Improving the Duration of Airborne Isolation for Suspected Pulmonary Tuberculosis: Cost-Effectiveness Analysis

by

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Abstract

Background: Airborne isolation (AI) is an effective way to prevent the spread of tuberculosis (TB). When healthcare facilities are faced with patients with suspected pulmonary TB, they place patients in AI and order at least 3 specimens for acid-fast bacilli (AFB) smears and culture. The specimens are collected 8-24 hours apart with at least one morning specimen. When 3 consecutive specimens are negative on smears or another diagnosis is made, AI is discontinued. However, there is a significant delay in discontinuation of AI. Effective strategies are needed to shorten the duration in AI.

Public Health Significance: Delayed deisolation is associated with significant avoidable cost for the hospitals and patients without health insurance and related with preventable negative health effects on patients over-isolated.

Aims: The objective is to evaluate current practice of AI and improve the efficiency of deisolation for patients without contagious TB.

Method: Demographic and clinical information was reviewed from Jan 2015 to Dec 2017 at a 495-bed university-affiliated medical center. Cost-effectiveness analysis was performed to compare isolation with no isolation. TreeAge Pro 2018 Software was used to build a decision tree and make a sensitivity analysis.

Result: The positive rate of respiratory specimens is 6.3%. 93 patients had contagious TB excluded successfully with 3 consecutive negative AFB smears. AI is always cost-effective than no isolation despite the variation of its effectiveness. The average LOS in AI is 4.8 days. If LOS can be reduced to 2 days, the cost saving is $3,122 per patient. The total cost saving for 93 patients is $290,160.

Conclusion: This study shows a significant delay in deisolation for patients without contagious TB. More effective measures are needed to rule out TB timely. Improved efficiency in deisolation can contribute to a significant cost saving. Cost-effectiveness analysis will be a powerful aid to decision making that could engage hospital administration to improve the efficiency of deisolation.

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Preface

I would like to thank Dr. Mattila who is a good advisor and mentor for his support and valuable suggestions. He is always willing to offer help when I encounter problems. His encouragement lights my way and helps me to achieve my goals step by step. I would like to thank Dr. Yassin who offers this great opportunity to work with him in UPMC Mercy. He is always patient and kind to meet with me to give me guidance and clear my questions. He offered data and helped to build decision tree and cost-effectiveness analysis for this project. Without his help, I was unable to complete this project. I would like to thank Dr. Chen for providing the information about practicum, so I was able to contact with Dr. Yassin. I really appreciate her unconditional help and giving valuable advice to me.

1.0 Introduction

Tuberculosis (TB) is one of the world's top ten leading causes of death. The number of deaths caused by TB exceeds the numbers caused by HIV/AID (World Health Organization, 2018). According to World Health Organization (WHO), there were 10.4 million people newly infected with TB and an estimated 1.7 million people died from this disease in 2016 (World Health Organization, 2017, p. 1). 53 million people's lives were saved during 2000-2016 (World Health Organization, 2017, p. 1).

WHO End TB strategy plans to end the global TB epidemic by 2035. Patients living with TB can be cured if they are diagnosed early enough and treated properly. Hence TB detection plays an important role in reducing mortality rates. Missed and delayed detection of TB can result in increased TB transmission and poor outcomes.

When healthcare facilities are faced with suspected patients, they perform sputum specimens for acid-fast stain and culture. Suspected TB patients are placed in airborne infection isolation room (AIIR). Three consecutive negative sputum smears for acid-fast bacilli (AFB) collected 8-24 hours apart or other diagnoses are required for discontinuing isolation (Centers for Disease Control and Prevention, 2013, p. 84). Among these specimens, at least one should be obtained in the early morning (Centers for Disease Control and Prevention, 2013, p. 84). Negative smears suggest that no infection is present or there are a low load of mycobacteria which are not sufficient enough to be seen under microscope (Centers for Disease Control and

Prevention, 2013, p. 84). Patients with negative AFB smears are considered at low risk of disseminating TB.

Airborne isolation (AI) is necessary to prevent the spread of TB. TB exposure in the medical center leads to exposed health care workers (HCWs) and patients which is associated with significant monetary and workforce attrition. In low TB incidence countries, the annual incidence rates of latent tuberculosis infection (LTBI) and TB disease among HCWs ranges from 1% to 4% (Baussano et al., 2011; D. Menzies, Joshi, & Pai, 2007). HCWs have a greater risk of becoming infected than the general population because the nature of their work leads to persistent exposure to *M. tuberculosis* (Nathavitharana et al., 2017). Although the incidence of TB in health care facilities is low, it's essential to continue AI for patients with suspected infectious TB in order to prevent the transmission of TB.

Actually only 4% - 10% of patients isolated have TB (Curley, 2015; Leonard et al., 2006). However, only 18% suspected patients end their isolation within 48 hours (Thomas, Bello, & Seto, 2013). Patients without medical insurance and hospital are facing the financial burden due to excessive time of AI. In addition, the longer the duration of AI, the greater the risk that patients will experience nosocomial infections and mental health problems. These issues make it necessary to discontinue isolation in a timely manner.

The objective of this study is to evaluate current practice of AI and improve the duration in AI for patients suspected with TB. This research focuses on answering following questions: What's the average time that patients with suspected infectious TB spend in AI? Is there any delayed discontinuation of isolation? What can be done to improve the duration of AI? How much money could be saved from these measures?

1.1 Clinical Manifestations of TB

TB is a contagious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB) which is spreading via the aerosol route. TB mainly affects the lungs (pulmonary TB) but can also infect other tissues or organs outside of the lungs (extra-pulmonary TB). According to the Centers for Disease Control and Prevention (CDC), patients with active TB show clinical features such as a cough for 3 weeks or longer, hemoptysis, night sweats, unexplained weight loss, fever, and fatigue (Centers for Disease Control and Prevention, 2011). Patients with active TB can infect others. If they are left untreated, TB can be transmitted to 10-15 persons per year (World Health Organization, 1999). The most common form of active TB, pulmonary TB, is very contagious because TB bacteria can be easily expelled by coughing, sneezing or speaking and the bacilli can remain in the air for hours (Centers for Disease Control and Prevention, 2016b).

