

2017

# Tuberculosis Screening in New Healthcare Employees: A Comparison of QuantiFERON®-TB Gold In-Tube Test and Tuberculin Skin Test

Mary C. Giovannetti  
*University of South Carolina*

Follow this and additional works at: <http://scholarcommons.sc.edu/etd>



Part of the [Nursing Commons](#)

---

## Recommended Citation

Giovannetti, M. C. (2017). *Tuberculosis Screening in New Healthcare Employees: A Comparison of QuantiFERON®-TB Gold In-Tube Test and Tuberculin Skin Test*. (Doctoral dissertation). Retrieved from <http://scholarcommons.sc.edu/etd/4195>

This Open Access Dissertation is brought to you for free and open access by Scholar Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact [SCHOLARC@mailbox.sc.edu](mailto:SCHOLARC@mailbox.sc.edu).

Tuberculosis Screening in New Healthcare Employees: A Comparison of  
QuantiFERON®-TB Gold In-Tube Test and Tuberculin Skin Test

by

Mary C. Giovannetti

Bachelor of Science in Nursing  
Marshall University 1994

Master of Science in Nursing  
Marshall University 1998

---

Submitted in Partial Fulfillment of the Requirements

for the Degree of Doctor of Nursing Practice in

Nursing Practice

College of Nursing

University of South Carolina

2017

Accepted by:

Stephanie Burgess, Major Professor

Karen Kane McDonnell, Committee Member

Abbas Tavakoli, Committee Member

Stephanie Barnhill, Committee Member

Cheryl L. Addy, Vice Provost and Dean of the Graduate School

©Copyright by Mary C. Giovannetti, 2017  
All Rights Reserved

## **DEDICATION**

I dedicate this manuscript first to my Lord and Savior Jesus Christ.

I would like to dedicate this project to my husband Sean and my children Bethany, Sean Christopher, Emily and Olivia who supported and put up with me throughout this journey. Without your understanding, I would not have achieved my goal. I love each of you very much and am looking forward to more free time to spend with you so that I can cheer each of you on in your gifts and own educational endeavors. And to my parents Dana and Tess Gullett who worked so hard, so that I could have an education when I was younger, I will be forever grateful of all you did for me, I love you.

## **ACKNOWLEDGEMENTS**

Thank you to my committee chair, Dr. Stephanie Burgess, along with my committee members Dr. Karen McDonnell, and Dr. Abbas Tavakoli for your editing, guidance, and encouragement throughout this process. Your countless hours spent on this project are much appreciated. Thank you to my secondary investigator and committee member Stephanie Barnhill for taking the time to help collect the large amount of data that seemed insurmountable. Your assistance helped me finish on time.

Thank you to the Employee Health staff who are the hands and feet for implementation of the QFT®-GIT for new hire screening processes, and for tracking the new hire logs. Thank you to Kathy Sinclair and SRHS administration for your support of this project. Also, thanks to Frankie Rice, Robbie Ford, Rachel Dattilo, Kathy Bryant, Todd Bridges, Denise Smith, Laurie Wybenga, Betty Warlick, and Kim Coggins for your assistance. To all my coworkers, friends, and family who listened, thank you.

## ABSTRACT

**Background:** Streamlining onboarding processes for new hires to maximize efficiency and reduce costs while meeting regulatory requirements is a constant challenge for healthcare systems' Employee Health staff. Health screening is a required step and includes obtaining a detailed health history, tuberculosis screening, drug screens, immunizations, fit for duty examinations, obtaining medical records, clarification of disability accommodations, pre-work screens, and other tests which are time consuming and result in delays in hire dates. Faced with a high volume of potential new employee hires a major southeast healthcare system was concerned about delays in new hire start dates. The two-step tuberculin skin test administration and follow-up process was identified as a potential area for concern to improve onboarding efficiency.

**Method:** A quality improvement study was designed and implemented to compare baseline testing for new employees with an Interferon-Gamma Release Assay (IGRA) known as QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD Tuberculin Skin Test (TST) for tuberculosis screening time, overall onboarding time, compliance with screening within 10 days of hire date, and associated costs. A retrospective electronic record review included a sample of 484 new hire employees.

**Results:** Results showed that the QFT®-GIT for tuberculosis screening in comparison to the TST testing significantly reduced tuberculosis screening time for new hire employees (TST = 8.03 days, QFT®-GIT = 4.11 days;  $p < .0001$ ) and overall

onboarding time (TST = 7.92 days, QFT®-GIT = 5.07 days;  $p < .0001$ ) while improving compliance with tuberculosis screening within 10 days of hire date (TST = 92.92%, QFT®-GIT = 100%;  $p < .0001$ ).

**Conclusions:** The utilization of QFT®-GIT for tuberculosis screening of new employees significantly reduced screening and onboarding time while improving compliance with screening within 10 days of the hire date. Anecdotal feedback from hiring managers and senior management indicated improved satisfaction with the Employee Health hiring process.

**Implications:** Healthcare systems should consider implementation of an IGRA to streamline processes for onboarding new employees. New processes require negotiations between healthcare systems and lab vendors, changes in policies and procedures, and employee health and laboratory staff development. Future research should focus on cost analyses, as well as, IGRA use for annual screenings.

## TABLE OF CONTENTS

|                                       |     |
|---------------------------------------|-----|
| DEDICATION .....                      | iii |
| ACKNOWLEDGEMENTS .....                | iv  |
| ABSTRACT .....                        | v   |
| LIST OF TABLES .....                  | x   |
| LIST OF ABBREVIATIONS .....           | xii |
| CHAPTER 1: INTRODUCTION .....         | 1   |
| Description of Clinical Problem ..... | 1   |
| Scope of the Problem .....            | 3   |
| Analysis of Current Practices .....   | 6   |
| Practice Innovation .....             | 11  |
| Purpose .....                         | 14  |
| Project Question/PICOT .....          | 14  |
| Assumptions .....                     | 16  |
| Summary .....                         | 17  |
| CHAPTER 2: LITERATURE REVIEW .....    | 18  |
| Introduction .....                    | 18  |
| Literature Search Strategy .....      | 19  |
| Literature Analysis .....             | 22  |
| Synthesis of Literature .....         | 67  |
| Discussion .....                      | 77  |



|   |     |
|---|-----|
| CHAPTER 3: PROJECT DESIGN AND PLAN .....      | 78  |
| Introduction .....                            | 78  |
| Conceptual Framework .....                    | 79  |
| Project Design .....                          | 81  |
| Justification for Need .....                  | 81  |
| Feasibility .....                             | 82  |
| Summary .....                                 | 85  |
| Intervention Plan .....                       | 85  |
| Timeline .....                                | 86  |
| Evaluation Plan .....                         | 89  |
| Data Collection Procedure .....               | 92  |
| Data Management and Analyses Procedures ..... | 93  |
| Human Subjects .....                          | 94  |
| Summary .....                                 | 95  |
| CHAPTER 4: FINDINGS AND CONCLUSIONS .....     | 97  |
| Introduction .....                            | 97  |
| Findings .....                                | 98  |
| Conclusions .....                             | 106 |
| Implications for Practice .....               | 108 |
| Future Research .....                         | 108 |
| Dissemination .....                           | 109 |
| REFERENCES .....                              | 110 |
| APPENDIX A: EVIDENCE TABLE .....              | 115 |

|  |     |
|--|-----|
| APPENDIX B: EVIDENCE LEVEL AND QUALITY GUIDE .....                   | 144 |
| APPEDIX C: CONCEPTUAL FRAMEWORK .....                                | 147 |
| APPENDIX D: INSTITUTIONAL REVIEW BOARD APPROVALS .....               | 149 |
| APPENDIX E: NURSING RESEARCH COUNCIL<br>PROPOSAL AND APPROVALS ..... | 151 |
| APPENDIX F: POSTER ABSTRACT .....                                    | 158 |
| APPENDIX G: CONFERENCE PRESENTATION APPLICATION .....                | 160 |
| APPENDIX H: JOURNAL MANUSCRIPT .....                                 | 166 |

## LIST OF TABLES

|  |     |
|--|-----|
| Table 1.1: Costs per Visit for New Hire Screening in Employee Health .....                                   | 10  |
| Table 1.2: Estimated Costs for New Hire Screening with QFT®-GIT .....  | 13  |
| Table 1.3: PICOT .....   | 15  |
| Table 1.4: PICOT Definitions .....   | 15  |
| Table 2.1: Keywords .....  | 20  |
| Table 2.2: Criteria for inclusion/exclusion .....  | 21  |
| Table 2.3: Quality ratings per evidence level .....  | 23  |
| Table 2.4: Journal/Sources .....   | 24  |
| Table 2.5: Categories of Articles .....  | 24  |
| Table 3.1: Required sample size for Ttest analysis with 80% power,<br>Different effect size, and alpha ..... | 94  |
| Table 4.1: Frequency distribution for demographic variables (n=485) .....                                    | 99  |
| Table 4.2: N, means, standard deviation, minimum, maximum for select variables .....                         | 100 |
| Table 4.3: N, mean standard deviation for select variables by group .....                                    | 101 |
| Table 4.4: N, mean standard deviation for select onboarding variables by group .....                         | 102 |
| Table 4.5: Correlation of selected variables for onboarding clearance days .....                             | 103 |
| Table 4.6: Frequency distribution for clear within 10 days .....   | 104 |
| Table 4.7: Average estimated costs based on data collection .....  | 106 |
| Table A.1: Evidence Table Abbreviation Guide .....   | 115 |
| Table A.2: Evidence Table .....  | 116 |

|  |     |
|--|-----|
| Table B.1: Evidence and quality guide .....  | 144 |
| Table H.1: Frequency distribution for demographic variables .....                            | 185 |
| Table H.2: N, means, standard deviation, minimum, maximum<br>for select variables .....      | 186 |
| Table H.3: N, mean, standard deviation for select variables by group .....                   | 186 |
| Table H.4: N, mean, standard deviation for select onboarding<br>Variables by group .....     | 187 |
| Table H.5: Spearman Correlation of selected variables for onboarding<br>clearance days ..... | 187 |
| Table H.6: Frequency distribution for clear within 10 days .....                             | 188 |

## LIST OF ABBREVIATIONS

|                |   |
|----------------|---|
| BCG .....      | Bacille Calmette-Guerin Vaccine                               |
| CDC .....      | Centers for Disease Control and Prevention                    |
| DHEC .....     | South Carolina Department of Health and Environmental Control |
| IGRA .....     | Interferon Gamma Release Assay                                |
| LTBI .....     | Latent Tuberculosis Infection                                 |
| PICOT .....    | Population, Intervention, Comparison, Outcome, Time           |
| PPD .....      | Purified Protein Derivative                                   |
| QFT®-GIT ..... | QuantiFERON®-TB Gold In-Tube Test                             |
| TB .....       | Tuberculosis  |
| TST .....      | Tuberculin Skin Test  |

# CHAPTER 1

## INTRODUCTION

### Description of Clinical Problem

Occupational health nurses in healthcare settings are challenged with promoting the health and safety of employees. This includes practicing current evidence-based interventions to prevent the spread of communicable disease including tuberculosis (TB) (Massante & Stinson, 2014). Healthcare workers are at increased risk for contracting mycobacterium tuberculosis (TB) from “sharing air space” with infected patients through airborne droplet transmission (Jensen, Lambert, Iademarco, & Ridzon, 2006). The Department of Health and Human Services Centers for Disease Control and Prevention (CDC) recommends that all healthcare workers receive initial screening for TB upon hire by a 2-step tuberculin skin test (TST) (Jensen et al., 2006). The TST is performed by injecting tuberculin purified protein derivative (PPD) intradermally. If someone has been exposed to TB, they will develop induration at the injection site which is measured in millimeters in 48-72 hours. According to CDC guidelines for interpretation of healthcare worker TST results, a reading of  $\geq 10$  mm of induration is positive. However, if the healthcare worker has HIV or other immune compromised conditions, a positive reading is  $\geq 5$  mm of induration. A positive result can indicate active TB, latent TB (LTBI), or may be due to history of vaccination with Bacillus Calmette-Guerin (BCG) vaccine or exposure to other non-tuberculin mycobacteria. Healthcare workers are at risk for spreading TB if they are not tested and unaware that they have latent TB and are

asymptomatic. Latent TB can be reactivated and the healthcare worker can then spread infection endangering the safety of patients and the community (Jensen et al., 2006).

There are three main categories of problems with utilization of the two step tuberculin skin test: extended screening time, noncompliance, and potential inaccuracy in placement and results. Problems with extended screening time and noncompliance occur due to the multiple steps that are required to complete the two step tuberculin test. The two step baseline tuberculin skin test requires 4 steps including: step 1- Intradermal placement of PPD, step 2- read the result in 48-72 hours, step 3- placement of second step in 1-3 weeks after the first step, and step 4- read the second step in 48 to 72 hours (Jensen et al., 2006). If the patient is noncompliant with returning for PPD reading, then the PPD must be replaced. Accuracy of the two step tuberculin skin test occurs due to variation in skin test placement, subjective reader interpretation, false-positive results, and false-negative results. Proper placement of the TST should include injection of 0.1ml of PPD solution injected intradermally on the inner forearm creating a pale skin elevation (wheal) of 6-10 mm. If a wheal does not appear, then the test is incorrectly placed and should be repeated. Inaccurate placement can lead to false-negative results when an untrained healthcare worker inadvertently places the skin test too deep or too shallow. Furthermore, errors in reader interpretation can lead to false-negative or false-positive results. Tuberculin skin tests results should measure millimeters of induration which is a raised, palpable area (Jensen et al., 2006). Often, inexperienced readers may inaccurately measure erythema rather than induration resulting in false-positive results. These false-positives may result in unnecessary anxiety for the patient and may lead to the patient taking LTBI treatment medications which have potential strong adverse side effects. In

contrast, some readers who are inexperienced or who do not understand the importance of accurate interpretation, may interpret results as negative which are really positive. In this case, the patient who needs treatment for LTBI will be left at risk for TB activation. Further compounding problems with false-positive results, tuberculin skin tests also react to Bacille Calmette-Guerin (BCG) vaccination and other non-tuberculous mycobacteria leading to false-positives (Swindells, Aliyu, Enoch, & Abubakar, 2009). Additionally, TST can give false negative results in immune suppressed individuals. In summary, the two step TST is subject to issues with extended screening time, noncompliance, and inaccuracies due to required multiple visits, variation in placement and readings, results, and false-positive or false-negatives (Swindells et al., 2009).

The purpose of this DNP project was to compare baseline testing for new healthcare employees with QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD TB skin test in regards to tuberculosis screening time, overall onboarding time, compliance with tuberculosis screening within 10 days of orientation, and costs. This quality improvement project assessed whether implementation of the QFT®-GIT in place of the two step TST, met the organizational goal to reduce the number of days to complete tuberculosis screening, reduce overall Employee Health onboarding clearance time, and improve compliance with completion of tuberculosis screening within 10 days of hire date, while maintaining cost-effectiveness.

### **Scope of the Problem**

Tuberculosis remains a major threat in the world with 9 million new cases each year. TB is the leading cause of death by an infectious disease, killing 1.5 million people



annually and 4,100 daily. This represents a 50% decrease in TB deaths globally (“National Action Plan to Combat Multidrug-Resistant Tuberculosis,” 2015). Death rates in the United States have fallen below 10,000 annually largely due to implementation of CDC recommended infection control measures (Jensen et al., 2006; “National Action Plan to Combat Multidrug-Resistant Tuberculosis,” 2015). In 2015, South Carolina had 104 cases of active TB, and 14 in the Upstate with less than 5 of those being in Spartanburg, South Carolina with a rate of 1.36 cases per 100,000 (South Carolina Department of Health and Environmental Services, 2016). Even though death rates are falling, it is estimated one third of the world’s population are infected with latent TB and are at risk for converting to active TB. Multidrug-resistant tuberculosis has also emerged threatening this progress. Action must be taken to prevent the spread of this drug resistant strain of TB. If efforts to prevent and diagnose latent and active TB are not actively continued, TB can spread rapidly around the world and to the United States and reverse decades of infection control measures (“National Action Plan to Combat Multidrug-Resistant Tuberculosis,” 2015).

Healthcare workers have up to 3 times higher risk of TB than the general population (Verkuijl & Middelkoop, 2016). The healthcare system accepts patients with TB and confines noncompliant TB patients for direct observed therapy. The healthcare system treated two patients with TB in 2015. Employees of the healthcare system may care for patients whose TB status is initially unknown for several days without respiratory protection and can unknowingly develop latent TB infection (Kathy Bryant, personal communication, November 2015). If an employee with undetected latent TB develops active TB, this employee can transmit TB to 10-15 other patients, coworkers,

family or community. This can be costly to the organization and the employee. If the TB strain is drug-susceptible then treatment consists of a four drug regimen for 6 months and can cost up to \$17,000. However, if it is drug resistant, treatment is more complex and expensive costing \$150,000 to \$482,000. Compounding drug resistance, adherence to drug regimens is difficult due to side effects and length of required treatment. If an employee acquires active TB, then the employee is subject to lost work time up to 4 months accounting for 30 percent of their income (“National Action Plan to Combat Multidrug-Resistant Tuberculosis,” 2015). Moreover, the organization can incur additional costs such as increased worker’s compensation benefits and interrupted staffing schedules or locum tenens coverage. Legally, the organization can also expect citations or sanctions by DHEC or other regulatory agencies if it is determined that proper infection control measures were not in place. From a public relations perspective, the organization may expect a tarnished reputation or at least some employee and public backlash that may instill a lack of trust or confidence as a healthcare institution or employer.

Healthcare systems must continue to monitor CDC recommendations and DHEC regulations to prevent spread of TB. Detection of latent or active TB in new employees plays a large role in this effort. Healthcare systems are required to maintain stringent respiratory protection plan that includes appropriate ventilation of TB patient rooms, N-95 mask fit testing, exposure follow up plans, and periodic testing of employees(Verkuijl & Middelkoop, 2016). Employee Health staff must refer all employees with positive tuberculosis screening to the health department for appropriate evaluation and treatment. Through appropriate surveillance, early detection of TB, and infection control measures

the organization can reduce the TB burden to the community, patients and employees (Jensen et al., 2006).

### **Analysis of Current Practices**

The healthcare system currently employs approximately 6,800 employees and had experienced a 15% employee turnover rate in 2015 and 2016 which led to staffing issues and utilization of expensive locum tenens temporary contract employees (Kathy Sinclair, personal communication, March 2016). The hospital has 78 locum tenens Registered Nurses which costs the healthcare system \$119,600 per RN or total 9.33 million annually. Hiring a permanent RN would save \$46,782 per position (Rachel Datillo, personal communication, July 2016). This does not include costs for non RN locum tenens employees. New hire RN orientation only occurs one time per month. If the new hire RN orientation is delayed due to incomplete tuberculosis screening or other requirements in Employee Health, then a locum tenens nurse will need to fill that spot for another month. The average full time RN salary is approximately \$30 per hour, but locum tenens RNs cost approximately \$60 per hour for 160 hours, totaling \$10,800 for one month of locum tenens. Therefore, a one-month delay would cost \$5,400 per month additional to the healthcare system. If only 2 RNs per month have delayed orientation, this would cost the healthcare system \$129,600 per year.

Further contributing to short staffing concerns, the process for hiring positions requires multiple time consuming steps. Managers must go through a position committee for approval of any job postings. This process can take 1-3 weeks or more. Recruitment then must post the job, actively recruit, screen applications, and submit top applications

to the manager for review which can take 1-2 weeks or more. The Manager must then conduct interviews and select the candidate. Recruitment must then obtain the pay rate from the compensation department and negotiate the offer with the candidate which can take a few days. The average amount of days it takes to fill positions from job posting to job offer in 2015 was 51 days (47 for RNs), and the January to February 2016 average was 58 days (Rachel Dattilo, personal communication March, 2016). The 2016 days to fill job offers ended wrapped up at 47 days compared to the national standard of median of 48 days (Rachel Dattilo, personal communication, March 2017). Following this, it can take 1-2 weeks to get an appointment in Employee Health for pre-placement assessments. Once the new employee has an appointment in Employee Health, it could take 3 days to 30 days to clear the employee for orientation. Clearance for orientation includes, health assessment, labs, immunization titers, drug screens, tuberculosis screening, review of medical records, and in some cases pre-work screen lift tests and fit for duties with a provider. This process could take 2 to 30 days with the Fall 2015 average being 15 days from time of first appointment to health clearance for orientation. Orientation only occurred twice per month except for RNs which was monthly, and new hires were required to attend. It was requested that new hires come to Employee Health at least 10 days prior to orientation, so that orientation will not be delayed due to waiting for drug screen results, for completion of 2 step PPD tuberculin skin test, and fit for duty appointments. If drug screen results were not back in time, fit for duties are not completed or the employee does not complete the PPD tuberculin skin test process prior to orientation, then the employee would not be able to start work until the next orientation in 2-3 weeks. Delays in orientation only compounded the short staffing concerns. Senior

management asked the Employee Health department as well as Recruitment to assess procedures for expediting new employee total onboarding time.

The healthcare system Employee Health examined its processes to determine measures to contribute to this reduction in new employee onboarding time. In 2015, Employee Health screened approximately 100 to 125 new hire employees monthly. Employee Health completed tuberculosis screening with the two step PPD skin test. This process took 2-4 visits and sometimes took 10 days to 4 weeks or more to complete. The first visit took approximately 2 hours and cost \$48.70 in staff time (5 min for PPD placement is \$2.58 of time) plus \$4 for the PPD test and 0.36 for the syringe and needle. This does not include the cost for other supplies, and lab processing. The second visit for PPD reading number one cost \$10.15 in staff time. The third visit which would include PPD placement number 2 and lab result review cost total \$10.15 in staff time (5 min of time for the PPD placement) plus \$4.36 for PPD. The fourth visit which would include PPD reading cost approximately \$10.15 in staff time (see Table 1.1). New employees were required to have at least 1 PPD skin test placed and read prior to orientation. New employees sometimes failed to return for first PPD reading which resulted in the need for replacement and delay in orientation. Therefore, if the new employee failed to complete this first skin test prior to orientation, then the employee could not start work for 2 or more weeks, or 1 month for RNs. The second step of the tuberculin PPD skin test is also problematic. New employees were required to have the second PPD skin test placed and read within 10 days of orientation. However, 6-10% of new employees do not return for this second PPD which caused Employee Health staff to spend additional time contacting the new hire to request a return visit and replacement of the PPD. If the Employee Health

RN spent 15-30 min per noncompliant new hire employee contacting the employee and scheduling another visit, it cost approximately \$7.75-\$15.50 in salary time per person that is non-compliant. If the average non return rate of 10% which would result in \$1,550 - \$3,100 cost for contacting approximately 200 new hires to reschedule visits. An extra PPD placement visit cost \$14.51 per person or \$2,902 for 200 new hires in staff time and supplies. This figure grows if you consider the costs of replacing 10% of 6,800 employees for annual PPD skin tests. Noncompliance with completion of two step PPD within 10 days of orientation can also result in citation by the Department of Health and Environmental Services (DHEC), or other regulatory agencies (Jensen et al., 2006). Recent DHEC surveys have resulted in survey staff questioning Employee Health's past practice of not reading step one. one A DHEC survey discovered one second step PPD not being read which could result in citation or penalty. A citation will reflect negatively on the organization and Employee Health. In fall of 2015 and early 2016, the Employee Health department reevaluated current practices and implemented processes to expedite new hire onboarding time, reduce tuberculosis screening time, improve new hire and manager satisfaction, and streamline processes. Some of these changes included adding appointment times, additional staffing, and renovation of a storage room to create another exam room. However, the largest change was implementation of an IGRA for tuberculosis screening.

Employee Health began verifying all positive tuberculin skin tests with a QFT®-GIT approximately 2 years before implementation of this study at the advice of the local department of health. If the test and symptom review were negative, then the employee did not have to be referred to DHEC for evaluation and treatment of LTBI. The test was

also utilized for tuberculosis screening for new employees who reported a history of a positive tuberculin skin test, but who did not have proper documentation. Staff were already familiar with the test and a contract was already in place with a local lab called external Lab. The initial cost for QFT®-GIT was \$85 per test.

Table 1.1  
*Costs per Visit for New Hire Screening in Employee Health*

---

*Employee Health average staff salary*

|          |         |
|----------|---------|
| RN       | \$31    |
| OHT      | \$14    |
| Clerical | \$14.79 |
| LPN      | \$20    |

---

*Visit 1 Costs*

|               |        |  |
|---------------|--------|--|
| Clerical      | 15 min | \$3.70                                 |
| OHT           | 1 hr.  | \$14.00                                |
| RN            | 1 hr.  | \$31.00 (PPD placement, 5 min, \$2.58) |
| Plus PPD cost |        | <u>\$4.36</u>                          |
| Total visit 1 |        | \$53.06                                |

*Visit 2 Costs*

|               |        |               |
|---------------|--------|---------------|
| Clerical      | 5 min  | \$1.23        |
| OHT           | 5 min  | \$1.17        |
| RN            | 15 min | <u>\$7.75</u> |
| Total visit 2 |        | \$10.15       |

*Visit 3 Costs*

|               |        |                                       |
|---------------|--------|---------------------------------------|
| Clerical      | 5 min  | \$1.23                                |
| OHT           | 5 min  | \$1.17                                |
| RN            | 15 min | \$7.75 (PPD placement, 5 min, \$2.58) |
| Plus PPD cost |        | <u>\$4.36</u>                         |
| Total visit 3 |        | \$14.51                               |

*Visit 4 Costs*

|               |        |               |
|---------------|--------|---------------|
| Clerical      | 5 min  | \$1.23        |
| OHT           | 5 min  | \$1.17        |
| RN            | 15 min | <u>\$2.58</u> |
| Total visit 4 |        | \$10.15       |

*Total costs all 4 visits (cost of labs excluded)*                    **\$87.87**

*Annual cost new hire visits 2,000 new hires per year* **\$175,740**

*Missed visits 10% average (10% of average 2,000 new hires annually)*

Contacting noncompliant patient staff time 30min15.50 = \$3,100 per year

Cost of one Replacement visit \$14.51 per patient = \$2,902 Additional Cost of visits for noncompliant 200 employees = **\$6,002**

**Total costs new hire screening including noncompliant**                    **\$181,742**

---

## **Practice Innovation**

Tuberculin skin test was the only available test for TB screening until 2001 when Interferon gamma release assays (IGRA) were developed. Interferon gamma release assay are blood tests for TB which specifically measure interferon-gamma which is released by T cells in response to tuberculosis antigens (Swindells et al., 2009). The first approved IGRA was the QuantiFERON®-TB test (QFT®) in 2001, followed by the QuantiFERON®-TB gold test (QFT®-G) in 2005, QuantiFERON®-TB Gold In-Tube (QFT®-GIT) test in 2007 and the T-SPOT® in 2008. In 2010, the CDC published updated guidelines for use of IGRA's and approved both the QFT®-GIT and the T-SPOT®. TB for healthcare worker TB screening (Mazurek et al., 2010). IGRA's can potentially overcome issues with TST tuberculosis clearance screening time and compliance, as well as problems with inaccurate results. In contrast to TST, IGRA's do not react to nontuberculous mycobacteria or BCG vaccination. IGRA's can also be completed in one visit and eliminate the need for multiple visits. Furthermore, IGRAs have been found to have a higher correlation to TB exposure than TSTs improving accuracy. IGRA's are more expensive than TST's, but utilization is expect to reduce costs associated with staffing requirements, inadequate testing results, poor employee



compliance follow up, and potential DHEC citations for organization noncompliance (Mazurek et al., 2010).

When a person is exposed to TB, they develop a white blood cell response (WBC). When white blood cells are re-exposed to TB, they secrete a small amount of interferon-gamma (TFN- $\gamma$ ) protein in response. The QFT®-GIT measures the TFN- $\gamma$  protein response which is a marker for cell mediated immune response to mycobacterium tuberculosis. The procedure for testing includes drawing one milliliter of blood is collected in 3 tubes including the nil (negative control), TB antigen, and mitogen (positive control). The antigen peptides include ESAT-6, CFP-10, and TB7.7. All tubes are gently shaken 10 times and must be transferred to a 37°C $\pm$ 1 incubator within 16 hours. Results are measured by TB antigen minus nil and positive is  $\geq$  0.35 IU/ml. The advantages of this test include completion in one visit, result is unaffected by BCG vaccination, test has positive and negative controls, and interpretation of results is objective (Nienhaus, 2013).

A potential barrier to implementation of IGRAs is the high cost of the lab test. The healthcare system microbiology department lab manager was contacted in 2015 to investigate the costs and acceptability associated with implementation of the QFT®-GIT or the T-SPOT®.TB for all new hires. The manager advised that the QFT®-GIT would be preferred for the healthcare system due to availability of a local external lab that is already conducting the test for the organization. This external lab has staff that are experienced with the testing and are better able to have consistent test performance than the in house lab. Experienced lab personnel conducting the test will ensure accurate, quality results and reporting. Furthermore, the manager reported that the T-SPOT®.TB

would require extra staff time for packaging to ship. It was discussed that the lab would have adequate facilities for incubating the tubes of blood (Frankie Rice, personal communication, September 2015). With the assistance of the lab manager, the price for the QFT®-GIT was negotiated from \$85 to \$53. While the QFT®-GIT is more expensive than the PPD, cost savings is found when you factor in staff time, and cost savings from not having delays in orientation, decreasing the amount of time locum tenens staff are utilized, and avoiding regulatory penalties. Onboarding just 2 full time RNs 1-month sooner every month would save the organization \$129,600 in salaries. Another advantage of utilizing the QFT®-GIT is that new hire visits can be completed in 1 visit and therefore reducing Employee Health workload and reduced salary costs to track down each non-compliant new hire. Reducing each new hire visit from 4 to 1 visit opened up additional available appointment times for new hire and other visits increasing visit volume capacity in Employee Health. Potentially, this decrease in number of required visits would also improve new hire satisfaction with the process. Cost of implementation of QFT®-GIT can be a barrier or a benefit, while process improvement is a potential benefit for new hires and Employee Health staff.

Table 1.2  
Estimated Cost for New Hire screening with QFT®-GIT

---

|                            |               |  |
|----------------------------|---------------|--|
| <i>Visit 1 Costs</i>       |               |  |
| Clerical                   | 15 min        | \$3.70                                       |
| OHT                        | 1 hr., 5 min. | \$15.16 (blood draw additional 5 min \$1.16) |
| RN                         | 55 min        | \$28.41                                      |
| QFT®-GIT                   |               | <u>\$53.00</u>                               |
| Total visit 1              |               | \$100.27                                     |
| Result follow up LPN 5 min |               | \$1.66                                       |

Total new hire screening cost (titers, routine labs excluded) \$101.93

|  |                  |
|--|------------------|
| <b>Total cost 2,000 new hires annual with QFT®</b>                   | <b>\$203,860</b> |
| Minus Cost of one locum tenens RN per month delayed by 2 step        | <u>\$64,800</u>  |
| Total annual cost of new hire screening                              | \$139,800        |
| Minus cost of two locum tenens RN monthly due to delayed orientation | -\$129,600       |
| Total annual cost of new hire screening                              | <b>\$74,260</b>  |

*Comparison*

|                                |                  |                           |
|--------------------------------|------------------|---------------------------|
| Annual cost new hire screening |                  |                           |
| <b>with 2 step PPD</b>         | <b>\$175,740</b> | <b>with QFT® \$74,240</b> |

---

**Purpose**

The purpose of this DNP project was to compare baseline testing for new healthcare employees with QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD TB skin test in regards to tuberculosis screening time, overall onboarding time, compliance with tuberculosis screening within 10 days of orientation, and costs. This quality improvement project assessed whether implementation of the QFT®-GIT in place of the two step TST, met the organizational goal to reduce the number of days to complete tuberculosis screening, reduce overall Employee Health onboarding clearance time, and improve compliance with completion of tuberculosis screening within 10 days of hire date, while maintaining cost-effectiveness.

**Project Question/PICOT**

As a foreground question, among all adult newly hired healthcare employees at a healthcare system, how does baseline testing with QuantiFERON®-TB Gold In-Tube test (QFT®-GIT) compare with two step PPD TB skin test in regards to time for completion of tuberculosis screening, overall onboarding screening time, and compliance with screening within 10 days of orientation over a 2-month time frame (see Tables 3 and 4)?

Table 1.3  
*PICOT*

| PICOT        | PICOT components   |
|--------------|--|
| Population   | New hire employees at Spartanburg Regional Healthcare System   |
| Intervention | QuantiFERON®-TB Gold In-Tube test (QFT®-GIT) for TB screening  |
| Comparison   | 2 step tuberculin PPD skin test for TB screening   |
| Outcome      | Reduction in completion time for TB screening reduction on overall onboarding time, and increased compliance with completion within 10 days of orientation |
| Time         | 2 months: chart review of 2 months with 2 step PPD standard of care, compared to 2 months with QFT®-GIT  |

PICOT definitions (Melnik & Fineout-Overholt, 2015)

Table 1.4  
*PICOT Definitions*

| Key Terms              | Definitions  |
|------------------------|--|
| New Hire Employee      | Any person newly hired to work scheduled for health assessment in employee health after offer, prior to orientation.                                   |
| QFT®-GIT               | QuantiFERON®-TB Gold In-Tube blood test screening for latent tuberculosis infection  |
| PPD                    | Purified protein derivative intradermal skin test for TB screening   |
| Tuberculosis screening | Time for employee to complete TB screening. For Tb skin test- time from first skin test to reading of second test. QFT®- time from lab draw to result. |
| Onboarding Time        | Number of days from first visit to completion of all requirements to begin work including at least one TST   |

placement and reading or QFT®-GIT result, drug screen result, lab results, pre-work screen, fit for duty, documentation, fit for duties

Compliance

Completion of PPD skin test or QFT®-GIT TB screening within 10 days of orientation. Also, completion of Chest X-Ray and/or retesting prior to orientation if + PPD or QFT®-GIT.

---

**Assumptions**

It was assumed that the new employee, employee health employees as well as hospital administration prefer for the amount of time it takes to clear employee health prior to orientation to be as short as possible. It was inferred that other healthcare organizations will prefer this shortened time as well. Another assumption is that the procedures in the hospital lab and external lab will be standardized and followed. It was assumed that laboratory staff were proficient and have achieved competency in all procedures for QFT®-GIT and lab equipment is in working order. It was assumed that lab interpretation of positive or negative results was accurate. Likewise, it was assumed the Chest X-ray procedures and interpretation was accurate.

The Centers for Disease (CDC) is recognized as national experts in tuberculosis control. It was assumed that this is true and that recommendations from CDC are best practice. Likewise, it was assumed that DHEC regulations are best practice and employees of DHEC have expert knowledge.

## Summary

The healthcare system is required to complete tuberculosis screening on all new hire employees through tuberculin skin tests or blood assays for mycobacterium tuberculosis (Jensen et al., 2006). Employee Health has traditionally completed the 2 step PPD as a method of screening all new hires. Processes for completion of this 2 step process can be problematic due to compliance with visits, and false-positives due to BCG vaccination or reader interpretation. The 2 step PPD can take 10 days to weeks or longer to complete delaying orientation dates for new hires. Employee health was tasked with review of regulations and processes to expedite new hire clearance. Tuberculosis screening was targeted in this process review. QuantiFERON®-TB Gold In-Tube test is a blood test for latent TB and was identified as a possible method to overcome barriers to TSTs and would help expedite new hire clearance (Mazurek et al., 2010). Tuberculosis remains a threat to employees and to the community (South Carolina Department of Health and Environmental Services, 2015). Early detection of TB is essential to stop the spread of TB (“National Action Plan to Combat Multidrug-Resistant Tuberculosis,” 2015). This project examined whether baseline testing with QuantiFERON®-TB Gold In-Tube test would reduce tuberculosis screening time, overall onboarding time, and improve compliance while remaining cost effective in comparison to the 2 step PPD skin test.

