postpartum period [7]. Active TB infection during pregnancy is associated with increased likelihood of maternal and fetal morbidity and mortality [8]. It is therefore recommended that all women who are high risk for TB be screened at the initiation of prenatal care, and those with active TB infection be treated, whereas treatment for LTBI can be deferred to the post-partum period [9]. Factors considered to be high risk for TB infection are recent contact with people with active TB, being from a country with a high prevalence of TB, and living or working in a high-risk setting such as a correctional facility or long-term care facility. A large proportion of this study population from inner-city Newark, New Jersey is considered high-risk for TB, primarily due to country of origin, which led to our institution creating a policy of TB screening for all patients in the prenatal period.

In 2014, the WHO announced its “End TB Strategy” with a goal of ending the global TB epidemic by the year 2035 [10]. The treatment of LTBI is a core intervention in achieving the goal of tuberculosis elimination, but it is a multifaceted process with many challenges. There are several steps involved in the process of treating LTBI which are

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collectively referred to as the cascade of care. Each step must be completed, and the completion of these steps is dependent upon collaboration between multiple providers and the patient. Patients are lost at various stages within this cascade, and improvement in the management of LTBI requires a programmatic approach to fixing the losses at each step [11]. Previous studies into non-completion of LTBI treatment noted that a 'one size fits all' approach to maintaining treatment adherence does not work [12]. Therefore, interventions to improve a LTBI cascade of care should be individualized to its specific population and shortcomings.

The steps in a LTBI cascade of care are generally: initial testing for TB infection, chest x-ray (CXR) to evaluate for active TB if the individual tests positive, referral for LTBI treatment, physician evaluation, initiation of treatment, and finally treatment completion. Reasons for failure to complete treatment could be failure of providers to report test results, order a CXR or refer the patient for TB treatment. There could also however be failure of the patient to get a CXR, attend clinic appointments, or adhere to treatment. Initially, an increase in attention was given to improving the tolerability of medications used to treat LTBI, leading to a transition from isoniazid-based therapy to rifamycin-based treatments [13]. With improvement in the medical therapy itself, more recently, the reasons for failure to complete LTBI treatment are believed to be associated with systems level factors. The goal of this study was to identify the causes for failure to pass through the LTBI cascade of care amongst patients screened in the prenatal clinic of our institution, an inner-city U.S. hospital, and to propose solutions to improve completion of LTBI treatment in this patient group.

2. Methods

To obtain the sample for this study, we first performed an electronic health record search to identify all patients who delivered at University Hospital in Newark, New Jersey in 2021, giving 1,267 patients. We then queried the QuantiFERON Gold (QFN) test result for these patients, yielding 990 patients with a negative result, 100 patients with a positive result, and 177 patients without a test result. The 177 patients without a QFN result were patients who gave birth at our institution, but did not receive antepartum care in our prenatal clinic, and were therefore not screened for LTBI. Of the 100 patients with a positive QFN, 1 had previously received treatment for LTBI, leaving 99 patients for inclusion in our final analysis.

Our institution's policy regarding the cascade of care for these patients at the time of the study was as follows. All patients receiving prenatal care at our institution were screened for LTBI with a QFN test during a prenatal clinic visit. Patients with a positive QFN underwent CXR to evaluate for active TB, and if the CXR was negative, were diagnosed with LTBI. After giving birth, patients with LTBI were then referred to the institution's TB clinic for treatment. If CXR had been performed greater than 3 months before the evaluation by the TB clinic, a second CXR was requested to rule out active TB prior to initiating treatment. After the evaluation at the TB clinic, patients who were candidates for treatment were prescribed shorter course rifamycin based regimens, 12 dose weekly rifapentine plus isoniazid, or 120 dose daily rifampin [14]. All encounters were conducted in the patients' preferred language with the use of interpretation services when necessary.

The medical records of identified patients were reviewed for timing and completion of the milestones in the LTBI cascade of care. Milestones in the cascade of care were defined as: 1. QFN order 2. QFN result 3. CXR order 4. CXR result 5. Referral to TB clinic 6. Appointment scheduling 7. First appointment 8. Treatment start 9. Treatment completion. The interval between each milestone reached within the cascade of care was documented for each patient. Percentages reported for completion of each milestone were calculated by dividing the number of patients completing the milestone by the total number of patients in the original study sample. Plots were made using Python 3.8.5. Bivariate statistical analysis was done using Pearson's Chi-square and Fisher's exact tests in Prism 8.