About a quarter of the world's population has latent TB and doesn't exhibit the signs and symptoms of TB and don't have the ability to infect others (Houben & Dodd, 2016). But latently-infected individuals have a 5-15% risk of progress to active TB depending on their age, immune system function and the period of the latent TB of the patients (Comstock, Livesay, & Woolpert, 1974). The risk of developing active TB is reduced by 80% if infected individuals receive treatment timely (Kato & Kuwabara, 2014).

Bacillus Calmette-Guérin (BCG) vaccination is the only available vaccine against TB, but the efficiency of BCG varies widely due to a variety of geography and age (Fine, 1995). Even though it protects against TB in some population, it shows little protective effect in other population, and protection declines after adolescence. (Nguipdop-Djomo, Heldal, Rodrigues, Abubakar, & Mangtani, 2016; Rodrigues, Mangtani, & Abubakar, 2011)

1.2 Diagnosis of TB

Making the diagnosis of TB typically needs a review of medical history, physical examination and the Mantoux skin test which is known as purified protein derivative test (PPD test), tuberculin skin test (TST) or tuberculosis test (TB test) (Centers for Disease Control and Prevention, 2016a). A patient with a positive reaction to TST doesn't necessarily have TB. It requires a chest radiograph and microbiology testing to confirm the result such as AFB smear microscopy and culture (Centers for Disease Control and Prevention, 2016a).

1.2.1 TST and Interferon-γ Release Assays (IGRAs)

TST and IGRAs both can be used to detect latent tuberculosis infection (LTBI). TST is cheap and easy to perform, so it is the most frequently used. But it also has deficiency because of a low specificity which means a low ability to tell a patient without TB (Campbell, Krot, Elwood, Cook, & Marra, 2015). Estimated 10-29% of persons have a false negativity and 30% of persons have a false positivity (Auld et al., 2013; Khawcharoenporn et al., 2016). The high false positivity is mainly attributed to common antigens shared with BCG vaccination and nontuberculous mycobacteria (NTM). A negative TST also is related with 2 to 3-fold increase in the risk of death from TB because it indicates a weaker immune function to control TB infection (Auld et al., 2013).

IGRAs are commercially available. There are two licensed IGRAs: QuantiFERON TB Gold and T-SPOT. It has higher specificity but more expensive than TST (Andersen, Munk, Pollock, & Doherty, 2000). The sensitivity of IGRAs (78%-92%) is higher than that of TST (65%-77%) (Goletti, Sanduzzi, & Delogu, 2014). They are favored especially when people have

BCG vaccination because they don't share common species with BCG vaccination and NTM. But IGRAs is not sensitive enough to rule out TB. It is recommended that to use IGRAs in TST positives and to perform a chest X-ray (CXR) in those IGRA positives. TST can be an alternative where IGRAs are unavailable or too expensive (Lewinsohn et al., 2017). However, neither test distinguishes between latent TB and active TB and they have poor predictive value for the development of active TB (Greenaway, Pareek, Abou Chakra, Walji, Makarenko, Alabdulkarim, Hogan, McConnell, Scarfo, Christensen, Tran, Rowbotham, Noori, et al., 2018).

1.2.2 AFB Smear Microscopy and Sputum Culture

AFB smear microscopy is one of the most important pieces of evidence for clinical preliminary TB diagnosis which has been used for over 100 years. It can be used to detect MTB and nontuberculous mycobacteria (NTM) and provides the final test result within one day (Boehme et al., 2011). The sensitivity and specificity are 88.4-95% and 99.3-99.7% respectively (Melese et al., 2016; Mosissa et al., 2016). The result indicates the risk of TB transmission. The risk increases as more AFB are detected which is also related with more extension of lung affected (Ralph et al., 2010). It is considered as a technique relatively simple, rapid and economical so it is widely used and available in most hospitals. But it cannot detect the resistance of TB-causing bacteria to antibiotics. It needs additional clinical examinations to confirm its result (Noori et al., 2016).

Fewer half of TB cases are identified by the presence of AFB in sputum smears (Pai, Ramsay, & O'Brien, 2008). Even though smear-negative TB patients are less contagious than those with smear-positive TB, they may transmit TB bacteria to others. Patients with smear-negative but culture-positive TB are usually in an early and less infectious stage and have a low load of bacteria burden, which contribute to 12-17% TB transmission (Behr et al., 1999; Hernandez-Garduno et al., 2004; Tostmann et al., 2008). There are 6% - 14% specimens positive in AFB smears but negative in culture (Chao et al., 2015; Lee et al., 2008; Mnyambwa et al., 2017). It may attribute to laboratory technical failure and NTM because of their similar morphology (Jun et al., 2009). False positive results will lead to unnecessary anti-TB treatment, adding to financial burden as well as psychological burden for patients. The performance of AFB smear microscopy is also hampered by HIV coinfection because of the presence of other microorganism causing infection and the lower sputum concentration of *M. tuberculosis* (Rewata et al., 2009).

Culture is regarded as a gold standard for TB diagnosis and used as a reference to evaluate other technologies (Cain et al., 2010). For smear microscopy, the limit of detection (LOD) is around 5,000-10,000 colony forming units (CFU) per milliliter, while for culture in liquid media LOD ranges from 10 to 50 CFU per milliliter (Olaru, Heyckendorf, Grossmann, & Lange, 2014). Compared with AFB smear microscopy, the sputum culture is more expensive, time-consuming and laborious. It takes up to 4 days to 12 weeks to get the result (Centers for Disease Control and Prevention, 2013). Solid culture usually takes 3-8 weeks while liquid cultures take 4-14 days (Centers for Disease Control and Prevention, 2013; Pfyffer & Wittwer, 2012). Therefore, it is not suitable to be used as a rapid diagnostic test. It may identify other bacteria as AFB by mistake in immunocompromised patients (Dinic et al., 2013). But it has a significantly higher sensitivity compared with smear microscopy. Time to culture positivity has a negative correlation with CFU which means time to culture positivity becomes longer with the treatment of TB (Bark et al., 2011).