## **CHAPTER 2**

### **LITERATURE REVIEW**

#### **Introduction**

A literature search was conducted in order to determine if a blood assay for mycobacterium tuberculosis would be acceptable for implementation of tuberculosis screening of new hires in a healthcare system Employee Health in place of the two-step PPD skin test. The primary purpose of the literature review was to answer the PICOT question: As a foreground question, among all adult newly hired healthcare employees at a healthcare system, how does baseline testing with QuantiFERON®-TB Gold In-Tube test (QFT®-GIT) compare with two step PPD TB skin test in regards to time for completion of tuberculosis screening, overall onboarding screening time, and compliance with screening within 10 days of orientation over a 2-month time frame? The literature review focused on articles that pertained to healthcare workers and screening in low incidence countries since the United States is considered to be low incidence overall. The healthcare system was considered to be low risk by CDC standards, however has been medium risk in the past. Therefore, studies that included medium or middle tuberculosis incidence were included in the review. The literature review examined whether blood assays for tuberculosis met with CDC and DHEC regulations, would be more efficient than the two-step tuberculin skin test process, have equal or better accuracy than TSTs, and be cost-efficient.

## **Literature Search Strategy**

In order to make evidence-based practice change, clinicians should conduct a thorough search of peer-reviewed research (Melnyk & Fineout-Overholt, 2015). Thomas Cooper Library database links were used to browse different databases including CINAHL, PubMed and Science Direct. Keyword searches included a combination of IGRA, Interferon gamma, tuberculosis screening, quantiferon, employee, healthcare worker, and tuberculosis (see table 4). An initial search on Science Direct of “IGRA” revealed too many results which needed to be filtered to obtain applicable evidence. A search on Science Direct for keywords “Tuberculosis screening” and “employees” revealed 2,095 results. When this result was filtered for 2010-2016 there were 32 articles found, but these did not meet the inclusion criteria. Science Direct was searched for Quantiferon which revealed 2,181 results. Many of these results were not specifically about quantiferon and some were in other languages. The search was for 2016 and found 65 results. The strategy was adjusted and this author searched keywords “quantiferon” and “employee”, 2008 to present and found 87 results with a few relevant articles. Then PubMed was searched for keywords “IGRA” and “Tuberculosis” and found 596 results. Filters of 5 years and newer was then added which narrowed it to 450 results. When a third keyword of “employee” was added in addition to “IGRA” and “Tuberculosis”, PubMed revealed 4 results with 1 applicable study. PubMed was searched for keywords “Quantiferon” and “healthcare workers” for the most recent 5 years and found 77 results. CINAHL proved to be the most user friendly for this author and all of the above the search strategies were utilized with multiple results found. A search for keywords “tuberculosis” and “IGRA” revealed 120 results with a few articles selected. The most



specific search that was helpful was “tuberculosis” and “employee” and “interferon gamma” which revealed 10 good results (see Table 2.1). Reference lists from the reviewed articles were also utilized to identify a few selected articles. Any articles that this author could not find full text articles for were obtained through the Thomas Cooper Library interlibrary loan request. During the course of the peer review, this author contacted South Carolina Department of Health and Environmental Control (DHEC) for guidance regarding a cluster of positive QFT®s with borderline results. The Columbia DHEC office referred this author to Dr. F Richard Ervin, regional TB clinician district 4 who emailed relevant articles regarding QFT® cutoff and conversions which was incorporated into the table (Dr. F Richard Ervin, personal communication, March 2016). Initially selected articles included approximately 40 articles that were reviewed and ultimately included 23 articles that were included in this evidence table (see appendices A).

Table 2.1  
*Keywords*

| Keyword                | Combination of keywords                        |
|------------------------|--|
| IGRA                   | IGRA and Tuberculosis                          |
| Tuberculosis screening | Tuberculosis screening and employees           |
| Quantiferon            | Quantiferon and employee                       |
| Employee               | Quantiferon and healthcare worker              |
| Healthcare worker      | Tuberculosis and IGRA                          |
| Tuberculosis           | IGRA and tuberculosis and employee             |
| Interferon gamma       | Tuberculosis and employee and interferon gamma |

Table 2.2  
*Criteria for inclusion/exclusion*

| Inclusion criteria                  | Exclusion criteria                      |
|-------------------------------------|---|
| English                             | Non-English                             |
| Low or Medium TB risk setting       | Single study primarily in High TB risk  |
| Published in 2005 and newer         | Published prior to 2005                 |
| Included any version QFT®           | Only examined TST                       |
| Included T-SPOT®.TB                 | Studies including only children         |
| IGRAs related to healthcare workers | Studies including only immunosuppressed |

Inclusion criteria included studies published in English conducted in low or medium TB incidence settings from 2005 to present with relevant information to IGRA testing in healthcare workers including QFT®, QFT®-TB Gold, QFT®-GIT, or T-SPOT®.TB. Studies were excluded that were conducted primarily in high TB incidence settings, did not include healthcare workers, were published in other languages, and those that were primarily about children or immune compromised patients (see table 5). The Centers for Disease Control updated guidelines were examined first to determine if utilization of Interferon Gamma Release Assays (IGRA) would meet required regulations before proceeding with the PICOT and literature search (Mazurek et al., 2010). Initially this author tried to limit articles to 5 years but did not find the required number of relevant articles. Since the QuantiFERON®-TB Gold was developed in 2005 and the CDC guidelines were written in 2005, articles were limited to those published in 2005 to present with focus on newer articles. The main inclusion articles of interest were studies that examined baseline IGRA testing of healthcare workers. Articles were included that examined IGRA alone with single or multiple retests, or IGRA with Tuberculosis skin test (TST) conducted separately or simultaneous. Studies that only examined non-

healthcare workers were excluded unless this was a small portion of a larger study. Studies were included that examined IGRAs in low or moderate incidence countries since the setting for this project is in a low to medium TB risk setting. Studies that looked at IGRAs in high-incidence settings or countries were excluded unless they were part of a larger study that also included low-incidence setting. Articles on cost-effectiveness of IGRAs were also included in order to examine financial feasibility for the project. There were not many articles directly related to new hire tuberculosis screening time and compliance, but two specific ones were found. Due to the concern regarding false-positives and at the direction of DHEC, studies regarding QFT®-GIT cutoff values and retesting were included (see Table 2.2). Overall, there was good evidence to continue on with the PICOT question and study (see Appendices A for full evidence table).

### **Literature Analysis**

Twenty-three studies were included in the review of the literature. The articles were classified into levels I through IV according to John Hopkins Research and Non-Research evidence appraisal tools (Dearholt & Dang, 2012). Level I includes experimental studies, II quasi-experimental, III Non-experimental, IV clinical practice guidelines, consensus or position statements, and level V literature review, expert opinion, community standard, clinician experience, and consumer preference (see Appendices B for level and quality guide). Of the 23 articles analyzed there were four level II articles, seven level III, two level IV, and 10 level V (see Table 2.3). Quality of the articles were also analyzed as shown in table 5 according to John Hopkins appraisal tools with ratings of A- high quality, B- Good quality, and C- Low Quality (Dearholt & Dang, 2014). All of the studies were conducted in the United States with the exception of

two in Germany that report that the study was conducted in low incidence settings (Diel, Loddenkemper, Meywald-Walter, Gottschalk, & Nienhaus, 2009; Schablon, Nienhaus, Ringshausen, Preisser, & Peters, 2014). Most of the studies focused on healthcare workers with the exception of 4 studies that included healthcare workers as well as other groups such as close contacts but all were published in English (Banaei, Gaur, & Pai, 2016; Diel et al., 2009; Pai, Zwerling, & Menzies, 2008; Rangaka et al., 2012). The 23 articles were published by 18 different journals or sources (see table 2.4). The articles reviewed were classified according to type of study which includes quality improvement, clinical practice guidelines, quasi-experimental, systematic review, financial, program evaluation, expert opinion/literature review, and case report (see table 2.5).

Table 2.3

*Quality Ratings per evidence level*

---

# of Articles in Quality Rating

| <u>Level</u> | <u>A-High</u> | <u>B-Good</u> | <u>C-Low</u> |
|--------------|---------------|---------------|--------------|
| II           | 1             | 3             | 0            |
| III          | 3             | 4             | 0            |
| IV           | 2             | 0             | 0            |
| V            | 2             | 8             | 0            |

---

Table 2.4  
*Journals/Sources*

|  |           |
|--|-----------|
| American Journal of Respiratory Critical Care Medicine | 2         |
| Annals of Internal Medicine                            | 1         |
| Archives of Internal Medicine                          | 1         |
| BMC Health Services Research                           | 1         |
| Chest  | 2         |
| Infection Control & Hospital Epidemiology              | 1         |
| Journal of American College Health                     | 1         |
| Journal of Clinical Microbiology                       | 1         |
| Journal of Hospital Infection                          | 1         |
| Journal of Occupational & Environmental Medicine       | 1         |
| Journal of Occupational Medicine & Toxicology          | 1         |
| Lab Medicine   | 1         |
| Lancet Infectious Disease                              | 1         |
| MMWR   | 2         |
| PLoS One   | 1         |
| Qiagen   | 2         |
| Thorax   | 1         |
| Workplace Health & Safety                              | 2         |
| <b>Total</b>   | <b>23</b> |

Table 2.5  
*Categories of Articles*                      *Total*

|                              |   |
|------------------------------|---|
| Case Report                  | 1 |
| Clinical Practice Guidelines | 2 |
| Correlational                | 1 |
| Expert Opinion/Lit. review   | 3 |
| Financial                    | 1 |
| Program Evaluation           | 2 |
| Quality Improvement          | 3 |
| Quasi-Experimental           | 4 |
| Systemic Review              | 6 |

## **Evidence level II, high quality (A) articles.**

A longitudinal study of healthcare workers at four organizations undergoing tuberculosis screening from February 2008 through March 2011 was conducted (Dorman et al., 2014). The purpose of this study was to assess the performance of IGRAs for serial testing of healthcare workers compared to tuberculin skin test (TST). The sample included 2,563 healthcare workers in Denver, Colorado; Houston, Texas; Baltimore, Maryland; and New York City. Healthcare workers with a history of TB, TST within the past 6 months, and those with history of anaphylactic reactions to TST reagents were excluded from the study. Initially participants were interviewed regarding demographics, occupations, TB exposure, history of LTBI and BCG status. Then blood was drawn for T-SPOT®.TB and QFT® followed immediately by TST. Participants had a second TST in 1-3 weeks if they did not have another TST in the past 12 months. Participants had repeat interview, QFT®, T-SPOT®.TB and TST at 6, 12, and 18 months. Those with a positive TST were asked to have a repeat TST. There was a sub-study wherein participants had blood drawn two weeks apart without a TST in-between and by drawing two sets during a single blood draw. It is important to note that mid-study, participants had repeat ELISA testing for all positive tests because there was a higher than expected rate of conversion. Another sub-study was conducted in which participants with baseline negative IGRAs had repeat IGRA in 7-21 days. Statistical analysis included K coefficient for agreement, two-proportion Z-test for independent proportions and McNemar's test for dependent proportions. Multiple comparisons were assessed by Holm-Bonferroni method and mean changes were compared by t test. Linear mixed-effects models were used and confirmed by residual plots. SAS 9.2 was used for calculations. Results show a 6.1%

(138 of 2,263) conversion rate for QFT®-GIT, 8.3% (177 out of 2,137) conversion for T-SPOT®.TB, and 0.9% (21 out of 2,293) for TST. There was a statistically significant difference in conversion rate of QFT®-GIT compared to TST ( $p < 0.001$ ). Baseline testing results showed 125 positive TSTs (5.2%), 118 positive QFT®-GIT (4.9%) and 144 positive T-SPOT®.TB (6.0%). The rate of positives in the IGRA groups was not significantly higher than the TST groups. Agreement of test results for those with triple positives was high with agreement between TST and QFT®-GIT 93.2%, 91.2% for TST and T-SPOT®.TB, and 93.8% between QFT®-GIT and T-SPOT®.TB (95% CI for all comparisons). There was a higher rate of baseline positive TST and negative IGRAs in BCG vaccinated participants (odds ratio 33.4). There was a 53.7% reversion of baseline positive TSTs in 29 out of 54 participants. Likewise, there was baseline reversion from positive to negative for QFT®-GIT of 56.8% (67 of 118) and 63.9% for T-SPOT®.TB (92 of 144) without statistically significant differences in comparison between the groups. Those with higher baseline values for QFT®s had lower rates of reversions but there was no difference in the T-SPOT®.TB group. Test conversions during this study were 0.9% for TST, 6.1% QFT®-GIT, and 8.3% for T-SPOT®.TB which was significant for TST vs QFT®-GIT and for T-SPOT®.TB ( $p < 0.001$ ) but no significant difference between QFT®-GIT and T-SPOT®.TB. When converters were retested in 6 months, 76.4% (81 of 106) QFT®-GIT positive tests reverted and 77.1% (91 of 118) of T-SPOT®.TB. It is important to note that not one participant converted in all three tests at once and there was no association with TB exposure for any of the conversions. In the sub study that was retested in 2 weeks, 7.5% of QFT®-GITs changed from negative to positive and 8.1% for T-SPOT®.TB. In the positive testes, 33.3% and 52.6% reverted for QFT®-GIT and T-

SPOT®.TB respectively. In the sub study that had two sets of blood drawn in one visit, there were discordant results in 5.8% for QFT®-GIT and 6.5% for T-SPOT®.TB (p=.39). When a subset of samples was retested by ELISA in 8 days, all negatives remained negative, but 27 out of 114 positives turned negative. An intervening TST boosted QFT®-GIT in 9.1% and 11.3% for T-SPOT®.TB and those with baseline positive TST a boosting affect. The authors conclude that conversions of IGRAs over 18 months occurred 6-9 times more often than TST which demonstrates false-positives and a need for retesting of converters. The authors did not feel that changing the cut point would be helpful since this only attributed to 15-18% of conversions in this study (Dorman et al., 2014).

The prospective study by Dorman et al. (2014) is a level II comparative study, quality A high study. This is an example of a prospective comparison study of which there are few for IGRAs. The authors analyzed several conversion factors by statistical methods. The sample size was sufficiently large and spanned different areas of the US but each were in larger metropolitan areas. The authors report the limitations of limited generalizability to groups with immunosuppression and limited generalizability for other higher incidence countries. There was also some attrition in the TST repeat groups (Dorman et al., 2014). This study was very thorough and has good applicability to this project. However, this study does point to the necessity for retesting of any positive QFT®s.



## **Evidence level II, Good quality (B) articles.**

The Switch study was conducted to determine what cost an IGRA would need to be in order to cost less overall than the tuberculin skin test for health care employees (Wrighton-Smith, Sneed, Humphreys, Tao, & Bernacki, 2012). All of the actual costs for materials and employee health staff labor costs involved with tuberculosis screening were gathered from a large healthcare facility's finance records. The setting was John Hopkins in Baltimore, Maryland that screens about 18,000 employees annually with the TST. Secondly, 393 random employee encounters were selected for time motion study to measure the time it takes to complete each step with the TST including data entry as well as time for the IGRA lab draw as well as how much time away from work the employee had to take for testing. This study also randomly invited new hire and annual employees to participate in parallel testing of T-SPOT®.TB and TST with a total sample of 750 (473 annual, 270 new hires). Of the 113 employees (69 foreign born) with a previous history of positive TST, two thirds had negative IGRA. The nonreturn rate for TST was 10%, while only 0.4% of IGRA results were unavailable. The IGRA test also showed a lower rate of positive results than the TST in new hires. Questionnaires completed by participants revealed that 62.3% preferred the IGRA to the TST. The cost model revealed that when considering non return rates, the average cost for TST for annuals was \$73.20 and \$90.80 per new hires. The IGRA costs overall \$78.05 per annual screening when adding in labor and supplies, and \$64.47 for new hires. The IGRA would save money if the test costs \$54.83 or less per test for each new or current employee. A sensitivity analysis was also conducted to determine which of 38 variables had the most effect on the cost model. None of the variables had much effect beyond 0.75 cent except for labor

cost. Labor costs would impact the overall cost due to higher costs for time off work. If employees made 20% higher salaries, then IGRA would save money if it was \$61.16 per test (p value not provided). The sensitivity analysis of variables was shown in a bar graph and statistical significance was not revealed. In conclusion, the authors report that the IGRA saves money and improves compliance rates for health care employee tuberculosis screening (Wrighton-Smith et al., 2012).

This Switch study was rated level II and quality B. The strengths of this study include that the study did have some elements of random selection and it did a parallel comparison of the TST and T-SPOT®.TB. The study also supports the conclusion that non-return rates for the TST affect cost. There may be potential bias in this study since the manufacturer of T-SPOT®.TB, Oxford Immune provided the test free of charge and provided John Hopkins a grant of \$49,300 for the study (Wrighton-Smith et al., 2012). The salaries had to be weighted and estimated to give an estimate of the average hourly wage. This could have skewed the results. A more accurate direct measure would have been to use the exact salary of each participant. The authors report the limitation that the study considered the TST and IGRA to be equally accurate. Descriptive statistics were described, rather than statistically significant testing. This is probably not necessary for the cost result, but would be important to ascertain for parallel testing of results. Overall, this is a good study to support this project.

Cummings et al. (2009) conducted a study of newly hired healthcare workers at West Virginia University prospectively comparing the tuberculin skin test and QFT®-GIT. A convenience sample of 182 out of 266 invited new hires from June 2007 to February 2008 was obtained by offering 2 QFT®-GITs to all new hires who were having

a TST. The QFT®-GIT was drawn first, followed by the first TST up to 3 weeks later, followed by a second QFT®-GIT and second TST if needed 1 week later. A unique feature of this study was that any indeterminate or positive QFT®-GIT was retested in the lab by ELISA. If the positive results agreed, then the result was confirmed. If the results did not agree, a third test was conducted and the mean of the values was used. In order to determine specificity, the study assumed that participants who had no risk factors for TB did not have latent TB. The study used mixed-model repeated measure analysis of variance (ANOVA) to compare results of first and second QFT®-GIT results and timing of TST was considered as a variant. The sample included 96% born in the US, 93% without BCG vaccination, and 62% having no risk factors reported for TB. For initial testing, the TST and QFT®-GIT had 96% agreement of negative results (both results were negative) but no agreement on positive results (none had both positive TST and QFT®). It was determined that specificity for the TST was 99% and QFT®-GIT 98% for healthcare workers that reported no risk factors. Eighty-five participants completed the second blood test and out of these two of the participants with initial negative QFT®-GIT results had subsequent positive results. The authors considered both blood test results and found that 4 had positive blood tests but negative TST, while 3 had positive TSTs but negative QFT®-GIT results. Only one participant had both a positive QFT®-GIT and TST. Sixteen indeterminate results were repeated in the lab by ELISA and 11 remained indeterminate while 5 were negative. The study found that employees with diabetes or who were on immunosuppressive therapy had greater odds of having an indeterminate result (rate 6.8, 95% confidence interval). Out of the 5 positive results, 2 were confirmed positive. This study did not find any statistically significant difference between the first

and second QFT®-GIT results. The INF $\gamma$  result for participants that had only 1 TST showed a mean increase of 0.02 which was statistically different ( $p=0.04$ ). The authors conclude that overall agreement and specificity for the TST and QFT®-GIT was good due to the fact that there was a high rate of negative results, but positive results did not agree. Retesting of samples in the lab may improve diagnostics due to the reversion of follow up testing. There was a small boost in IFN- $\gamma$  results from the TST which may limit testing. Immune status of participants should also be considered due to increase in indeterminate results. The authors state that the QFT®-GIT may be beneficial due to fewer visits required for QFT®-GIT as compared to multiple visits for the TST (Cummings et al., 2009).

This study by Cummings et al. (2009) is level II with rating of good quality. The study is good in that it compared both QFT®-GIT and TST tests and included statistical analysis. The authors have clear discussion of the results, but do not assert which testing is recommended. However, the study had important findings to consider when determining whether to retest employees when QFT®-GIT are positive or indeterminate. This setting is low- incidence which is relevant to this project, but would limit generalizability to other settings. A limitation is that the study lacks randomization and only 47% returned for the second blood test resulting in attrition bias (Cummings et al., 2009). The authors assumed that employees without risk factors for tuberculosis did not have LTBI which could have skewed results. The sample included 96% United States born and 93% did not have BCG vaccination which could limit generalizability to other countries (Cummings et al., 2009).

Diel, Loddenkemper, Maywald-Walter, Gottschalk, and Nienhaus (2009) conducted a study to assess agreement between the QFT® and T-SPOT®.TB in comparison to people with positive TSTs who had recently been exposed to tuberculosis. The sample included 2,004 people who were close contacts of patients with culture confirmed tuberculosis, which were reported to the Hamburg Public health department from December 2006 through February 2008. Six people were excluded from the study because they had already had contact investigations, and seven did not follow up for testing. Eight hundred and forty-two contacts tested positive by TST and had subsequent QFT® and T-SPOT®.TB testing. Twenty-two were eliminated because the T-SPOT®.TB could not isolate sufficient lymphocytes. Results were indeterminate for 7 T-SPOT®.TB and 1 QFT®. The final sample was 812 TST positive contacts who were exposed to 123 tuberculosis patients. The results revealed 245 (30.2%) positive QFT®s and 233 (28.7%) positive T-SPOT®.TB. The rate of negative IGRA results significantly increased in the BCG vaccinated groups with 140 negative T-SPOT®.TB (versus 93 positive) and 146 negative QFT®s (versus 99 positive) ( $p < 0.0001$ ). Statistical analysis revealed high agreement between the QFT® and T-SPOT®.TB with  $k$  value of 0.852, 95% confidence interval. Furthermore, QFT® and T-SPOT®.TB were more statistically likely to be positive if the patient coughed in the presence of the contact ( $p < 0.0001$  for each). There was also a statistically higher rate of IGRA positive results for those with higher exposure time ( $p < 0.0001$ ) and those with contact with AFB positive patients ( $p < 0.0001$ ). Those with exposure  $> 40$  hrs. to AFB positive patients had a 6 times higher positive rate than those with  $\leq 8$  hours of exposure and twice as likely in the AFB smear negative sources. It appeared that higher cutoffs for TST positive results showed greater

association with positive IGRAs. Those with TST result of >15 mm had 68.3% positive QFT® and 87% for T-SPOT®.TB. However, this agreement decreased to 56.7% and 54.4% for patients with TST positive results of 11-15 mm and decreased further to 14.2% and 12.9% for those with TST of 6-10 mm. Multiple regression analysis showed a statistically significant relationship between increase age ( $p=.003$ ), and foreign birth ( $p<0.001$ ), source AFB-positive contacts ( $p<0.001$ ) and positive QFT® and T-SPOT®.TB results. Overall, the QFT® and T-SPOT®.TB had good agreement of 93.9% and were associated with increasing exposure risk factors. Metanalysis revealed the QFT® to be more specific for active TB than the T-SPOT®.TB but less sensitive, however in actuality there were more positive QFT®s found than T-SPOT®.TB. Specificity of the TST was poor (64.5%) for those with TST cutoff of >5 mm if you consider that patients with positive results to both QFT® and T-SPOT®.TB had true infection. The authors conclude that the QFT® or T-SPOT®.TB is more accurate indicators of LTBI than TST and utilization would decrease the number of patients with suspected LTBI by 70% (Diel et al., 2009).

The article by Diel et al. (2009) is rated level II, good quality. There is excellent prospective comparison of the TST and QFT® and T-SPOT®.TB. Not many studies have conducted these analyses with statistically significant results. This was a convenience sample which can lead to some selection bias. There was just a small attrition in this study. Multiple statistical tests were applied which result in statistically significant results by chance (Melnik & Fineout-Overholt, 2015). This article is relevant to this project in that it shows that QFT® is associated with greater likelihood of exposure to tuberculosis.

### **Evidence level III, high quality (A) articles.**

Schablon, Nienhaus, Ringshausen, Preisser, and Peters (2014) performed a large scale study of serial QuantiFERON® Gold in Tube (QFT®) tests on 3,823 healthcare workers in Germany. Participants included a convenience sample selected by occupational health physicians from 32 different hospitals, nursing homes and out-patient centers from 2006 through 2013. Each participant signed a written informed consent and physicians collected information regarding age, gender, reason for the test, exposure to TB, work history, history of TB, birth country, and tuberculosis screening results. Statistical analyses were performed by SPSS version 21 and included Chi-square, adjusted odds ratios, 95% confidence intervals, and logistic regression models. At baseline, there were 318 positive QFT®s ( $\geq 0.25$  IU/ml) which is 8.3% of the sample. There were four variables found to be associated with positive QFT®s including age  $> 55$  with odds ratio 6.89 (95% CI), foreign birth odds ratio 2.39 (95% CI), personal or family history of TB with odds ratio 6.23, and place of work. Interestingly, there was no association with job title (RN versus MD, etc.) or with the reason for the testing (screening versus contact investigation). Out of the sample, 817 had repeat QFT® testing from 7 days to 48.6 months apart. The amount of time between testing had no difference in conversion, reversion, or results that did not change. 97.2% of those with negative baseline tests had consistently negative QFT® results (721 out of 742) and 62.5% were consistently positive (47 of 75). The odds of remaining positive increased from 2% to 18% for those over 55 years of age. Age did not appear to affect conversion or reversion rates. Those who were foreign born outside of Germany had higher reversions rates of 7.8% versus 2.7% German born. Conversions on serial testing after baseline occurred in

2.8% (21 out of 742) and reversion rate of 37.3% (28 out of 75). If the definition of QFT® result was changed to a borderline zone of 0.2 to <0.7 IU/ml, then conversions would decrease to 1.1% and reversions to 18.8%. If the definition of conversion was changed to 1.0 or 3.0, then conversion rates decreased even further to 1.0% or 0.4% respectively and the reversion rate changed to 18.6% or 11.1%. The authors conclude that a borderline interpretation zone of 0.35 to 0.7 or 1.0 IU/ml would be safe and reduce the number of chest x-rays for healthcare workers without symptoms of TB in countries with low TB incidence (Schablon et al., 2014).

This study by Schablon et al. (2014) is a level III correlational, quality B Good study. The authors discuss the limitations of using a convenience sample with selection bias. The occupational health physicians did not have a strict study protocol for schedules of retesting or selection of groups to test (Schablon et al., 2014). There appears to be a preconceived bias by the authors that there should be a borderline testing zone, however it does not appear that the authors directed the physicians to retest participants in this zone. There was no specific inclusion or exclusion criteria for participant selection to control for any variables. The sample size was sufficiently large at 3,823.

Generalizability to US healthcare workers could be limited since this study was conducted in Germany and authors report that from literature there is a historical positive rate of TSTs to be 24-50% in healthcare workers. This would not be the general result that is found in the US. Furthermore, 45.5% of participants had BCG which did not affect the odds ratio for positive QFT®s (Schablon et al., 2014). This high rate of BCG vaccination might not be found in the US. It would be helpful to know the number of



foreign born US participants in this study. A comparison with TST would strengthen this study.

Lamberti et al. (2015) conducted a system review of the literature with meta-analysis with the purpose of reviewing healthcare worker screening with TST and QFT® test agreement and association with BCG vaccination and TB incidence. The authors searched PubMed for articles from January 2004 through October 17, 2013 with combination of search words “workers”, “tuberculosis”, “TB infection”, “TB disease”, “TB”, “tuberculin skin test”, “Tuberculin skin testing”, and “quantiferon”. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was utilized for the review and meta-analysis. Studies included were cross-sectional or longitudinal articles about screening of healthcare workers with TST and QFT®, and comparison of the tests as well as those with vaccination information. Studies were excluded that were case reports and those that were about patients with immune system diseases or HIV. Twenty-nine studies were chosen out of 1,430 abstracts. The authors considered the QFT®-TB Gold and the QFT®-GIT to be QFT® for purposes of analysis. Cohen’s  $k$  was used with a confidence interval of 95% calculated. Meta-regression was used to examine the covariates. The selected articles included 10 studies in low TB incidence settings, 7 intermediate and 7 high incidence settings. Studies were excluded that did not define a positive PPD at cutoff of 10 mm. The sample size was 10,314 with patients with indeterminate results being excluded. Results regarding agreement between the tests showed that 6,893 tests agreed for TST and QFT®, while 3,421 did not. TST positive and QFT® negative occurred four times more often than TST negative and QFT® positive. The Cohen’s  $K$  for agreement between the TST and QFT® overall was 0.28 with 95%

Confidence Interval which the authors report is low and shows that 33% of the time the tests do not agree. However, this improved to 0.38 for high incidence settings while intermediate was 0.19 and low incidence 0.25 Cohen's  $k$ . The intermediate group had the worst agreement and was significantly different than the high incidence ( $p=0.041$ ). However, the intermediate group had the highest BCG vaccination rate. When the sample was divided by low and high BCG vaccination rates, the group of studies with the lower rate (15 studies) had a Cohen's  $k$  of 0.34 and the higher group (9 studies) was 0.17. The authors conclude that TST should be used in areas with low vaccination rates or high incidence of TB, while QFT® is helpful in settings with high incidence of TB. Providers should consider that the QFT® higher specificity for mycobacterium tuberculosis may be causing the differences in test results because the TST reacts to nonspecific antigens (Lamberti et al., 2015).

The systematic literature review by Lamberti et al. (2015) is a level II study with a quality rating of A High. This study applied statistical analyses to multiple articles to generate new statistics. A table is provided with the variables of interest for each study. The sample size was very large. The review included articles dated to 2004, but all studies were relevant to QFT® testing in healthcare workers. One limitation is assuming that the TST which measures nonspecific antigens is a valid indicator of LTBI when comparing agreement with QFT® which tests specific mycobacterium antigens. Therefore, the QFT® should reduce false-positives which would result in discordant agreement between the tests. Another limitation of the review was the combined testing of the QFT®-G and QFT®-GIT. It would be beneficial to examine whether there was a difference between the QFT®-G and QFT®-GIT improved testing.

Zwerling et al. (2012) completed a systematic review of the literature regarding IGRAs for healthcare worker screening. The authors searched PubMed, Embase, Biosis and Web of Science for all articles up through 2010 and included sources from conferences, article references, and references from experts and test manufacturers. A total of 50 articles were reviewed with 44 that examined LTBI prevalence and incidents, agreement of IGRA results or agreement between IGRA and TST. Three of the studies were included regarding cost-effectiveness and three on feasibility. Of the 44 main studies, 35 studied QFT® only, 3 T-SPOT®.TB only and 6 studied both. Five of the studies were conducted in high incidence settings. The total sample across the studies was 11,963 healthcare workers. Fisher exact 95% confidence interval was calculated for prevalence estimates. Three cross sectional studies from India, Russia and Vietnam were included, but the Russian study did not perform TST. The India and Vietnam studies showed a high positive rates for IGRA in healthcare workers of 40-60%. The rate of IGRA positives was only slightly lower than TST positive in the two studies. The prevalence between the TST and IGRA was only statistically significant (statistic not provided) in the Vietnam study which had a lower BCG vaccination rate of 37.3% compared to 71% in the India study. Thirty-one of the studies were from low or intermediate risk settings. Out of 25 studies, 24 showed lower prevalence of positive QFT® or T-SPOT®.TB compared to TST with 17 statistically significant (p value not provided). There did not appear to be an association between BCG vaccination and higher prevalence of positive TST or difference between the tests. Agreement between the TST and IGRA was weak with more common TST positive and IGRA negative results with kappa values from 0.05 to 0.56 with agreement improving if TST cutoff was

increased to 15 mm. In 14 studies in low incidence countries, there was an association between positive IGRA results and occupational risk factors for TB such as working in high risk TB units, working in TB clinics or geriatric areas and longer employment duration with two studies not finding this association. Four studies showed relationship between foreign birth or history of living in high TB incidence country and positive QFT® results with 3 showing correlation with TST positive. One study did not find this association with foreign birth but it was the only study that used T-SPOT®.TB. Two studies in high incidence settings showed IGRA conversion rates of 11.6% and 21%. Only four studies examined conversion rates in low incidence settings and ranged from 1.8 to 14%. Three studies showed reversion rates for IGRAs to be 40-52.9%. Two more recent studies showed that conversion and reversion rates were more stable when the IGRA results were higher than those close to the cutoff. The authors concluded that use of IGRAs for baseline would result in lower positive rates and few treated for LTBI, however conversions for serial testing may result in healthcare workers taking preventative medications on subsequent testing. The authors conclude that guidelines for serial testing of IGRAs should be reviewed due to issues with conversions and reversions.

The study by Zwerling et al. (2012) is a level II systematic review that is rated A high quality. The search strategy was comprehensive and the sample size large. Characteristics of each study are displayed in tables with an online supplement for review. The authors report limitations of the study including lack of reporting of HIV prevalence in the studies, inherent publication bias, and a lack of evidence at the highest hierarchy. A limitation was noted in the review of all studies that combined QFT®s together as one test methodology. The review included studies from different countries

which could limit generalizability to US populations. The study would have been strengthened by meta analysis. Overall, this article is high quality and relevant to this project.

Rangaka et al. (2012) conducted a systematic literature review with meta-analysis to assess whether IGRAs can predict the development of active TB compared to TST. This review included 15 studies found through search of PubMed, Embase, Biosis, Web of Science, bibliographies from other reviews, and expert recommendations. Studies included longitudinal studies of adults or children who did not have active TB at the study onset with the primary objective of predictability of IGRAs for TB by ELISA, ILISPOT, commercial or noncommercial assays. Statistical analysis included Newcastle-Ottawa quality assessment scale, incidence rate ratios, calculated risk ratios, DerSimonian and Laird random-effects with 95% CI. Seven of the reviewed studies showed a higher rate of positive IGRAs at baseline for those that developed TB (n=9,530, IRR 2.10, 95% CI). In five studies there was no statistically significant difference between the progression to active TB for people with TST positive versus IGRA positive results (IRR 2.11, 95% CI). Studies that used ELISPOT showed a sensitivity of 72% (95% CI) for developing active TB and specificity of 50% with TST sensitivity of 72% and specificity of 41%. The risk for developing active TB in positive IGRA people was low. The authors concluded that the association between IGRAs and active TB development is weak to moderate and no test is available that has high prognostic value, and therefore, decisions regarding testing should be based on logistics, population type, cost and patient preference (Rangaka et al., 2012).

The study by Rangaka et al. (2012) is a level III systematic review with meta-analysis high quality. The study had a very large sample size. The application of statistical analyses provides value and strength to the study although the article is very technical and difficult to understand. The authors noted that most of the reviewed studies had bias by not accounting for risk factors for TB, and did not fully answer whether IGRAs are predictive of TB. The authors also note that most studies were not in high income countries and most had industry involvement (Rangaka et al., 2012).

**Evidence level III, good quality (B) articles.**

Swindells, Aliyu, Enoch, and Abubakar (2009), conducted a literature review of 82 articles related to healthcare workers and interferon-gamma release assays. PubMed was used to find articles published from 1990 through 2008 with the combination of search words health care, health care worker, doctors, nurse, medical staff, tuberculosis, TB, quantiferon, elispot, IFN, interferon, IFN $\gamma$  assays, t cell assays, ESAT-6, CFP10, or rd1 antigens. The results were published in narrative and no meta-analysis was conducted. A total of 22 articles met the inclusion criteria with 2 about T-SPOT®.TB and 20 QFT® articles. Out of 11 articles, 9 found that the TST and QFT® results did not have good agreement while two found good agreement in high incidence countries (CI 95%). The studies that were examined regarding healthcare worker and BCG vaccination status had varied results. Two of the studies found agreement between TST and QFT® in those without BCG vaccination (kappa 0.676, kappa 0.649) but poor agreement in BCG vaccinated (Kappa 0.090 and 0.029). But two studies did not find any difference in results according to BCG status (84.2% concordance without BCG and 80.2% with BCG). Three of the studies did find that positive QFT®s was more closely related to

increasing TB exposure for healthcare workers (p value not provided). Another reviewed study also found that the QFT® was more likely to be positive for healthcare workers that were older and had worked longer in health care. Likewise, a Swiss study reviewed showed that healthcare workers in higher risk departments were more likely to have a positive QFT® (p= 0.03). One Italian study did not agree with this assessment and did not find any correlation between professional category and QFT® result (p value not provided). Studies that examined contact investigations found that positive QFT®s were more likely associated with exposure than positive TSTs (p < 0.05). When examining articles regarding conversions/reversions, there was one that showed a 24% QFT® reversion rate, one showed good QFT® reproducibility, and one that reported a significant increase in QFT® results in repeat testing over time (CI 95%). The authors reported that overall there was poor agreement between the TST and QFT® in healthcare workers in high incidence countries, however this discordance most likely is due to false positive TSTs in BCG vaccinated individuals. The authors report that the QFT® was a good marker of TB exposure in contact investigations. It was concluded that IGRAs are important to screening and prevention of tuberculosis for healthcare workers (Swindells et al., 2009).