3. Results

In 2021, 1,090 patients received prenatal care and gave birth at our institution. All of these patients were screened for LTBI with QFN during their prenatal course. 100 of the 1,090 patients screened had a positive QFN, giving a screen positivity rate of 9.17 %. One patient was previously treated for LTBI, leaving 99 patients for analysis of the LTBI cascade of care.

The study cohort was 45.5 % black and 54.4 % other race (Table 1). 51.5 % were Hispanic or Latino. There were no patients with multiple reported race/ethnic identities. 47.5 % had Spanish as their preferred language as compared to 36.4 % with English as their preferred language.

Of the n = 99 patients who had a positive QFN, 96.7 % had a CXR ordered by their provider (Fig. 1). 95.6 % of patients completed a CXR. 82.8 % of patients were referred to the TB clinic with an average of 53.1 days between completing the CXR and getting the referral. 44.4 % of patients scheduled an appointment with the TB clinic. 23.2 % of patients attended an appointment at the TB clinic. 21.2 % of patients started medical treatment of LTBI. 17.2 % of patients completed LTBI treatment with an average of 129.0 days between starting and ending treatment.

There was no significant difference in the rate of treatment completion amongst patients who were requested to get a second CXR compared to patients who only had one CXR (Table 2). There was no difference in the rate of treatment completion amongst patients who had their first CXR during their admission for delivery as compared to those who had the CXR before their admission for delivery. There were no differences in treatment completion with regards to preferred language. No cases of active TB developed in the study population.

4. Discussion

The goal of this study was to evaluate the effectiveness of screening for LTBI in the prenatal clinic of an inner-city hospital. The purpose of screening was to rule out active TB in pregnancy, and to treat patients with LTBI after pregnancy to prevent reactivation TB. The findings from this study of the LTBI cascade of care showed that most patients from the prenatal clinic with a positive screening result do not complete LTBI treatment. Most patients were lost during the steps that transition them from obstetric care to the care of the TB clinic. Only 23.2 % of patients attended an appointment in the TB clinic. These findings are consistent with other studies which found that 5–42 % of women with LTBI during pregnancy actually complete treatment, with attrition occurring due to lack of referral, gaps in adherence to appointments, and non-adherence with treatment [15,16]. Without treatment, it is estimated that 5–10 %

Table 1
Characteristics of Study Population.

Variable	Mean	Standard Deviation
Age (years)	33.5	6.5
Gestational Age at Screening (days)	115.3	48.1
Category	**Number**	**Percentage**
Preferred Language	36	36.4
English	47	47.5
Spanish	11	11.1
Haitian Creole	2	2.0
Portuguese	2	2.0
French	2	2.0
Other	1	1.0
Race		
Black	45	45.5
Other Race	54	54.5
Ethnicity		
Hispanic	51	51.5
Non-Hispanic	48	48.5