1.2.3 Chest Radiograph and Xpert MTB/RIF (Xpert)

The chest radiograph is a good tool to detect active TB cases in low-incidence regions (Curtis, 2016; Paquette et al., 2014). To make good use of it, it requires an experienced reader (Cain et al., 2010). The sensitivity of chest radiography was high (98%) to detect chest abnormality related to pulmonary TB, while the specificity was moderate (75%) (Greenaway, Pareek, Abou Chakra, Walji, Makarenko, Alabdulkarim, Hogan, McConnell, Scarfo, Christensen, Tran, Rowbotham, van der Werf, et al., 2018). It has a high negative predictive value in immunocompetent patients whereas a negative result cannot rule out TB in immunocompromised patients (van Cleeff, Kivihya-Ndugga, Meme, Odhiambo, & Klatser, 2005). In addition, old TB cannot be distinguished from new active TB by using chest radiographs alone. Hence, it is recommended to perform microbiological testing to confirm chest radiographs suggestive of TB.

In 2010, WHO first recommended adopting Xpert which is a nucleic acid amplification test that can reliably and quickly detect MTB complex as well as rifampicin resistance within 2 hours (World Health Organization, 2011a). Now Xpert is widely implemented and it is considered as the initial test of diagnosis for persons with signs and symptoms of TB or living with HIV (Steingart et al., 2014; World Health Organization, 2013). When testing a single sample, Xpert demonstrates the sensitivity is about 85% (59.3%-72.5% for smear-negative and 96.7%-98.2% for smear-positive cases) and specificity is about 99% (Kirwan, Cardenas, & Gilman, 2012; Luetkemeyer et al., 2016). One additional Xpert increases the overall sensitivity from 85% to 91% (Luetkemeyer et al., 2016). For patients living with HIV, the sensitivity is 79% (Steingart et al., 2014). LOD is about 130 CFU/ml much lower than that with smear microscopy. Compared with smear microscopy and liquid culture, Xpert has a higher sensitivity that means it can detect more TB cases (Balcha et al., 2014). It also has low number needed to screen and high positive predictive value when following the Chest X-ray (CXR) screening (Van't Hoog, Onozaki, & Lonnroth, 2014).

The advantages of Xpert including increased case-detection and timely treatment lead to a decrease in mortality and morbidity of TB and potentially reduced LTBI (Boehme et al., 2011; N. A. Menzies, Cohen, Lin, Murray, & Salomon, 2012). Due to its relatively expensive cost, it may be cost-effective only in high-income countries.

1.3 Cost-Effectiveness of Screening Strategies

A systematic literature review shows the cost of TB diagnosis ranges from $0.5 for sputum smear microscopy (SSM) to $175 for intensified case detection by Xpert for per patient suspected (de Siqueira-Filha, Legood, Cavalcanti, & Santos, 2018). Xpert is considered as the most cost-effective method to diagnose TB in the United States (Choi, Miele, Dowdy, & Shah, 2013). Using the TST or IGRAs to detect LTBI cost varied from $10.9 to $31.5 and from $22.5 to $97.1 respectively (World Health Organization, 2015). When it comes to people living with HIV/TB co-infection, it becomes more difficult to rule out TB (de Siqueira-Filha et al., 2018; Padmapriyadarsini, Narendran, & Swaminathan, 2011). In consequence, TB diagnosis for immunosuppressed persons becomes more expensive.

Using IGRA-alone strategy and using IGRAs in TST positive strategy are more cost-effective than TST (Nienhaus, Schablon, Costa, & Diel, 2011). Although the pre-screening cost of IGRAs is higher than TST, the post-test cost of IGRAs is lower than TST due to the cost savings for the treatment of undetected infectious TB and LTBI progresses to active TB. In the previous study, IGRAs were less cost-effective when compared with CXR in low TB burden country (Kowada, Deshpande, Takahashi, Shimbo, & Fukui, 2010). In contrast, IGRAs which was about 15 quality-adjusted life-years (QALYs) were more cost-effective than CXR in intermediate- and high- TB incidence countries (Kowada et al., 2010). Symptom screening combined with Xpert is highly cost-effective in high TB-burden countries (Adelman et al., 2018). And IGRAs following TST positive was the most cost-effective in high prevalence TB countries (Oxlade, Schwartzman, & Menzies, 2007).

When considering using the most cost-effective strategy, it is necessary to take the risk of disease in the areas into account. In regions where the TB prevalence is lower than 2%, it's more important to pay attention to increase the specificity to reduce the large number needed to screen which will result in a high financial cost in screening TB.

1.4 Airborne Isolation (AI)

Although TB prevalence is declining in most developed countries, transmission of TB is still a risk in hospitals. Not only patients but also HCWs were involved in multiple TB outbreaks in healthcare facilities (Balmelli et al., 2014; Baussano et al., 2011; Nigorikawa et al., 2012). Some of them have drug resistance.

TB is a kind of occupational disease for HCWs. The risk for infection with TB among HCWs is globally higher than the risk among the general population because of HCWs' potential contact with infectious individuals (Baussano et al., 2011). TB cases in the healthcare setting among HCWs were about 50%, 30% and 80% in low, intermediate and high TB burden countries respectively (Baussano et al., 2011). The rates can be decreased if effective infection control measures are taken. TB infection control measures including administrative controls (e.g. management measures), environmental controls (e.g. ventilation system and AI) and personal respiratory protection (e.g. N-95s respirators) play essential roles in the reduction of TB incidence among HCWs (Centers for Disease Control and Prevention, 2016c). Administrative controls are of the first essential among these measures (Centers for Disease Control and Prevention, 2016c).

Appropriate isolation precautions for persons with suspected of communicable diseases are of the essence to prevent disease transmission. AIIR is a negative pressure and single-bed room designed to prevent the infectious airborne pathogens from escaping into public areas which decreases the risk of TB disease in healthcare facilities. The ventilation system in the AIIR helps to provide a gentle air flow sent into the room and moves exhaust air into the atmosphere where the infectious air can be diluted (Centers for Disease Control and Prevention, 2007). Or using the HEPA filters directs the air in AIIR before it is introduced into other spaces (Centers for Disease Control and Prevention, 2007). This method diluting and removing the infectious air represents the primary environmental control. It's recommended that the ventilation system should have at least six air changes per hour to reduce the concentration of infectious droplets effectively, and recently twelve air changes per hour has been advised for new buildings (Centers for Disease Control and Prevention, 2003). The requirement in airflow showing the secondary environmental control is the difference between the general negative-pressure rooms and AIIRs. The ventilation system with the specific location of a supply and exhaust air can significantly reduce the concentration of the airborne pathogens in the room which prevents the spread of infectious droplets (Jafari et al., 2015).