The study by Swindells et al. (2009), is a level III systematic review of the literature rated good. The literature review used a reputable database (PubMed) and had clear criteria for inclusions and exclusion. However, the reviewed articles were published within the past 18 years which is longer than recommended. This long period of time may have been necessary due to limited research regarding QuantiFERONS® since the test itself was fairly new at the time of publication. The authors published results in Euros and

did not report p values or confidence intervals. Several assumptions were made regarding specificity and sensitivity of the TST and QFT®. The authors did not specify which QFT® was used in the reviewed studies and QFT®s only became approved in 2001. Different types of QFT® could have altered the results since newer versions of the test are considered to be more accurate. The authors did not discuss the limitations of the articles reviewed. The authors mentioned that there were only 2 studies that assessed the T-SPOT®.TB and therefore there was not adequate evidence for its use in healthcare workers at the time. Another limitation was that the review included articles published in different countries which may have different TB incidence rates. Overall this was a good study, but would have been strengthened by conducting some form of meta analysis.

Nienhaus, Schablong, Costa, and Diel (2011) conducted a systematic review of the literature to evaluate cost effectiveness of utilizing IGRAs to replace TST in tuberculosis screening. The authors searched Medline and Embase for search terms cost, interferon, and tuberculosis for articles in English and German. 76 studies were identified and narrowed down to 13 articles that met inclusion criteria of studies regarding cost, included high risk groups such as healthcare workers, immigrants, contacts, included TST and/or IGRA. In five cost analysis studies, two found the QFT®-GIT to be less costly than TST only, and in three studies the QFT® after positive TST was less costly than IGRA only. In all five cost analysis studies, the TST only method costs more than IGRA alone. Eight cost effectiveness studies were reviewed with one study examining TST only versus IGRA and seven studies comparing TST only, IGRA after TST, and IGRA only methods. One of these examined T-SPOT®.TB and one examined both T-SPOT®.TB and QFT® (4 QFT®-G, 1 QFT®-G and QFT®-IT, 3 QFT®-GIT). In all cost-



effectiveness studies, the TST only strategy was found to be the most expensive method of tuberculosis screening. In four of the studies, IGRA after TST was the least expensive and in two the IGRA only testing was least expensive. The authors conclude that there is strong evidence that IGRAs are cost-effective for tuberculosis screening in high risk healthcare workers, immigrants, close contacts, or those from high incidence countries. Cost savings is found in less frequency of chest x-rays and less preventive therapy for LTBI. The IGRA only strategy would be the least expensive if it is proven to predict progression to active TB more accurately, however more studies are needed to prove this assumption (Nienhaus et al., 2011).

The study by Nienhaus et al. (2013) is a level III systematic review rated B good quality. This study used a comprehensive search strategy with clear inclusion and exclusion criteria and followed the prisma guidelines. The article lists the different articles in tables for a clear view of differences. The authors discuss the limitation of the studies lacking consistency in assumptions regarding test parameters and specificity, progression rates, and different models for cost analysis. While the studies all targeted high risk groups such as healthcare workers and immigrants, the studies were in different countries and therefore, cost ratios had to be calculated (Nienhaus et al., 2011). This could limit generalizability of the conclusions. This study would be strengthened by applying meta analysis but overall it is a good study to support cost savings for use of IGRAs.

Pai, Zwerling and Menzies (2008) conducted a meta-analysis of 38 studies examining sensitivity and specificity of QuantiFERON®-TB Gold, QuantiFERON®-TB Gold IN-Tube, and T-SPOT®.TB. This is an update to a previous study adding 20 newer

studies with stricter inclusions criteria compared to the previous study. Eight of the previous studies were excluded due to noncommercial assays, fewer than 10 participants, articles that only studied immune compromised patients, or that used an older antigen for testing. The authors used PubMed to search for articles published through March 2008. Studies were included that assessed sensitivity by microbiologically confirmed cases of tuberculosis (by culture). Studies were also included that assessed specificity by including samples of healthy low- risk people without tuberculosis exposure. Studies with fewer than 10 participants were excluded from the review. The statistical method included a calculation of sensitivity or specificity with 95% confidence intervals and displayed results in forest plots. MetaDiSc software was used for fixed-effects meta-analysis which corrected for variability between studies. Chi-square and  $I^2$  tests were used to test heterogeneity. This analysis included 22 studies of QFT® with 1369 participants and 13 T-SPOT®.TB studies with 726 sample size. Three of the QFT® studies were from high incidence countries, while none of the T-SPOT®.TB studies were. The results showed pooled sensitivity for all QFT® studies to be 76% (95% CI). For each study investigating QFT®, sensitivity of the QFT®-TB Gold was 78% (CI 73-82%), QFT®-TB GIT 70% (CI 63-78%), and T-SPOT®.TB was 90% (CI 86-93%). Six out of seven studies found that T-SPOT®.TB had higher sensitivity than QFT® (3-25% difference) while one showed equal sensitivity between the tests (CI 95%, p value not specified). There were 16 studies from low or incidence countries that examined specificity of QFT® with 8 of them including BCG vaccinated and 8 non vaccinated with a sample of 1624 participants. There were 2 studies that examined specificity for T-SPOT®.TB and 4 that used ELISpot with a sample of 290. Specificity for all QFT® was

98% (CI 96-99%), QFT® non-BCG was 99% (CI 98-100%), and 96% (CI 94-98%) for BCG vaccinated. T-SPOT®.TB and TB/ELISpot specificity was 93% (CI 86-100%) overall with T-SPOT®.TB alone being 87% (CI 80-92%). T-SPOT®.TB sensitivity in relation to BCG was not reported, but one study included BCG vaccinated participants. TST sensitivity from 20 studies was 77% (CI 71-82%) and specificity in non-BCG vaccinated in 6 studies of 97% (CI 95-99%). Specificity for TST in BCG vaccinated participants was low. The authors concluded that IGRAs have excellent specificity that is not influenced by BCG vaccination status particularly for QFT®s but there are few studies on T-SPOT®.TB. TSTs were found to have high specificity for those not vaccinated with BCG but specificity was variable for BCG vaccinated participants (Pai et al., 2008).

This article by Pai et al. (2008) is a B good quality level III systematic review with meta-analysis. The authors list the limitation that most of the studies examined were small and the studies had different cutoffs for testing results. The authors also report that studies were not included that examined TST alone which could alter the TST analysis. The authors also report that interpretation of the usefulness of sensitivity and specificity is limited since there is no gold standard for latent tuberculosis diagnosis. Not all of the studies reported sensitivity and specificity. The authors caution that results regarding T-SPOT®.TB should be carefully interpreted since there were few studies. The authors clearly discussed limitations of their studies which is important for readers to ascertain strength. The analyses included scatter plots in the appendix with information about each article's sensitivity/specificity results as well as tables comparing BCG vaccinated versus non-vaccinated (Pai et al., 2008). This improves this studies validity. The meta analysis

rather than just systematic review is a strength of this study. The results of this study are comparable to many other articles found in this review of the literature and contribute to considerations for policies and procedures for the project.

**Evidence level IV, high quality (A) articles.**

Jensen, Lambert, Iademarco, and Ridzon (2006), published recommendations for preventing tuberculosis in healthcare settings. These are the recommendations that are approved by the CDC and that DHEC require to be followed. This article is 141 pages long and the aspects that pertain to this project will be summarized for brevity. This article discusses healthcare workers that should be screened, epidemiology and transmission of tuberculosis. The authors report that tuberculosis may be transmitted in healthcare settings and healthcare workers are at risk. Therefore, healthcare facilities should implement infection control measures. The article describes in detail the infection control measures including administrative controls, environmental controls, and respiratory protection controls in detail (Jensen et al., 2006).

The article outlines methods for determining risk level in health care settings and describes the required screening for low, medium and healthcare workers with potential ongoing transmission settings (Jensen et al., 2006). According to recommendations, healthcare workers in low risk settings should receive two step tuberculosis skin testing on hire or a single blood assay. Those with positive tests should have a chest x-ray to rule out TB. Healthcare workers in medium risk settings should have the same baseline screening but should have annual TB screening. Baseline testing with a single blood assay is acceptable. Facilities should complete only one test without overlapping the

blood test and TST except for a trial period of evaluation for 1-2 years. The article reviews care of patients with TB and managing exposures. Proper TST procedures include first step followed by a trained designated reader in 48-72 hours. The second step should be placed in 1-3 weeks and read in 48-72 hours. If a patient does not return for reading within 72 hours and the result is negative, the test must be repeated. Positive results can be read up to 7 days after placement. The second step is necessary because an initial TST may be falsely negative while the second step boosts a person with LTBI's ability to react to the TST with subsequent positive test. Healthcare workers must have a trained health care professional to read the TST result. Reading is determined by measuring mm of induration perpendicular to the forearm. The QFT®-G blood assay for mycobacterium tuberculosis (BAMT) is reported as an alternative to the TST and this article reports that the test reacts to two specific proteins found in mycobacterium tuberculosis "(M. tuberculosis, M. Bovis, M. africanum, M. microti, M. canetti, M. caprae, and M. pinnipedii)" but not to m. bovis found in BCG vaccine. The blood test interpretation is less subjective than the TST, may be more cost effective, efficient, and eliminate two step testing. The TST is subject to variability in placement and reading but healthcare professional TST administration training can help overcome these barriers. The authors report that the likelihood that a positive TST represents TB infection in low risk settings is low but the specificity improves in higher prevalence settings. The authors report that one single negative BAMT is all that is needed to determine if a healthcare worker is not infected with tuberculosis. Conditions that reduce immune function could reduce the predictive value of a negative BAMT or TST (Jensen et al., 2006). BAMTs may result in indeterminate results if the IFN- $\gamma$  antigen response is low or if the antigen

response is not at least 50% of the Nil (Jensen et al., 2006). Some reasons for indeterminate BAMT results include low immune response, improper storage or transport of blood, lab error, or other illness in the healthcare workers. BAMTs or TSTs should be completed within 10 days of hire for baseline screening (Jensen et al., 2006). Healthcare workers with positive blood assays or positive TSTs should be referred for healthcare evaluation and testing (Jensen et al., 2006). Treatment options for healthcare workers with positive test results should be guided by considering test results, epidemiologic factors, risk factors and by diagnostics including chest x-ray or bacteriology, and histology (Jensen et al., 2006).

Prior to making any changes in tuberculosis screening in healthcare settings, the Centers for Disease Control and Prevention recommendations must be reviewed and followed. Therefore, this was the first resource reviewed prior to considering this project. While the date of publication is 2006, this article had to be included as it is still the most current guidelines with the addendum on IGRAs published in 2010. There is clearly expert input in the article including CDC, experts in TB and infection control as well as experts in respiratory protection and occupational health (Jensen et al., 2006). A list of departments for which the experts come from are given, however a specific list of who these experts are is revealed. There is a comprehensive list of 487 references is given. The authors did not specify their method of obtaining the references for review. Overall, Jensen et al. (2006) is rated a high quality A level IV study of clinical practice guidelines.

The literature search revealed that the CDC gathered a group of experts and published an article in 2010 regarding guidelines for IGRAs (Mazurek et al., 2010). This group of experts reviewed 96 out of 152 articles published through 2008 which examined

agreement between QFT®-GIT and T-SPOT®.TB or with TST, sensitivity or specificity of QFT®-GIT or T-SPOT®.TB, QFT®-GIT and T-SPOT®.TB in relation to TB risk, and use of QFT®-GIT or T-SPOT®.TB in contact investigations. The authors searched PubMed as well articles from the test manufacturers. The purpose was to provide guidance for use of IGRAs for tuberculosis diagnosis for healthcare providers, public officials, and laboratory workers. The result is a lengthy article with discussion of the strengths and limitations of QFT®-GIT and T-SPOT®.TB. The review of articles by the authors showed varying results regarding sensitivity of the QFT®-GIT and T-SPOT®.TB, however, in general sensitivity is similar to the TST. Pooled QFT®-GIT sensitivity was reported as 81-83%. Out of 11 studies that examined confirmed active tuberculosis patients, six studies showed no statistically significant difference between QFT®-GIT and TST, three showed greater sensitivity for TST, and two showed greater sensitivity for QFT®-GIT ( $p < 0.01$ ). Pooled T-SPOT®.TB sensitivity was about 90-91%. Pooled QFT®-GIT specificity for those not likely to have TB was 99% and for TST 85%, and 86% for T-SPOT®.TB. The authors caution that the reviewed articles for specificity have varied risk for infection and test methods and interpretation may vary. Tables are available in this article listing the p values for each study by country. The articles which the experts reviewed showed varied results with regards to agreement among tests due to differences in test interpretation criteria, estimates of exposure, BCG status, TST status, and coexisting conditions. The review did reveal that in contact investigations, positive IGRAs were more strongly associated with recent exposure and longer duration of exposure or infectiousness as compared to the TST. Therefore, IGRAs may be better at detecting more recent infection with TB than the TST. There have been few studies to

examine whether IGRAs will predict development from LTBI to active TB. However, a few have reported that the QFT®-GIT performed better than TST at predicting conversion to active TB. There is limited data regarding using QFT®-GIT for immunocompromised persons, but two found that QFT®-GIT sensitivity was 81-88%. Further study is recommended for all aspects of IGRA use. The authors suggest that ultimately the organization should consider logistical factors such as single visits for IGRAs, quicker results and less error with reading of results, and cost factors (Mazurek et al., 2010).

Mazurek et al. (2010) gives guidelines for general use of IGRAs and approve use for surveillance. It is recommended that quantitative and qualitative results be utilized. It is recommended that organizations evaluate cost, availability, and benefits of each test in order to choose which test to implement as studies vary as to which test is better regarding sensitivity and specificity. IGRAs are preferred for individuals who have a low rate of return for TST reading and for those who have received a BCG vaccine. An IGRA or TST may be used without preference for contact investigations and period screening for occupational exposure. It is mentioned that repeat of an IGRA may be useful if the result is indeterminate or borderline. After testing, a person with a positive IGRA should be assessed for likelihood of active TB versus LTBI based on risks, exam, history, chest x-ray and symptom assessment. A single positive IGRA should not be used as reliable evidence that someone has tuberculosis as false-positives do occur (Mazurek et al., 2010). Overall, use of IGRAs are acceptable and approved by the CDC for tuberculosis screening in healthcare workers.



**Evidence level V, high quality (A) articles.**

A study comparing the cost-effectiveness of the QFT®-G, QFT®-GIT, and the TST for new health care workers was conducted based on data from the Veterans Healthcare Administration in 2007 (dePerio, Tsevat, Roselle, Kralovic, & Eckman, 2009). The study conducted a Markov state-transition decision analytic model and measured quality adjusted life years (QALYs) in relation to direct costs, missed work time and probabilities. A hypothetical sample of 35-year old RNs was used for this study. The analysis ran decisions for those with and without BCG vaccination, those with and without LTBI. The study also accounted for those that fail to return for TST readings. Also, analyzed was whether isoniazid treatment might be indicated for 9 months and whether medication induced hepatitis might develop as a result of INH treatment. Direct and indirect costs were considered, including costs for conducting the tests missed time from work. Sensitivity analysis was conducted to examine all probabilities and changes in age. Final results indicated that for all models IGRAs were less expensive than TSTs. According to the sensitivity analyses, the IGRAs were less costly as long as tests were conducted in batches of at least 12 for non BCG vaccinated and at least 4 for BCG vaccinated. For batch QFT® testing, in order to cost less than the TST, the cost for the QFT®-G should be \$32 or less and for the QFT®-GIT \$36 or less. The authors demonstrated that the IGRAs were less costly than TST 100% of the time, but the rate of LTBI did not change this result. It is concluded that the QFT®-GIT is less costly than the QFT®-G if it is more sensitive. The authors conclude that the QFT®-G or the QFT®-GIT can lower costs in comparison to the TST for tuberculosis screening of new healthcare workers and have “superior clinical outcomes” (dePerio et al., 2009).

The study by de Perio (2009) is level V Financial evaluation with a quality rating of high. This study analyzed multiple hypothetical variables to assess cost of QFT®s in comparison to TST and the results were very clear that the IGRAs were less costly. Limiting the age to 35 could have skewed the results, however the authors did vary the age in some of the models and there were no changes in the result. The figures for salary could vary by institutions which could change the outcome of this study. The study also only considered RN salary which is the largest employed group in the hospital, however this could have skewed the results by not considering lower and higher paid staff. It is important to note that this study was published in 2009 and the salary and costs for testing would be considerably higher today. The authors mention the limitation that decision analyses are dependent on quality and accuracy of the model parameters. The authors attempted to use pooled data from multiple studies to help overcome this. However, readers need to understand QALYs definitions. The study could be strengthened by including decisions regarding cost of subsequent annual TST testing as well as analyzing actual versus hypothetical data.

An article by Banaei, Gaur, and Pai (2016) discuss the literature regarding variability for IGRA results and recommendations. According to the authors, studies have shown some issues with reproducibility and conversion rates with respect to variability. Factors that contribute to this variability including pre-analytical, post-analytical, manufacturing, and immunological problems. A pre-analytical source of variability is timing of the blood draw since QFT®-GIT results tend to be higher when blood is drawn in the evening rather than morning. Also, if the blood collection tube and the skin is not properly disinfected, there can be contamination causing

immunomodulatory response from bacteria. If the blood is not drawn in the correct order of nil, antigen, and then mitogen tubes, then there could be contamination of the antigen tube from the mitogen giving a false-positive or from the nil tube with mitogen causing false-negative. The volume of blood and vigorous shaking can affect results as well. The higher volume of blood can result in false-negatives. Excess shaking can cause increased IFN- $\gamma$  response and false- positive or negatives depending on whether it was the nil or antigen tube shaken too much. The authors report that literature shows that delay in incubation can cause false negative or indeterminate results due to reduction in mitogen response for QFT®-GIT. For T-SPOT®.TB, indeterminate results are more common in fall and winter perhaps due to lower temperature during transport of the blood. Longer incubation does not appear to affect results. Analytical sources of variability can be due to pipetting that is not precise, errors with centrifugation, washing steps and operator incorrect measurements. The authors report that studies have shown variability in results of  $\pm 0.6$  overall and a variability of  $\pm 0.24$  IU/ml for those with initial results close to cutoff levels. Post-analytical errors can be the result of error in clerical data entry. Manufacturing errors can be due to faulty antigen tubes or bacterial contamination causing false-positive or faulty mitogen tubes causing indeterminates. Immunological variability may be due to boosting from TST causing conversions. Contamination from microorganisms on skin or in the environment can cause microbe-associated molecular patterns that increase the TB response. Staphylococcus aureus contamination in the antigen tube can cause increase in false-positive results. Recommendations to reduce variability include: proper disinfection, correct collection tube order, standardize order of blood draws standardize filling of tubes to 1 ml, gentle shaking of QFT®-GIT tubes,

prompt incubation, use of automated instruments, quality assurance equipment calibrations, and draw blood within 72 hours of TST placement (Banaei et al., 2016).

The article by Banaei et al. (2016) is a level V, high quality expert opinion with some literature review. Recommendations are very clear and helpful for policy and procedures for QFT®-GIT implementation. References are comprehensive and recent. This article was not primarily a literature review, but did discuss the literature. The article did not discuss the limitations of the articles presented in the expert review. Overall, this is an excellent article which provides clear guidance to avoid variability in IGRA results.

#### **Evidence level V, good quality (B) articles.**

Weddle, Hamilton, Potthoff, Rivera, and Jackson (2014), conducted a study with the purpose of determining performance of the QFT®-GIT in healthcare employees in a children's hospital setting determined to be in a low TB incidence. Secondly, the study examined whether repeat testing of positive QFT®s was useful to determine TB infection. The study utilized occupational health records to retrospectively review 758 employees screened for TB in 2010-2011. Out of 47 who had positive QFT®s, 34 had repeat testing with 64.7% (22) positive on repeat and 35.5% (12) negative on repeat. The mean QFT® result of those who had positive repeat testing was 1.19 and 0.92 on initial testing. The initial mean and median of negative repeat testers was 0.61 and 0.5. This revealed that the negative repeat individuals had a statistically significant ( $p=.01$ ) lower IFN $\gamma$  results than those with positive results. The authors did not reveal which statistical test was used to compute the findings. There was no statistically significant difference in

reported risk factors between the repeat negative and repeat positive groups ( $p=.86$ ). Out of the 707 negative QFT® employees, 37.9% had risk factors for TB and 36.2% of the positive QFT® individuals had risk factors for TB. The authors conclude that the QFT®-GIT is useful for tuberculosis screening in healthcare workers, however false positive may occur when results are less than 1IU/ml and repeat testing should be considered (Weddle et al., 2014).

Overall, this study is level V quality improvement with a quality rating of good. While statistical analyses were conducted, the authors did not reveal which tests were employed. The authors give a clear discussion of implications for repeat testing. However, the authors do not discuss the results of the risk stratification. This study would have been strengthened by a larger sample of positive repeaters. Comparing 707 negative employees to 47 positive employees may have skewed results unless this was adjusted for in the statistical analysis. This study is important to consider when designing policies and procedures for repeat testing.

Foster-Chang, Manning, and Chandler (2014), conducted a study at the Veteran's Administration health care facility to determine if an IGRA was acceptable in lieu of the TB skin test to improve processes for pre-placement assessments. This medical center employees 3,500 with 64% in the 41-60 age group. It was reported that many employees were foreign born and had BCG vaccination but the total number or percent was not given. This study included a convenience sample of 100 new employees hired from March 19 through May 30,2013 who were asked to have a T-SPOT®.TB instead of the TST during pre-placement assessment. Data from this group was compared to retrospective electronic chart review of 100 new employees who had the TST in the

previous time periods of 2011 and 100 new employees in 2012. The study examined compliance with completing the entire pre-placement process within 14 days. Compliance in the T-SPOT®.TB group was 97% while compliance in the PPD group was 77%. Chi-square goodness of fit tests showed statistically significant difference between the TST group and the T-SPOT®.TB group compliance rates with  $p < .001$  for 2012 compared to 2013 and  $p < .0001$  for 2011 compared to 2013. The study also reviewed the clearance for work time defined as the time from pre-placement assessment to provider signed clearance to start work. The average clearance for work time for the T-SPOT®.TB group was 5.91 days while the average for the TST groups was 12.67 in 2011 and 13.18 in 2012. There was statistically significant difference in clearance time by Kruskal-Wallis equality of populations rank test between the T-SPOT®.TB and the TST groups regardless of whether the employee in the TST group brought prior TB documentation ( $p < .001$ , 95% confidence interval, Chi-square 30.981) or did not ( $p < .001$ , 95% confidence interval, chi-square 28.479). Cost comparison for the IGRA with cost of TST process was \$78.53 per person versus \$47.02 per person in the T-SPOT®.TB group (Foster-Chang et al., 2014). No statistical analyses were conducted for the cost estimates. The authors conclude that IGRAs are acceptable in place of the TST for new employees and will improve tuberculosis screening processes (Foster-Chang et al., 2014).

The strengths of this article by Foster-Chang et al. (2014) included good precision with results that were statistically significant for compliance and screening time with adequate sample size of 300. Another strength of the study is that the purpose and design are closely related to the PICOT questions for this project, however the authors used the T-SPOT®.TB rather than QuantiFERON®-TB Gold In-Tube-Test. External validity is

good in that conclusions can be applied to similar healthcare settings, however the fact that the sample may have a higher percentage of foreign born employees who may have received BCG vaccination could affect the generalizability. For construct validity, other facilities might interpret clearance time different than this organization. One weakness is that the authors admit that reliability could have been affected due to the physician signed clearance with impending vacation plans, a chart for a T-SPOT®.TB employee was misplaced and discovered 21 days later, and two employees chose not to have blood drawn on date of pre-placement assessment, returning 2 weeks later (Foster-Chang et al., 2014). These factors could have affected the results causing increase in clearance time and reduction in compliance. Furthermore, data from misplaced charts were probably not readily available for data analysis of the TST groups. This study was not a controlled experiment which affects internal validity. Investigators may have also had bias due to the expected reduction in clearance times at the start of the study. A strength in the internal validity is that the T-SPOT®.TB group had no attrition. Overall the evidence level for this study is V quality improvement with quality rating of B Good. This article supports that implementation of an IGRA is acceptable for new healthcare employees.

Gonzalez and Conlon (2013) described how their organization developed a needs assessment to determine which tuberculosis surveillance program would meet the needs of the facility. The hospital is described as moderate sized and has 4,300 employees with a low risk assessment per CDC guidelines. Approximately 25% of the employees had previous BCG vaccination. TB screening is conducted by TST annually for those without previous BCG vaccination or previous positive. This organization was originally exempting pregnant employees from screening and conducted annual symptom

assessments. The organization also conducted an annual symptom review and a chest x-ray every 5 years for those with a history of positive TST. The authors admit that these practices were outdated and did not meet current CDC guidelines as pregnant women do not need to be excluded and an x-ray every 5 years is not necessary. New employees were screened with two-step TST. The organization developed a 12 item table comparing the attributes of the TST, QFT®-GIT, and the T-SPOT®.TB. The organization eliminated the T-SPOT®.TB as an option due to the lack of on-site lab testing and the time limitations for the specimens. The authors' literature review revealed that QFT® and TST had comparable sensitivity and specificity when BCG vaccinated people are not included in the TST data. The authors were concerned about the report reversion rates with the QFT® and the laboratory preparation and incubation time. The organizations lab did not conduct testing on the weekend which would limit QFT® testing due to the 16-hour time limit for processing. The QFT® can be conducted in one visit which saves money in lost productivity. Ultimately the organization chose to continue two step TSTs for new hires without BCG vaccination and for annual testing. The organization chose QFT® for BCG vaccinated new hires but only a symptom assessment for annuals. The organization will utilize QFT® additionally for exposures, pregnant employees and immunocompromised employees. This article provides an example of how organizations should consider all of the variables when deciding on which tuberculosis screening test to implement (Gonzalez & Conlon, 2013).

The article by Gonzalez and Conlon (2013) is a level V Organizational Experience/Quality Improvement quality B good article. This is a non-research article that provides useful information to consider when choosing a tuberculosis screening tool.



The article had a small amount of literature included but certainly is not comprehensive. The decisions in this tool cannot be generalized but the techniques for decision making can be applied. A concern, is that they continue to exclude pregnant workers from their standard TST, rather choosing to use the QFT® demonstrates an improvement in standards. Decision making for tuberculosis screening is certainly complex and unique for each organization due to multiple variables such as demographics and geographics.

Veesser, Smith, Handay, and Martin (Veesser, Smith, Handy, & Martin, 2007) evaluated the results, acceptability and costs for QFT®-G implementation at the University of Tennessee Health Science Center at Memphis. There are approximately 2,200 students and 6,000 direct patient care employees that are screened for tuberculosis. The authors conducted a retrospective chart review for those that were screened for tuberculosis with QFT®-G from June 2005 through August 2006 through University Health Services (UHS). The organization began using the QFT®-G in 2005 for special groups included those that reported a history of positive TST but did not have documentation from the health department, those with questionable history of positive TST, people who had been BCG vaccinated and those that tested positive by TST at UHS. The sample size was 109 including 55 employees and 54 students. Out of the sample, 84 had negative QFT®-G, 10 positive and 5 indeterminate. Out of the 10 positive results, 7 were students who had BCG vaccination and 1 that reported a history of undocumented positive TST. One was an employee that had documented past positive TST and one employee had history of undocumented positive TST. The 5 people that had indeterminate results were tested a second time and had indeterminate results again. One case study is discussed in which one employee had a positive TST after years of negative

testing and was referred for treatment. The authors state she was tested with both methods but do not report if the QFT®-G was positive. There were 3 people who had a past +TST but negative QFT®-G result. The authors state that this may have been due to improper readings, or thimerosal reactions. The authors conclude that the QFT®-G is acceptable and provides operational improvements. The authors report that phlebotomy was acceptable to the patients. At this facility the QFT®-G costs \$62.60 and the TST is \$9.79 but report that patient time requirements could make the QFT®-G cost effective. The authors report that the cost of one false-positive TST would be \$445 to \$1,195 for chest X-ray, office visits, lab monitoring, and medications. In this organization implementation of the QFT®-G was successfully implemented for specific groups (Veesser et al., 2007).

The study by Veesser et al. (2007) is a level V program evaluation rate B good quality. This study had clear recommendations and clearly described the program. However, there was no attempt to complete statistical analyses of the results. The sample lacked randomization, and there was not control for extraneous variables. The conclusions regarding the past positive TST but negative QFT®-G is presumptive and not objective. The conclusions regarding acceptability of phlebotomy is not verified by any objective information that is provided in the article. Logistical improvements were discussed but this conclusion would have been improved by tracking objective data. This study could be strengthened by including statistical analysis and further measures of logistical improvement and acceptability surveys for the patients.

Slater, Welland, Pai, Parsonnet and Banaei (2013) conducted a retrospective study to examine the reproducibility of QFT® in healthcare workers at Stanford University Medical Center (SUMC). SUMC has 10,000 employees and averages 14 cases of TB per

year between 2006 and 2011. The TST conversion rate in 2006 was 0.4%. SUMC screens employees for TB annually and in 2006 began using the QFT®-G for screening and changed to QFT®-GIT in 2008. SUMC clinic screened all employees with QFT® regardless of previous history of LTBI or positive results. Anyone who had a conversion was retested in 6 weeks. The study period was from June 1, 2008 through July 31, 2010 and the sample size was 9,153 healthcare workers who had at least 2 QFT®s. Data was obtained from lab databases and no information was obtained regarding previous test results or risk factors. Statistical analysis included independent group t test for comparison of variables, z for proportions, linear regression, and kappa statistic performed using Stata. The results showed that when those with initial positive QFT®s (1,223) were retested 67.5% (n=828) remained positive. When employees who had negative initial QFT®s (8,277) were retested, 4.4% (361) converted to positive. There was a statistically significant ( $p < .001$ ) increase in conversions and reversions in groups that had results between 0.35 and 1.0 IU/ml compared to those who were persistently positive. Three hundred and sixty-one healthcare workers that converted to positive and retested 262 (72.3%) retested within 60 days and reverted to negative, and 38 people tested negative after 60 days, while 11.1% (40) failed to retest. Twelve out of 16 Healthcare workers who received a second repeat test reverted to negative. If the cutoff for positive results was changed to 1.0 IU/ml, 67% of discordant results would be eliminated, however 33.7% of the persistent positive results would have been missed. In order to obtain the same 0.4% conversion result as with the TST, the cutoff for QFT® would have to be 5.3. The authors conclude that QFT® cutoff values result in increased conversion rates and conversions suggest false-positive results (Slater et al., 2013).

The article by Slater et al. (2013) is a level V organizational experience, quality good study. The authors discuss the limitations of a lack of gold standard, the lack of information regarding TB risk factors for this study, and intervals between retests were not standardized. The authors also mention the limitation of possible changes in lab practices over the years (Slater et al., 2013). This study did include a large sample size which improves validity. There was some attrition bias as 11.1% of positive testers did not follow up for repeat testing. There was no randomization for this study. The authors did not do any comparison for the QFT®-G versus the QFT®-GIT which might have provided some helpful information. Information regarding previous BCG vaccination status and risk factors would have improved interpretation of results.

Loddenkemper, Diel, and Nienhaus (2012) wrote an expert opinion article that discuss a few studies. The authors report that the specificity of IGRAs is well established and sensitivity for diagnosis of active TB is higher than with the TST. IGRAs are useful for identifying who will benefit from preventive treatment, however research on the positive predictive value is still small. The few studies that have examined serial IGRA testing have found high reversion rates for positive IGRAs and simple negative or positive result interpretation can overestimate reversion and conversions. Some studies have suggested using a gray interpretation zone of 0.35 to 1.0 IU/ml, but that figure has not been validated. The authors conclude that positive IGRAs should be repeated for routine screening of healthcare workers. Chest x-rays are not needed if healthcare workers with positive IGRAs are asymptomatic and the IGRA reverts (Loddenkemper et al., 2012).

This article by Loddenkemper et al. (2012) is a level V Expert opinion, quality B article. The article is short but contains 13 references. It is too short to discuss all the limitations of the studies mentioned. The authors appear to be experts from German Central Committee Against TB, Department of Pulmonary Medicine Medical School and a physician from University Medical Center Hamburg-Eppendorf as well as being authors of other articles reviewed in this literature review (Loddenkemper et al., 2012). The conclusions would be more credible if the authors were able to specify frequency for when IGRA results should be repeated, but as they state, there is no validated recommendations at this time (Loddenkemper et al., 2012).

Nienhaus (2013) provides expert opinion and a short literature review regarding use of QuantiFERON®-TB Gold (QFT®) in healthcare workers. This article discusses the risk for tuberculosis in healthcare workers which is still a concern globally. Ongoing screening for TB is essential for TB control. The advantages of IGRAs include one visit, clearer interpretation, results are not affected by BCG vaccination, and objective results. The authors report that studies show that IGRAs have superior specificity in comparison to TST in low incidence countries with QFT® offering the highest specificity of 99.2%. Utilization of QFT®s would reduce the number of chest x-rays by 25 to 98% as shown in a head to head comparison (Nienhaus, 2013). The author reports that QFT® can predict the development of active TB better than TST and reduce the number of patients needing chemotherapy. QFT® results should not be compared to TST or Elispot due to different cutoff levels and methods as well as the TST has non-return rates and Elispot invalid results are usually not published. The author reports that studies have shown IGRAs to improve cost-effectiveness. The article reviews the criteria for interpreting negative and

positive with a flowchart. If TB Antigen Minus Nil is  $\geq 0.35$  IU/ml and that result is  $\geq 25\%$  of the Nil value and the Nil is  $\leq 8.0$  IU/ml, then the result is positive. Healthcare workers are usually more accepting of taking medications for positive IGRA results versus TST results. The author discusses that studies show that healthcare workers do have a higher rate of reversion from positive to negative IGRA results, and therefore, should have retesting if positive and TB is not suspected. Some studies have suggested a borderline retesting zone of 0.35 to 1.0 IU/ml but the FDA has not approved a change in cut off (Nienhaus, 2013).

The article by Nienhaus (2013) is level V expert opinion/literature review quality B good. Recommendations and review are clear and concise. This article is published by QIAGEN® which is a limitation that could introduce bias. The number of references is large at 63. The number of articles discussed in depth is smaller at 10. The article does not review limitations of articles but the main purpose of the article is expert opinion. Expert opinion is evidence since the author is a Professor and occupational physician in Germany and has written several other studies on QFT® testing. Overall, this article is useful for providing guidance for QFT® testing in employees.

Graban and Filby (2015) discussed a case study of a 'lean' process applied to a healthcare facility's evaluation for utilizing the QuantiFERON®-TB Gold test for tuberculosis screening of new hires. 'Lean' processes aim to improve work flows, reduce delays and other barriers to completion of work. The health system has 5,000 employees and hires about 1,000 new employees annually with an employee turnover rate of 15-20%. The system currently uses a 2 step TST process for new hire screening requiring four different visits for each new hire. According to data, new hires do not follow up for

TST readings which delays onboarding. This further contributes to the need for temporary staffing or locum tenens and additional recruitment efforts to fill employee vacancies. The organization has a goal of completing onboarding within 30 days and the 2 step process can delay this. The one step QFT® can reduce ‘waste of transportation’ in ‘lean’ terminology which means it reduces the number of visits improving efficiency. If the QFT® has a false positive rate that is less than TST then there may be a reduction in ‘waste of defects’. QFT® results are reported within 1-3 days which can reduce tuberculosis clearance by 7-9 days. Reduction in Chest X-rays and medications for false-positive can also reduce waste. More objective results reduce waste. Reduction in ‘over-processing’ and ‘talent’ occurs when staff do not have to spend time following up on new hires who don’t return for TST readings. QFT®s may reduce costs by reducing, and therefore, reduce temporary staffing or locum tenens needs. The authors conclude that QFT® testing of new hires for screening can reduce waste (Graban & Filby, 2015).