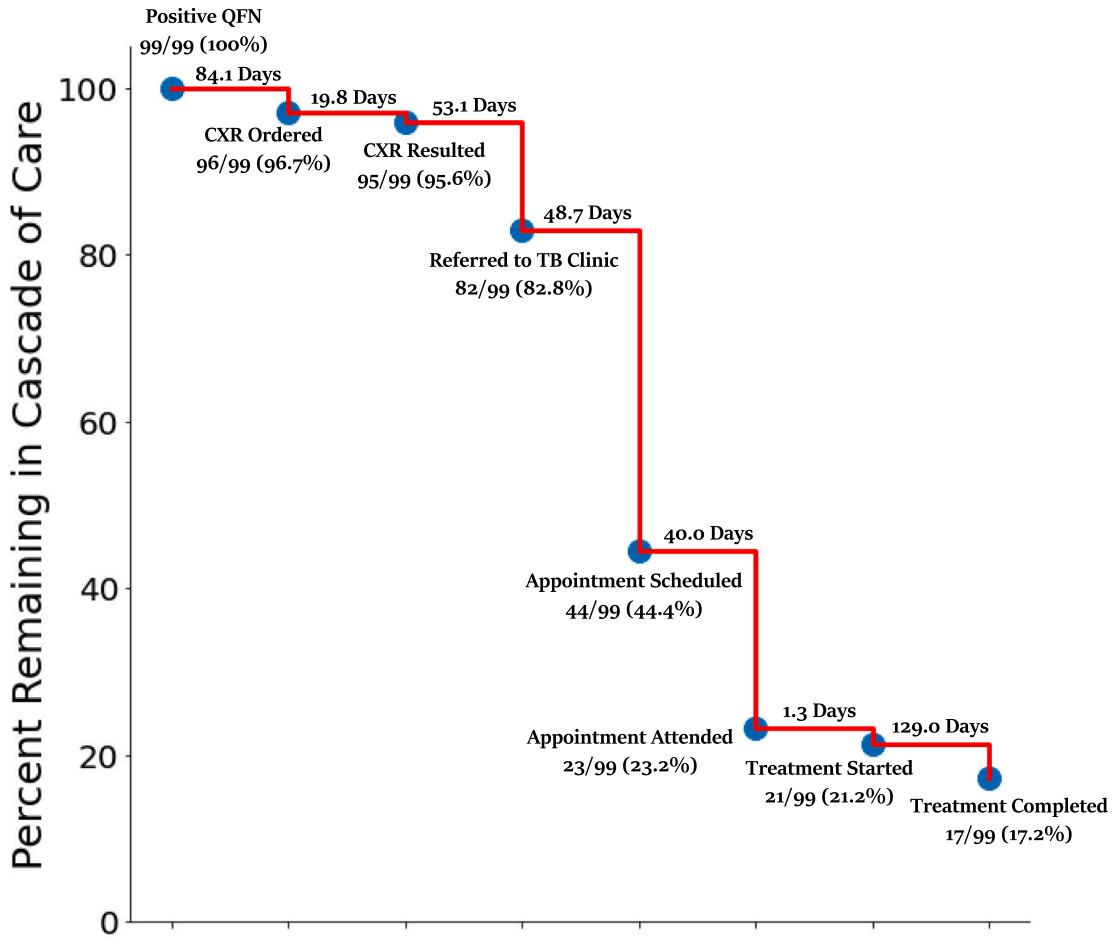

Fig. 1. Cascade of care for LTBI in prenatal clinic. Number on bar indicates average time between steps of the cascade of care.

Table 2
Relationship of Demographic and Cascade Related Factors to Treatment Completion.

Variable	Number Completing Treatment (%)	Number Not Completing Treatment (%)
Preferred Language		
English	8 (22.2)	28 (77.8)
Spanish	8 (17.0)	29 (83.0)
Haitian Creole	1 (9.0)	10 (91.0)
Portuguese	0 (0.0)	2 (100.0)
French	0 (0)	2 (100.0)
Other	0 (0)	1 (100.0)
p-value for all languages	0.82	
p-value for English vs. non-English	0.41	
Asked for 2nd CXR		
Yes	8 (22.2)	28 (77.8)
No	9 (14.3)	54 (85.7)
p-value	0.41	
CXR During Delivery Admission		
Yes	5 (13.5)	32 (86.5)
No	12 (20.7)	46 (79.3)
p-value	0.42	

p-value is result of χ^2 test for independence.

of the untreated patients will develop active TB at some point later in life, which carries significant risk for morbidity, mortality, and transmission [17].

Although 96.7 % of patients with a positive QFN were ordered a CXR, 39 % of those patients did not complete the CXR until they were admitted for delivery. With this latency, one important objective of this strategy, which is to rule out active TB during pregnancy, is not met. All patients with a positive QFN should be counseled on the importance of completing a CXR prior to delivery, specifically by highlighting the risk active TB carries for the patient and the pregnancy. The patients diagnosed with LTBI should additionally be educated on the risks of leaving LTBI untreated after delivery, as there is evidence to suggest that improvement in the retention of patients in the cascade of care can be achieved with appropriate education [18,19]. Additionally, we speculate that reducing latency between LTBI diagnosis and establishing a treatment plan could help retain more patients in the cascade of care.

In this institution's current practice, referral to the TB clinic was most often done during the patients' post-partum period in the hospital, and personnel from the TB clinic would subsequently call the patient to schedule an appointment after discharge. Evidence from previous studies of LTBI in pregnancy shows that patients who received care from the same physician antepartum and postpartum were more likely to complete LTBI treatment than those who saw different physicians [16]. This suggests that there is merit to establishing a relationship in the antepartum period with the physician who will treat LTBI. Moreover, after the patient delivers, her focus likely shifts away from her own health and towards caring for the newborn. Shifting the referral and initial evaluation of patients by the TB clinic to before delivery would move the patient further along the cascade of care, before the diagnosis of LTBI becomes less salient to the patient. Alternatively, the obstetrician could initiate LTBI treatment at the first postpartum visit. A caveat to changing the time of the first TB clinic appointment is that adding an additional appointment in the prenatal period could be challenging for

patients already negatively affected by social determinants of health such as difficulty getting transportation to appointments and arranging child care. The engagement of patient navigators has also shown promise in retaining patients within care [20]. Although our patients did have an obstetrics navigator, the navigators were not involved in LTBI care at the time of this study.