1.5 Discontinuation of Airborne Isolation

1.5.1 The Average Duration of AI

When making decisions on AI discontinuation according to 3 consecutive negative AFB smears results, the duration in AI varies in different studies. The average time for AI discontinuation is 4 to 7 days (Curley, 2015). It was also reported that patients spent an average of 6.6 days in AI (Harmon & Roche, 1995). The median time from specimen collection to the report of laboratory result is 1 day for AFB smear-positive patients and 21 days for AFB smear-negative patients (Pascopella et al., 2004). The results of Thomas's study showed only 18% of patients ended their AI within 2 days and about a half were within 3 days by using smear microscopy. (Thomas et al., 2013). The median duration in AI was 68 hours in a tertiary medical center (Lippincott, Miller, Popowitch, Hanrahan, & Van Rie, 2014). If specimen collection follows the CDC protocol, the duration in AII is expected not more than 2 days (Thomas et al., 2013).

1.5.2 Causes for Delayed Discontinuation of AI

Delayed laboratory report is one of the important factors contributing to the delays in discontinuation of isolation as well as delays in initiation of medical therapy (Thomas et al., 2013). There were 27% delayed laboratory reports for smear-positive patients and 47% for smear-negative patients (Pascopella et al., 2004). Some delayed reports are attributable to delayed transports of specimen to laboratory performing testing. Inability to produce sputum explains 15% of non-timely discontinuation (Thomas et al., 2013).

1.5.3 Negative Effects of Delayed Deisolation

Isolation precautions for patients with presumptive pulmonary TB are tended to reduce nosocomial infection. For prevention the spread of MTB, they are placed in AIIR and most of time restricted to stay in the room. There is an inevitable barrier between HCWs and isolated patients. Inpatients' level of quality of life, depression and anxiety are not influenced by the short-term isolation which is less than 4 days (Wassenberg, Severs, & Bonten, 2010).

However, excessive isolation exerts potential adverse impacts on patients. They are associated with higher rate of patients neglect which is reflected in less documented care, less frequent and shorter contact with clinicians during rounds and lower rate of satisfaction (Stelfox, Bates, & Redelmeier, 2003). When HCWs enter AIIR, they should wear an appropriate PPE (e.g. N95 masks) making patients care cumbersome. Isolated patients are more likely to have adverse events (Abad, Fearday, & Safdar, 2010; Stelfox et al., 2003). Their mental well-being is negatively influenced such as an increased rate of depression and anxiety. These mental problems result from uncertainty, loss of control and lack of communication with others (Gammon, 1998). These negative emotions can lead to weak immune system and become vulnerable to infection, or contribute to angina, ulcers and hypertension these secondary diseases (Gammon, 1998).

Verlee et al. study concludes that delayed discontinuation of isolation leads to annual 4,000 days unnecessarily spent in AI and $141,000 avoided from overuse of supplies and HCWs' time (Verlee, Berriel-Cass, Buck, & Nguyen, 2014). Isolation precautions are related to longer hospital length of stay (LOS) and higher costs in comparison with general medicine inpatients (Tran et al., 2017). In comparison to general medicine patients, the incremental length of stay

(LOS) is one day and the incremental direct cost is $3,339 for patients isolated for respiratory illness (Wachter, 2017).

Over-isolation affects patients' physical and psychological health, wastes resources for excess PPE and causes financial problems for hospitals and patients without health insurance. For patients with no risk of spreading TB, they should be taken out of AIIRs timely. Benefits could be gained from the improved efficiency in discontinuation of isolation such as increased patient satisfaction, higher bed availability and increased cost avoidance without adding to the risk of infection. Cost-effectiveness analysis will be a powerful aid to decision making that could engage hospital administration to improve the efficiency of discontinuing AI.

2.0 Methods

We performed observational retrospective study reviewing electronic medical records of inpatients with suspected active TB from January 2015 to December 2017. It was conducted at a 495-bed university-affiliated medical center in Pennsylvania. The number of TB rates in Pennsylvania was 1.6 per 100,000 persons in 2015 (Centers for Disease Control and Prevention, 2015). There were 173 cases of TB reported in 2016 and 192 cases reported in 2017 with the 11% increase (PA Department of Health, 2017).

This medical center follows conventional CDC guidelines for discontinuation of isolation. AI will be discontinued if either of conditions is satisfied: (1) there are three consecutive negative AFB sputum smears collected 8-24 hours apart and at least one obtained in the early morning (Centers for Disease Control and Prevention, 2013); (2) another diagnosis is made (Centers for Disease Control and Prevention, 2013).

AI is initiated based on a screening tool. A significant number of initial AI were discontinued based on clinical assessment after approval from infection control department. Decision to AI depends on TB program criteria. The criteria for AI are listed in **Table 1**. Patients who meet the criteria will be placed in AIIRs. Typically, these patients remain in AI for no more than 1 day. They may get one sample for AFB stain and culture. These patients are not included in this study. This screening tool is too sensitive to pick any suspected TB cases, but not specific enough.

The study focuses on the patients who remain in AI and had three specimens for AFB stain and culture. The patients who have three AFB negative smears are considered not high-risk for disseminating TB and are taken out of AI. The cost-effectiveness analysis was performed to compare patients with airborne isolation from patients with no isolation. The cost-effectiveness of AI was evaluated by using decision tree model. Probabilities and costs were obtained by the local hospital data.

Table 1 Criteria for Airborne Isolation

1. Prolonged cough (3 weeks or longer)
2. Hemoptysis (coughing up blood)
3. Chest pain
4. Anorexia (loss of appetite)
5. Unexplained weight loss
6. Night sweats
7. Fever
8. Fatigue
9.Chest radiograph suggestive of TB

2.1 Population

TB identification is done by the screening tool as well as if TB is suspected by the treating physicians. There were 457 episodes of AI for suspected pulmonary TB identified from January 2015 to December 2017. 364 patients excluded because 3 of them were outpatients and 361 inpatients whose initial isolation was discontinued and decision to discontinue isolation for these patients was made by Infection Control Department after clinical assessment. 93 inpatients having TB excluded with 3 negative AFB smear results were included in this study.