The article by Graban and Filby (2015) is a Good B quality level V case report. This article reviews how ‘lean’ business principles can be applied to QFT® for new hires, but does not report any actual statistical results. This would add value and validity to this article. This article was published by QUIAGEN which could result in bias. There were only 6 references for this article which is small limiting validity. This article has good generalizability with principles that can be applied to many different healthcare facilities.

## **Synthesis of Literature**

### **Tuberculosis screening process.**

Studies suggest that organizations should conduct a needs assessment prior to selection and implementation of IGRAs (Gonzalez & Conlon, 2013; Graban & Filby, 2015). The first step in the needs assessment is to make sure that the tuberculosis screening method meets regulatory requirements. The Federal Drug Administration (FDA) and the CDC has approved IGRA's for screening of workers who may have occupational exposure to tuberculosis (Jensen et al., 2006; Mazurek et al., 2010). Studies show that organizations should choose the appropriate test based on availability, costs, logistics, population TB risk, BCG Vaccine status, staffing, and organization resources (Gonzalez & Conlon, 2013; Graban & Filby, 2015; Lamberti et al., 2015; Mazurek et al., 2010; Rangaka et al., 2012). Healthcare employee health offices should examine current processes and any impact the change would make to the organization. After impact to the organization has been identified, the organization can then individualize the test selection and process plan (Gonzalez & Conlon, 2013).

Logistics and adherence of utilizing IGRAs in place of TB skin tests should be considered (Foster-Chang et al., 2014; Gonzalez & Conlon, 2013; Graban & Filby, 2015; Mazurek et al., 2010; Rangaka et al., 2012). IGRAs do have the advantage of one single visit rather than 4 visits for two step TB skin tests. Studies report that IGRAs improve compliance and expedite completion of tuberculosis screening (Cummings et al., 2009; Foster-Chang et al., 2014; Graban & Filby, 2015; Mazurek et al., 2010). Lean processes applied to analyzing logistical processes for tuberculosis screening and can help with



improving flow, work time, and efficiency. The required four visits for tuberculosis screening is inconvenient to new hires and can result in noncompliance and hiring delays. Hiring delays can result in further understaffing which can lead to stress and increased turnover and costs due to temporary agency staffing. One study showed that onboarding of associates in an organization with 5,000 employees with a 15-20% turnover rate rarely resulted in meeting the onboarding goal of completion in less than 30 days. The QFT® presents a possible contributing solution for reduction in onboarding time since results can be received within 1-3 days and the candidate can be cleared 7-9 days sooner than with the 2 step TST (Grabau & Filby, 2015). Studies have shown that use of IGRA's can indeed increase compliance, reduce tuberculosis screening time and improve compliance (Foster-Chang et al., 2014; Veerer et al., 2007; Wrighton-Smith et al., 2012). Veerer, Smith, and Martin (2007), successfully implemented QFT®-TB Gold tests for students and employees of a health science college and saw improved completion rates. Likewise, Wrighton-Smith et al. (2012) conducted parallel testing of healthcare workers at a large healthcare system and reports that only 0.4% of IGRA test results were unavailable in comparison to the typical rates of noncompliance with TST follow up to be 20%. This shows an improvement in tuberculosis screening compliance from 80% to 99.6% with utilization of IGRAs (Wrighton-Smith et al., 2012). Foster-Chang et al. (2014), revealed successful implementation of the T-SPOT®.TB for all new hire hospital workers. This study showed that use of the T-SPOT®.TB for new employees improved overall employee health clearance to work time from 13.18 to 5.91 days showing a reduction of 7.27 days. Compliance with completion of the pre-placement process within 14 days also increased from 77% to 97% (Foster-Chang et al., 2014). This demonstrates that

implementation of an IGRA for new hires can significantly reducing overall onboarding time and improve compliance. It would be expected that the QFT®-GIT should yield similar results with increased compliance and reduced onboarding time. However, if QFT®-GIT is selected, the facility must have resources and staff to draw the blood, and incubate or send the specimens to a lab for incubation within 16 hours (Banaei et al., 2016; Gonzalez & Conlon, 2013). The T-SPOT®.TB has similar process issues such as need to process fresh blood within 5 hours (Gonzalez & Conlon, 2013; Mazurek et al., 2010). If procedural difficulties are overcome, IGRA results are quicker and not subject to reader bias which can improve efficiency in the employee health department (Grabán & Filby, 2015; Mazurek et al., 2010)

Of high importance is that studies found use of IGRAs was found to be acceptable by patients (Foster-Chang et al., 2014; Veaser et al., 2007; Wrighton-Smith et al., 2012). One study administered a questionnaire to healthcare workers who were enrolled in a study with parallel TST and IGRA testing. This study revealed that 62.3% of participants preferred the IGRA and had better confidence in IGRA results (Wrighton-Smith et al., 2012). One visit is more convenient than 2 or 4 visits for employees. Improved employee satisfaction with use of IGRAs can lead to reduced turnover, improved compliance, faster onboarding, and provide logistical benefits to employee health offices (Grabán & Filby, 2015).

### **Cost.**

Cost-effectiveness of using an IGRA versus TST was evaluated in several studies and found to be cost-effective (dePerio et al., 2009; Grabán & Filby, 2015; Mazurek et

al., 2010; Nienhaus, 2013; Nienhaus et al., 2011; Wrighton-Smith et al., 2012) The IGRA costs more than the TST on the surface, but savings can be found in staff time, less missed work time, less treatment of false positive results, and reduced turnover (Foster-Chang et al., 2014; Graban & Filby, 2015). In a high quality financial evaluation utilizing a Markov state-transition decision analytic model, QFT®-TB Gold and QFT®-GIT were both found to be less costly and more effective than TSTs for healthcare workers regardless of BCG vaccination status. This study measured direct and indirect costs including quality-adjusted life-years (QALYs) which considers missed work time into costs and analysis revealed reduced costs (dePerio et al., 2009). Foster-Chang et al. (2014) conducted a quality improvement study in which new hires had IGRAs. When salaries, supplies, staff time, failure to return for TST, and monitoring of positive results were considered in cost analysis, there was a reduction in costs of 38% to 40% in comparison to the TST. Costs were reduced from \$7,852.70 for 100 new employee TSTs in 2011 to \$4,699.50 for 100 new employees with IGRA (Foster-Chang et al., 2014). Veerer et al. (2007) found similar results when QFT®-G was implemented for health science students and employees which revealed reduction in costs related to less false positive results and follow up. They estimated that the cost of one single false-positive TST to be \$445 to \$1,195 for chest x-rays, medications, and follow up (Veerer et al., 2007).

The SWITCH study was conducted at John Hopkins Healthcare system employee health which screens 18,000 employees annually with the purpose of determining the price at which IGRA becomes less costly than TST. This study analyzed material and labor costs, conducted a time-motion study of 393 patients and assessed labor costs, and

thirdly 743 health care workers had TST and IGRA parallel testing. Material costs, employee health labor costs, employee labor costs, employee health staff time, and employee time off work were considered. When considering all these factors, switching to IGRA for annual as well as new hires there would be savings if the IGRA costs \$54.83 or less per test. When considering only new hires, switching to IGRA would result in savings if the IGRA costs \$81.16 or less per test (Wrighton-Smith et al., 2012).

Nienhaus, et al. (2011) conducted a systematic review of 13 studies and found that TST's were the most expensive method for tuberculosis screening while utilization of IGRAs decreased costs in all scenarios. Only two of the studies reviewed examined T-SPOT®.TB while the other studies examined QFT®-TB gold or QFT®-GIT. Four of seven of these studies this review examined revealed that IGRA after positive TST was the least expensive. The authors concluded that there was strong evidence that IGRAs including QFT® or T-SPOT®.TB are cost effective in high risk groups including healthcare workers, high incidence country immigrants and close contact with tuberculosis (Nienhaus et al., 2011). Literature review by Nienhaus (2013) also revealed that studies that considered that TST sensitivity is well below 100% for countries with low incidence of TB, found that IGRA alone will improve cost-effectiveness. The evidence shows that screening with IGRA can be cost-effective if cost of the test is controlled and staff time, labor costs and adherence are considered (dePerio et al., 2009; Nienhaus, 2013; Nienhaus et al., 2011; Wrighton-Smith et al., 2012).

## **Accuracy.**

Several studies examined the sensitivity and specificity of IGRAs as well as agreement between TSTs and IGRAs with varied results. Sensitivity assessments attempt to determine whether positive tests results are truly positive. Assessment of sensitivity of IGRAs is complicated by the fact that there is no “gold standard” test to confirm culture negative latent tuberculosis infection (LTBI). IGRAs are indirect tests that measure immunologic response rather than testing for the organism. Published reports vary in test methods and interpretation criteria further confounding interpretation analysis of the literature (Mazurek et al., 2010). Some of systematic reviews and single studies that were reviewed found that agreement between TST and IGRA to be low in regards to sensitivity with predominance of positive TST compared to negative IGRA (Cummings et al., 2009; Dorman et al., 2014; Lamberti et al., 2015; Swindells et al., 2009). However, positive TST can likely be the result of false-positives from BCG vaccination status, immune factors, boosting or poor reader interpretation (Dorman et al., 2014; Lamberti et al., 2015; Rangaka et al., 2012; Swindells et al., 2009). Pai et al. (2008) conducted a meta- analysis of 20 studies and reports inconsistent results of sensitivity for IGRAs, but does report 70% sensitivity for QFT®-GIT. The authors do admit that the studies analyzed were small and had varying TST methods and cutoffs (Pai et al., 2008). However, Mazurek et al. (2010) report that when studies consider sensitivity of the QFT®-GIT in patients with active tuberculosis, the combined data show QFT®-GIT combined sensitivity of 81% in comparison to 70% for studies that use meta-analysis. Furthermore, analysis shows that when QFT®-GIT is compared to TST in culture positive patients, QFT®-GIT sensitivity is 83% while TST is 89% (Mazurek et al., 2010).

Assessment of specificity (likelihood that a true negative test result is negative) of IGRAs shows more consistency in results. Specificity of IGRAs appears to be high (Cummings et al., 2009; Mazurek et al., 2010; Nienhaus, 2013). This high specificity is to be expected since IGRAs and QFT®-GITs in particular do not react with BCG vaccination or other nontuberculous mycobacteria (Mazurek et al., 2010). Cummings et al. (2009) conducted a study comparing QFT®-GIT in low risk healthcare workers with tuberculin skin tests and found high agreement and specificity. Two QFT®-GITs were offered to newly hire healthcare workers who were having TSTs. Specificity of the QFT®-GIT was 98% for healthcare workers without risk factors (Cummings et al., 2009). One systematic review found that QFT® have 99% specificity in patients not BCG vaccinated and 96% in BCG vaccinated (Pai et al., 2008). Nienhaus (2013) reports that a review of the literature supports that QFT®s have superior specificity in comparison to TSTs especially in countries with low TB incidence. In particular, results of pooled studies show QFT®-GIT show specificity of 99% while TST was 85% (Mazurek et al., 2010). This shows a higher rate of specificity for QFT®-GIT than TST supporting its use in low risk areas.

Risk factors, BCG vaccination status and exposure risk should be considered when choosing testing methods. Several studies agree that IGRAs are the test of choice for individuals vaccinated with BCG (Foster-Chang et al., 2014; Jensen et al., 2006; Lamberti et al., 2015; Mazurek et al., 2010; Rangaka et al., 2012; Wrighton-Smith et al., 2012). The CDC reports that IGRA is the preferred method for tuberculosis screening for individuals who have received the BCG vaccine and for those who are unlikely to return for follow up (Jensen et al., 2006; Mazurek et al., 2010). IGRAs have been correlated

with exposure risk including length of employment in healthcare, age, foreign born, and exposure level (Diel et al., 2009; Nienhaus, 2013; Swindells et al., 2009; Zwerling et al., 2012). In one quasi-experimental study, close contacts of tuberculosis culture confirmed sources were tested with IGRAs and found that IGRAs were a better indicator of latent tuberculosis in relation to exposure risk in comparison to TST (Diel et al., 2009).

Mazurek et al. (2010) had similar findings when reviewing the literature and found that positive IGRA results were more closely associated with greater recent exposure measured by exposure duration. Therefore, IGRAs should be chosen over TST in situations when the individual is BCG vaccinated or has high risk of exposure.

#### **Conversions, reversions and result cutoffs.**

Several studies examined conversion (change from negative to positive) and reversion (change from positive to negative) rates and discussed possible need for change in IGRA cutoffs (Banaei et al., 2016; Cummings et al., 2009; Dorman et al., 2014; Loddenkemper et al., 2012; Schablon et al., 2014; Slater et al., 2013; Weddle et al., 2014; Zwerling et al., 2012). This evidence will be important to consider when designing processes for interpretation and implementation of QFT®-GITs. Weddle et al. (2014) conducted repeat QFT®-GITs in healthcare employees who had positive QFT®-GITs. Of the 34 QFT®-GIT positive employees who had repeat testing 64.7% had positive repeat tests and 35.3% had negative on repeat tests. The mean result of the repeat positive testers was 1.19 while the mean repeat negative test results was 0.61. This article suggests that healthcare workers with QFT®-GIT results of 0.35 to 1 IU/ml should have repeat testing to avoid false-positives (Weddle et al., 2014). Zwerling et al. (2012) also examined four studies that addressed conversion and reversion rates in healthcare

workers in low incidence settings. Rates of conversions and reversion in IGRA results upon repeat varied in results due to different cutoff definitions. The studies had higher rates of conversions and reversions if a simply positive or negative cutoff was used (Zwerling et al., 2012). Slater et al. (2013) conducted a retrospective evaluation of QFT®-GIT results for 9,153 healthcare workers in relation to conversions and reversions. Three hundred sixty-one (4.4%) of healthcare workers with baseline negative QFT®-GIT converted to positive over 2 years. Of 261 healthcare workers with positive QFT®-GITs, 169 (64.8%) reverted back to negative when retested within 60 days. This article states that a result cutoff of 5.3 IU/ml would result in a conversion rate of 0.4% similar to the institutions tradition rate of conversion (Slater et al., 2013). Dorman et al. (2014) found similar results when healthcare workers with QFT®-GIT test conversions were retested 6 months later, 76.4% reverted to negative. Schlabon et al. (2014) showed a small conversion rate of 2.8% and reversion of 37.3% when healthcare workers were screened with QFT®-GIT. This study found that an interferon cutoff result of <0.2 to >0.7 IU/ml would decrease the conversion to 1.2% (Schablon et al., 2014). Similarly, Cummings et al. (2009) found that of 5 positive QFT®-GITs, only 2 were confirmed on repeat testing. Loddenkemper et al. (2012) also reports that a cutoff for QFT®-GIT results may be warranted. The author suggests a gray zone of 0.35 to 1.0 IU/ml and states that treatment medications should not be given for IGRA results of  $\leq 0.1$  IU/ml (Loddenkemper et al., 2012). CDC recommendations agree that repeat IGRA testing with another blood sample may be useful if the result is borderline or invalid. However, ultimately treatment should be based on likelihood of infections, risk factors and symptoms (Mazurek et al., 2010).



Indeterminate results should also be considered when choosing IGRAs. Cummings et al. (2009) repeated ELISAs on the same blood sample for indeterminate testers. Of 16 indeterminate results due to low mitogen response, 11 (69%) remained indeterminate and 5 (31%) converted to negative. Healthcare workers with diabetes or immunosuppression had a greater odds ratio (6.8) of having a confirmed indeterminate result. It is also important to note that there was found to be statistically significant higher IFN- $\gamma$  concentrations in QFT®-GIT results when healthcare workers had 1 intervening TST regardless of the time between tests (Cummings et al., 2009).

There are some sources of variability in lab procedures that can contribute to false-positive QFT®-GITs that should be considered when making recommendations. Sources of variability include time of day the blood is drawn, inadequate disinfection/contamination of tubes, vigorous shaking, blood volume, processing delays, and incubation issues. It is possible that contamination with bacteria can lead to higher IFN- $\gamma$  concentration. Vigorous shaking of the tubes may also lead to false positive or negative results. The blood should be collected in the proper order, nil, antigen, and then mitogen as tube contamination may be a factor in results. Incubation delays could potentially decrease antigen response. Processes for disinfection, tube order, and 1 ml blood fills should be standardized to eliminate variability. All 3 tubes should be gently shaken together. Processing delays should be minimized. As mentioned above TSTs can boost IGRAs and therefore IGRAs should be drawn within 72 hours of placement. Standardization can assist with variability concerns (Banaei et al., 2016).

## Discussion

Analysis of the literature revealed pros and cons to choosing the QFT®-GIT for TB skin testing for new healthcare workers. There are a number of positive logistical factors that would provide value for employee health offices while improving cost-effectiveness. Since QFT®-GITs are completed in one test, new hire onboarding and tuberculosis clearance time should be reduced. This will also reduce the burden on employee health staff time spent on tuberculosis clearance activities, and enhance convenience to the new hire (Foster-Chang et al., 2014; Graban & Filby, 2015; Veesser et al., 2007). Cost analysis revealed that IGRAs are cost effective (dePerio et al., 2009; Foster-Chang et al., 2014; Graban & Filby, 2015; Nienhaus, 2013; Nienhaus et al., 2011). The QFT®-GIT has high specificity but there are some concerns about sensitivity (Banaei et al., 2016; Cummings et al., 2009; Dorman et al., 2014; Loddenkemper et al., 2012; Schablon et al., 2014; Slater et al., 2013; Weddle et al., 2014; Zwerling et al., 2012). However, sensitivity of the QFT®-GIT improves with consideration of patients with active tuberculosis (Mazurek et al., 2010). Some studies have shown that there can be issues with conversions and reversion and a borderline cutoff with retesting may be appropriate (Dorman et al., 2014; Loddenkemper et al., 2012; Mazurek et al., 2010; Schablon et al., 2014; Slater et al., 2013; Weddle et al., 2014; Zwerling et al., 2012). When interpreting results, the immunologic status of the patient should also be considered with indeterminate results (Cummings et al., 2009). Standardization of lab procedures can help overcome some of the variability in results (Banaei et al., 2016). Overall, there is good evidence to implement QFT®-GITs in new hire healthcare workers while considering all the interpretation factors.

## **CHAPTER 3**

### **PROJECT DESIGN AND PLAN**

#### **Introduction**

Employee Health was faced with the dilemma of increasing volume of new hires coming for pre-placement assessment appointments and increasing frustration by management regarding delays in orientation. Employee Health management formed a new hire committee in Fall of 2015 to investigate the factors involved with delays in orientation. One factor identified that contributed to orientation delays was the amount of time it takes for new employees to complete the two-step TST. The literature was reviewed and multiple steps were taken to investigate the ability for Employee Health to offer an IGRA for all new hires in order to reduce the amount of time it takes to be cleared for orientation. In February of 2016, Employee Health implemented the QFT®-GIT in place of the two-step TST for tuberculosis screening of all new hire employees. This project evaluated the success of this implementation by retrospective review of the data to compare the two methods of tuberculosis screening in regards to tuberculosis clearance time, overall onboarding time, compliance, and costs. The study utilized a descriptive comparative non-research design Data collection for this project was designed to protect the privacy of the subjects and was guided by a comprehensive framework.

## **Conceptual Framework**

### **Triggers**

*The Iowa Model of Evidence-Based Practice to Promote Quality Care (Iowa Model)* was utilized to guide implementation of the project. This model begins with identification of “triggers” that are problem or knowledge focused. These triggers occur when the clinician questions current practices. Problem focused triggers in the Iowa Model include process improvement data (Melnik & Fineout-Overholt, 2015). The initial process improvement problem that triggered this project was the initial question of whether processes for onboarding new hires could be more efficient. The demand for new hire appointments exceeded the available appointments in Employee Health, which led to delays in orientation dates. Knowledge focused triggers in the Iowa Model includes new research and standards. IGRAs are relatively new and represent a potentially new standard of care. Along with new standard of care, new research has been generated to assess utilization of the tests.

### **Priority.**

The Iowa Model has been utilized for clinical and operational programs (Melnik & Fineout-Overholt, 2015). After the triggers for change are identified, the question is formulated. The next step is to ask whether this is a priority for the organization (Melnik & Fineout-Overholt, 2015). The need to reevaluate onboarding practices was instigated by upper management which resulted in this project. The Vice-President of Human Resources asked this author to make this a priority for the department. According to the Iowa Model, if the change is a priority for the organization, then a team should be formed to develop and implement the change including stakeholders (Melnik & Fineout-

Overholt, 2015). A new hire committee was formed including managers who had expressed concern about onboarding delay, recruitment staff and management, education management, operations director and information services. Problems were discussed and ideas were shared for improvement in the overall onboarding process. This author listened to the ideas and implemented some of them and discussed why we could not implement others. This author knew about the QuantiFERON® lab test but also knew that implementation had been rejected in the past due to the high cost.

### **Research and Implementation.**

The next steps in the Iowa Model include research and analysis of the literature. After the team agreed that utilization of the QuantiFERON® may be a good idea, this author began to review the literature. The next step in the Iowa Model includes asking whether the literature show a sufficient base for the change (Melnyk & Fineout-Overholt, 2015). If the answer is yes, then the change should be piloted. Outcomes will be chosen, baseline data collected, change pilot implemented and outcomes evaluated. If the pilot reveals that the change is appropriate for practice, then the change should be instituted in practice. The structure, process and outcome data should be monitored. Last, results should be disseminated (Melnyk & Fineout-Overholt, 2015). The literature review did reveal that there was sufficient base for change in tuberculosis screening processes. Preliminary baseline data of implementation of the IGRA indicated that the new processes was increasing available appointments and appeared to be reducing onboarding time. This study represents a full analysis of outcomes for the IGRA implementation.

## **Project Design**

The design of this project will be evidence-based a descriptive comparative level III non-experimental design. Four outcomes will be measured (1) tuberculosis screening time for new hires, (2) overall onboarding time, (3) compliance with tuberculosis screening within 10 days of hire date, and (4) cost-effectiveness comparing the traditional two-step PPD tuberculosis screening versus screening with QFT®-GIT.

## **Justification for Need**

At the organization level, Employee Health was asked by senior management to improve time efficiency for TB clearance in order to onboard a larger volume new hires more efficiently. At the department level, Employee Health was unable to accommodate the volume of appointments needed to process the increased volume of new hires. Furthermore, Employee Health was having difficulty getting some new hires to return for appointments to complete the 2-step PPD skin test. This resulted in delays in orientation and could have led to DHEC and other regulatory agency citations or penalties. The 2-step tuberculin skin test requires 4 visits which was inconvenient to the new hire employee and filled available appointments in Employee Health. Department Managers seeking to hire potential applicants expressed frustration with delays in orientation for their new hires which left the departments short staffed. Thus, management requested measures to improve efficiency, new hire satisfaction, and reduce costs. Investigation of changes included use of interferon gamma release assays and was a priority for the organization. At a larger level, there is minimal research and data regarding implementation of interferon gamma release assays for new employees.

## **Feasibility**

### **Stakeholder support.**

Feasibility for implementation includes examination of stakeholder support (Melnyk & Fineout-Overholt, 2015). Leadership and stakeholder support is essential to success of the study. This project for implementation of QFT®-GIT and for the subsequent retrospective data analyses was supported by the Vice President of Human Resources, Recruitment Director, Director of Operations, and managers part of the new hire committee. Approval was obtained in January of 2016 for implementation of QFT®-GIT beginning February 2016 for all new hires. Continued support was critical to ongoing success of the project and for continued implementation beyond the study. The Vice President of Human Resources is currently in favor in continuing with the QFT®-GITs due to preliminary findings of a reduction in Employee Health clearance time. Initially, nursing staff were concerned about procedural and process difficulties with having only one pre-placement visit. A meeting was convened with the nursing staff to talk through and agree upon processes. One area that was resolved was how to provide follow up on all lab results since the new employee would not follow up with a second visit in Employee Health. It was determined that staff would mail the lab results to the employee's home and call the employee for any significantly abnormal results per a revised protocol. Approval from risk management was obtained prior to mailing the lab results. Employee Health staff were educated regarding the benefits of testing and how to draw the blood. Initially staff were hesitant to accept the change, but after several months, staff members realized the benefits of the process for the new employees and for themselves. They discovered that they had to spend less time trying to complete

tuberculosis testing and less time trying to obtain compliance with testing. Employee health staff now support QFT®-GITs for new employees. Meetings were initially convened monthly with the new hire committee and Employee Health staff in order to review progress and to maintain support. The Employee Health manager continued ongoing conversations with the microbiology lab manager to continue to problem solve and maintain support. Preliminary non-statistical data regarding increased volume in new hire visits and reduction in onboarding clearance time in Employee Health was shared with the VP of Human Resources and this author was asked to present the data at the quarterly leadership meeting.

#### **Sample size and accessibility.**

Access to an adequate sample size enhances feasibility (Melnyk & Fineout-Overholt, 2015). Adequate sample size was easily obtained since the data was collected retrospectively and all new hires were required to complete tuberculosis screening for employment. There were approximately 100-125 new hires per month in 2015 and 150-180 in 2016.

#### **Financial resources.**

Financial resources for implementation of the QFT®-GIT and for this DNP project was examined. While a TST only costs \$4, factoring in staff time and supplies for four visits would cost approximately \$87. The QFT®-GIT is an expensive test, however this author was able to negotiate a reduced price from its original price of \$85 to \$53 which enhanced feasibility. This was not in the budget to implement but senior management believed that the extra expense would be offset by the benefits of reducing



onboarding time. Although difficult to directly measure, implementation ultimately contributed to cost savings in the form of reduced employee health staff time, reduced onboarding time and subsequent reduction in locum tenens staffing. If the current high turnover rate slows or upper management cuts budget for the lab tests, then a more thorough cost benefit analysis will need to be conducted to continue with QFT®-GIT testing. There were no direct costs for the retrospect data collection and analyses other than time for this author and the secondary researcher to collect the data.

### **Time and expertise.**

Data collection for this DNP project was time consuming. One Employee Health staff member was enlisted to assist with collection of the data ensuring no breaches in HIPPA or IRB protocols. This secondary researcher completed all training requirements from the IRB and was added to the project committee. Utilization of QuantiFERON® is a new process for the author and for the organization, but knowledge barriers were overcome through the literature review, and utilization of resources such as consultation with DHEC experts and microbiology staff.

### **Legal and Ethical Implications.**

CDC and DHEC regulations in regards to tuberculosis screening were monitored and it was determined that QFT®-GITs were acceptable for tuberculosis screening of healthcare workers. There was little risk to the subjects since the data was collected retrospectively for the project. Measures were taken to ensure confidentiality by removing all identifiers from the data.

## **Summary**

Stakeholder support, sample access and size, financial, legal and ethical resources were substantial. An adequate sample size was easily obtained through the retrospective chart review. Benefits of QFT®-GIT and dissemination of results of the project will be provided to stakeholders including senior management, the healthcare system's research council members, and Employee Health. Presentations to senior management was provided. Limitations such as time, knowledge barriers, and budget concerns were overcome. Since findings will be important to the organization, Literature, DHEC staff, and laboratory management was consulted for any knowledge gaps.

## **Intervention Plan**

### **Design.**

The design of this project was evidence-based quality improvement project that is descriptive comparative level III non-experimental. Data was collected retrospectively. Tuberculosis screening time for new hires, overall onboarding time, compliance with screening within 10 days of hire date, onboarding time, and costs was compared between the traditional two-step PPD tuberculosis screening versus screening with QFT®-GIT.

### **Sample.**

The sample included a convenience sample of all new hire employees that are completed pre-placement assessment at the healthcare system Employee Health in April and May 2015 and 2016.

## **Setting.**

The healthcare system consisted of 3 acute care hospitals, a post-acute facility, hospice house, home health, multiple outpatient offices, and other healthcare services. The healthcare system Employee Health serves over 6,800 employees in addition to volunteers, staff providers, and contract workers. The healthcare system is state supported and is designated as a health professional service area and critical shortage facility. Employee Health staff performed pre-placement assessments including tuberculosis screening for all newly hired employees in the Employee Health department post offer but prior to orientation up until February 2016, when implementation of QFT®-GIT.

## **Timeline**

- September 2015:
  - Formed new hire committee to review new hire processes and garner support from key stakeholders including: recruitment staff, education staff, key managers, employee relations manager and staff, outpatient office directors, employee health staff, and Information Services staff.
- October through December 2015
  - Reviewed current processes and data regarding onboarding time and rate of new hire appointments.
  - Reviewed regulations for interferon gamma release assays
  - Compared literature regarding available types of assays

- Reviewed lab procedures and recommendations with healthcare system lab managers
- Began literature review
  
- January 2016
  - Negotiated price and procedures with external lab
  - Obtained permission from VP to proceed with testing
  - Reviewed process and procedures with Employee Health staff
  - Updated policies in Employee Health
  - Ordered lab supplies-QFT kits
  - Reviewed staffing needs and incubation procedures with lab
  - Completed competencies for Employee Health staff completed
  - Ongoing literature review
  
- February 2016
  - Began QFT®-GIT for all new hires
  - Conducted ongoing literature review
  - Developed tracking methods for new hire log
  
- March 2016
  - Contacted DHEC for recommendations and update policies to retest in borderline result range
  
- March-May 2016
  - Testing continued for new employees
  - Completed CITI training

- Summer 2016
  - Planned project
- September 2016
  - Presented poster of literature review at conference
- Fall 2016
  - Reviewed healthcare system's requirements for nursing research council
  - Reviewed IRB requirements for healthcare system and University of South Carolina
  - Reviewed new hire volumes and onboarding times
  - Completed Healthcare system CITI requirements
- January 2017
  - Completed DNP project proposal defense
  - Presented DNP project to Nursing Research Council and obtained scientific reviews and approval
  - Submit IRB application to University of South Carolina and obtained approval
  - Received approval from healthcare system IRB.
- February 2017
  - Completed Retrospective data collection
  - Completed data analyses
- March 2017
  - Defend dissertation University of South Carolina
- April 2017

- Final edits and submission to graduate school
- Submission of manuscript to Association of Occupational Health Professionals Journal
- September 2017
  - Potential Conference presentation

### **Resources.**

Retrospective data was compiled in excel spreadsheets in a password protected s-drive folder that is only accessible by the primary and secondary investigators. Information was obtained from the paper new hire logs and Agility electronic medical record. No further technology assistance was required. The QFT®-GIT cost was accepted mid-budget year with VP understanding that lab cost budget would exceed budget in fiscal year 2016.

### **Evaluation Plan**

#### **Questions/Outcomes/Evidence-based measures**

Q1. Did implementation of QFT®-GIT reduce the number of days to complete tuberculosis screening for new hires?

- Retrospective data was collected from electronic and paper Employee Health records. This data was stored on a password protected spreadsheet and all identifiers were removed prior to submission for analyses.
- Tuberculosis screening time included the number of days to complete TST screening from the time of placement of step 1 to reading of the 2<sup>nd</sup> step. If the new hire brought documentation of step 1, then only time for

completion of step 2 was recorded. If the new hire failed to complete a step and had to be replaced, then that additional time was also included in the number of days for clearance.

- Tuberculosis screening clearance time for subjects who completed the QFT®-GIT included the date of blood draw to date the result was reviewed. If the QFT®-GIT needed to be repeated for borderline positive result, this time was included in overall screening time.
- If any test was positive, the amount of time for result of a chest x-ray was also including in tuberculosis screening time.
- Those with a previous positive TST will be included with days to clearance being 0 days since the symptom review was completed on the day of pre-placement. However, if the subject did not bring the documentation on day one, then the number of days it took to bring in the documentation was recorded.
- Data was analyzed by simple t test. Nonparametric testing and frequency was completed to analyze and describe demographic variables.
- The time for completion of DHEC evaluation for positive testers was not included in screening time.

Q2. Did implementation of QFT®-GIT for new hires reduce the overall number of days to complete onboarding?

- Time for onboarding include days from first appointment to completion of all requirements including tuberculosis screening, assessments, fit for duties, lab results, and review of any requested records. Completion of

immunizations and Hepatitis B waivers were not included because those are not completed until after orientation.

- Data was analyzed by t test, and spearman correlation.

Q3. Did implementation of QFT®-GIT improve compliance with completion of tuberculosis screening within 10 days of orientation?

- Compliance included completion of both steps of the 2 step PPD tuberculin skin test within 10 days of orientation or completion of QFT®-GIT results along with any required repeat results, symptom reviews, or chest x-rays.
- The data was analyzed by chi-square testing.

Q4. Was implementation of QFT®-GIT be cost-effective?

- A simple review of associated costs with QFT versus PPD including staff time was reviewed. Actual average salary of employees in Employee Health in relation to the time it takes to complete testing and assessment requirements, phone calls to contact non-compliant employees, and call employees with results of lab testing will was considered. Cost of supplies will include the cost for the PPD derivative, the syringe/needle, and cost of lab charges for QFT®-GIT. Labor costs from missed work for the new hire will not be considered since the new hire is not yet working for the organization and current salary cannot be determined.
- Data was collected regarding average staff salary and the amount of time for each step of the assessment process and was described without statistical analyses.



## **Data Collection Procedure**

Data was collected retrospectively from electronic medical record chart review, review of paper new hire logs, and by the human resources data system. Data was compiled in a password protected excel spreadsheet initially separated into months of the year. Data was collected for subjects that came to Employee Health for pre-placement assessments during the months of April and May of 2015 and 2016. In 2015, TST was the standard of care and in 2016, QFT®-GIT. Data collected in the spreadsheet included: pre-placement date, hire date, gender, race, age at hire, job titles, dates for placement or reading of TSTs, dates for QFT®-GIT results, dates for Chest X-ray results, dates for completion of screening and overall onboarding, and whether the employee brought documentation of previous positive or negative TST or IGRA results. The number of days to complete each step were calculated manually and by excel spreadsheet. Anything completed on the date of first pre-placement visit was counted as zero days. Tuberculosis screening time with TST was defined as the number of days from first placement of PPD in Employee Health to reading of second PPD. If the employee brought in documentation of first step PPD within previous 12 months, only the time for the one step was recorded for tuberculosis screening time. If the new hire employee failed to return for a reading or placement, the time it takes for the employee to complete the entire screening process was included in total screening time. The definition for tuberculosis clearance time with QFT®-GIT was defined as the number of days between blood draw and result including any repeat QFT®-GIT for borderline results of 0.25 to 1.0 IU/ml. If the new hire required a chest x-ray for a positive PPD or QFT®-GIT, the time to complete x-ray and receive result as well as completion for symptom questionnaire was included. The time for the

patient to complete any DHEC appointments or treatment was not included because this is often lengthy, unpredictable and cannot be controlled by employee health. Compliance with completion of tuberculosis screening within 10 days of hire date was also recorded as yes or no, and if the new hire failed to complete at least one TST placement/reading or QFT prior to orientation was recorded.

In addition to tuberculosis screening time and compliance within screening within 10 days of hire date, dates and time for completion of other onboarding requirements was recorded. Data for overall onboarding time was recorded including dates and number of days to complete: overall tuberculosis screening, drug screens, fit for duty examinations, pre-work screens, required medical records/provider notes, and any other requirements for orientation clearance. A simple review and comparison of costs associated with TST and QFT®-GIT was conducted including Employee Health staff labor costs, lab fees, PPD fees. Data for volunteers, and for employees who did not begin work due to declination of the position, positive drug screens, failed pre-work screens or fit for duties or those who did not start for unknown reasons were removed from the final spreadsheet submitted for analyses. However, the primary investigator kept notes regarding the number of subjects excluded and the reasons.