Prior to the data collection, it was hypothesized that patients who were asked to get a second CXR by their obstetrician after delivery would be less likely to complete treatment because this effectively adds an extra step to the cascade of care. The reasoning behind this policy was to ensure that the patient did not have active TB when initiating LTBI treatment. Interestingly, these patients actually had a non-significant increase in completion rate. This could possibly be due to the fact that asking the patient to get a second CXR refreshes the salience of her LTBI diagnosis, thereby encouraging the patient to attend her appointment and complete treatment.

Taking into account the results of this study, previous literature, and the needs of this population, the modified cascade of care begins with performing the QFN at the first prenatal clinic visit, and having the CXR done as soon as possible if the QFN is positive. If the CXR does not show active TB, the patient should be educated about LTBI by the obstetrician and via educational materials regarding LTBI and its treatment in the postpartum period. At this time, with the help of a patient navigator who will develop a relationship with the patient over the course of the pregnancy, the patient should be referred to the TB clinic, with an appointment scheduled for within 1 month after the estimated date of delivery. During the admission for delivery, the patient should have another CXR to rule out active TB prior to beginning LTBI treatment. This will also serve to ensure that the CXR is recent enough to initiate LTBI treatment at the time of the clinic appointment. At the first appointment in the TB clinic, the patient will be started on treatment for LTBI. This modified approach provides a framework for smooth transition from obstetric care to the care of the TB clinic by establishing an appointment with the TB clinic prior to delivery. Additionally, it leverages the proven benefits of educating patients about LTBI and involving patient navigators in LTBI care. Lastly, it has the added benefits of evaluating for active TB in the period with high risk for reactivation TB and refreshing the salience of LTBI diagnosis.

After implementing these modifications to our institution's policy, it will be imperative to reevaluate the cascade of care to see if the changes are effective. The analysis will follow a similar framework to what was performed for this study, and will elucidate if additional interventions are required. Future directions could involve having the obstetrician initiate LTBI treatment, or engaging the newborn's pediatrician in encouraging the patient to receive LTBI treatment.

The estimated LTBI positivity rate for the general population in the U.S. is 2.7 % [3]. Previous studies of LTBI in pregnancy showed higher prevalence in minority populations [21]. The positivity rate for LTBI in this majority Hispanic and black population was 9.17 %, supporting the strategy to screen all patients for TB in the prenatal clinic. Pregnancy and the perinatal period are times of increased interaction with the healthcare system, and are therefore opportunities to address chronic health issues. Improved retention of patients within the cascade of care will make the screening intervention a more effective tool for reducing the burden of TB.

5. Conclusion

Systematic analysis of the cascade of care elucidates correctible deficiencies which led to patients not getting treatment for LTBI. Particularly, the transition from obstetric care to that of the TB clinic is the major source of losing patients at our institution. This deficiency was most likely due to the referral and scheduling process overlapping with delivery and the immediate post-partum period. Moving forward, this will be corrected by shifting the process to immediately after the diagnosis of LTBI is made. It will also be supplemented by providing patients with more education about the significance of LTBI. Patient navigators will also be engaged to facilitate movement through the cascade of care. Additionally, it was shown that having patients receive a second CXR and doing a CXR during admission for delivery does not negatively affect treatment completion. As a result, an additional CXR during admission for delivery to rule out active TB will be added. These interventions aimed at decreasing latency between steps of the cascade, establishing therapeutic relationships, and increasing the salience of the diagnosis of LTBI may improve rates of treatment completion.

Ethical statement

This study was approved by the Institutional Review Board committee at Rutgers New Jersey Medical School, Approval Number: Pro2022000688. All data was collected with strict confidentiality measures, and HIPAA compliant software. The data presented in this manuscript do not contain any identifying information. The contents of the manuscript reflect the work of only the authors, and no other persons. None of the authors have any financial disclosures or conflicts of interest.

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Jay Phansalkar: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rajas Karajgikar:** Investigation, Data curation, Conceptualization. **Jai Patel:** Investigation, Data curation. **Shauna Williams:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Lisa Gittens-Williams:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization. **Alfred Lardizabal:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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