2.2 Data Collection

Demographic and clinical information were obtained from electronic medical records by year. The collected data include patients' age, length of stay (LOS), the duration of AI, the type and result of AFB smears and culture. LOS is calculated by subtracting the admission date from the discharge date. The duration of AI is defined as the time between the initiation and the discontinuation of AI. For each patient, the duration of AI is the amount of time a person spends in AI and it is defined with the unit "days". It is counted according to the electronic isolation lists which recorded patients in AI every half day. If total time for a patient in AI is equal to or less than 1 day or specimen collections are less than 3 times, the patient will be excluded. Outpatients are excluded. If the duration is 1.5 days, it will round to 2 days. The specimens only include respiratory samples, which are bronchoalveolar lavage, pleural fluid, respiratory tract fluid and sputum.

The average salary costs per day associated with these patients placed in AIIR is shown in **Table 2**. The information is based on data available in Health Catalyst for medical patients who spent their entire stay in the Intensive Care Unit or General Medicine. Salaries include regular salary, overtime salary, benefits and central benefits.

Table 2 The Average Hospital Costs per Day by Departments

Department	Hospital Cost per Day ($)	ICU ($)
Ancillary	100.82	239.69
Cardiology	10.95	15.52
Emergency Room	16.30	20.37
Imaging	23.10	39.53
Labs	36.60	83.94
Nursing	305.03	1146.61
Pharmacy	50.15	115.41
Surgery	10.21	12.04
Other	236.21	186.30
Total	**789.37**	**1859.40**

2.3 Data Analysis

TreeAge Pro 2018 software was used to build a decision tree and sensitivity analysis. The decision tree model in **Figure 1** was structured based on the screening tools by which HCWs identified patients with suspected infectious TB. AI strategy is labeled as the first branch of the model, and the no isolation (NI) strategy is labeled as second branch. This model calculated the cost and probability for each strategy and compared with each other. The outcomes for both strategies are patients with contagious TB and patients without contagious TB. In both AI and NI strategy, patients with positive AFB stain can indicate having contagious TB as well as not having contagious TB. Because AFB smears cannot distinguish NTM and MTB. Positive AFB stain can be resulted from the presence of NTM. Negative AFB stain suggests there is no TB infection or there is a low load of mycobacteria burden. Patients with negative AFB stain are considered at no or low risk for the spread of TB. When 3 consecutive specimens are negative on AFB smears, patients can be taken out of AI. The effectiveness is the number of detected infectious TB and an average value is 50,000 in this study. Only isolating a patient with contagious TB is effective, so the others effectiveness is zero. Conditional probabilities of different scenarios and related costs for different events are presented in detail in **Table 3**. The costs were assessed from healthcare facilities perspectives. Only costs for the general medicine and TB related costs were included which are shown in the end of each decision path.

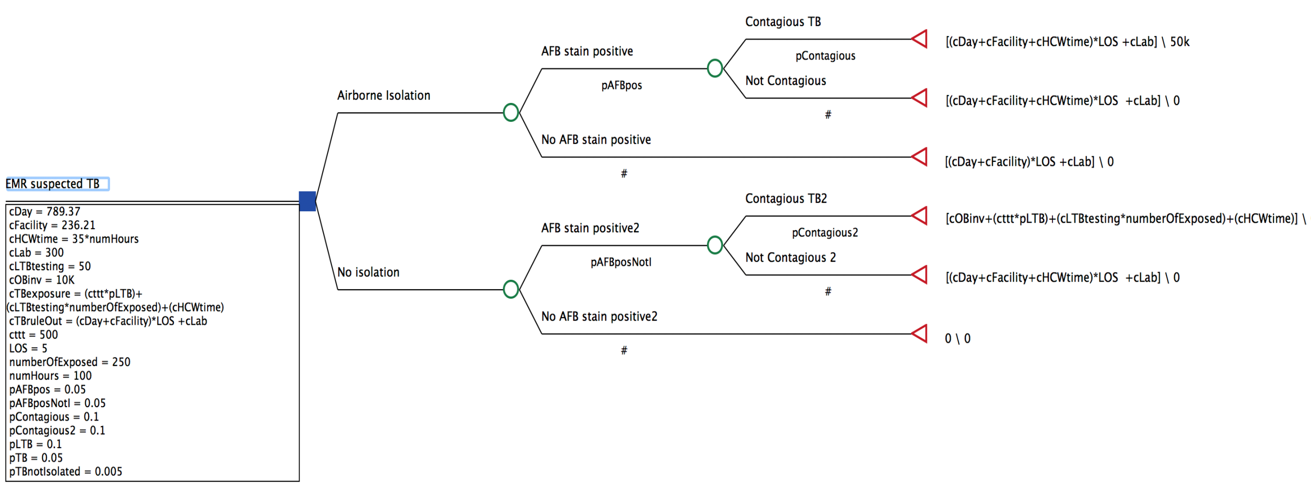

Figure 1 Decision Tree Model for the Airborne Isolation Strategy

A square node, a circle node and a triangle node represent the decision node, the chance node and the terminal node respectively. The decision node shows a decision to be made. The chance node represents the probabilities of a certain event. The terminal node is the result of a decision path.

Table 3 Model Parameter in Decision Tree Model

Model parameter input	Description of parameters	Value
pAFBpos	The probability of positive AFB stain	0.05
pAFBposNotI	The probability of positive AFB stain for patients without isolation	0.05
pContagious	The probability that patients isolated have contagious TB	0.1
pContagious2	The probability that patients without isolation have contagious TB	0.1
pLTB	The probability of people who converted to latent TB infection	0.1
cDay	Hospital cost per day including cost for ancillary, emergency room, cardiology, imaging, labs, nursing, pharmacy, surgery and others.	$789.37
cFacility	Facility cost per day	$236.21
cHCWtime	Cost of HCWs hours per day	$3500
cLab	Cost of laboratory testing	$300
cLTBtestinig	Cost of testing for latent TB	$50
cOBinv	Cost of outbreak investigation including employee work hours, communications, lab testing for exposed people and excluding any negative advertisement or litigation.	$10,000
cttt	Cost of TB treatment	$500
cTBruleOut	Cost of patients who were successfully “ruled out” by 3 consecutive negative AFB stain	$5428
cTBexposure:	Cost resulting from TB exposure	$16,050
LOS	Length of stay in AI	5 days
numberOfExposed	The average number of people exposed to TB	250
numHours	The number of hours	100 hours

The expected values in decision tree are shown in **Figure 2**. The summary of costs and effectiveness of TB were shown in **Table 4**, including hospital cost per day, facilities, HCWs hours worked, TB treatment, laboratory tests and outbreak investigation. The total cost is the same among patients with positive AFB stain in AI and patients who have positive AFB stain but not having contagious TB in NI, which is $22,928. The cost for patient with negative AFB stain in AI is only $5,428 due to exclusion of HCWs hours. The cost for Patients without contagious TB in NI is the most expensive, because it includes the outbreak investigation, HCWs hours, latent TB testing and treatment. If patients neither have contagious TB nor have being isolated, the cost is zero.