### **Data Management and Analyses Procedures**

Once the survey data was entered into the excel spreadsheet and the identifiers removed the investigator in collaboration with the committee statistician, reviewed the data and, organized the data in the form that would be useable in SAS for analyses. Data analysis included both descriptive and inferential statistics using SAS 9.4. Frequency distribution was included for categorical variables. The continuous variable statistics

included measures of central tendency (mean and median) and measures of spread (standard deviation and range). Inferential statistics included T-test, spearman correlation, and nonparametric testing. P-values less than or equal to .05 were considered significant. A power analysis at 80% power was conducted and revealed that a sample size of 300 would be sufficient for statistical significance (see Table 3.1).

Table 3.1  
*Required sample size for Ttest analysis with 80% power,  
 Different effect size, and alpha.*

| <b>Effect Size</b>  | <b>Alpha = 0.05</b> | <b>Alpha = 0.01</b> |
|---------------------|---------------------|---------------------|
| <b>0.2 (Small)</b>  | <b>788</b>          | <b>4676</b>         |
| <b>0.3</b>          | <b>352</b>          | <b>524</b>          |
| <b>0.4</b>          | <b>200</b>          | <b>296</b>          |
| <b>0.5 (Medium)</b> | <b>128</b>          | <b>192</b>          |
| <b>0.60</b>         | <b>90</b>           | <b>134</b>          |
| <b>0.7</b>          | <b>68</b>           | <b>100</b>          |
| <b>0.8 (Large)</b>  | <b>52</b>           | <b>78</b>           |

## **Human Subjects**

The primary and secondary investigators completed CITI training for the University of South Carolina and for the healthcare system. After the committee approved the DNP proposal, the primary investigator presented the project to the healthcare system’s Nursing Research Council for approval. Two members of the committee provided scientific review of the proposal and the committee approved the study (see Appendices D). An application for exempt status was submitted to the University of South Carolina and exempt from human subjects research was obtained (see Appendices D). The Healthcare System IRB agreed to accept the IRB decision from

the University of South Carolina and approved the secondary investigator. After approval, the investigator began data collection. The primary and secondary investigators are employees of the Employee Health department and are in charge of routinely collecting data regarding onboarding times and have access to the electronic medical records. The investigators only retrieved data essential for project. The excel spreadsheet was saved in the primary investigator's access limited S-drive folder, with a password protected spreadsheet. All computers were password protected and all data on the healthcare system's computers are encrypted. The health reasons for any required fit for duties or pre-work screens, as well as substance found in the results of drug screens was not noted on the spreadsheet. Notations were made regarding any positive TST or QFT®-GIT results, required chest x-ray dates and results, symptom review dates, and DHEC referrals. However, there was no record included on the spreadsheet to identify subjects.

## **Summary**

The Iowa Model was utilized as a framework to evaluate the effectiveness of the quality project implementation and comparison of new hire tuberculosis screening with TST and QFT®-GIT (Melnyk & Fineout-Overholt, 2015). The quality improvement project arose out of a need to improve efficiency within the Employee Health department. Senior level management supported the decision to implement QFT®-GIT for new hires. IRB and the Healthcare System approved this study to assess differences in TST and QFT®-GIT methods for tuberculosis screening for new employees in regards to tuberculosis screening clearance time, overall onboarding time, compliance with screening within 10 days of hire date, and, costs. Data was collected without identifiers to

protect the health information of the subjects.

## CHAPTER 4

### FINDINGS AND CONCLUSIONS

#### Introduction

The purpose of this chapter is to present the findings and conclusions, implications for nursing practice and future evidence-based projects and dissemination activities for this quality improvement project. The purpose of this DNP project was to compare baseline testing for new healthcare employees with QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD TB skin test in regards to tuberculosis screening time, overall onboarding time, compliance with tuberculosis screening within 10 days of orientation, and costs. This quality improvement project assessed whether implementation of the QFT®-GIT in lieu of the two step TST, met the organizational goal to reduce the number of days to complete tuberculosis screening, reduce overall Employee Health onboarding clearance time, and improve compliance with completion of tuberculosis screening within 10 days of hire date, while maintaining cost-effectiveness. The findings will be presented in relation to the primary questions discussed in chapter three.

The data was collected by Agility medical record chart review and from new hire spreadsheets in Employee Health. When hire data or job title was not available in agility, data was obtained from the Human Resources Capital Management system. For statistical analyses, race was identified as white, black or other. For comparison purposes, data was

divided into two groups including the “TST group” and the “QFT group”. The 2015 sample included subjects who had tuberculosis screening with the two step tuberculin skin test as a standard of care was identified as the TST group. The 2016 sample was screening with the QFT®-GIT as the standard and was identified as the QFT group. The data was analyzed by descriptive and inferential statistics utilizing SAS 9.4. Descriptive statistical analysis included frequency procedures, measures of central tendency and spread. Inferential statistics included T-test, Pearson correlation, fisher exact test, general linear model (GLM) and chi-square. P-values of less than or equal to .05 were considered to be significant. Power analysis was conducted to determine an appropriate sample size.

## **Findings**

### **Sample.**

The initial sample included 537 subjects who had pre-placement assessments at the healthcare system’s Employee Health department in April and May of 2015 and 2016. Subjects were excluded from the study if they were volunteers (n=40), new hire subjects with positive drug screens (n=6), subjects who failed to report for employment (n=4) or failed fit for duty examination (n=1), and subjects who failed pre-work screen (n=1) or did not show for pre-work screen (n=1). The final sample included 484 new hire employees comprising 81.4% female subjects (see Table 1). The three most frequently hired age groups included ages 21, 25, and 27 years. The mean age for the sample was 35.08 (n=484) (see Table 1). There were 323 Caucasian subjects (66.73%), 112 African American (Black) (23.14%), 13 Hispanic (2.69%), 12 Asian (2.48%), and 24 other (4.96%). The most frequent job title for the sample was registered nurses (n=111),

followed by nursing support (n =62). Of the sample, 227 had TST testing and 257 had QFT Testing (Table 4.1).

Table 4.1  
*Frequency distribution for demographic variables*

| <b>Sample demographic variables</b> | <b>N</b> | <b>%</b> |
|-------------------------------------|----------|----------|
| <b>Gender</b>                       |          |          |
| Male                                | 90       | 18.60    |
| Female                              | 394      | 81.40    |
| <b>Age: Most frequently hired</b>   |          |          |
| 25 yrs.                             | 24       | 4.96     |
| 27 yrs.                             | 24       | 4.96     |
| 21 yrs.                             | 23       | 4.75     |
| Other                               | 413      | 85.33    |
| <b>Race</b>                         |          |          |
| White                               | 323      | 66.73    |
| Black                               | 112      | 23.14    |
| Hispanic                            | 13       | 2.69     |
| Asian                               | 12       | 2.48     |
| Other                               | 24       | 4.96     |
| <b>Job</b>                          |          |          |
| RN                                  | 111      | 23.03    |
| Nursing Support                     | 62       | 12.86    |
| EMS/Transport                       | 32       | 6.4      |
| Resident physicians                 | 15       | 3.11     |
| Epic/IS                             | 14       | 6.64     |
| Other                               | 245      | 47.96    |

The mean number of days for completing all onboarding requirements to begin orientation was 6.40 days. The mean number of days to complete tuberculosis screening by TST was 8.06, ranging from 0-36 days. One hundred twenty-four subjects supplied documentation of at least one previous TST, thereby reducing the number of days



required for subsequent testing. Seven subjects required repeated TST's due to failure to follow up for TST reading. TB clear days included the amount of time required for tuberculosis screening and was 5.92 mean days for the TST and the QFT groups. However, Quantiferon® testing yielded an average 4.11 days to complete testing with a range of 1 to 10 days. There were four positive QFT® results with 3 of those being borderline less than 1.0. The mean number of days for drug screen results was 2.71 days with a maximum of 19 days resulting from subjects who had 2 dilute drug screens, necessitating a hair drug screen. Thirty-six employees were required to have pre-work screen tests, averaging 5.68 days to complete. Six subjects were required to bring documentation from their personal health care provider regarding work status. Nonparametric testing did not demonstrate was a statistically significant relationship between race and number of clear days ( $p=0.0942$ ), fit for duty days ( $p=0.1823$ ), drug screen days ( $p=0.0712$ ), QuantiFERON® result days ( $p=0.9555$ ), TB clear days ( $p=0.0718$ ), TST clear days ( $p=0.0879$ ), and pre-work screen days ( $p=0.9920$ ) (Table 4.2).

Table 4.2  
*N, means, standard deviation, minimum, maximum for select variables*

| <b>Variable</b> | <b>Label</b>      | <b>N</b> | <b>Mean</b> | <b>Std Dev</b> | <b>Minimum</b> | <b>Maximum</b> |
|-----------------|-------------------|----------|-------------|----------------|----------------|----------------|
| age             | Age               | 484      | 35.08       | 11.54          | 18.00          | 67.00          |
| cldy            | Clear days        | 481      | 6.40        | 5.08           | 1.00           | 30.00          |
| tstcldy         | TST clear days    | 223      | 8.06        | 7.16           | 0.00           | 36.00          |
| tbclrd          | TB clear days     | 481      | 5.92        | 5.35           | 0.00           | 36.00          |
| qftdy           | # days result QFT | 255      | 4.11        | 1.26           | 1.00           | 10.00          |
| dsdy            | d/s days          | 481      | 2.71        | 2.27           | 1.00           | 19.00          |
| ffddy           | FFD days          | 36       | 7.94        | 4.26           | 2.00           | 18.00          |
| pwsdy           | PWS days          | 31       | 5.68        | 4.77           | 0.00           | 21.00          |
| pcpndy          | PCP note days     | 6        | 7.17        | 8.57           | 1.00           | 24.00          |

**Question 1. Did implementation of QFT®-GIT reduce the number of days to complete tuberculosis screening for new hires?**

There was a statistically significant difference in number of days to complete tuberculosis screening for the QFT® group in comparison to the TST group ( $p < .0001$ ) (see Table 3). The average mean number of days to clear tuberculosis screening was 8.03 for TST and 4.11 for the QFT®. When comparing age between the two groups for testing completion days, there was no statistically significant difference ( $p = 0.0849$ ) (see Table 4.3)

Table 4.3  
*N, mean, standard deviation for select variables by group*

| Variable                          | TST group |       |       | QFT group |       |       |
|-----------------------------------|-----------|-------|-------|-----------|-------|-------|
|                                   | N         | Mean  | Std.  | N         | Mean  | Std.  |
| Age <sup>a</sup>                  | 227       | 34.11 | 11.78 | 257       | 35.93 | 11.27 |
| TB screen clear days <sup>b</sup> | 224       | 8.03  | 7.16  | 257       | 4.08  | 1.29  |
| QFT complete days                 | 0         | .     | .     | 255       | 4.11  | 1.26  |
| TST complete days                 | 223       | 8.06  | 7.16  | 0         |       |       |

a. t-test  $p = 0.0849$

b. t-test  $p < .0001$

**Question 2. Did implementation of QFT®-GIT for new hires reduce the overall number of days to complete onboarding?**

Findings indicated a statistically significant difference in the overall number of days to complete Employee Health screening for the QFT®-GIT in comparison to the

TST group ( $p < .0001$ ), even when factoring in other new hire screening requirements. A reduction in number of onboarding days was demonstrated when using the QFT method as compared to the TST group (7.92 TST group; QFT® group 5.07,  $p < .0001$ ). There was no statistically significant difference between the TST and the QFT® groups in the number of days to complete drug screens ( $p = 0.8009$ ), fit for duties ( $p = 0.8009$ ), or pre-work screens ( $p = 0.1265$ ) (see Table 4.4).

Table 4.4  
*N, mean, standard deviation for select onboarding variables by group*

| Variable                          | TST group |       |      | QFT group |      |      |
|-----------------------------------|-----------|-------|------|-----------|------|------|
|                                   | N         | Mean  | Std. | N         | Mean | Std. |
| Clear days <sup>a</sup>           | 223       | 7.92  | 6.54 | 256       | 5.07 | 2.68 |
| Drug screen days <sup>b</sup>     | 225       | 2.74  | 2.84 | 256       | 2.68 | 1.61 |
| Fit for duty days <sup>c</sup>    | 11        | 10.18 | 5.10 | 25        | 6.96 | 3.52 |
| Pre-work screen days <sup>d</sup> | 20        | 6.6   | 5.0  | 11        | 4.00 | 4.00 |
| PCP note days                     | 6         | 7.17  | 8.57 | 0         | .    | .    |

- a. t-test  $p < .0001$
- b. t-test  $p = 0.8009$
- c. t-test  $p = 0.0768$
- d. t-test  $p = 0.1265$

Data was further analyzed to determine if there was a correlation between onboarding clearance time and age, TST clear days, QFT®-GIT clear days, drug screen days, fit for duty days, pre-work screen days, or PCP note days. A weak but positive correlation was demonstrated between overall onboarding time and age ( $r = 0.10094$ ,  $p = 0.0268$ ) (see Table 14). However, findings showed a statistically significant stronger positive relationship between overall onboarding time and number of days to complete

TST screening ( $r=0.71838$ ,  $p<.0001$ ) and number of days for clearance by QFT® ( $r=0.62275$ ,  $p<.0001$ ). A positive relationship was also found between onboarding clearance time with number of days to complete drug screens ( $r=0.30298$ ,  $p<.0001$ ). There was also a positive relationship between the number of days and fit for duties ( $r=0.76433$ ,  $p<.0001$ ), however, only 36 subjects were required to complete the examination. For onboarding time with the number of days to complete pre-work screens, a positive correlation was found among six subjects ( $r=0.68600$ ,  $p<.0001$ ) but none was found between onboarding clearance time and the number of days to supply documentation clearance from the PCP ( $r=0.40584$ ,  $p=0.4247$ ) (see Table 4.5).

Table 4.5  
*Spearman Correlation of selected variables for onboarding clearance days*

| Variable                          | Onboarding Clear Days |             |
|-----------------------------------|-----------------------|-------------|
|                                   | N                     | Correlation |
| Age <sup>a</sup>                  | 481                   | 0.10094     |
| TST clear days <sup>b</sup>       | 223                   | 0.71838     |
| QFT days <sup>b</sup>             | 255                   | 0.62275     |
| Drug screen days <sup>b</sup>     | 479                   | 0.30298     |
| Fit for duty days <sup>b</sup>    | 36                    | 0.76433     |
| Pre-work screen days <sup>b</sup> | 31                    | 0.68600     |
| PCP note days <sup>c</sup>        | 6                     | 0.40584     |

a.  $p=0.0268$

b.  $p<.0001$

c.  $p=0.4247$

**Question 3. Did implementation of QFT®-GIT for new employees improve compliance with completion of tuberculosis screening within 10 days of**

**orientation?**

Analyses showed a statistically significant improvement in compliance with the QFT® group in comparison to the TST group ( $p < .0001$ ). Overall, the compliance rate for completing the tuberculosis screening was 99.29% in the TST group and 100% the QFT group. There was no statistical difference for tuberculosis screening compliance between races. However, there was a statistically significant difference in compliance between genders with an increase in compliance among female employees (97.96%;  $p = .0010$ ) (see Table 6). Three employees failed to complete two step TSTs. Ten employees failed to have at least one TST read prior to orientation. Sixteen employees in the TST group failed to complete tuberculosis screening within 10 days of orientation. No QFT group subjects failed to complete screening within 10 days of hire date Table 4.6).

Table 4.6  
*Frequency distribution for clear within 10 days*

| Variables                 | Yes |       | No |      |
|---------------------------|-----|-------|----|------|
|                           | N   | %     | N  | %    |
| <b>Gender<sup>a</sup></b> |     |       |    |      |
| Female                    | 385 | 97.96 | 8  | 2.04 |
| Male                      | 82  | 91.11 | 8  | 8.89 |
| <b>Race<sup>b</sup></b>   |     |       |    |      |
| White                     | 309 | 95.96 | 13 | 4.04 |
| Black                     | 109 | 97.32 | 3  | 2.68 |
| Other                     | 49  | 100   | 0  | 0    |
| <b>Group<sup>c</sup></b>  |     |       |    |      |
| TST                       | 210 | 92.92 | 16 | 7.08 |
| QFT                       | 257 | 100   | 0  | 0    |

- a. Fisher exact test p value= .0010
- b. Fisher exact test p value= .3092
- c. Fisher exact test p value<.0001

#### **Q4. Was implementation of QFT®-GIT cost-effective?**

The average cost for a two-step TST in Employee Health was estimated at \$87.87 per person and for QFT® \$101.66 (cost of lab test, supplies, staff time for review of results). At initial glance, the QFT®-GITs appears to cost more per person (\$13.79). However, further consideration is warranted when factoring other variables. Ten subjects failed to have at least one TST read and had to be replaced which required a second TST at an additional cost of \$30.01- \$37.76 per person (total costs of \$377.60). Sixteen subjects failed to complete screening within 10 days of orientation which resulted in an increase in Corporate cost to allocate Employee Health staff time recalling these new hired employees (\$25 per hour x 8 hours per week used for recalls = \$200.00 per week). If the 16 noncompliant new hire employees were RNs and were delayed start dates, Corporate would have had to contract with a staffing agency for 16 locum tenens nurses while waiting for the new hire employees to begin work. This locum tenens contract would have resulted in an additional potential cost of \$76,800 per month (\$30/hr. for each locum tenens for full time x 160 hours in month = \$4,800 x 16 employees = \$76,800). Four subjects in the TST group did not complete both steps of the two-step tuberculin skin test within the specified time frame, which potentially placed the system at risk for DHEC penalties ranging from \$100 for the first violation and up to \$5,000 for a third violation (S.C. Department of Health and Environmental Control, 2015). Occupational Health Safety Administration penalties could be 12,675 to 126,749 each (OSHA, 2017). Fortunately, Employee Health staff were vigilant in their efforts to have new hires complete the testing but again allocating staff time was costly to Corporate.

Accounting for the QFT® cost is easily done as a single test in comparison to

TST testing which includes other cost variables such as staff time incurred for noncompliant new hires in regards to follow up and TST re-testing and overall costs for locum tenens use to fill temporary vacancies. Overall, the costs are for utilizing the QFT® for new hire screenings demonstrated a cost savings to the healthcare system (see Table 4.7).

Table 4.7  
Average estimated costs based on data collection

| Estimated Annual TST screening cost      |                  | Estimated Annual QFT®-GIT cost  |                  |
|--|------------------|---------------------------------|------------------|
| For 2,000 compliant                      | \$175,740        | For 2,000 compliant             | \$203,320        |
| + cost of noncompliant replace           | 8,823            | + Repeat QFT®-GIT 1 monthly     |                  |
| <b>Total</b>                             | <b>\$184,563</b> |                                 | <b>656</b>       |
| Minus brought hx step 1                  | 18,347           | Minus hx +PPD \$53x 60/yr.=     |                  |
| Minus hx +PPD                            | 1,479            |                                 | 3,180            |
| <b>Total</b>                             | <b>\$164,737</b> | <b>Total</b>                    | <b>\$200,796</b> |
|  |                  | Minus savings on locum tenens - |                  |
| Plus locum tenens cost                   | \$576,000        |                                 | \$576,000        |
| Plus DHEC fines x 20= \$2,000 -          |                  |                                 |                  |
| \$100,000                                |                  |                                 |                  |
| Plus OSHA fines 20 x \$12,675= \$253,500 |                  |                                 |                  |

## Conclusions

Data analyses revealed that utilization of the QFT®-GIT for tuberculosis

screening of new hire healthcare employees in place of the TST significantly reduced tuberculosis screening and onboarding time while improving compliance with tuberculosis screening within 10 days of hire date ( $p < .0001$ ). The mean tuberculosis screening time for both screening methods combined was 5.92, while TST screening time was 8.03 days and 4.11 days for the QFT® group. TST screening can be completed within 2 days for those that bring in documentation of previous TST, however the range in TST screening time was from 0 to 36 days. In contrast, screening time with the QFT®-GIT was 1-10 days with the average of 3-4 days. The only QFT® group subjects that required 10 days or more for repeat testing were due to borderline positive test results. Overall, the healthcare system was able to increase the number of pre-placement visits in Employee Health from 104 pre-placement visits in September of 2015 to 187 in July of 2016. This 56% increase in volume contributed to improved satisfaction for the senior management and hiring managers by increasing the volume and decreasing delays in orientation.

More efficient onboarding time has been shown to improve employee satisfaction and retention, although not measured in this DNP project. Anecdotal feedback back from hiring managers and senior management indicated an improvement in satisfaction with the Employee Health new hire process. They fully appreciated the decrease in onboarding time, quicker start dates for new hires, less delays in orientation, and an increase in volume of new hire visits. Employee Health manager admits to receiving less complaints regarding appointment availability for screening processes and orientation start dates for new hires. Streamlining processes also facilitated regulatory site visits with DHEC because the QFT®-GIT data is more easily retrievable and accurate. Clearly,



the cost of QFT®-GIT is more than a TST, but as a single test but agencies should account for other variables in the cost analyses including staffing costs, lab testing, and locum tenens use. Streamlining processes and improved efficiency are critical to Corporate overhead costs and compliance.

### **Implications for Practice**

Employee and Occupational health staff confront barriers with processes and compliance with tuberculosis testing with TSTs for new hire employees. The QFT®-GIT significantly reduced screening time and onboarding time and improve compliance. Organizations should consider implementation of an IGRA in order to streamline processes for onboarding new hires. Of course, new processes require negotiations between hospital departments and lab vendors, changes in policy and procedures, and Employee Health staff development for IGRA testing procedures in order to facilitate new hires and onboarding.

### **Future Research**

Future research should include detailed cost analyses comparing screening with TST versus QFT®-GITs for both new hires and annual testing. A pilot study could provide foundation for future research to compare annual screening with QFT®-GIT and TST. Analyses could include measurements of process improvement, screening time, and employee satisfaction surveys for onboarding. Another area of future study would be implementation of an IGRA for patients being transferred to nursing homes or other long term care facilities to determine costs associated with extended hospital stays. Similarly,

IGRA's might prove useful in reducing hospitalization days for other patients awaiting transfer to other facilities. Additionally, more studies are needed to analyze whether IGRAs predict active tuberculosis. Further study should be conducted to determine the predictive serum levels for borderline GRA and factors yielding false-positive or false-negative results. Other studies in a variety of higher risk settings should be duplicated and further examined.

### **Dissemination**

The review of the literature for this study was presented at the Fourteenth Annual Research Symposium: Research Impacting Clinical Practice sponsored by Upstate AHEC on September 30, 2016. Introduction to the problem, purpose of the review and methods for literature search were presented. Results of the literature review included process improvement, cost effectiveness, accuracy and conversions/reversions was shared. Discussions involved comparison of the TST and QFT® were reviewed (see Appendix D). A manuscript for the for Association of Occupational Health Professionals Journal (AOHP Journal) will be submitted for publication. An abstract of this quality improvement project has also been submitted for presentation at the AOHP conference in Denver, Colorado in September of 2017 (see Appendix E). Results will be shared with the new hire committee, the Vice-President of Human Resources, Employee Health, and in house lab staff.

## REFERENCES

- Banaei, N., Gaur, R. L., & Pai, M. (2016). Interferon Gamma Release Assays for Latent Tuberculosis: What Are the Sources of Variability? *Journal of Clinical Microbiology*, *54*(4), 845–850. <https://doi.org/10.1128/JCM.02803-15>
- Cummings, K. J., Smith, T. S., Shogren, E. S., Khakoo, R., Nanda, S., Bunner, L., ... Weissman, D. N. (2009). Prospective comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube assay for the detection of latent tuberculosis infection among healthcare workers in a low-incidence setting. *Infection Control & Hospital Epidemiology*, *30*(11), 1123–1126. <https://doi.org/10.1086/644754>
- Dearholt, S. L., & Dang, D. (2014). *Johns Hopkins Nursing Evidence-Based Practice : Models and Guidelines (2)*. Indianapolis, US: Sigma Theta Tau International. Retrieved from <http://site.ebrary.com/lib/alltitles/docDetail.action?docID=10540866>
- dePerio, M. A., Tsevat, J., Roselle, G. A., Kralovic, S. M., & Eckman, M. H. (2009). Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. *Archives of Internal Medicine*, *169*(2), 179–187. <https://doi.org/10.1001/archinternmed.2008.524>
- Diel, R., Loddenkemper, R., Meywald-Walter, K., Gottschalk, R., & Nienhaus, A. (2009). Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. *CHEST*, *135*(4), 1010–1018. <https://doi.org/10.1378/chest.08-2048>
- Dorman, S. E., Belknap, R., Graviss, E. A., Reves, R., Schluger, N., Weinfurter, P., ... Daley, C. L. (2014). Interferon-[gamma] Release Assays and Tuberculin Skin Testing for Diagnosis of Latent Tuberculosis Infection in Healthcare Workers in the United States. *American*

- Journal of Respiratory & Critical Care Medicine*, 189(1), 77–87.  
<https://doi.org/10.1164/rccm.201302-0365OC>
- Foster-Chang, S. A., Manning, M. L., & Chandler, L. (2014). Tuberculosis Screening of New Hospital Employees: Compliance, Clearance to Work Time, and Cost Using Tuberculin Skin Test and Interferon-Gamma Release Assays. *Workplace Health & Safety*, 62(11), 460–467. <https://doi.org/10.3928/21650799-20140902-02>
- Gonzalez, M., & Conlon, H. A. (2013). Updating a Tuberculosis Surveillance Program Considering All of the Variables. *Workplace Health & Safety*, 61(6), 271–278.  
<https://doi.org/10.1177/216507991306100606>
- Grabam, M., & Filby, D. (2015). Lean-the-new-Hire-Onboarding-Process-for-Healthcare-Workers - QIAGEN. Retrieved April 22, 2016, from  
<https://www.qiagen.com/us/resources/resourcedetail?id=a17784e8-d734-434e-a26a-4e39945aa55d&lang=en>
- Jensen, P. A., Lambert, L. A., Iademarco, M. F., & Ridzon, R. (2006). Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care settings, 2005. *MMWR: Morbidity & Mortality Weekly Report*, 54(51&52), 1–102.
- Lamberti, M., Uccello, R., Monaco, M. G. L., Muoio, M., Feola, D., Sannolo, N., ... Chiodini, P. (2015). Tuberculin skin test and Quantiferon test agreement and influencing factors in tuberculosis screening of healthcare workers: a systematic review and meta-analysis. *Journal of Occupational Medicine & Toxicology*, 10(1), 1–13.  
<https://doi.org/10.1186/s12995-015-0044-y>
- Loddenkemper, R., Diel, R., & Nienhaus, A. (2012). To Repeat or Not to Repeat-That Is the Question!: Serial Testing of Health-care Workers for TB Infection. *CHEST*, 142(1), 10–11. <https://doi.org/10.1378/chest.12-0045>
- Massante, L., & Stinson, L. (2014). *Getting started: occupational health in healthcare settings*. Warrendale, PA: Association of Occupational Health Professionals in Healthcare.

- Mazurek, G. H., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., & Castro, K. (2010). Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection -- United States, 2010. *MMWR Recommendations & Reports*, 59(RR-5), 1–26.
- Melnyk, B. M., & Fineout-Overholt, E. (2015). *Evidence-Based Practice in Nursing & Healthcare: A Guide to Best Practice 3rd edition* (3rd ed.). Philadelphia: LWW.
- National Action Plan to Combat Multidrug-Resistant Tuberculosis. (2015, December). Retrieved May 21, 2016, from <http://www.cdc.gov/mmwr/preview/mmwrhtml/00031159.htm>
- Nienhaus, A. (2013). Clinical review of literature pertaining to the use of interferon-gamma release assays for tuberculosis screening in healthcare workers: Evidence base and clinical experience with QuantiFERON-TB Gold (QFT). *Qiagen Clinical Review*. <https://doi.org/QM31635290A>
- Nienhaus, A., Schablon, A., Costa, J. T., & Diel, R. (2011). Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Services Research*, 11(1), 247–247.
- OSHA. (2017). OSHA Penalties | Occupational Safety and Health Administration. Retrieved February 22, 2017, from <https://www.osha.gov/penalties/>
- Pai, M., Zwerling, A., & Menzies, D. (2008). Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Annals of Internal Medicine*, 149(3), 177–184.
- Rangaka, M. X., Wilkinson, K. A., Glynn, J. R., Ling, D., Menzies, D., Mwansa-Kambafwile, J., ... Pai, M. (2012). Predictive value of interferon-[gamma] release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infectious Diseases*, 12(1), 45–55.

- S.C.Department of Health and Environmental Control. (2015). R.61-16, Minimum Standards for Licensing Hospitals and Institutional General Infirmaries. Retrieved from <https://www.scdhec.gov/Agency/docs/health-regs/61-16.pdf>
- Schablon, A., Nienhaus, A., Ringshausen, F. C., Preisser, A. M., & Peters, C. (2014). Occupational Screening for Tuberculosis and the Use of a Borderline Zone for Interpretation of the IGRA in German Healthcare Workers. *PLOS ONE*, 9(12), 1–16. <https://doi.org/10.1371/journal.pone.0115322>
- Slater, M. L., Welland, G., Pai, M., Parsonnet, J., & Banaei, N. (2013). Challenges with QuantiFERON-TB Gold Assay for Large-Scale, Routine Screening of U.S. Healthcare Workers. *American Journal of Respiratory & Critical Care Medicine*, 188(8), 1005–1010. <https://doi.org/10.1164/rccm.201305-0831OC>
- South Carolina Department of Health and Environmental Services. (2015). South Carolina tuberculosis incidence rate by county 2010-2014. South Carolina Department of Health and Environmental Services. Retrieved from [http://www.scdhec.gov/Health/docs/SC\\_TB\\_13.pdf](http://www.scdhec.gov/Health/docs/SC_TB_13.pdf)
- South Carolina Department of Health and Environmental Services. (2016). South Carolina Tuberculosis Incidence Rates by Count, 2011-2015. Retrieved from [http://www.scdhec.gov/Health/docs/TB\\_SC\\_Stats\\_2011\\_15.pdf](http://www.scdhec.gov/Health/docs/TB_SC_Stats_2011_15.pdf)
- Swindells, J. E., Aliyu, S. H., Enoch, D. A., & Abubakar, I. (2009). Role of interferon-gamma release assays in healthcare workers. *Journal of Hospital Infection*, 73(2), 101–108. <https://doi.org/10.1016/j.jhin.2009.05.005>
- Veeser, P. I., Smith, P. K., Handy, B., & Martin, S. (2007). Tuberculosis screening on a health science campus: use of quantiFERON-TB Gold test for students and employees. *Journal of American College Health*, 56(2), 175–180.

- Verkuyl, S., & Middelkoop, K. (2016). Protecting Our Front-liners: Occupational Tuberculosis Prevention Through Infection Control Strategies. *Clinical Infectious Diseases*, 62(suppl 3), S231–S237. <https://doi.org/10.1093/cid/civ1184>
- Weddle, G., Hamilton, M., Potthoff, D., Rivera, D., & Jackson, M. A. (2014). QuantiFERON-TB Gold In-Tube Testing for Tuberculosis in Healthcare Professionals. *Laboratory Medicine*, 45(3), 207–210. <https://doi.org/10.1309/LMLSJ4BVXS66WJHS>
- Wrighton-Smith, P., Sneed, L., Humphreys, F., Tao, X., & Bernacki, E. (2012). Screening Health Care Workers With Interferon- $\gamma$  Release Assay Versus Tuberculin Skin Test. *Journal of Occupational & Environmental Medicine*, 54(7), 806–815. <https://doi.org/10.1097/JOM.ObO>
- Zwerling, A., van den Hof, Scholten, J., Cobelens, F., Menzies, D., & Pai, M. (2012). Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. *Thorax*, 67(1), 62–70.