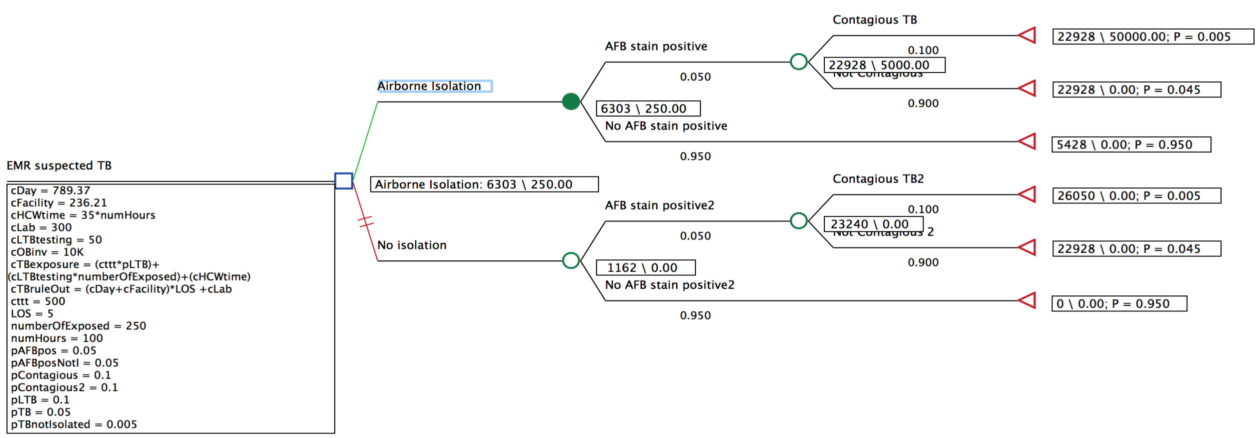

Figure 2 Expected Values in Decision Tree Model

Table 4 Costs and effectiveness of Two Strategies in Six Outcomes

Costs incurred in outcomes	Contagious TB detected by AFB stain	False positivity of AFB stain	TB ruled out	Contagious TB detected by AFB stain	False positivity of AFB stain	No contagious TB
	In airborne isolation			No isolation		
Costs	$22,928	$22,928	$5,428	$26,050	$22,928	$0
Effectiveness	50,000	0	0	0	0	0

3.0 Results

3.1.1 Basic Statistical Analysis

The demographic and clinical data are shown in **Table 5** including total specimens, total positive specimens, respiratory specimens, respiratory positive specimens, total patients with suspected active TB, patients with discontinuation of isolation before rule-out, patients ruled out, the average LOS in AI, the average age of patients and the average hospital stay. The overall positive rate of specimens is 4.6%. The positive rate of respiratory specimens takes up to 6.3%. 361 (79.5%) patients that their isolation was discontinued before ruled out were excluded from this study. It was based on the clinical assessment and infection control that made the conclusion that AI for them was unnecessary. 93 (20.5%) patients were successfully ruled out by 3 consecutive negative AFB smears results. The LOS in AI decreases over the last three years and the average is 4.8 days.

Table 5 Demographic and Clinical Data

Metric		2015	2016	2017	Total
Total specimens		2358	670	629	3657
Total positive specimens		107 (4.5%)	31 (4.6%)	30 (4.8%)	168 (4.6%)
Respiratory specimens		748	290	290	1328
Positive respiratory specimens		37 (5.0%)	29 (10.0%)	18 (6.2%)	84 (6.3%)
Total patients with suspected active TB		191	131	132	454
Patients with discontinuation of isolation before rule-out		159 (83.2%)	102 (77.9%)	100 (75.8%)	361 (79.5%)
Patients ruled out		32 (16.8%)	29 (22.1%)	32 (24.2%)	93 (20.5%)
LOS in AI (days)		5.3	4.7	4.4	4.8
The average hospital stay (days)	**All patients**	13.5	12.6	12.3	12.8
	Patients ruled out	11.4	9.5	9.4	10.1
The average age (years-old)	**All patients**	64.2	63.4	60.6	62.7
	Patients ruled out	59.0	54.7	59.6	57.8

3.1.2 Cost-Effectiveness Analysis

Table 6 shows one-way sensitivity analysis for cost-effectiveness of different duration in AI. It evaluates how the changes of LOS in AI impact the cost. If ruling out TB can be achieved within 2 days, it will cost about $2880. The average duration in AI is 4.8 days which costs $6000. If the LOS in AI can be reduced from 4.8 days to 2 days, the cost saving is $3,120 per patient. The total cost saving for 93 patients is $290,160. In addition, when AI strategy is compared with NI strategy for the same LOS. AI costs more than NI. The incremental cost for patients isolated is $4,892 ($6,003 vs $1,111) when the LOS is 4.8 days.

Table 6 One-way Sensitivity Analysis for Cost-effectiveness of Different Duration in AI

LOS[a]	Strategy	Cost
1.5	NI[b]	$449.23
	AI	$2100.87
2.15	NI	$581.60
	AI	$2881.25
2.8	NI	$713.97
	AI	$3661.62
3.45	NI	$846.35
	AI	$4442.00
4.1	NI	$978.72
	AI	$5222.38
4.75	NI	$1111.10
	AI	$6002.76
5.4	NI	$1243.47
	AI	$6783.13

[a]LOS = Length of stay

[b]NI = No isolation

Sensitivity analysis shows the change of incremental cost-effectiveness ratio (ICER) in terms of effectiveness of TB ranging from 10,000 to 100,000 in **Figure 3**. No isolation is base case scenario. Only isolating a patient with contagious TB is considered effective. ICER for NI is fixed on zero, while ICER for AI is always higher than zero. AI is more cost-effective than NI despite the variation of effectiveness.

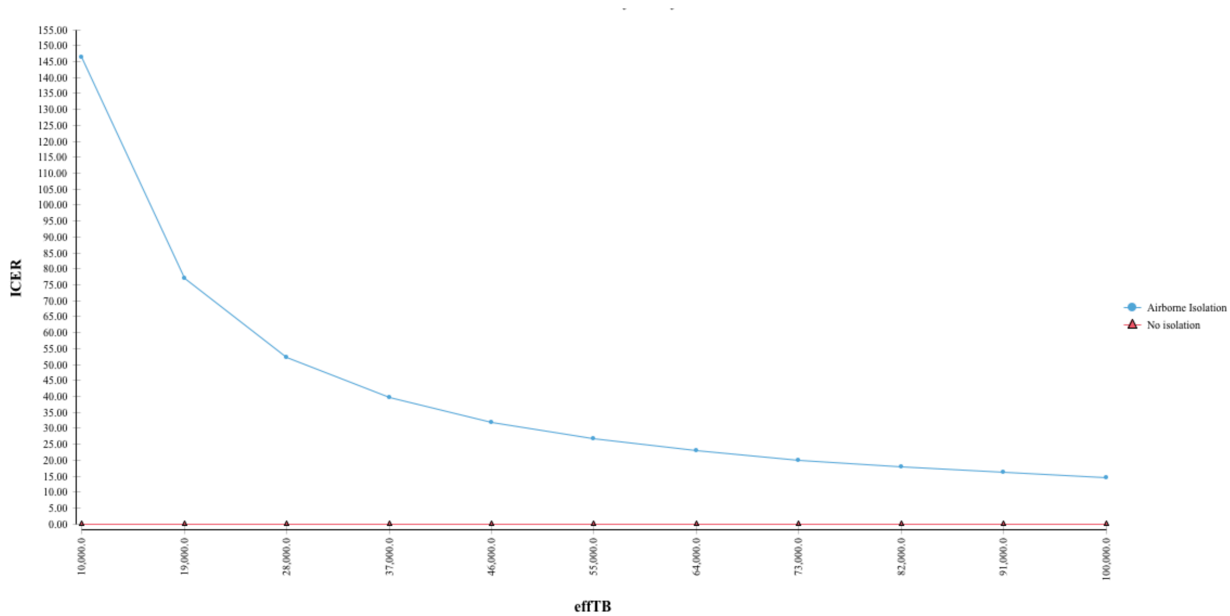

Figure 3 Sensitivity Analysis of Probability of Effectiveness of TB

4.0 Discussion

TB is the leading killer for people living with HIV (Centers for Disease Control and Prevention, 2017). TB incidence in United States has been on the decline in recent years and it has reached the lowest in 2017 since the beginning of national TB surveillance (Stewart RJ, Tsang CA, Pratt RH, Price SF, & AJ, 2017). A three-year review of all AI in this study reveals that TB positive rate in the hospital which is about 4 - 6% is consistent with nationwide data (4 - 10%). TB still threatens public health. In addition to the treatment of LTBI, ongoing control measures are still important for the purpose of TB elimination, especially in high-risk groups such as healthcare workers and people in homeless shelters (Stewart RJ et al., 2017). Factors leading to a higher TB infection rate in healthcare settings include delayed diagnosis and treatment of TB disease, delayed initiation of AI practices and lack of adequate airborne precautions and so on (Paul A. Jensen, Lauren A. Lambert, Michael F. Iademarco, & Ridzon, 2005). Decreased reports of TB outbreaks in health care settings related with the implementation of AI shows AI is useful in controlling the transmission of MTB. However, it often leads to excess isolation. The average duration in AI is 4.8 days according to the data collected from the hospital which shows a fair good job in discontinuing AI by following CDC guidelines. But there certainly has room for improvement.

AI is always more cost-effective than NI in spite of the variation of its effectiveness. According to the CDC protocol, the LOS in AI for patients without contagious TB is expected no more than 2 days (Thomas et al., 2013). By reducing LOS in AI from 4.8 to 2 days, there will be $3,120 saved per patient. The total cost saving for 93 patients over the last three years is up $290,160. In addition, when LOS for patients in NI and patients in AI is the same, AI costs $4,892 more than NI. This result is consistent with Wachter's study (Wachter, 2017).

Administration control is the major factor in successfully controlling TB. Even though hospitals policies for discontinuation of isolation are effective, they are certainly not efficient enough. Over-isolation of patients reflects this problem. Because the screening tool is too sensitive to capture patients without contagious TB. AIIRs in hospital usually are in high demand. Improved efficiency in ruling out patients from AI can increase bed turnover rate. These patients ruled out in a timely manner would spend less time in AIIR, and subsequently, reduce their time in hospital. This would be a large cost saving for the hospitals and patients without health insurance, and the results in this study confirm this point. Meanwhile, psychological problems and adverse events resulting from isolation for patients will be mitigated and the patient satisfaction will be increased.

Delayed discontinuation of isolation is associated with delayed specimen collection, transport and report (Pascopella et al., 2004). Delayed discontinuation of AI caused by these reasons could be addressed by effective interventions. When they are unable to have productive cough, an easy method to induce sputum is inhaling hypertonic saline which dose a favor in increasing the efficiency of collecting specimens (Centers for Disease Control and Prevention, 2013). Another way is gastric aspiration which is sometimes used in children who are incapable to induce adequate sputum (Centers for Disease Control and Prevention, 2013). Continuous training and re-training for laboratory workers involved in AFB microscopy enhance the quality of AFB smears results (Reji, Aga, & Abebe, 2013). Laboratory professionals who have been trained previously do better at work and make fewer mistakes compared with those have never been trained (Reji et al., 2013). A good operation of AFB microscopy ensures obtaining test results rapidly and accurately for prompt treatment or discontinuation of unnecessary isolation and avoids isolation due to false positive errors. In addition to coaching laboratory worker, it is necessary to train nursing staff to raise their awareness of timely performance of specimen collection and delivery. The importance of discontinuing AI without delays is likely to be underrepresented. For hospitals, they should evaluate the effectiveness of these interventions.