**APPENDIX A**  
**EVIDENCE TABLE**

Table A.1  
*Evidence Table Abbreviation Guide*

---

|          |  |
|----------|--|
| IGRA     | Interferon Gamma Release Assay             |
| TST      | Tuberculosis Skin Test                     |
| QFT®-GIT | QuantiFERON®-TB Gold In-Tube Test          |
| LTBI     | Latent Tuberculosis Infection              |
| BAMT     | Blood Assay for Mycobacterium Tuberculosis |
| CDC      | Centers for Disease Control                |
| BCG      | Bacillus Calmette-Guerin vaccine           |
| HCW      | Healthcare Worker                          |
| INH      | Isoniazid                                  |

---



| Table A.2<br>Evidence Table   |   |   |   |   |
|---|---|---|---|---|
| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>  | <u>Findings</u>   | <u>Conclusions</u>  |
| <p>Article 1</p> <p>Foster-Chang, S. A., Manning, M. L., &amp; Chandler, L. (2014). Tuberculosis screening of new hospital employees: Compliance, clearance to work Time, and cost using tuberculin skin test and Interferon-Gamma Release Assays. <i>Workplace Health &amp; Safety</i>, 62(11), 460-467. doi:10.3928/21650799-20140902-02</p> <p>(Foster-Chang et al., 2014)</p> <p>Level <b>V</b>- Organization Experience/Quality Improvement<br/>Quality <b>B Good</b>- purpose is clearly stated, findings are relevant, recommendations clear, consistent results in a single setting, good literature review<br/>(Dearholt &amp; Dang, 2014)</p> | <p>Sample: Convenience Sample</p> <p>IGRA sample size =100<br/>Sample size using retrospective chart review using TST in 2011=100</p> <p>Sample from 2012 with TST= 100</p> <p>Procedure:<br/>A) New employees offered IGRA or TST for screening: all chose IGRA between March 19 and May 30,2013<br/>B) Retrospective chart review of new employees using TST for screening in 2011 and 2012</p> <p>Statistical analysis:<br/>Chi-square goodness of fit</p> <p>Lab tests:</p> | <p>Conclusion Validity-reasonable, lists limitations. Sample size is good -100 with IGRA compared with 100 sample in 2012 and 100 in 2011= 300 sample size</p> <p>Internal Validity- Not a controlled study so there are other variables that could be the cause of the result. Some investigator bias- expected the decrease in clearance and increase in compliance. No attrition</p> <p>External Validity- The conclusion can apply to similar sized healthcare settings with similar age group of employees but perhaps not to other employers or healthcare settings in other countries. The author did not overly generalize.</p> <p>Construct validity- Good. Measured clearance time as stated.</p> <p>Reliability- It was admitted that clearance time was affected by vacation of the provider that signs off on clearance, and a chart was misplaced. Failure to return rate was estimated and could be higher or lower than expected and affect cost estimates.</p> | <p>There was a reduction in time to clearance with average reduction from 13.18 days 2011 w TST to 5.91 days. Time to clearance based on screening method with and without prior TB screen significant <math>p &lt; .0001</math>.</p> <p>Statistically significant compliance rates – 77% to 97% -2011/2013 <math>p &lt; .0001</math> and 2012/2013 <math>p &lt; .001</math>. Meaning statistically increased compliance rate with IGRA vs TST. Compliance= completions of pre-placement process within 14 days or less.</p> <p>Cost savings found 78.53 vs 47.02 per person. No statistical analysis with several assumptions regarding failure to return rate, staffing costs.</p> <p>38-40% reduction in cost for TB screening</p> | <p>Reports as “useful insights for new employee TB screening programs”</p> <p>Mentions- intra-subject variability with IGRA results confusing management. Lack of “true gold standard for latent TB”.</p> <p>IGRAs attractive diagnostic aid</p> <p>IGRA potentially expedites and improves new hire tuberculosis screening process</p> |

|   |  |   |   |   |
|---|--|---|---|---|
|   | - T-SPOT®.TB used for IGRA   | Precision- statistically significant result p<.0001 for clearance time. 95% confidence interval   |   |   |
| <b><u>Reference, Type, Quality</u></b>  | <b><u>Methods</u></b>  | <b><u>Threats</u></b>   | <b><u>Findings</u></b>  | <b><u>Conclusions</u></b>   |
| <p>Article 2</p> <p>Mazurek, G.H., Jereb, J., Vernon, A., LoBue, P. Goldberg, S., &amp; Castro, K. (2010). Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection- United States. <i>MMWR Recommendations and Reports</i>, 59(RR-5), 1-24. Retrieved from <a href="http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm">http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm</a></p> <p>(Mazurek et al., 2010)<br/>Evidence <b>Level IV</b> Clinical Practice<br/><b>Quality A High</b><br/>(Dearholt &amp; Dang, 2012)</p> | <p>Group of experts reviewed 96 out of 152 reports to develop recommendations for IGRA's. Studies included sensitivity/specific of GFT-GIT/ T-SPOT®.TB , agreement of tests with each other or with TST, association with risk for TB. Meeting convened to review study results, descriptive studies, explanations, commentaries from test manufacturers. Multiple appropriate experts used- AAP, Am Thoracic Society, Advisory Council elimination of TB, Assoc Public Health lab, CDC, FDA, Infectious Disease Society, Army, Air Force, VA, clinicians, labs, experts, etc.</p> | <p>Internal Validity- Threat includes the use of package inserts and test company information that is subject to bias. There is some discussion about confounds in some of the examined studies in some of the discussion. This Article size would be too large to discuss all of them. Study included some non-experimental studies/articles which limits the validity.</p> <p>External Validity- the volume of studies reviewed and number of experts reviewing should limit threats to external validity.</p> <p>Reliability- Reviews large number of articles and compares results in multiple tables enhancing reliability of recommendations.</p> | <p>Recommendations given for <i>General use of IGRAs</i>- may be used for surveillance, qualitative &amp; quantitative interpretation should be used, evaluate feasibility, do not use low risk in general;</p> <p><i>Test Selection, Situations which IGRA preferred</i>- groups w low return rates, BCG vaccine; <i>TST preferred</i>- children &lt;5;</p> <p><i>Either TST or IGRA may be used without preference</i>- recent contacts with TB, periodic occupational exposure to TB;</p> <p><i>Testing with IGRA &amp; TST may be considered</i>- when risk or progression increased, when initial test positive and second test encourages compliance, low risk for infection and progression, repeat when result indeterminate, borderline or invalid;</p> <p><i>Medical Management after testing</i>- Diagnosis of TB should not be based on IGRA or TST alone, +TST or IGRA should be evaluated for likelihood TB infection, LTBI- exclude active dx with symptoms exam &amp; Chest x-ray, discordant test results- individualized judgement</p> <p>Specificity QFT®-GIT- 99%</p> | <p>IGRA may be used for surveillance, multiple recommendations.</p> <p>Further study to focus on value and limits of IGRA</p> |

|  |  |  |  |  |
|--|--|--|--|--|
|  | Systematic reproducible literature search described. |  | Sensitivity QFT®-GIT-81%                               |  |
|  |  |  | Recent exposure strongly associated with positive IGRA |  |

| <u>Reference, Type, Quality,</u>  | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>   |
|---|---|--|---|--|
| <p>Article 3</p> <p>Wrighton-Smith, P., Sneed, L., Humphrey, F., Tao, X., &amp; Bernacki, E. (2012, July). Screening health care workers with interferon-γ release assay versus tuberculin skin test: impact on costs and adherence to testing (the Switch study). <i>Journal of Occupational and Environmental Medicine</i>, 54(7). doi: 10.1097/JOM.0b013e318254620f (Wrighton-Smith et al., 2012)</p> <p>John Hopkins Dearholt &amp; Dang (2012) evidence <b>level II: Quasi-Experimental</b>-includes intervention, standard of care as a control, and some randomization. <b>Quality: B- Good</b>, sufficient sample size, some control, reasonable recommendation, some references to scientific evidence</p> <p>Dearholt, S. L., &amp; Dang, D. (2012). Johns Hopkins Nursing Evidence-Based</p> | <p>Setting: 18,000 employees of John Hopkins.</p> <p>Purpose- measure cost &amp; adherence annual and new hire screening.</p> <p>-Measured material &amp; labor costs- average labor cost.</p> <p>-2<sup>nd</sup>- time motion to measure time with all steps using TST or IGRA-393 randomly selected patients,</p> <p>-3<sup>rd</sup>- 743 cohort new hire and annual tested in parallel (random invitation, voluntary participation) with TST and IGRA to gather data on positivity rates.</p> <p>Also questionnaire on views of TST or IGRA. Decisions trees.</p> <p>Retrospective</p> | <p>Potential Bias- Oxford Immune provided tests free of charge and education grant to John Hopkins of \$49,300- manufacturer of T-SPOT®.TB</p> <p>Internal validity- Participation voluntary.</p> <p>Possible validity threat- Employee Labor costs estimated</p> <p>External Validity- salary had to be estimated which could slightly skew results. I'm not sure I would include employee time away from work in measurement of the cost but it is an interesting approach to consider.</p> <p>Precision -Multiple hypothesis measured could account for significant p value by chance</p> <p>Precision-This study did an excellent job testing 38 other variables to see if they impacted test cost and they did not!</p> <p>I did not see statistical analysis of significance</p> <p>Reliability- there will be different salary structures in different organizations.</p> | <p>Cost of TST \$54.09 per annual and \$81.38 two step new hire- most due to staff time, and patient time off work. Adding in follow up of positives and symptom screens= \$73.20 per person and new hire 90.80pp – nonreturn rate considered.</p> <p><b>TST overall cost per person \$73.20</b></p> <p>TST Adherence 99.1%, 97.53%-total 98.54%</p> <p>IGRA Annual \$78.05, new hire- \$64.47 (did not add in cost of missing work)</p> <p><b>IGRA overall cost \$73.20</b></p> <p>IGRA Adherence 99.98 (annual) and 100% (new)</p> <p>Overall costs of screening with IGRA is the same as</p> | <p>TST program costs are high due to staff burden- \$73.20 per person</p> <p>IGRA results in better adherence and saves if the test is \$54.83 or less per test</p> <p>Positivity tests showed high rate of those with prior known TST positives are false-positives- more than 50%</p> <p>Questionnaire showed employee preference of IGRA vs TST</p> <p>Costly- those who do not follow up for reading- adherence 70.8- 98.5% would save \$366,793 per year</p> <p>-IGRA positive rate lower than TST -parallel- 62.5%</p> |

|  |  |   |   |   |
|--|--|---|---|---|
| <p>Practice: Models and guidelines (2nd Edition). Indianapolis, IN, USA: Sigma Theta Tau International. Retrieved from <a href="http://www.ebrary.com">http://www.ebrary.com</a></p> | <p>epidemiological statistics of TB screens over 1 year to estimate cost and adherence rates</p> | <p>Limitations Mentioned by author- did not consider accuracy of TST vs IGRA. IGRA conversion rate assumed equal to TST because serial testing not conducted. Enrollment bias in positivity portion- impractical to test all employees with both TST and IGRA</p> <p>New baseline IGRAs needed for serial testing</p> | <p>TST”</p> <p>IGRA- test cost at which it becomes cost savings- \$54.83.</p> | <p>preferred IGRA, 6.5% TST -18.5% blood draw undesirable</p> |
|--|--|---|---|---|

| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>  |
|---|---|--|---|---|
| <p>Article 4</p> <p>Swindells, J. E., Aliyu, S. H., Enoch, D. A., &amp; Abubakar, I. (2009). Role of interferon-gamma release assays in healthcare workers. <i>J Hosp Infect</i>, 73(2), 101-108. doi:10.1016/j.jhin.2009.05.005</p> <p>(Swindells et al., 2009)</p> <p>Level <b>III</b> –Systematic review of mixed types of articles</p> <p>Quality <b>B Good</b>- results reasonably consistent, references to scientific literature. Conclusions were a little confusing</p> <p>(Dearholt &amp; Dang, 2012)</p> | <p>Systematic review- of 82 studies, 29 suitable, 7 excluded non-English. 2 re T-SPOT®.TB, 20 QFT®. Pubmed</p> <p>Examined agreement between IGRA &amp; TST; Agreement IGRA &amp; TST in BCG naïve; IGRA on long term exposure; IGRA in contact investigation; IGRA &amp; sequential testing; correlation between IGRA &amp; C-X-ray</p> <p>They do not specify difference in articles that examine older QFT® vs newer QFT®-GIT.</p> | <p>Used a valid search strategy- pub med and listed search terms. However, searched studies from 1990-2008- older studies may not be as reliable since IGRA’s only began use in 2001 with the most recent in 2008. Authors do separate T-SPOT®.TB articles from QFT® but I cannot tell that they separated the older QFT®, QFT® gold vs QFT®-GIT. This can affect validity and reliability.</p> <p>Also, included studies from different countries which can affect generalizability.</p> <p>Only 2 reviewers- there could be some bias.</p> <p>The authors do not discuss the limitations of the articles reviewed.</p> | <p>Poor agreement between IGRA and TST in low incidence countries-but related to BCG vaccination. Higher correlation in 2 higher TB incidence countries.</p> <p>IGRA’s did show better correlation with markers of TB exposure during contact investigation than TST.</p> <p>States T-SPOT®.TB has not been adequately assessed. This is probably due to date of this study of 2009 and the development of T-SPOT®.TB was 2008. The few studies did show increased specificity of T-SPOT®.TB.</p> | <p>Role of IGRA for chemoprophylaxis unclear but may be alternative to TST for detecting conversions. T-SPOT®.TB not adequately studied at the time of this article.</p> <p>Positive QFT® associated greater exposure to TB.</p> <p>Discordance between TST and QFT® probably related to false positive TST due to BCG- only cites 2 studies to back up this conclusion.</p> <p>Studies on boosting of TST show conflicting results.</p> <p>States role of IGRA in healthcare workers appears favorable but more studies are needed. Predictive values are conflicting. But then states specificity for IGRA is improved compared to TST and will help prevent inappropriate prophylaxis. These statements are a bit contradictory.</p> |

| <u>Results, Type, Quality</u>  | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>  | <u>Conclusions</u>  |
|--|---|--|--|---|
| <p>Article 5</p> <p>Weddle, G., Hamilton, M., Potthoff, D., Rivera, D., &amp; Jackson, M. (2014). QuantiFERON-TB gold in-tube testing for tuberculosis in healthcare professionals. <i>Lab Medicine, 45(3)</i>, 207-210. doi: 10.1309/LMLSJ4BVXS66WJHS</p> <p>(Weddle et al., 2014)</p> <p>This study combined to areas of assessment with one part being non-experimental cohort and the second part quasi-experimental- mixed method. I will use the non-research appraisal tool. Level per John Hopkins appraisal tool:<br/><b>Level V</b> Quality Improvement<br/>Quality <b>B Good-</b> purpose is clear, findings clear and relevant, recommendations clear and linked to findings. Description of methods a little unclear.<br/>(Dearholt &amp; Dang, 2012)</p> | <p>Purpose- to determine performance of QFT®-GIT in employees of children's hospital w low incidence of TB and to determine need for repeat testing for employees with positive result. Cohort study- retrospective convenience sample approved by IRB. Reviewed occupational health records for TB risk factors. Collected repeat QFT®-GIT in 34 employees who had positive QFT®-GIT</p> | <p>Conclusions regarding repeat testing of + QFT® is related to the results of the study leading to good conclusion validity. The results were statistically significant P= .01</p> <p>However, no recommendation was really given as to what to do with the result of no association with risk factors and QFT® result.</p> <p>Internal Validity- It is unclear as to whether the repeat QFT®-GIT was looked at retrospectively or done at the time of this study. 34 of the 47 positive testers followed up. There is no discussion as to why the other 13 did not follow up- some attrition bias.</p> <p>External Validity-good conclusion, however would only generalize to low incidence areas which is not clearly spelled out in abstract findings.</p> <p>Construct validity- It is clear that the researchers are measuring what they intend to measure.</p> <p>Reliability- For the repeat QFT® the sample is relatively small- 34- reliability would be enhanced with larger sample and improve statistical significance</p> <p>Precision- appropriate application of p values however which statistical test was used is not listed. Confidence interval not discussed.</p> <p>There is a larger sample size for the retrospective portion which examines risk factors- 707 employee records assessed which improves reliability and precision and generalizability.</p> | <p>Interferon gamma IFN<math>\gamma</math> mean lower for those with repeat negative results compared to repeat positive. P= .01</p> <p>No statistical difference for risk factors between + or - QFT®-GIT result. P=.86</p> | <p>False-positives can occur for healthcare providers with QFT®-GIT borderline 1 IU/ml or less. Repeat testing recommended. However, there was overlap and cutoff for positive should not be changed. Hypothesized that other clinical conditions or minor infections could have activated T-cells. Did cite studies that supported this finding.</p> <p>Risk factors for TB such as birth country, contact with high-risk persons and hx of 1 + TB test was not significantly associated with prediction of QFT®-GIT test results. The study did not mention association or assessment of those with BCG vaccination which would have been important to look at in this study.</p> |

| <u>Reference, Quality, Type</u>   | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>  |
|---|---|--|---|---|
| <p>Article 6</p> <p>Cummings, K., Smith, T., Shogren, E., Khakoo, R., Sharmilarani, N., Bunner, L., ... Weissman, D. (2009, November). Prospective comparison of tuberculin skin test and QuantiFERON-TB gold in-tube assay for detection of latent tuberculosis infection among healthcare workers in a low-incidence setting (Cummings et al., 2009)</p> <p>Evidence level II<br/>Quasi- Experimental<br/><b>B Good Quality</b>-consistent results, reasonable sample size for this study, reasonable conclusions.</p> <p>(Dearholt &amp; Dang, 2012)</p> | <p>Convenience sample: June 2007 to Feb 2008, WVU new hire health care workers</p> <p>182 sample size which was 68% of 266 invited.</p> <p>Procedure:<br/>1. Informed Consent written.<br/>2. Blood draw first QFT®-GIT.<br/>3. Up to 3 weeks later step 1 TST. 4. Second QFT®-GIT 1 week later. Also second TST if needed.</p> <p>Research Approvals:<br/>-IRB approval obtained<br/>-National Institute Occupational Safety &amp; Health approval obtained</p> <p>-Any ELISA QFT®-GIT that was positive or indeterminate was repeated. If tests agreed, results were confirmed. If tests disagreed, 3<sup>rd</sup> test was completed and confirmed result from mean of all values.</p> <p>Analyses:<br/>-Calculated % agreement TST and first QFT®-GIT.<br/>-specificity determined by no reported risk factors.</p> | <p><i>Threat to external validity</i>-Lacks randomization. Selection bias- convenience sample</p> <p><i>Threat to precision &amp; Validity</i><br/>Used Tubersol &amp; Aplisol brands for TST which can have variation. Aplisol has shown higher rates of false-positives.</p> <p><i>Internal validity threat</i><br/>Did the reader interpret the TST result accurately?<br/>4 reports as positive.<br/>3 QFT®-GIT positives- study calculated % agreement as low but there were not many positives to measure<br/>-only 85 (47%) showed for second QFT®-GIT- attrition bias</p> <p><i>Precision threat</i><br/>It is unclear if the TST is what caused the result of 2 2<sup>nd</sup> QFT®-GIT to be positive</p> <p>- <i>Enhances reliability</i>- 96% born in US, 93% did not have BCG vaccine, 62% no report of risk factors.</p> | <p>-agreement between TST and QFT®-GIT for those without risk factors on negative results= 99%</p> <p>-Agreement of positive results = 0%</p> <p>-2 with negative 1<sup>st</sup> QFT®-GIT had positive QFT®-GIT</p> <p>-4 had positive QFT®-GIT but negative TST</p> <p>-3 +TST but – QFT®-GIT</p> <p>-1 +TST and +QFT®-GIT</p> <p>-69% of indeterminate QFT®-GIT were confirmed by second ELISA (11 of 16, the other 5 negative)</p> <p>-HCW w DM or Immuno therapy had greater odds of confirmed indeterminate (6.8 odds ratio, CI 95%)</p> <p>-Days between TST and 2<sup>nd</sup> QFT®-GIT- no statistical significant difference.</p> <p>-there was higher IFN-<math>\gamma</math> concentration on second QFT®-GIT after 1 TST (56 HCW)</p> | <p>-Agreement between QFT®-GIT good</p> <p>-Tests did not agree on + results</p> <p>-most disagreement was +TST with negative QFT®-GIT</p> <p>-reanalysis of 5 QFT®-GIT that had + results, only confirmed 2- conclusion that reanalysis may identify initial + test results as negative.</p> <p>-immunosuppression consistent with low response to mitogen</p> <p>-effect of difference in QFT®-GIT after TST is questionable clinical significance</p> <p>-Fewer visits for QFT®-GIT valuable</p> <p>Author listed limitations:<br/>-short follow up time<br/>-limited sample size<br/>-variation in timing of tests and brands of PPD<br/>-Some HCW agreed to test but did not follow up</p> |

|  |  |  |  |  |
|--|--|--|--|--|
|  | <p>Likelihood ratio X2<br/>         -compared results 1<sup>st</sup> and 2<sup>nd</sup> QFT®-GIT by mixed-model repeated measures of analysis of Variance (ANOVA)<br/>         - covariate-duration of time between 1<sup>st</sup> TST and second QFT®-GIT<br/>         -compared effect of 1 intervening TST with 2 intervening TST</p> | <p><i>Reliability Threats:</i><br/>         - large age range 28-62 years<br/>         -8 had diabetes or recent immunosuppressive therapy which can affect results of TST or QFT®-GIT (false-negatives)</p> |  |  |
|--|--|--|--|--|



| <u>References, Type, Quality</u>   | <u>Methods</u>   | <u>Threats</u>  | <u>Findings</u>   | <u>Conclusions</u>  |
|--|--|---|---|---|
| <p>Article 7</p> <p>Perio, M. A., Tsevat, J., Roselle, G., Kralovic, S., Eckman, M. (2009, January 26). Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. <i>Journal of American Medical Association: Internal Medicine</i>, 169(2), 179-187. Doi: 10.1001/archinternmed.2008/524</p> <p>(dePerio et al., 2009)</p> <p><b>Level V</b> Financial Evaluation (cohort)<br/> <b>A High Quality</b>- clear objective, consistent results, good lit review, thorough methods (Dearholt &amp; Dang,2012)</p> | <p>Estimates based on RN salaries at VHA in 2007</p> <p>Markov state-transition model w societal perspective &amp; lifetime horizon 1yr</p> <ul style="list-style-type: none"> <li>- No LTBI, no INH,</li> <li>-No LTBI, INH partial,</li> <li>-No LTBI, INH complete,</li> <li>-LTBI, no INH,</li> <li>-LTBI, INH partial,</li> <li>-LTBI, INH complete</li> </ul> <p>-effectiveness measured in quality-adjusted life years (QALYs)</p> <p>-hypothetical 35 yr old HCW, pay based on RN</p> <p>-compared TST, QFT®-G, QFT®-GIT</p> <p>-analysis vaccinated BCG vs not</p> <p>-accounted for indeterminate QFT® or failure to return for TST reading</p> <p>-used statistics from VHA for probabilities of return for TST read/placements</p> <p>-direct &amp; indirect costs considered including missed work</p> <p>-software- Decision Maker 4.0; beta version</p> | <ul style="list-style-type: none"> <li>- Used hypothetical scenario</li> <li>-age 35 but did run analysis for ages 25-55 with same results</li> </ul> <p>Construct validity- attempted to generalize to entire HCW population based on hypothetical results</p> <ul style="list-style-type: none"> <li>-study is in 2009 so figures for salary and cost of IGRA are not equivalent to today</li> <li>-good-performed probabilistic sensitivity analysis by Monte Carlo simulation</li> <li>-used only RN pay for calculations- does not consider other pay scales</li> </ul> <p>Author listed</p> <ul style="list-style-type: none"> <li>-did not assess transmission of TB &amp; costs/benefits</li> <li>-did not examine subsequent annual TST or QFT®</li> </ul> | <ul style="list-style-type: none"> <li>-TST costlier &amp; less effective for all models</li> </ul> <p>-if QFT®-GIT sensitivity is better than QFT®-G then QFT®-GIT becomes more cost effective</p> <ul style="list-style-type: none"> <li>-less cost if QFT®-G kit is \$32, QFT®-GIT \$36 or less</li> </ul> <p>-QFT®-G &amp; QFT®-GIT cost savings compared to TST in 00% of 10000 Monte Carlo simulations</p> <ul style="list-style-type: none"> <li>-non-BCG- cost savings 30% of time</li> <li>QFT®-G, QFT®-GIT- 3%</li> <li>BCG vaccinated- QFT®-G 21%, QFT®-GIT-18%</li> </ul> | <ul style="list-style-type: none"> <li>-QFT®-G &amp; QFT®-GIT are more effective &amp; less costly compared to TST for detecting LTBI in HCW</li> <li>-time costs saved with less missed work time and QALYs.</li> <li>-IGRAs less costly if run in batches of 12 for non BCG and 4 for BCG-vax</li> <li>-QFT®-GIT least costly and most effective</li> </ul> |

| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>  | <u>Conclusions</u>   |
|---|---|--|--|--|
| <p>Article 8</p> <p>Lamberti, M., Uccello, R., Monaco, M. G. L., Muoio, M., Feola, D., Sannolo, N., Nienhaus, A., &amp; Chiodini, P. (2015). Tuberculin skin test and QuantiFERON® test agreement and influencing factors in tuberculosis screening of healthcare workers: a systematic review and meta-analysis. <i>Journal of Occupational Medicine and Toxicology</i>, 10(2),1-13. doi: 10.1186/s12995-015-0044-y</p> <p>(Lamberti et al., 2015)</p> <p>Level <b>III</b> Systematic review with meta analysis of combo RCT and Quasi-experimental, non-experimental</p> <p>Quality- <b>A High</b>- used statistics to generate a new effect size, listed inclusion and exclusion criteria, complete flow diagram of studies, large sample size, comprehensive review (Dearholt &amp; Dang, 2012)</p> | <p>-Preferred Reporting Items for Systematic Reviews and Meta-Analysis.</p> <p>-PubMed</p> <p>Search terms-workers and tuberculosis or TB infection or TB disease or TB and tuberculin skin test or tuberculin skin testing and Quantiferon®- 2004-2013</p> <p>-inclusion-screening LTBI in HCW w TST &amp; QFT®, comparison between TST &amp; QFT®, sample vaccine rates, English</p> <p>-Excluded- duplicates, case reports, editorials, close contacts, immunologic or lab, NTM, HIB, chronic rheumatologic, infl bowel.</p> <p>-29 included out of 1,430</p> <p>-10 mm cutoff +PPD only</p> <p>-Cohen's K applied to each study</p> | <p>-Validity/precision- lumped QFT®-G with QFT®-GIT</p> <p>-study assumed that TST is an accurate test for LTBI.</p> <p>-review went back a little far 2004</p> <p>Author- should include longitudinal studies in future study</p> | <p>-One third of TST &amp; QFT® results discordant. K value random effect 0.28 (CI 95%)</p> <p>-K 0.25 (95% CI)TST &amp; QFT® agreement in low incidence group, 0.19 intermediate, 0.38 in high group</p> <p>-best agreement in high incidence group</p> <p>-worst agreement intermediate (highest vaccine rate)</p> | <p>-overall agreement TST &amp; QFT® low</p> <p>-QFT® reproducibility unclear</p> <p>-lower rate of QFT® positive attribute to higher specificity than TST- higher specificity to mycobacterium tb</p> <p>-BCG vaccination reduced agreement- TST + increasing risk of false positives</p> <p>-discordant QFT® + vs TST negative increased with age over 40 and 50</p> <p>-increasing working year and positivity of both tests</p> <p>-TST should continue for low prevalence of vaccination or high incidence of TB infection</p> <p>-QFT® is helpful for areas w higher BCG vaccination</p> <p>-physicians should consider TB incidence, vaccination status, age and working seniority when choosing tests.</p> |

| <u>References, Type, Quality</u>   | <u>Methods</u>   | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>  |
|--|--|--|---|---|
| <p>Article 9</p> <p>Jensen, P. A., Lambert, L. A., Iademarco, M. F., Ridzon, R., &amp; Cdc. (2005). Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. <i>MMWR Recomm Rep</i>, 54(RR-17), 1-141. Retrieved from <a href="http://www.ncbi.nlm.nih.gov/pubmed/16382216">http://www.ncbi.nlm.nih.gov/pubmed/16382216</a></p> <p>(Jensen et al., 2006)</p> <p><u>Evidence Level IV Clinical Practice Guidelines</u><br/> <u>Quality: A High even though not developed in the past 5 years. There is an addendum that is 2010. Sponsored by CDC this is nationally recognized guidelines based on scientific evidence</u><br/> (Dearholt &amp; Dang, 2012)</p> | <p>-update of 1994 guidelines</p> <p>-based on epidemiology reports, evidence-based science and content experts- experts in TB, infection control, environmental control, respiratory protection and occupational health</p> | <p>Very lengthy document and lengthy list of references that would be difficult for one person to review.</p> <p>-not updated in the past 5 years except for an addendum</p> <p>-did not list search strategy</p> <p>-expertise is evident</p> | <p>-lengthy document listing practice guidelines for preventing Tb including screening of healthcare workers and infection control for patients. I will focus on applicable sections for screening in my setting due to length of this article.</p> <p>-Low risk facilities-<br/> New hires- 2 step PPD or 1 BAMT<br/> If hx positive- symptom review<br/> No annual screening required</p> <p>-outlines how to complete 2 step and when to read</p> <p>-2 step minimizes boosting leading to unwarranted suspicion of TB with subsequent testing</p> <p>-baseline tests should be within 10 days of HCW starting employment</p> <p>-medium risk-<br/> Same for new hires<br/> Annual PPD or BAMT for all HCW</p> <p>-states BAMT is more specific than skin testing</p> <p>-BAMT recommended for BCG vaccinated</p> <p>-Outlines follow up for exposures</p> <p>-HCW with + should have Chest X-ray and be assessed for LTBI treatment</p> | <p>Guidelines require 2 step PPD or 1 BAMT for new hires regardless of risk.</p> <p>IGRA's- QFT® or T-SPOT®.TB are acceptable per 2010 addendum</p> |

| <u>Reference, Type, Quality</u>  | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>  | <u>Conclusions</u>   |
|--|---|--|--|--|
| <p>Article 10</p> <p>Gonzalez, M., &amp; Conlon, H. A. (2013). Updating a tuberculosis surveillance program: considering all of the variables. <i>Workplace Health &amp; Safety</i>, 61(6), 271-278. doi: 10.3928/21650799-20130516-05</p> <p>(Gonzalez &amp; Conlon, 2013)</p> <p>Level V Quality Improvement. Quality- B Good- clearly stated aims, single setting only, good references (Dearholt &amp; Dang, 2012)</p> | <p>-organizational needs assessment based on: CDC requirement, resources, needs of employees, logistics</p> <p>Steps:</p> <ol style="list-style-type: none"> <li>1. Identify specific organization elements and processes</li> <li>2. Match organizational elements to testing methods</li> <li>3. 13 item chart was created to compare each methods attributes</li> </ol> <p>Evaluate employee population and decide which test meets surveillance needs considering resources of organization</p> | <p>-reliability threat- results can really only be generalized to this practice setting but method of determining which method TST or QFT® to use can be applied.</p> <p>-Validity threat- some author bias- attempts to make results easier for the setting</p> | <p>This organization chose:</p> <ul style="list-style-type: none"> <li>-TST for annual testing of all without BCG vaccine.</li> <li>-annual for those with BCG-signs &amp; symptoms</li> </ul> <p>Pre-employment</p> <ul style="list-style-type: none"> <li>-no BCG-TST</li> <li>-BCG- QFT®</li> <li>-visiting physician-QFT®</li> <li>-employee exposure to TB-QFT®</li> <li>-Pregnant employee- QFT®</li> <li>-Immunocompromised-QFT®</li> </ul> | <p>-I don't know that I agree with this organizations choices. The evidence does not point to doing QFT®'s just because someone is pregnant. CDC recommendations are not to just do a symptom assessment on BCG vaccinated. The article did not say it was for BCG vaccinated with +TST. I do realize this organization has lab limitations that our organization does not have.</p> <p>-my take away for this article is the process to assess the organization specific needs.</p> |

| <u>Reference, Type, Quality</u>  | <u>Methods</u>   | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>  |
|--|--|--|---|---|
| <p>Article 11</p> <p>Diel, R., Loddenkemper, R., Meywald-Walter, Gottschalk, R., &amp; Nienhaus, A. (2009). Comparative performance of tuberculin skin test, QuantiFERON®-TB-gold in tube assay, and T-SPOT®.TB . TB test in contact investigations for tuberculosis. <i>Chest</i>, 135(4), 1011-1018. doi: 10.1378/chest.08-2048 (Diel et al., 2009)</p> <p>Evidence level <b>II</b> Quasi-experimental<br/><b>Quality B</b> good-reasonable conclusions, large sample size, reproducible (Dearholt &amp; Dang, 2012)</p> | <p>-started with 2004 close contacts of culture confirmed TB.</p> <p>-eliminated 6 w hx prior +TST and 2 with prior tx for active tb.</p> <p>-842+ TST &gt; 5mm had blood drawn for QFT® and T-SPOT®.TB</p> <p>-22 of those T-SPOT®.TB result could not be determine- not enough lymphocytes, 7 indeterminate T-SPOT®.TB</p> <p>-1 indeterminate QFT®</p> <p>-none had immunosuppression, HIV, hemodialysis</p> <p>-convenience sample</p> <p>-215 recalled case coughing</p> <p>-more than half BCG vaccinated</p> <p>-321 household/intimate contacts</p> <p>-291 coworkers</p> <p>-87 pupils/teachers</p> <p>-51 healthcare workers</p> <p>-44 nonintimate friends</p> <p>-11 copatients</p> <p>-5 sports club members</p> <p>-multiple regression analysis</p> | <p>Reliability- may not be able to reproduce due to high rate of BCG vaccination in this group</p> <p>-increased age and foreign born was associated with higher rate IGRA positive despite trying to exclude those with prior TB exposure- could be confounding variable</p> <p>-this study was focused on community more than HCW so less applicability to my setting</p> <p>Validity threats-</p> <p>-not a random sample</p> <p>-small attrition bias-</p> <p>-attempted to control confound variable of being household or intimate contact but was not significant variable.</p> | <p>-Agreement between QFT® and T-SPOT®.TB high 93.9% k value 0.852 w CI 0.78 to 0.92</p> <p>-BCG vaccination was associated with negative IGRA p&lt;0.0001</p> <p>-contacts who report coughing of source more likely + IGRA- QFT® 49.8%, T-SPOT®.TB 23.1%p, 0.0001</p> <p>-no significant + IGRA and cumulative exposure time of contacts p &lt; 0.0001</p> <p>-contacts of AFB-positive more likely IGRA + than AFB negative p &lt; 0.0001</p> <p>-contact with AFB-positive &gt;40 hrs were 6x higher rate of +IGRA</p> <p>- Higher cutoff of TST &gt;15 mm was more likely associated for IGRA positive suggesting high specificity.</p> <p>- Significant association between + IGRA and increase age, foreign origin, AFB positive source, source case cough and exposure time</p> <p>-Discordant results between QFT® and T-SPOT®.TB improved with increasing cutoffs to 9 spots for T-SPOT®.TB , QFT® IU/mL 0.6 but only slight gain of 4.8%</p> | <p>-IGRA reduce LTBI screening to those truly infected and is better for contact investigation</p> <p>-Using QFT® or T-SPOT®.TB would reduce LTBI suspects to be investigated by 70%</p> <p>-IGRA more accurate indicator of LTBI than TST</p> <p>-QF®T and T-SPOT®.TB show excellent agreement</p> |

| <u>Reference, type, quality</u>   | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>   |
|---|---|--|---|--|
| <p><b>Article 12</b></p> <p>Veeseer, P. I., Smith, P. K., Handy, B., &amp; Martin, S. R. (2007). Tuberculosis screening on a health science campus: use of QuantiFERON®-TB gold test for students and employees. <i>Journal of American College Health</i>, 56(2), 175-180. Retrieved from <a href="http://eds.b.ebscohost.com/pallas2.tcl.sc.edu/ehost/pdfviewer/pdfviewer?sid=3265610b-2bae-4881-bdc1-8fa0f87a2448%40sessionmgr113&amp;vid=5&amp;hid=120">http://eds.b.ebscohost.com/pallas2.tcl.sc.edu/ehost/pdfviewer/pdfviewer?sid=3265610b-2bae-4881-bdc1-8fa0f87a2448%40sessionmgr113&amp;vid=5&amp;hid=120</a></p> <p>(Veeseer et al., 2007)</p> <p><b>Evidence Level 5</b><br/>Program Evaluations<br/>Quality- <b>B Good</b><br/>Clear objectives, some scientific evidence<br/>(Dearholt &amp; Dang, 2012)</p> | <p>-Retrospective Chart Review June 2005 to Aug 2006</p> <p>-QFT® use for- past positive but not documented by health dept, questionable report past +, hx BCG, UHS TST +</p> <p>-Setting University of Tennessee Health Science Center- 2,200students, 6,000 employees</p> <p>-109 subjects- 55 employees, 54 students</p> | <p>-did not control extraneous variables</p> <p>-External validity/conclusion threat- small sample size</p> <p>-lacks randomization</p> <p>-Did not run any statistical analysis</p> | <p>-94 nonreactive, 10 reactive (8 students &amp; 2 employees), 5 indeterminate</p> <p>-7 reactive students had BCG, 1 undocumented past + TST</p> <p>-1 employee reactive with documented +TST and 1 employee undocumented past + TST</p> <p>-85% of tested nonreactive, 9% reactive, 5% indeterminate</p> | <p>-Successful implementation of QFT®-TB gold for students and employees for listed situations.</p> <p>-3 with past +TST but nonreactive QFT®-G may have had improper readings or reaction to thimerosal.</p> <p>-benefits in completion rates of TB screening, result reporting and surveillance capacity</p> |

| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>  | <u>Findings</u>  | <u>Conclusions</u>   |
|---|---|---|--|--|
| <p>Article 13</p> <p>Zwerling, A., van den Hof, S., Scholten, J., Cobelens, F., Menzies, D., &amp; Pai, M. (2012). Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. <i>Thorax</i>, 67, 62-70. doi: 10.1136/thx.2010.143180</p> <p>(Zwerling et al., 2012)</p> <p>Evidence <b>level III</b><br/>Systematic review<br/>combination of quasi-experimental and non-experimental<br/>Quality- <b>A High</b><br/>Clear objectives, multiple databases used, details of studies presented, conclusions logical<br/>(Dearholt &amp; Dang, 2012)</p> | <p>-Systematic Review of studies:<br/>1-compare IGRA performance in HCW<br/>2- IGRA correlation to occupational exposure to TB compared to TST<br/>3- Rate of IGRA conversions &amp; Reversions in relation to IGRA and occupational exposure compared to TST<br/>4- summarize cost-effectiveness studies</p> <p>-Databases-PubMed, Embase, Biosis, Web of Science up to Oct 2010.<br/>-reviewed bibliographies of reviews &amp; guidelines on IGRA<br/>-conference proceedings<br/>-Experts contact<br/>-detailed search string</p> <p>-Created hierarchy of reference standards- no studies found at 2 highest. From low to high: Concordance with TST, Sensitivity &amp; Specificity in active TB, Correlation w exposure, Predictive value of IGRA for active TB, Efficacy of preventive therapy based on IGRA results figure 1.</p> <p>-calculated Fishers exact 95% CI or prevalence estimates</p> <p>-separated studies by high, intermediate, low incidence settings</p> <p>-50 total studies:<br/>42 IGRA studies in IGRA w main outcomes of interest<br/>3 cost-effectiveness</p> | <p>Authors note publication bias is always a concern.<br/>-note lack of evidence at highest hierarchy</p> <p>Threats-Lumped all QFT®'s together when the QFT®-GIT is more specific.</p> <p>-contact test manufacturers for citations- bias threat</p> <p>-included different countries which could affect reproducibility</p> | <p>-high incidence- TST and IGRA positivity rates high, IGRA slightly lower<br/>Low &amp; Moderate- 25 studies- lower prevalence of + QFT® or T-SPOT®.TB than TST with statistically significant difference in 17.</p> <p>Concordance weak between TST &amp; IGRA. Agreement is improved with higher TST cutoff of 15 mm</p> <p>TST-/IGRA-predominant discordance</p> <p>-low incidence-14 studies show positive association between IGRA + and risk factors- high risk ward work, Work in TB clinic or geriatric care, increased length of healthcare employment.</p> <p>-conversion rates vary</p> | <p>-IGRAs well correlated with TB infection risk factors in low &amp; intermediate incidence</p> <p>-One-time screening may result in lower prevalence of + tests and less LTBI tx.</p> <p>-prevalence of +IGRA lower than TST</p> <p>-IGRA higher rate reversions and conversions if using simple cutoffs of positive/negative. Caution when interpreting. Consider absolute increase over baseline. Few studies examine this</p> |