Opening a dedicated airborne isolation infection (AII) unit with nursing staff trained in TB control can contribute to a great decrease in the duration of AI (Leonard et al., 2006). Before HCWs entering AIIRs, they should use respiratory protection such as N-95 respirators. AIIRs require appropriately adjusted and maintained ventilation system and air-handle system which is potential financial burden to the hospital (Centers for Disease Control and Prevention, 2005). In hospitals, AIIRs are usually scattered in different floors which increases the demand and workload on nursing staff who should monitor the air pressure daily when AIIRs is in use. This dedicated AII unit improves the efficiency of excluding TB by the concerted effort of HCWs and brings significant cost saving in return.

In addition to AFB smear microscopy, there are techniques that are more efficient and cost-effective in minimizing the AI duration. Nucleic acid amplification tests (NAATs) can detect NTM so that smear-positive patients due to NTM could be avoided (Bourgi et al., 2017). Xpert as an automated NAAT not only offers test results within 2 hours, but also detect rifampicin resistance at the same time. Much research have been done to compare Xpert with SSM and show Xpert has higher sensitivity and specificity compared with AFB microscopy (Boehme et al., 2011; Luetkemeyer et al., 2016; Steingart et al., 2014). The implementation of

Xpert in evaluating patients with presumptive pulmonary TB saves 51 patient-hours in AII and up to $11,466 versus SSM and the laboratory processing time for Xpert is 2.5 times less than the SSM (Cowan et al., 2017; Lippincott et al., 2014). Combined with TB symptom screening, Xpert is considered as the most cost-effective testing in TB diagnosis in the United States (Choi et al., 2013). The 2-specimen or 3-specimen Xpert strategies are qualified for capturing TB cases. Their median AI time are 26.5 and 14 hours respectively less than the median AI time of SSM (Lippincott et al., 2014).

Patients with suspected TB are usually put in AI. International TB guidelines recommend that three consecutive negative smear samples for acid-fast bacilli (AFB) collected at interval of 8-24 hours are required for deisolation with at least one collected in early-morning (Mathew, Kuo, Vazirani, Eng, & Weinstein, 2002). According to conventional diagnosis strategy, patients should provide 3 specimens: one spot specimen, one in the early morning specimen and another one spot specimen collected the next day. The result cannot be obtained until two to three days after the patients' visit. Studies showed 11% additional diagnostic yield for the second sputum while the third specimen only has 2% - 5% the incremental yield (Bonnet et al., 2007; Mase et al., 2007; Yilmaz et al., 2008). In 2007, WHO recommended two specimens for SSM with good external and internal quality are qualified to detect TB cases. A large number of studies confirm the validness of two-specimen strategy for stopping AI (Bryan, Rapp, & Brown, 2006; Leonard et al., 2005; Wilmer, Bryce, & Grant, 2011; Yilmaz et al., 2008). One specimen is collected on the spot and another is collected in the early morning.

In 2009, WHO provided evidence to support same-day sputum microscopy namely front-loaded microscopy, which was to collect only 2 smears from one or more specimens at least one hour apart and obtained the results within one day, allowing more rapid discontinuation of isolation (World Health Organization, 2011b). The accuracy of AFB sputum smears collected in a single day is equivalent to those collected in 3 different days (Iwata, Doi, Nakamura, & Yoshida, 2015). The reduction in the number of specimens alleviates the workload for laboratories and reduces the cost for the hospitals (Bonnet et al., 2007). It has very similar sensitivity and specificity with the conventional method (Davis, Cattamanchi, Cuevas, Hopewell, & Steingart, 2013; Firdaus, Kaur, Kashyap, Avasthi, & Singh, 2017; Ndubuisi, Azuonye, Victor, Robert, & Vivian, 2016). However, Nayak et al stated a different opinion that is the same-day microscopy protocol isn't as sensitive as the conventional method (Nayak et al., 2013). WHO recommends countries that have already carried out the two-specimen SSM successfully can take same-day microscopy into account especially where patients are prone to default from the diagnostic process (World Health Organization, 2011b). A study shows the dropout rate during the diagnostic process in the conventional approach is more than 10 times as much as the rate in front-loaded microscopy (11% vs 0.7%) (Ndubuisi et al., 2016).

These modified strategies can quicken the process of diagnosis of TB and improve the efficiency of case-detection as well as isolation discontinuation without increasing the risk of premature deisolation. Ruling out patients in an efficient manner results in an amount of time saved, minimizing workloads for nursing staff and lab technicians and a significant cost saving for hospitals.

5.0 Conclusions

To increase the efficiency of discontinuation of isolation, it is essential to complete and report the result of TB test in a timely manner. In addition to implementing more effective strategies, it is important to raise physicians and nurses' awareness of the harm of delayed discontinuation of isolation (Thomas et al., 2013). This study shows significant delay in the current practice of deisolation of patients with suspected pulmonary TB in this hospital. More efficient measures can be taken to rule out patients who are at low risk to infect others. At the same time, it should be careful to carry out to prevent the premature deisolation of patients.

There are suggestions for shortening the duration in AI:

- If patients are unable to have productive cough, sputum induction can be implemented to collect sputum by inhaling hypertonic saline (Centers for Disease Control and Prevention, 2013).
- Using gastric aspiration in persons who are incapable to induce adequate sputum. (Centers for Disease Control and Prevention, 2013).
- Accelerating specimen collection, transport and report (Pascopella et al., 2004; Thomas et al., 2013).
- Refresher training of laboratory workers and nurse staff (Reji et al., 2013).

- If possible, installing a dedicated AII unit for more quick evaluation of patients admitted with suspected TB (Leonard et al., 2006).
- Using more rapid and effective techniques to detect the MTB, such as Xpert MTB/RIF (Dinic et al., 2013; Lippincott et al., 2014; Millman et al., 2013; Opota et al., 2016; World Health Organization, 2011a).
- Adopting 2-specimen sputum microscopy strategy instead of the conventional approach (Bryan et al., 2006; Leonard et al., 2005; Wilmer et al., 2011; Yilmaz et al., 2008);
- Using the same-day sputum microscopy strategy in areas where 2-specimen microscopy has been successfully implemented (Iwata, Doi, Nakamura, & Yoshida, 2015).

5.1.1 Limitation

Records for AI patients on weekend are unavailable. The duration of isolation is counted according to the number of days rather than the number of hours which exists roundoff errors. These factors contribute to the inaccuracy of the duration in AI. Using 3 consecutive negative AFB smears to rule out TB may be imperfect, although it indicates patients have low risk for disseminating TB. These patients still have chance to spread TB. The cost resulted from false negative results is unknown and it is not included in the decision tree model.

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