|  |  |  |  |  |
|--|--|--|--|--|
|  | <p>3 feasibility &amp; test implementation<br/>2 new studies after 10/2010</p> <p>-further details online supplement</p> <p>-79% of studies QFT® only (35), 7% (3) T-SPOT®.TB only, 14% both IGRAs<br/>-14% only IGRA testing<br/>11% (5) high incidence<br/>-study size 12 to 1313 HCW for total 11,963</p> |  |  |  |
|--|--|--|--|--|



| <u>Reference, Type, Quality</u>   | <u>Methods</u>   | <u>Threats</u>  | <u>Findings</u>   | <u>Conclusions</u>  |
|---|--|---|---|---|
| <p>Article 14</p> <p>Nienhaus, A., Schablon, A., Costa, J.T., &amp; Diel, R. (2011). Systematic review of cost and cost-effectiveness of different TB-screening strategies. <i>BMC Health Services Research</i>, 11(247). doi: 10.1186/1472-6963-11-247</p> <p>(Nienhaus et al., 2011)</p> <p>Evidence level <b>III</b><br/>Systematic review</p> <p>Quality- <b>B Good</b>- used comprehensive database and search strategy, inclusions criteria listed, articles up to 10 years old<br/>(Dearholt &amp; Dang, 2012)</p> | <p>Search strategy- Medline, Embase</p> <p>Search terms- cost+interferon +tuberculosis German &amp; English</p> <p>Identified 76 references, narrowed to 13</p> <p>Inclusion: study design cost analysis or cost-effectiveness. Population- high risk groups- HCW, immigrants, close contacts</p> <p>Outcome-cost, ratios</p> <p>Screening strategies- TST and/or IGRA</p> | <p>-construct validity-reviewed other groups besides HCW which can be a threat to generalizability for purposes of my study.</p> <p>-precision-had to calculate cost ratios for different countries to compare</p> <p>Author listed-</p> <p>-assumptions regarding TST specificity varied widely between the studies making comparison difficult</p> <p>-different cost ratio assumptions and test parameters between TST and IGRA varied and therefore cannot be directly compared</p> | <p>-in all studies the TST only strategy was most expensive'</p> <p>-all 13 studies showed decrease in costs with use of IGRAs</p> <p>-in 4 out of 7 dual step studies- IGRA after +TST- was least expensive and in 2 studies IGRA only was least expensive</p> | <p>-Studies show strong evidence in support of cost-effectiveness of using IGRA for screening high risk groups- HCW, immigrants from high-incidence countries, close contacts</p> |

| <u>Reference, Type, Quality</u>   | <u>Methods</u>   | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>   |
|---|--|--|---|--|
| <p>Article 15</p> <p>Pai, M., Zwerling, A., &amp; Menzies, D. (2008, August 5). Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. <i>Annals of Internal Medicine</i>, 149(30), 177-184. doi:10.7326/0003-4819-149-3-200808050-00241</p> <p>(Pai et al., 2008)</p> <p><b>Evidence level III</b><br/>Systematic review mixed with meta analysis</p> <p><b>Quality- B Good-</b><br/>Thorough literature searches of reputable databases, used statistics<br/>(Dearholt &amp; Dang, 2012)</p> | <p>-Search PubMed thru 2008<br/>-added 20 new studies to a previous analysis and eliminated those with less than 10 participants and those with known immunocompromised</p> <p>-Fixed effects meta-analysis with correction for over dispersion<br/>-Sensitivity- microbiologically confirmed active TB, not including immunocompromised<br/>-specificity- healthy low-risk participants without known exposure to tb</p> <p>-2 independent reviewers performed searches and selected articles</p> <p>-95% Cis<br/>-summarized results in forest plots<br/>-to pool estimated- fixed effects meta-analysis with correction of variability using MetaDiSc</p> <p>-evaluated heterogeneity with chi-square and I<sup>2</sup> tests</p> <p>Used 38 articles<br/>-15 QFT@-G, QFT@-GIT<br/>9 T-SPOT@.TB</p> | <p>-most studies small<br/>-no gold standard for dx of TB<br/>-variable TST methods and cutoff<br/>-data on T-SPOT@.TB limited</p> | <p>Sensitivity:<br/>78% QFT@-TB G (95%CI)</p> <p>70% QFT@-GIT (CI 63-78%)</p> <p>90% T-SPOT@.TB (CI 86-93%)</p> <p>Specificity:<br/>99% for non-BCG for both QFT@s (CI 98-100%)</p> <p>96% BCG vaccinated (CI 94-98%)</p> <p>T-SPOT@.TB 93% (CI 86-100%)<br/>TST97% (CI 95-99%)</p> | <p>-IGRAs have excellent specificity unaffected by BCG</p> <p>TST specificity high in non-BCG vax but low in BCG-Vax</p> <p>Sensitivity of IGRA &amp; TST not consistent but T-SPOT@.TB is more sensitive T-SPOT@.TB than QFT@ and TST</p> |

| <u>Reference, Type, Quality</u>  | <u>Methods</u>  | <u>Threats</u>  | <u>Findings</u>  | <u>Conclusions</u>   |
|--|---|---|--|--|
| <p>Article 16</p> <p>Slater, M., Welland, G., Pai, M., Parsonnet, J., &amp; Banaei, N. (2013, October 15). Challenges with quantiferon-TB gold assay for large-scale, routine screening of U.S. healthcare workers. <i>American Journal of Respiratory Critical Care Medicine</i>, 188(8), 1005-1010. doi: 10.1164/rccm.201305-0831OC</p> <p>(Slater et al., 2013)</p> <p>Evidence level <b>V</b><br/>Organizational Experience-Program evaluation<br/>Quality level <b>B Good</b>-<br/>project aim clearly stated, methods and results adequately described, clear interpretation.</p> <p>(Dearholt &amp; Dang, 2012)</p> | <p>-Retrospective review of QFT® results of HCW with 2 or more QFT® tests June 2008-July 2010 at SUMC.</p> <p>-SUMC-611 bed hospital, 14 cases TB per year</p> <p>-9,153 HCW annual QFT® results</p> <p>-new positives had repeated QFT® in within 6 weeks</p> <p>-2008 QFT®-GIT upgrade</p> <p>-independent group t tests to compare variables</p> <p>-z statistic for proportions</p> <p>-linear regression compare independent variables</p> <p>-kappa to assess agreement between QFT® assays</p> | <p>-attrition bias-11.1% n=40 did not follow up for repeat testing- staff turnover, refusal or preference</p> <p>-there is no clear standard for when to repeat QFT®s</p> <p>-construct-generalizability threat- lack of gold standard to dx LTBI</p> <p>-Lack of risk factor data in cohort- other variables could contribute such as exposures during the year.</p> <p>-precision- intervals between tests non-standardized</p> <p>-no randomization</p> <p>-changing lab practices over 25 months could cause variability.</p> | <p>-repeat QFT® conversion rate was 4.4% and short term reversion rate 64.8% (short term is testing &lt; 60 days between tests)</p> <p>-of 1,223 (13.4%) initially +QFT®, 67.5% stayed positive (828)</p> <p>-of 8,227 – QFT®, 4.4% (361) converted. High proportion fell between 0.35 to 1.0 IU/ml cutoff</p> <p>-positives were retested and 64% reverted short term. Long term tested 63% reverted</p> <p>-11.1% did not return for repeat testing</p> <p>-changing QFT® cutoff would help conversion rates</p> | <p>-short term retesting new QFT® conversions is feasible to reduce false-positives</p> <p>-Short term retesting of +conversions revealed 67% reversion to negative.</p> <p>-QFT® standardization is needed</p> <p>-cutoff variability needs examined.</p> <p>-Variability sources may include incubation time, ELISA between run, Manufacture related, immunologic factors</p> <p>-manufacturer definition of QFT® conversion is inflated and incompatible with low risk setting.</p> <p>-higher QFT® cutoff is needed</p> <p>-cutoff of 5.3 yields similar cutoff of institutions historical TST</p> |

| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>  | <u>Findings</u>   | <u>Conclusions</u>   |
|---|---|---|---|--|
| <p>Article 17</p> <p>Dorman, S. E., Belknap, R., Graviss, E. A., Reves, R., Schluger, N., Weinfurter, P., . . . Daley, C. (2014, January 1). Interferon-<math>\gamma</math> release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. <i>American Journal of Respiratory Critical Care Medicine</i>, (189)1, 77-87. doi <a href="https://doi.org/10.1164/rccm.201302-0365OC">10.1164/rccm.201302-0365OC</a></p> <p>(Dorman et al., 2014)</p> <p>Level <b>II</b> Quasi-experimental<br/>Quality <b>A high</b>-generalizable, consistent results, large sample size, conclusions derived from the results (Dearholt &amp; Dang, 2012)</p> | <ul style="list-style-type: none"> <li>- Longitudinal, cross- sectional</li> <li>- 2,563 HCW</li> <li>- 4 healthcare systems in US- Denver, Houston, Baltimore, New York City</li> <li>- Case rate low- 4-9 per 100,000</li> <li>- QFT®-GIT, T-SPOT®.TB, and TST (tubersol) baseline, 6 months, 18 months 2/2008 to 3/2011</li> <li>- QFT®-GIT, T-SPOT®.TB collected and TST immediately after phlebotomy (2 step if needed)</li> <li>- Interviewed at each visit</li> <li>- +TST were asked to repeat TST but counseled of risks</li> </ul> <p>Exclusion-</p> <ul style="list-style-type: none"> <li>- Current or prior TB</li> <li>- Prior anaphylaxis to TST</li> <li>- TST past 6 months</li> </ul> <p>Substudies-</p> <ul style="list-style-type: none"> <li>- 2 sets of IGRA 2 weeks apart without TST in between</li> <li>- Concordant negative or concordant positive baseline included</li> <li>- Repeat ELISA testing for all positives started midway through the study</li> </ul> <p>Boosting Sub study-</p> <ul style="list-style-type: none"> <li>- Repeat IGRA in 7-21 days after</li> </ul> | <p>-To prevent bias and improve reliability-the lab staff did not access clinical information or prior IGRA results and staff performing one type IGRA did not access result of other IGRA</p> <p>-Author did an excellent job of listing limitations/threats-</p> <p>-Absence of gold-standard</p> <p>-attrition- good-low rate of loss to follow up</p> <p>-reliability threat- cannot generalize study to immunosuppressed or areas with higher rates of TB</p> <p>-cannot generalize to Europe or areas with lower rate of + IGRA compared to TST- these areas may use different tuberculin and higher rates of BCG</p> <p>-not all +TST patients accepted repeat TST</p> <p>-Results could vary with different kinds of PPD</p> <p>-Varied lab practices could affect validity/reliability</p> | <p>-baseline +TST with – IGRA associated with BCG odds 25.1 (95%CI)</p> <p>-Test conversions 6.1% QFT®-GIT, 8.3% T-SPOT®.TB , 0.9% TST</p> <p>-of test converters- 76.4% QFT®-GIT reverted, 77.1% T-SPOT®.TB revert to negative at 6 months</p> <p>-sub study if IGRA retesting without TST</p> <p>-negative/positive discordance 8.8% QFT®-GIT, 12.6% T-SPOT®.TB at 2 weeks lab redraw</p> <p>-baseline + QFT®-GIT 3.8%, T-SPOT®.TB 5%, TST 1.8%</p> | <p>-majority of new positive TST and IGRAs were false-positive</p> <p>-reversions for all 3 tests were observed in 50% participants</p> <p>-none had conversions to all 3 tests at once</p> <p>-conversions were not associated with TB exposure risk</p> <p>-Sub study- half of new conversions by QFT®-GIT were not confirmed by ELISA</p> <p>-IGRA specificity in US HCW at low risk is less than previously reported by prior studies</p> <p>-borderline cutoff would not help clinically because only a small proportion 15-18% of converters were close to cut points</p> <p>-IGRAs play a role for HCW with BC vaccine as positive TST but negative IGRA was strongly associated.</p> <p>-false-positive conversions occur 6-9 times more w IGRA than TST – balance use with logistical advantages</p> <p>-repeat testing of new converters should be considered</p> <p>-repeat ELISA from stimulated plasma for QFT®-GIT + may be useful</p> |

|  |  |  |  |  |
|--|--|--|--|--|
|  | <p>baseline IGRA and TST</p> <p>Statistics-</p> <ul style="list-style-type: none"><li>- K coefficient- agreement measures</li><li>- Two-proportions z test</li><li>- McNemar's test- dependent proportions</li><li>- Holm-Bonferroni- multiple comparisons</li><li>- T test-compare mean changes IGRA</li><li>- Reproducibility &amp; repeatability sub studies used assess variability</li><li>- Linear mixed-effects models</li><li>- Within subject standard deviation and intraclass correlation coefficient</li></ul> |  |  |  |
|--|--|--|--|--|

| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>   |
|---|---|--|---|--|
| <p>Article- 18-<br/>Loddenkemper, R., Diel, R., &amp; Nienhaus, A. (2012, July). To repeat or not to repeat- that is the question! <i>Chest</i>, 142(1), 11. doi: 10.1378/chest.12-0045</p> <p>(Loddenkemper et al., 2012)</p> <p>Level- <b>V</b>- Literature Review/Expert opinion- editorial<br/>Quality <b>B</b>- fairly definitive conclusions. Short article with only one true article review</p> <p>Article recommended by region 4 DHEC TB control MD</p> | <p>Methods not discussed in this short article. Good research is referenced however. Discussed research that is in the same periodical. This is an editorial.</p> | <p>-small number of articles reviewed<br/>-no discussion of limitations of the research reviewed</p> | <p>-High income, low TB incidence countries- evidence points toward positive predictive values for IGRAs higher than TST.</p> <p>-gray zone 0.35 to 1.0 would reduce conversion to &lt;1%<br/>-using gray zone approximately every second HCW will revert to negative</p> | <p>-simple positive- negative interpretation of IGRA serial testing of HCW overestimates conversion and reversion rates</p> <p>-recommend preventive chemotherapy only for IGRA <math>\geq 1.0</math></p> <p>-IGRAs should be repeated in routine TB screening in + testers</p> <p>-Chest X-rays not needed in asymptomatic HCW with reversion in IGRA regardless of first positive IGRA concentration</p> |

| <u>Reference, Type, Quality</u>   | <u>Methods</u>   | <u>Threats</u>  | <u>Findings</u>   | <u>Conclusions</u>  |
|---|--|---|---|---|
| <p>Article 19<br/>Schablon, A., Nienhaus, A., Ringshausen, F. C., Preisser, A. M., &amp; Peters, C. (2014, December). Occupational screening for tuberculosis and the use of a borderline zone for interpretation of the IGRA in German healthcare workers. <i>PLoS One</i>, 9(12). doi: 10.1371/journal.pone.0115322</p> <p>(Schablon et al., 2014)</p> <p>Evidence <b>level II</b> Quasi-experimental<br/>Quality <b>B Good</b><br/>(Dearholt &amp; Dang, 2012)</p> <p>Article recommended by region 4 DHEC TB control MD</p> | <p>Convenience sample, cohort of screenings in HCW-hospital, nursing home, and outpatient- conducted in occupational health clinic<br/>3,823 had one QFT®<br/>817 had second QFT®- whether patients had second QFT® was not standardized- occupational health physician determined need based on exposure or working on high risk ward<br/>-questionnaire to assess risk<br/>-low incidence country</p> <p>SPSS statistical software<br/>Chi square<br/>Odds ratios<br/>Confidence intervals</p> | <p>-convenience sample – selection bias<br/>- second QFT® not standardized<br/>- German study- could be higher risk than is US but it is listed as low incidence.<br/>-This included serial testing, not just baseline.<br/>-Some author bias is apparent as they specifically examined articles regarding variability in results and cutoffs. I think there was an expectation of the cutoff being too high.<br/>-no inclusion or exclusion criteria</p> | <p>-Positive QFT® risk factors= age &gt;55, foreign birth, hx TB, internal medicine work, infection ward work, geriatric care work.</p> <p>-Conversion rate 2.8%<br/>-Reversion 37.3%<br/>-changing conversion definition to &lt;0.2 to &gt;0.7 decreases conversion rate to 1.2%</p> | <p>Borderline zone 0.2 to ≤ 0.7 may avoid X-rays and meds that are not needed.</p> <p>No case of active Tb found- screening should be restricted to HCW w unprotected contact</p> |

| <u>Reference, Type, Quality</u>  | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>  | <u>Conclusions</u>   |
|--|---|--|--|--|
| <p>Article 20</p> <p>Rangaka, M. X., Wilkinson, K. A., Glynn, J. R., Ling, D., Menzies, D., Mwansa-Kambafwile, J., . . . &amp; Pai, M. (2012, January). Predictive value of interferon-<math>\gamma</math> release assays for incident active tuberculosis: a systematic review and meta-analysis. <i>Lancet Infectious Disease</i>, 12, 45-55. doi: 10.1016/51473-3099(11)70210-9</p> <p>(Rangaka et al., 2012)</p> <p>Evidence level <b>III</b> – systematic review with meta analysis, combo type of studies</p> <p>Quality- <b>A High</b>- thorough literature search, conducted quality assessment, new statistics, definitive conclusions (Dearholt &amp; Dang, 2012)</p> <p>Article recommended by region 4 DHEC MD</p> | <p>-PubMed, EMBase, Biosis, Web of Science</p> <p>-studies up to 6/30/11 IGRA predictive value</p> <p>-2 independent reviewers</p> <p>-Quality assessment- Newcastle-Ottawa scale- study group selection, comparability of groups, exposure or outcome of interest</p> <p>-15 studies</p> <p>-26,680 participants</p> <p>-Statistics- Main interest- person-years incidence rates of disease</p> <p>-calculated incidence rate rations for disease progression in IGRA + vs – and also for TST</p> <p>-DerSimonian &amp; Laird random effects relative risk w 95% CI</p> <p>-heterogeneity-I<sup>2</sup> statistic</p> <p>-country level stratification- high income, low, middle</p> | <p>-did not limit articles to 5 years</p> <p>-most studies did not “fully answer” whether IGRA could predict active tb</p> <p>-Authors note- most studies have bias because they do not assess other risk factors for tb</p> <p>-could not do formal assessment of publication bias- assumed some bias</p> <p>-most IGRA studies have some “industry involvement” which may lead to bias</p> <p>-most studies did not examine high income settings</p> <p>This article made efforts to improve validity through quality assessment of articles and statistics applied, discussed limitations and listed no conflicts of interest</p> | <p>-moderate association between + result and TB</p> <p>-IGRA + and TST + were about the same for risk of tb</p> <p>-proportion of IGRA + was lower than for TST</p> | <p>-neither IGRA or TST have high accuracy prediction active TB</p> <p>-use of IGRA might reduce number of people who take preventive meds</p> <p>-Which test you use should be based on population, logistics, cost, patient preference rather than just predictive ability</p> |



| <u>Reference, Type, Quality</u>   | <u>Methods</u>  | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>   |
|---|---|--|---|--|
| <p>Article 21</p> <p>Banaei, N., Gaur, R. L., &amp; Pai, M. (2016). Interferon-<math>\gamma</math> release assays for latent tuberculosis: what are the sources of variability? <i>Journal of clinical Microbiology</i>. doi:10.1128/JCM.02803-15</p> <p>(Banaei et al., 2016)<br/>Evidence level <b>V</b> Expert Opinion/Literature Review</p> <p>Quality <b>A High</b>- clear expertise, definitive conclusions (Dearholt &amp; Dang, 2012)</p> <p>Article recommended by region 4 DHEC TB MD</p> | <p>-reviewed literature to summarize sources of variability</p> <p>-method of lit review nonspecific.</p> <p>Purpose of paper is more for expert opinion.</p> | <p>-did not discuss methods for conclusions but appears to be updating a previous review.</p> <p>-did not list method for search of articles</p> <p>-did not discuss limitations of studies reviewed</p> | <p>Higher rate of false- positives with IGRA</p> <p>Sources of Variability-</p> <p>-Preanalytical</p> <ul style="list-style-type: none"> <li>- evening blood draw related to higher response value with QFT@-GIT</li> <li>-Inadequate disinfection- can contaminate tubes</li> <li>-correct order of tubes may matter- nil, antigen, mitogen- tube contamination- antigen contaminated with mitogen = false +, contamination of nil tube with mitogen = false negative</li> <li>-volume of blood can alter result- inverse TB response</li> <li>- vigorous shaking may increase IFN-<math>\gamma</math> response- false + or false –</li> <li>- processing day 1-4 hr. before antigen stimulation can lower t cells</li> <li>-incubation delay- declines TB response</li> <li>-indeterminate results increase in autumn and winter- transport in lower temp may affect result-particularly with T-SPOT@.TB</li> <li>- longer incubation = does not increase TB response</li> </ul> <p>Analytical</p> <ul style="list-style-type: none"> <li>-biologic fluid uncontrolled factors</li> <li>-pipetting imprecision</li> <li>-centrifugation error</li> <li>-error in washing steps</li> <li>-operator error in measurement of signal</li> <li>-between run variability=<math>\pm</math> 0.6 for all, <math>\pm</math> .24 for those with initial borderline response</li> <li>-conversion 9%, reversion 7%</li> </ul> <p>Post-analytical</p> <ul style="list-style-type: none"> <li>-clerical error data entry</li> </ul> | <p>-neither IGRA or TST have high accuracy prediction active TB</p> <p>-use of IGRA might reduce number of people who take preventive meds</p> <p>-Which test you use should be based on population, logistics, cost, patient preference rather than just predictive ability</p> |

|  |  |  |   |  |
|--|--|--|---|--|
|  |  |  | <p>Manufacturing</p> <ul style="list-style-type: none"><li>- Some reports of false + in faulty antigen tubes</li><li>- Potential bacterial contamination</li></ul> <p>Immunologic</p> <ul style="list-style-type: none"><li>- Boosting by TST= increase</li></ul> <p>Immunomodulation microbes- skin microorganisms such as staff</p> |  |
|--|--|--|---|--|

| <u>Reference, Type, Quality</u>   | <u>Methods</u>   | <u>Threats</u>  | <u>Findings</u>   | <u>Conclusions</u>   |
|---|--|---|---|--|
| <p>Article 22</p> <p>Nienhaus, A. (2013). Clinical review of literature pertaining to the use of interferon gamma release assays for tuberculosis screening in healthcare workers: Evidence base and clinical experience with Quantiferon-TB Gold (QFT®). <i>HCW Clinical Review</i>. Retrieved from <a href="http://usa.quantiferon.com/irm/content/pdfs/ClinRev_QFT_HCW_EN_1013_QA_LR%20(1).pdf">http://usa.quantiferon.com/irm/content/pdfs/ClinRev_QFT_HCW_EN_1013_QA_LR%20(1).pdf</a></p> <p>(Nienhaus, 2013)</p> <p><b>Level V</b> Literature Review/Expert Opinion<br/>Quality <b>Good B</b></p> <p>Expertise credible, logical opinions for conclusions (Dearholt &amp; Dang, 2014)</p> | <p>-Discussion of TB, TST, IGRA pros and cons with literature review following</p> <p>-11 studies reviewed with main findings summarized in table.</p> | <p>-did not discuss inclusion or exclusion criteria</p> | <p>-HCW 2-5x increase risk if TB</p> <p>- study supports use of QFT® vs TST in neonates exposed to HCW w TB</p> <p>-greater specific of QFT® over TST</p> <p>-a single positive IGRA, may not be infection</p> <p>-QFT®-G and QFT®-GIT, more effective &amp; less costly than TST whether vaccinated with BCG or not</p> <p>-IGRA appropriate for serial screening HCW in low incidence country w high vaccination rates</p> <p>-IGRAs cost effective for screening high risk individuals in low incidence setting</p> <p>- specificity IGRA higher than TST, correlated w exposure better</p> <p>-IGRA reduces false-positives from BCG</p> <p>-good correlation betw occupational risk factors and IGRA +</p> | <p>-IGRA is appropriate for HCW tuberculosis screening</p> <p>-Advantages of IGRA:</p> <ul style="list-style-type: none"> <li>-single visit</li> <li>-use of positive &amp; -controls</li> <li>-unaffected by BCG vaccine</li> <li>-objective interpretation</li> </ul> <p>-Superior specificity over TST in countries with low TB burden</p> <p>-Saves 25-85% of chest x-rays</p> <p>-IGRA correlated with TB risk factors</p> <p>--improves cost-effectiveness</p> |

| <u>Reference type, quality</u>  | <u>Methods</u>   | <u>Threats</u>   | <u>Findings</u>   | <u>Conclusions</u>   |
|---|--|--|---|--|
| <p>Article 23</p> <p>Grabau, M., &amp; Filby, D. (2015). "Lean" the new hire onboarding process for healthcare workers: evaluating the Quantiferon™-TB Gold test. <i>Qiagen</i>. Retrieved from <a href="http://www.qiagen.com">www.qiagen.com</a></p> <p>(Grabau &amp; Filby, 2015)</p> <p>Level V Case Report<br/>Quality B Good<br/>Clear objectives for the article, consistent recommendations (Dearholt &amp; Dang, 2014)</p> | <p>Case study on how lean principles can improve new hire onboarding and TB screening process.</p> <p>-compares process to Toyota lean principles to address: Defects, Overproduction, Transportation, Waiting, Inventory, Motion, Over-processing, Talent</p> | <p>-published by Qiagen</p> <p>-did not directly report results of the hospital using the QFT®</p> | <p>-Use of QFT® can result in 7-9 days sooner clearance to work for new hires</p> <p>-Cost of unfilled positions, staff overtime can be significant in comparison to QFT®</p> <p>-labor costs savings for test administration</p> <p>-process is respectful of candidate's time</p> | <p>-QFT® less expensive, faster, less false positives, reduces waste, reduces hiring delays and potentially lost candidates.</p> <p>-QFT® is in line with lean principles and is more efficient and less expensive</p> |

**APPENDIX B**

**EVIDENCE LEVEL AND QUALITY GUIDE**

Table B.1 Evidence and quality guide

|   |  |
|---|--|
| <p><b>Level I</b> Experimental study, randomized controlled trial (RCT). Systematic review of RCTs, with or without meta-analysis</p>   | <p><b>A High Quality:</b> consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough references to scientific evidence</p> <p><b>B Good quality:</b> Reasonably consistent results, sufficient sample size for the study design, some control, fairly definitive conclusions, reasonably consistent recommendations based on fairly comprehensive literature reviews that includes some reference to scientific evidence</p> <p><b>C Low quality or major flaws:</b> Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn</p> |
| <p><b>Level II</b> Quasi-experimental study. Systematic review of combination of RCTs and quasi-experimental, or quasi-experimental studies only, with or without meta-analysis</p>   |  |
| <p><b>Level III</b> Non-experimental study. Systematic review of a combination of RCTs, quasi-experimental and non-experimental studies, or non-experimental studies only, with or without meta-analysis. Qualitative study or systematic review with or without a meta-synthesis</p> |  |

|  |  |
|--|--|
| <p><b>Level IV</b> Opinion of respected authorities and/or nationally recognized expert committees/consensus panels based on scientific evidence. Includes: clinical practice guidelines, consensus panels</p>                                   | <p><b>A High quality:</b> Material officially sponsored by a professional, public, private organization, or government agency; documentation of a systematic literature search strategy; consistent results with sufficient numbers of well-designed studies; criteria based evaluation of overall scientific strength and quality of included studies and definitive conclusions; national expertise is clearly evident; developed or revised within the last 5 years.</p> <p><b>B Good quality:</b> Material officially sponsored by a professional, public private organization, or government agency: reasonably thorough and appropriate systematic literature search strategic; reasonably consistent results, sufficient numbers of well-designed studies; evaluation of strengths and limitations of included studies with fairly definitive conclusions; national expertise is clearly evident; developed or revised within the last 5 years</p> <p><b>C Low quality or major flaws:</b> Material not sponsored by and official organization or agency; undefined, poorly defined, or limited literature search strategy; no evaluation of strengths and limitations of included studies, insufficient evidence with inconsistent results, conclusions cannot be drawn; not revised within the last 5 years</p> |
| <p><b>Level V</b> Based on experiential and non-research evidence. Includes: Literature reviews; quality improvement, program or financial evaluation; Case reports; Opinion of nationally recognized experts based on experiential evidence</p> | <p><b>Organizational Experience:</b></p> <p><b>A High Quality:</b> Clear aims and objectives, consistent results across multiple settings; formal quality improvement, financial or program evaluation methods used; definitive conclusions, consistent recommendations with thorough reference to scientific evidence.</p> <p><b>B Good quality:</b> Clear aims and objectives; consistent results in a single setting; formal quality improvement of financial or program evaluation methods used; reasonably consistent recommendations with some reference to scientific evidence</p> <p><b>C Low quality or major flaws:</b> Unclear or missing aims and objectives; inconsistent results; poorly defined quality improvement, financial or program evaluation methods; recommendations cannot be made.</p>   |

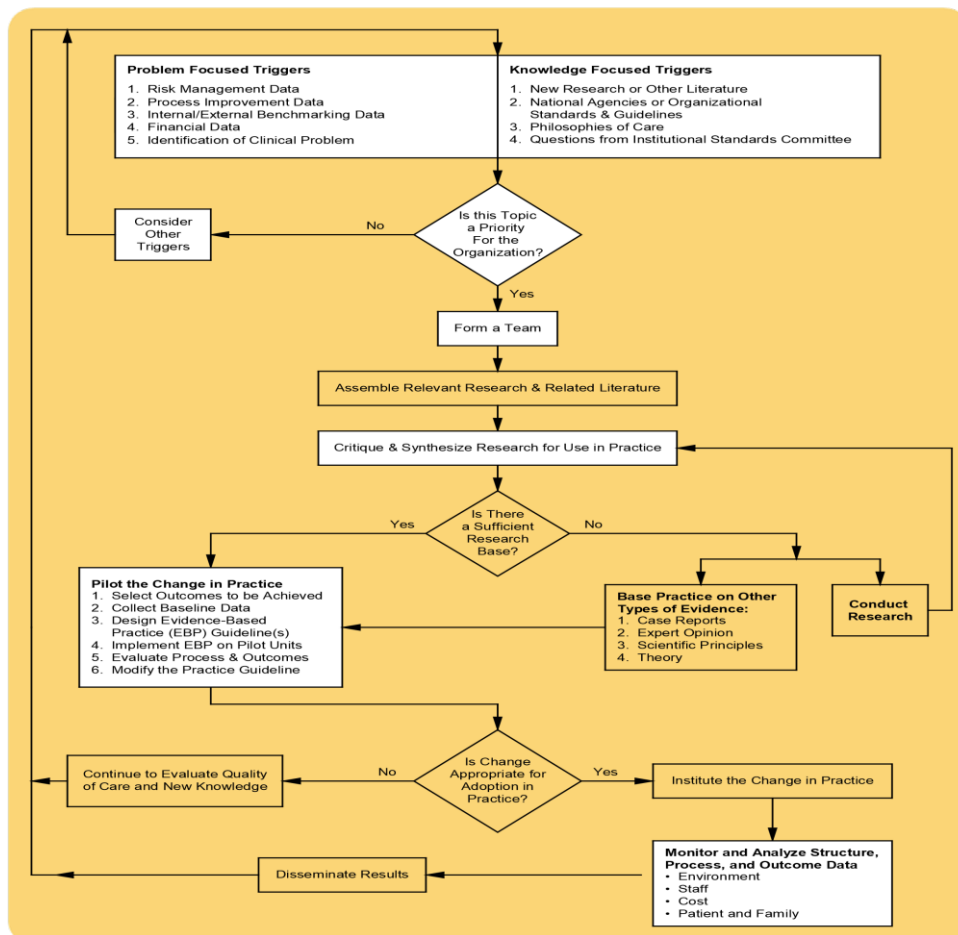
|  |   |
|--|---|
| <p>©The John Hopkins Hospital/The Johns Hopkins University<br/>(Dearholt &amp; Dang, 2014)</p> | <p><b>Literature Review, Expert Opinion, Case Report, Community Standard, Clinician Experience, Consumer Preference:</b></p> <p><b>A High Quality:</b> Expertise is clearly evident: draws definitive conclusions; provides scientific rationale: thought leader in the field</p> <p><b>B Good quality:</b> Expertise appears to be credible; draws fairly definitive conclusions: provides logical argument for opinions</p> <p><b>C Low quality or major flaws:</b> Expertise is not discernable or is dubious: conclusions cannot be drawn</p> |
|--|---|

## APPENDIX C

### CONCEPTUAL FRAMEWORK

- *Used/Reprinted with permission from the University of Iowa Hospitals and Clinics. Copyright 1998. For permission to use or reproduce the model, please contact the University of Iowa Hospitals and Clinics at (319)384-90*

### The Iowa Model of Evidence-Based Practice to Promote Quality Care



◇ = a decision point

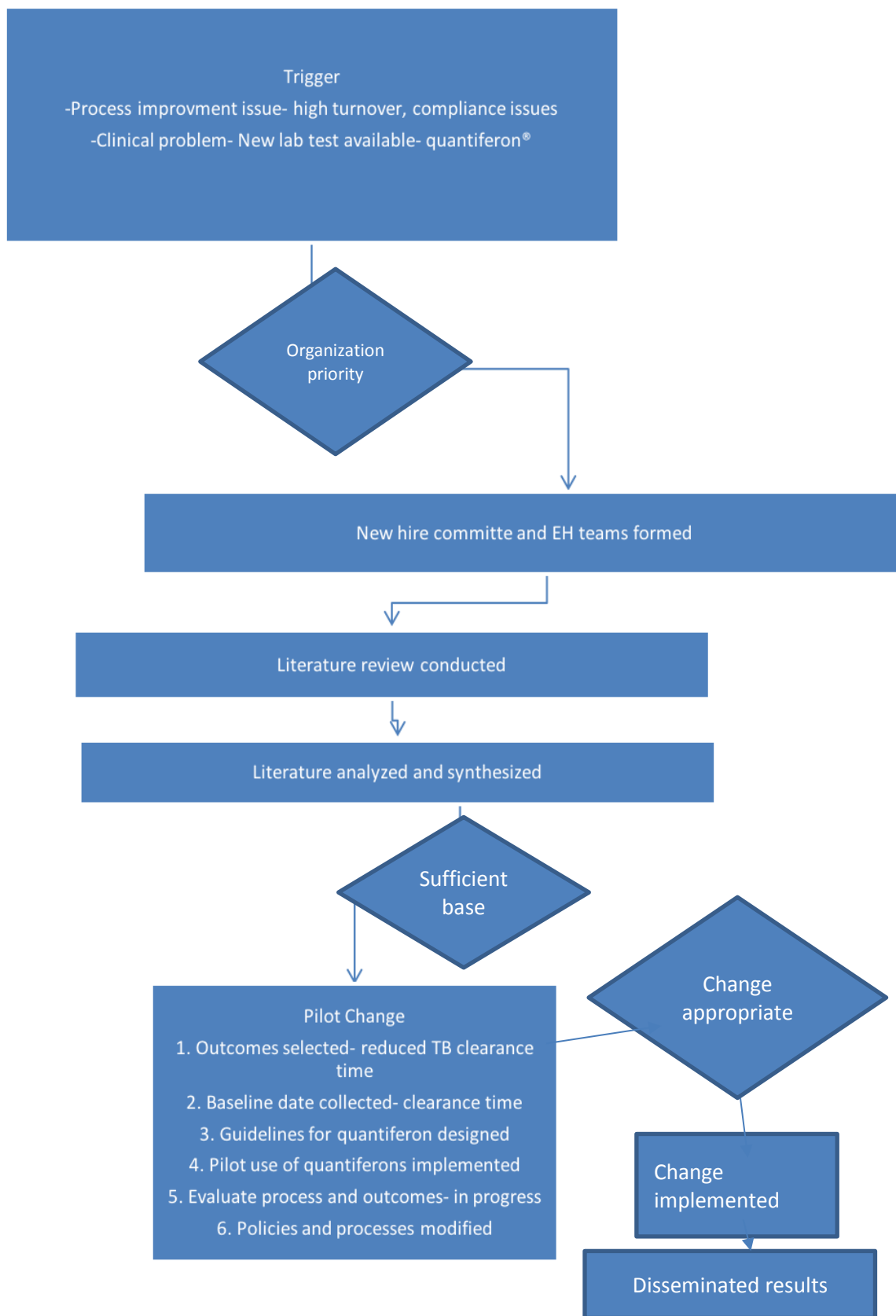
Titler, M.G., Kleiber, C., Steelman, V.J., Rakel, B. A., Budreau, G., Everett, L.Q., Buckwalter, K.C., Tripp-Reimer, T., & Goode C. (2001). The Iowa Model Of Evidence-Based Practice to Promote Quality Care. *Critical Care Nursing Clinics of North America*, 13(4), 497-509.

REQUESTS TO:  
Department of Nursing  
University of Iowa Hospitals and Clinics  
Iowa City, IA 52242-1009

DO NOT REPRODUCE WITHOUT PERMISSION

Revised April 1998 © UIHC





**APPENDIX D**

**INSTITUTIONAL REVIEW BOARD APPROVALS**

**OFFICE OF RESEARCH COMPLIANCE**

**INSTITUTIONAL REVIEW BOARD FOR HUMAN RESEARCH  
DECLARATION of NOT RESEARCH**

This is to certify that research proposal: **Pro00063801**

Entitled: *Tuberculosis Screening in New Healthcare Employees: A Comparison of QuantiFERON-TB Gold In-Tube Test and Tuberculin Skin Test*

Submitted by:

Principal Investigator: Mary Giovannetti  
College of Nursing  
1601 Greene Steet  
Columbia, SC 29208

was reviewed on **1/27/2017** by the Office of Research Compliance, an administrative office that supports the University of South Carolina Institutional Review Board (USC IRB), and has determined that the referenced research study is not subject to the Protection of Human Subject Regulations in accordance with 45 CFR 46 et. seq.

No further oversight by the USC IRB is required; however, the investigator should inform the Office of Research Compliance prior to making any substantive changes in the research methods, as this may alter the status of the project.

If you have questions, contact Arlene McWhorter at [arlenem@sc.edu](mailto:arlenem@sc.edu) or (803) 777-7095.

Sincerely,



Lisa M. Johnson  
IRB Manager

Email approval from Healthcare system IRB 2/1/17:

Mary, I spoke with Frank Stewart and he said to proceed with your study. Please upload this email as a private comment (this option is available on the left side of your eIRB screen when you click into your study) for confirmation.

Thanks,  
David

**David L. Suárez, MLIS**  
IRB Coordinator | Office of Research Compliance

101 East Wood Street | Spartanburg, SC 29303  
o: 864-560-6892 | f: 864-560-1950  
e: [dsuarez@srhs.com](mailto:dsuarez@srhs.com) | w: [SpartanburgRegional.com](http://SpartanburgRegional.com)

## APPENDIX E

### NURSING RESEARCH COUNCIL PROPOSAL AND APPROVALS

Evidence-Based Quality Improvement DNP Clinical Dissertation Project

Tuberculosis Screening in New Healthcare Employees: A Comparison of QuantiFERON®-TB Gold In-Tube Test and Tuberculin Skin Test

**Principle Investigator:** Mary Giovannetti, NP

**Co-Investigator:** Stephanie Barnhill, NP

**Faculty/Committee:** Dr. Stephanie Burgess, Dr. Karen McDonnell, Dr. Abbas Tavakoli

**To be conducted at:** Spartanburg Regional Healthcare System

**PICOT:** As a foreground question, among all adult newly hired healthcare employees at a healthcare system, how does baseline testing with QuantiFERON®-TB Gold In-Tube test (QFT®-GIT) compare with two step PPD TB skin test in regards to time for completion of tuberculosis screening and compliance with screening within 10 days of orientation over a 2-month time frame?

#### **Purpose**

The purpose of this quality improvement DNP project is to compare baseline testing with QuantiFERON®-TB Gold In-Tube test (QFT®-GIT) to the two step PPD TB skin test in regards to tuberculosis screening time, costs, overall onboarding clearance time, and compliance for new employees.

Spartanburg Regional Healthcare System (SRHS) currently employs approximately 6,800 employees and experienced a 15% employee turnover rate in 2015 and 2016 which led to staffing issues and utilization of expensive locum tenens temporary contract employees. There was an increase in hiring due to this turnover and an increased demand for Employee Health to expedite new hire clearance. Employee Health was asked to onboard new hires quicker and increase appointment availability. After careful review, it was found that the long process of tuberculosis screening contributed to the longer onboarding time for new hire employees.

The Department of Health and Human Services Centers for Disease Control and Prevention (CDC) recommends that all healthcare workers receive initial screening for TB upon hire by a 2-step tuberculin skin test (TST) (Jensen et al., 2006). There are three main categories of problems with utilization of the two step tuberculin skin test: extended screening time, noncompliance, and potential inaccuracy in placement and results. Employee Health completes tuberculosis screening with the two step PPD skin test. This

process takes 2-4 visits and can take 10 days to 3 weeks or more to complete. If the new employee fails to return for a placement or reading, orientation may be delayed.

Tuberculin skin test was the only available test for TB screening until 2001 when Interferon gamma release assays (IGRA) were developed. IGRA's can potentially overcome issues with TST tuberculosis clearance screening time and compliance, as well as problems with inaccurate results. In contrast to TST, IGRA's do not react to nontuberculous mycobacteria or BCG vaccination. IGRA's can also be completed in one visit and eliminate the need for multiple visits. Furthermore, IGRAs have been found to have a higher correlation to TB exposure than TSTs improving accuracy. IGRA's are more expensive than TST's, but utilization is expected to reduce costs associated with staffing requirements, inadequate testing results, poor employee compliance follow up, and potential DHEC citations for organization noncompliance (Mazurek et al., 2010). In February of 2016, Employee Health implemented QFT®-TB Gold In-Tube Test for all new hires in place of the 2 step PPD. Preliminary assessment revealed that implementation of QFT® for new hires along with other factors has led to increase in available appointments, decrease in screening and onboarding time. This project will further analyze the data for publication in dissertation and in journal publication.

## **Literature Review and Synthesis**

Twenty-three studies were included in the review of the literature. The articles were classified into levels I through IV according to John Hopkins Research and Non-Research evidence appraisal tools (Dearholt & Dang, 2012). Level I includes experimental studies, II quasi-experimental, III Non-experimental, IV clinical practice guidelines, consensus or position statements, and level V literature review, expert opinion, community standard, clinician experience, and consumer preference (see Appendices B for level and quality guide). Of the 23 articles analyzed there were four level II articles, seven level III, two level IV, and 10 level V. Quality of the articles were also analyzed as shown in table 5 according to John Hopkins appraisal tools with ratings of A- high quality, B- Good quality, and C- Low Quality (Dearholt & Dang, 2014).

Analysis of the literature revealed pros and cons to choosing the QFT®-GIT for TB skin testing for new healthcare workers. There are a number of positive logistical factors that would provide value for employee health offices while improving cost-effectiveness. Since QFT®-GITs are completed in one test, new hire onboarding and tuberculosis clearance time should be reduced. This will also reduce the burden on employee health staff time spent on tuberculosis clearance activities, and enhance convenience to the new hire (Foster-Chang et al., 2014; Graban & Filby, 2015; Veaser et al., 2007). Cost analysis revealed that IGRAs are cost effective (dePerio et al., 2009; Foster-Chang et al., 2014; Graban & Filby, 2015; Nienhaus, 2013; Nienhaus et al., 2011). The QFT®-GIT has high specificity but there are some concerns about sensitivity (Banaei et al., 2016; Cummings et al., 2009; Dorman et al., 2014; Loddenkemper et al., 2012; Schablon et al., 2014; Slater et al., 2013; Weddle et al., 2014; Zwerling et al., 2012). However, sensitivity of the QFT®-GIT improves with consideration of patients with active tuberculosis (Mazurek et al., 2010). Some studies have shown that there can be issues with conversions and reversion and a borderline cutoff with retesting may be appropriate (Dorman et al., 2014; Loddenkemper et al., 2012; Mazurek et al., 2010;

Schablon et al., 2014; Slater et al., 2013; Weddle et al., 2014; Zwerling et al., 2012). When interpreting results, the immunologic status of the patient should also be considered with indeterminate results (Cummings et al., 2009). Standardization of lab procedures can help overcome some of the variability in results (Banaei et al., 2016). Overall, there is good evidence to implement QFT®-GITs in new hire healthcare workers while considering all the interpretation factors.

## **Study Design**

Employee Health was faced with a dilemma of increasing volume of new hires coming for appointments and increasing frustrations by management regarding delays in orientation. Employee Health management formed a new hire committee in Fall of 2015 to investigate the factors involved with delays in orientation. One factor identified in orientation delays was the amount of time it takes for new employees to complete the two-step TST. The literature was reviewed and multiple steps were taken to investigate the ability for Employee Health to offer an IGRA for all new hires in order to reduce the amount of time it takes to be cleared for orientation. In February of 2016, Employee Health implemented a quality improvement project to reduce onboarding time for new hires by implementing the QFT®-GIT in place of the two-step TST.

This quality improvement evidence-based project will be utilized to satisfy requirements for DNP clinical dissertation. The design will be descriptive comparative non-experimental which will compare the two methods of tuberculosis screening in regards to tuberculosis clearance time, compliance, costs, and overall onboarding time.

## **Conceptual Framework and Feasibility**

*The Iowa Model of Evidence-Based Practice to Promote Quality Care (Iowa Model)* will be utilized to guide implementation of the project. Stakeholder support, sample access and size, financial, legal and ethical resources are substantial. An adequate sample size should be easily obtained through the retrospective chart review. This project should not incur any costs other than time for the investigator.

## **Procedure and Data Collection**

The sample will include a convenience sample of all new hire potential employees that are scheduled for pre-placement assessment at the healthcare system Employee Health beginning March, April, and May 2016 utilizing the QFT®-GIT, and all new hires from March, April and May 2015 through November 2015 utilizing the two-step PPD screening.

Data will be collected retrospectively by electronic medical record chart review by the primary investigator employed by the Employee Health Department. Data will be compiled in a password protected excel spreadsheet with all identifiers removed. Data collected on each subject will include: dates for each pre-placement visit and pre-placement follow up visits, dates for TST placement and readings, dates for QFT®-GIT collection and dates results were received, dates for orientation, and dates for final

orientation clearance. Data regarding dates for completion of requirements that could delay orientation will also be collected including dates fit for duties, dates documentation was received for provider work notes, pre-work screen dates, and drug screen collection result dates. Notations will be made regarding any positive TST or QFT®-GIT results, required chest x-ray dates and results, symptom review dates, and DHEC referrals.

## **Data Analysis**

Once the survey data is entered into the encrypted file, the investigator in collaboration with a statistician will review the data and, create data in the form that would be useable in SAS for analyses. Data analysis will include both descriptive and inferential statistics using SAS 9.4. Frequency distribution will be included for categorical variables. The continuous variable statistics will include measures of central tendency (mean and median) and measures of spread (standard deviation and range). Inferential statistics will include T-test, Pearson correlation, and simple linear model. Findings with p-values less than or equal to .05 will be considered significant.

## **Evaluation Plan**

### **Questions/Outcomes/Evidence-based measures**

Q1. Will implementation of QFT reduce the number of days to complete tuberculosis screening for new hires?

- Retrospective data will be collected from electronic and paper Employee Health records. This data will be stored on a password protected spreadsheet without patient identifiers.
- The number of days it takes to complete TST screening will include the time from placement of step 1 to reading of the 2<sup>nd</sup> step. If the new hire brought documentation of step 1, then only completion of step 2 will be recorded. If the new hire fails to complete a step and has to be replaced, then that time will also be included in the number of days for clearance.
- Total tuberculosis screening clearance time for those completing the QFT®-GIT will include date of blood draw to date the result was reviewed. If the QFT®-GIT needs to be repeated for borderline positive result, this time will be included in overall screening time.
- Those with a previous positive TST will be included with days to clearance being 1 day.
- Data will be analyzed by simple t test. Regression model will be completed to control for demographic variables.

Q2. Will implementation of QFT for new hires reduce the overall number of days to complete onboarding?

- Time for onboarding will include days from first appointment to

completion of all requirements including tuberculosis screening, assessments, fit for duties, lab results, and review of any requested records. Completion of immunizations and Hepatitis B waivers will not be included because those are not completed until after orientation.

- Data will be analyzed by t test

Q3. Will implementation improve compliance with completion of tuberculosis screening within 10 days of orientation?

- Compliance will be defined as completing both steps of the 2 step skin test within 10 days of orientation or completion of any required repeat QFT®-GITs, symptom reviews, or chest x-rays.
- The proportion test will be used to compare two proportions.

Q4. Will implementation of QFT be cost-effective?

- A simple review of associated costs with QFT versus PPD including staff time will be reviewed. Actual average salary of Employees in Employee Health in relation to time it takes to completion of testing and assessment requirements, phone calls to contact non-compliant employees, and call employees with results of lab testing will be considered. Cost of supplies will include the cost for the PPD derivative, the syringe/needle, and cost of lab charges for QFT®-GIT. Labor costs from missed work for the new hire will not be considered since the new hire is not yet working for the organization and current salary cannot be determined.

## **Timeline**

Upon approval of the Nursing Research Council, SRHS IRB, and USC IRB, data collection will begin. Data collection and analysis will be completed by the end of March 2017 with DNP defense March 31, 2017. Manuscript with summary of findings will be submitted to Association of Occupational Health or related journal for consideration of publication.

## **Human Subjects**

An application for exempt status will be submitted to two IRBs: the healthcare system and University of South Carolina. The University of South Carolina typically grants exempt status for quality improvement projects which are focused on improving outcomes/processes in the setting and are not research to generate new knowledge. After approval, the investigator will begin to collect data. The primary investigator is in charge of routinely collecting data regarding onboarding times and has access to the electronic medical records. The investigator will only retrieve data essential for project. The excel spreadsheet will be saved in the investigator's access limited S-drive folder, with a



password protected spreadsheet. All computers are password protected and all data on the healthcare system's computers are encrypted. All identifiers will be removed from the spreadsheets. The investigator has completed Collaborative IRB Training Initiative (CITI) courses. Data will be disseminated in the aggregate.

**Nursing Research Council  
Final Approval Form with Two Scientific Reviews**

(This completed form will be placed in the Principle Investigator's (eIRB) Smart Form)

Principle Investigator (PI): Mary Giovannetti, Nurse Practitioner      Date: 1/24/17

Study Name: ***Tuberculosis Screening in New Healthcare Employees: A Comparison of QuantiFERON®-TB Gold In-Tube Test and Tuberculin Skin Test***

(Required 2 Independent Peer Reviewers: See Scientific Review Tools for Comments)

| Reviewer's Name & Credentials  | Title                                       | Review Date |
|--------------------------------|---|-------------|
| Mary Alice Hodge, PhD, RN, CNL | Professor, USC<br>Upstate School of Nursing | 1/20/17     |
| Jo Vaughn, MSN, RN             | Corp Educ –Hospital<br>Educ                 | 1/20/17     |

The scientific review was completed by a minimum of two independent reviewers who are members of the Nursing Research Council. Members of the research team, PI, or data collectors cannot participate in the review. The Scientific Reviewer Tool for Nursing Research Proposals was used as a guide in the review process by the review team.

We attest that the above information is correct and that, to the best of our knowledge, scientific review and approval of this PI's research proposal has been performed by a group of independent peer reviewers.

Tim Fagan, MA, MSN, CPHQ      1/24/17  
Nursing Research Council – Co-chairperson's Signature      Date

Betty Warlick, MN, RN      1/24/17  
Nursing Research Council – Co-chairperson's Signature      Date

**Instructions for the Nursing Research Council:**

1. The Nursing Research Council's Co-chairpersons will complete this form & email it to the Principle Investigator (PI).

**Instructions for the Principle Investigator (PI):**

1. The PI will work with the IRB Manager to upload into the eIRB their Nursing Research Proposal. This form, the scanned Preliminary Approval for Research Form plus other forms will also be uploaded into the eIRB Smart Form on the last page "General comments."

- 
2. The PI will email the NRC's Co-chairpersons that they have uploaded these forms & completed the eIRB process.

2017

## APPENDIX F

### POSTER ABSTRACT

#### **QuantiFERON®-TB Gold In-Tube Test for Baseline Tuberculosis Screening in New Healthcare Employees: A Review of the Literature**

**Author:** Mary Giovannetti, MSN, APRN, BC-FNP,  
Manager, Spartanburg Regional Healthcare System Employee Health  
Nurse Practitioner, Medical Group of the Carolinas Occupational Health  
DNP Student, College of Nursing, University of South Carolina

**Contact:** [mgiovannetti@srhs.com](mailto:mgiovannetti@srhs.com), 864-497-4087 (cell phone)

**Additional Authors:** Stephanie Burgess, PhD, APRN, BC, FAANP,  
Clinical Professor, Associate Dean for Practice, Director  
DNP/MSN, College of Nursing, University of South Carolina

Karen McDonnell, PhD, RN, OCN  
Assistant Professor  
College of Nursing, University of South Carolina

#### **Abstract**

**Introduction:** The two step tuberculin skin test is recommended by Centers for Disease Control and Prevention for all new healthcare workers. The two step TST has limitations including compliance with both steps, subjective reader interpretation, and false-positive results. This can be problematic for Employee Health departments and cause delays in orientation. A systematic review of the literature was conducted to determine the evidence regarding implementation of Interferon Gamma Release Assays (IGRA) in Employee Health for new hire employees. This literature review is preliminary work for an evidence-based project to determine if baseline testing with QuantiFERON®-TB Gold In-Tube test (QFT®-GIT) will reduce tuberculosis screening time and improve compliance in new employees at Spartanburg Regional Healthcare System.

**Methods:** CINAHL, PubMed, and Science Direct were searched with keywords IGRA, Interferon Gamma, tuberculosis screening, quantiferon, employee, healthcare worker, and tuberculosis. Studies published in English, conducted in low or medium TB incidence settings which included information regarding IGRA testing in healthcare workers including QFT®, QFT®-TB Gold, QFT®-GIT, or T-spot from 2005 to present met the inclusion criteria.

**Results/Limitations/Conclusions:** Twenty-three studies were included in the literature review. The John Hopkins nursing evidence-based practice model and guidelines was utilized to rate the evidence and quality of the studies. There were five level II studies, six level III, two level IV and ten level V. Eight studies were high quality, and fifteen studies were rated good. Low quality studies were excluded. The analysis of the literature was grouped into topics of the tuberculosis screening process, cost, accuracy, and conversions/reversions. Synthesis of the literature revealed a number of positive logistical factors that would provide value for employee health offices including reduced number of visits for the new hire and reduced burden on employee health office staff time spent on tuberculosis clearance. The cost analysis revealed that utilization of IGRAs has been found to be cost effective and in some cases saves money. The literature showed that the QFT®-GIT has high specificity but there are conflicting reports on sensitivity. There may be reductions in false-positives due to elimination of subjective reader interpretation and IGRAs do not react to other non-mycobacterium tuberculosis. The review also showed that positive results in a borderline interpretation zone can have conversions and reversions with some studies recommending retesting. One limitation of this review is that there was no level I study found. In conclusion, the literature review showed that utilization of the QFT®-GIT has potential to improve tuberculosis screening processes, reduce costs, reduce false-positive results with improved specificity, and has the potential to contribute to reduced tuberculosis screening time and improve compliance.

**Implications for practice:** Employee Health and occupational health departments that are required to conduct tuberculosis screening for new hire employees should conduct a needs assessment in their organization and review the evidence to determine if IGRAs would improve processes, be cost effective, and align with organization priorities. Organizations implementing IGRAs for new hires should develop policies and procedures with consideration of the evidence with regards to sensitivity, specificity, conversions, and reversions with consideration for retesting guidelines.

### **Applying for Poster Presentation**

## APPENDIX G

### CONFERENCE PRESENTATION APPLICATION



### **CALL FOR SPEAKERS** **AOHP 2017 NATIONAL CONFERENCE**

*September 6-9, 2017*

*Sheraton Denver Downtown Hotel, Denver, CO*

Thank you for considering speaking at the AOHP 2017 National Conference. The speaker submission will be **in two phases.**

The **first submission** will help the committee decide if your presentation meets the needs of the conference. Please provide as much detail as possible in your submission, including a description of any relevant methods, techniques, tools, results, lessons learned, etc.

- **Deadline to submit: *January 31, 2017***
- **Successful applicants will be notified by April 24, 2017.**

All presentation submissions will be reviewed and selected by a committee of volunteer professionals according to the following evaluation criteria. Preference will be given to abstracts that include appropriate detail.

- ★ Originality of presentation
- ★ Overall quality of content
- ★ Relevance/timeliness to current issues
- ★ Well-defined focus

Please complete the form below with following:

- Presentation Title
- Presenter's Bio
- Topic Overview - Describe the basic content of the proposed presentation – a minimum of 50 words and maximum of 300 words is needed.
- Purpose – Describe as an outcome statement.
- Description of current state
- Description of desired achievable state
- Identify at least three objectives for the proposed presentation
- Provide an outline of the content for each objective
- Type of presentation, level and time frame.

Submission abstracts should be submitted to AOHP National Headquarters via email at [info@aohp.org](mailto:info@aohp.org) by **January 31, 2017.**

We appreciate your interest and welcome your submission. AOHP reserves the right to review and accept only those proposals deemed suitable for the program. The conference committee will review all valid submissions. The choice of a session will be based on the presentation of the session, its value to professionals, the location of the speaker to promote local experts, and comprehensiveness of the required information submitted. Speakers will be contacted individually about their submission, accepted or not.

Session speakers are asked to participate on a “gratis” basis. **Speakers receive FREE registration for the day of their presentation and one complimentary night hotel stay. To discuss alternative speaker compensation, please contact AOHP Headquarters at [info@aohp.org](mailto:info@aohp.org)**

We appreciate your time and look forward to working with you for the 2017 Conference.

Sincerely,

Dana Jennings Tucker, RN, BSN, CCM  
AOHP 2017 National Conference Chair

**Deadline to submit: [January 31, 2017](#) Successful applicants will be notified by [April 24, 2017](#).**

AOHP Headquarters: 125 Warrendale Bayne Road, Suite 375, Warrendale, PA 15086  
[www.aohp.org](http://www.aohp.org) Email: [info@aohp.org](mailto:info@aohp.org)

## SPEAKER SUBMISSION FORM

AOHP 2017 National Conference ❖ September 6 – 9, 2017  
Sheraton Denver Downtown Hotel ❖ Denver, CO

**PRESENTER**

Mary Giovannetti, APRN, DNP, C-FNP (I graduate May 6, if you  
publish before then use APRN, MSN, C-FNP)

**ADDRESS** 913 Palmdale Court

**CITY, STATE & ZIP** Boiling Springs, SC 29316

**PHONE** 864-497-4087      **EMAIL** mgiovannetti@srhs.com

**CURRENT POSITION & EMPLOYER** Manager/NP Spartanburg Regional Healthcare System  
Employee Health

**CO-  
PRESENTER**

Stephanie Barnhill, APRN, MSN, C-FNP

**ADDRESS** 236 Orchard Grove Road

**CITY, STATE & ZIP** Campobello, SC 29322

**PHONE** 864-497-5089      **EMAIL** sbarnhill@srhs.com

**CURRENT POSITION & EMPLOYER** NP Spartanburg Regional Healthcare System  
Employee Health

**CO-  
PRESENTER**

**ADDRESS** \_\_\_\_\_

**CITY, STATE & ZIP** \_\_\_\_\_

**PHONE** \_\_\_\_\_      **EMAIL** \_\_\_\_\_

**CURRENT POSITION & EMPLOYER** \_\_\_\_\_

**CO-  
PRESENTER**

(Please provide your full name with credentials that you prefer to show on our  
publications.)

**ADDRESS** \_\_\_\_\_

**CITY, STATE & ZIP** \_\_\_\_\_

**PHONE** \_\_\_\_\_      **EMAIL** \_\_\_\_\_

**CURRENT POSITION & EMPLOYER** \_\_\_\_\_

**Presentation Title**

Tuberculosis screening in New Healthcare Employees: A Comparison of QuantiFERON®-TB Gold In-Tube Test and Tuberculin Skin Test

**Presenter's Bio**  
**(Please provide a brief bio, not CV, for each presenter.)**

Mary Giovannetti graduated with BSN (1994) and MSN (1998) from Marshall University, and DNP from University of South Carolina (2017). She worked in family practice offices providing primary care from 1998 to 2006. In 2006, she joined SRHS Employee Health providing acute care services to employees, workers' compensation visits, fit for duties, and other occupational health exams. Dr. (or Mrs.) Giovannetti transitioned to Employee Health Manager in 2014 providing oversight of staff, employee health visits, workers' compensation, and Employee wellness. Dr. Giovannetti currently serves as state chapter AOHP Vice President.

Stephanie Barnhill graduated with BSN (2000) and MSN (2006) from Clemson University. She is currently enrolled in the University of South Carolina's DNP program. Mrs. Barnhill has worked in public health for the majority of her career, including tuberculosis management, adult health, and preventative medicine. In 2015, she joined SRHS employee health department working as a nurse practitioner providing acute care services, worker's compensation visits, fit for duties, and occupations health exams.

**Abstract/Presentation Overview** - Describe the basic content of the proposed presentation – a minimum of 50 words and maximum of 300 words is needed.

Authors: Mary Giovannetti, DNP, APRN, BC-FNP; Stephanie Burgess, PhD, APRN, BC, FAANP; Karen McDonnell, PhD, RN, OCN; Abbas Tavakoli, DrPH, MPH, ME; Stephanie Barnhill, MSN, APRN, BC-FNP

**Background:** Streamlining onboarding processes for new hires to maximize efficiency and reduce costs while meeting regulatory requirements is a constant challenge for healthcare systems' Employee Health staff. Health screening is a required step and includes obtaining a detailed health history, tuberculosis screening, drug screens, immunizations, fit for duty examinations, obtaining medical records, clarification of disability accommodations, pre-work screens, and other tests which are time consuming and result in delays in hire dates. Faced with a high volume of potential new employee hires a major southeast healthcare system was concerned about delays in new hire start dates. The two-step tuberculin skin test administration and follow-up process was identified as a potential area for improved onboarding efficiency.

**Method:** A quality improvement study was designed and implemented to compare baseline testing for new employees with an Interferon-Gamma Release Assay (IGRA) known as QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD Tuberculin Skin Test (TST) for tuberculosis screening time, overall onboarding time, compliance with screening within 10 days of hire date, and associated costs. A retrospective electronic record review included a sample of 484 new hire employees.

**Results:** Results showed that the QFT®-GIT for tuberculosis screening in comparison to the TST testing significantly reduced tuberculosis screening time for new hire employees (TST = 8.03 days, QFT®-GIT = 4.11 days; p<.0001) and overall onboarding time (TST = 7.92 days, QFT®-GIT = 5.07 days; p<.0001) while improving compliance with tuberculosis screening within 10 days of hire date (TST = 92.92%, QFT®-GIT =100%; p<.0001).



**Conclusions:** The utilization of QFT®-GIT for tuberculosis screening of new employees significantly reduced screening and onboarding time while improving compliance with screening within 10 days of the hire date.

**Implications:** Healthcare systems should consider implementation of an IGRA in order to streamline processes for onboarding new employees. New processes require negotiations between healthcare systems and lab vendors, changes in policies and procedures, and employee health and laboratory staff development.

**Learning Outcome:**

Learners will be able to describe how implementation of an Interferon Gamma Release Assay (IGRA) can be utilized for tuberculosis screening of new healthcare workers.

**Description of current state:**

Delays in orientation and health clearance due to long process of tuberculosis screening

**Description of desired achievable state:**

Reduce number of days needed to complete tuberculosis screening

| Identify at least three <b>objectives</b> for the proposed presentation. |   | <b><u>Provide an outline</u></b> of the content for each objective. It must be more than a restatement of the objective.  |
|--|---|---|
| 1.   | Discuss problems with tuberculosis screening for healthcare workers               | Review author's department experience with TST's and onboarding and have learners interactively discuss their experience with TST's or IGRA's for tuberculosis screening. |
| 2.   | Describe pros and cons of Interferon Gamma Release Assays                         | Summarize the Review literature results of 23 articles including: TB screening process, cost, accuracy, conversions/reversions  |
| 3.   | Identify steps for implementation of IGRAs for new healthcare employees           | Discuss how the healthcare system implemented the IGRA including successes and problem resolution.  |
| 4.   | Describe results of IGRA implementation for tuberculosis screening and compliance | Review results of data analysis for sample of 485 subjects.   |
| 5.   |   |   |

**What level do you consider your presentation?**

Basic

Intermediate

Advanced

**What time frame is needed? Check all that apply.**

- Workshop (2 to 8 hours): \_\_\_\_\_ hours
- General Session (60 minute included Q&A)
- Breakout Session (60 minute included Q&A)

**Type of presentation, check all that apply.**

- Case study       Topic discussion       Roundtable discussion
- Forum Discussion       Other \_\_\_\_\_

**Submission abstracts should be submitted to AOHP National Headquarters.**

**Email [info@aohp.org](mailto:info@aohp.org) by January 31, 2017.**

**Maximum of four speakers for workshops and two speakers for sessions.**

Session handouts will be made available to attendees for download and in notebook and CD format. AOHP reserves the right to request or make last minute changes to any program. Speakers who do not comply with given deadlines may be removed from the program.

***Disclaimer:*** AOHP 2017 National Conference sessions and workshops must be educational in nature. The conference objective is to provide participants with practical knowledge and tools that can be easily implemented in their own organizations. We believe that an objective presentation, one that meets the educational expectations of the audience, will enhance the credibility of the speaker, the speaker's employer and the event. No product or service promotion will be permitted. All presentations must avoid commercialism, promotion and advertising. Presentations that are a simple description of company products will NOT be allowed. Statements in the presentation are the sole responsibility of the author. No presenter statements should be viewed as, or considered representative of, any formal stance or position taken on any product, subject or issue by AOHP.

**APPENDIX H**

**JOURNAL MANUSCRIPT**

**Tuberculosis Screening of New Healthcare Workers utilizing an Interferon  
Gamma Release Assay (IGRA): Quality Improvement in Screening time,  
Onboarding time, and Compliance<sup>1</sup>**

---

<sup>1</sup>Mary Giovannetti, DNP, APRN, BC-FNP; Stephanie Burgess, PhD, APRN, BC, FAANP; Karen McDonnell, PhD, RN, OCN; Abbas Tavakoli, DrPH, MPH, ME; Stephanie Barnhill, MSN, APRN, BC-FNP

To be submitted to Association of Occupational Health Professionals Journal

## Abstract

**Background:** Streamlining onboarding processes for new hires to maximize efficiency and reduce costs while meeting regulatory requirements is a constant challenge for healthcare systems' Employee Health staff. Health screening is a required step and includes obtaining a detailed health history, tuberculosis screening, drug screens, immunizations, fit for duty examinations, obtaining medical records, clarification of disability accommodations, pre-work screens, and other tests which are time consuming and result in delays in hire dates. Faced with a high volume of potential new employee hires a major southeast healthcare system was concerned about delays in new hire start dates. The two-step tuberculin skin test administration and follow-up process was identified as a potential area for improved onboarding efficiency.

**Method:** A quality improvement study was designed and implemented to compare baseline testing for new employees with an Interferon-Gamma Release Assay (IGRA) known as QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD Tuberculin Skin Test (TST) for tuberculosis screening time, overall onboarding time, compliance with screening within 10 days of hire date, and associated costs. A retrospective electronic record review included a sample of 484 new hire employees.

**Results:** Results showed that the QFT®-GIT for tuberculosis screening in comparison to the TST testing significantly reduced tuberculosis screening time for new hire employees (TST = 8.03 days, QFT®-GIT = 4.11 days;  $p < .0001$ ) and overall onboarding time (TST = 7.92 days, QFT®-GIT = 5.07 days;  $p < .0001$ ) while improving compliance with tuberculosis screening within 10 days of hire date (TST = 92.92%, QFT®-GIT = 100%;  $p < .0001$ ).

**Conclusions:** The utilization of QFT®-GIT for tuberculosis screening of new employees significantly reduced screening and onboarding time while improving compliance with screening within 10 days of the hire date. Anecdotal feedback from hiring managers and senior management indicated improved satisfaction with the Employee Health hiring process.

**Implications:** Healthcare systems should consider implementation of an IGRA to streamline processes for onboarding new employees. New processes require negotiations between healthcare systems and lab vendors, changes in policies and procedures, and employee health and laboratory staff development. Future research should focus on cost analyses, as well as, IGRA use for annual screenings.

## **Introduction**

Employee health offices are challenged with streamlining onboarding processes for new hires to maximize corporate efficiency and reduce costs meeting regulatory requirements. Health screening is a key step and includes multifaceted components such as obtaining a detailed health history, tuberculosis screening, drug screens, immunizations, fit for duty examinations, obtaining medical records, clarification of disability accommodations, and other pre-work screens which are often time consuming resulting in delays in hire dates. A large healthcare system experienced a high volume new hires and concern regarding delays in new hire start dates. The Healthcare System Corporate Administration engaged the Employee Health Manager to assess and develop solutions for increased onboarding efficiency. A potential area identified as a concern

was the two-step tuberculin skin test administration and follow-up process. The purpose of this quality improvement study was to compare baseline testing for new healthcare employees with QuantiFERON®-TB Gold In-Tube Test (QFT®-GIT) to the two step PPD Tuberculin skin test (TST) for tuberculosis screening time, overall onboarding time, compliance with screening within 10 days of hire date, and associated costs.

### **Tuberculosis Screening**

Historically, the tuberculin skin test was the only available test for TB screening until 2001, when Interferon gamma release assays (IGRA) were developed. Interferon gamma release assays are blood tests which specifically measure the interferon-gamma released by T cells in response to white blood cells exposed to TB, thus releasing interferon-gamma (TFN- $\gamma$ )(Swindells, Aliyu, Enoch, & Abubakar, 2009) Two currently available IGRAs include the QuantiFERON®-Gold In-Tube Test (QFT®-GIT) and the T-SPOT®.TB. The T-SPOT®.TB measures the number of interferon gamma producing cells by counting spots and is collected in one blood tube (Foster-Chang, Manning, & Chandler, 2014). In contrast, the QFT®-GIT measures the TFN- $\gamma$  protein response quantitatively utilizing whole blood enzyme linked immunosorbent assay (ELISA). The procedure for testing includes drawing one milliliter of blood collected in 3 tubes including the nil (negative control), TB antigen (ESAT-6, CFP-10, and TB7.7), and mitogen (positive control). All tubes are gently shaken 10 times and must be transferred to a 37°C $\pm$ 1 incubator within 16 hours. Results are measured by TB antigen minus nil and positive is  $\geq 0.35$  IU/ml. Results are measured by TB antigen minus nil and positive is  $\geq 0.35$  IU/ml (Nienhaus, 2013).

IGRA's can potentially overcome barriers with TST extended tuberculosis clearance screening time, noncompliance, and inaccuracies in results. In contrast to TST, IGRA's do not react to nontuberculous mycobacteria or BCG vaccination. IGRA's can also be completed in one visit and eliminate the need for multiple visits. Furthermore, IGRAs were found to have a higher correlation to TB exposure than TSTs, thus, improving accuracy. IGRA's are more expensive than TST's, but utilization can reduce costs associated with onboarding, staff time for TST implementation and follow-up processes, and reducing potential regulatory citations for organizational noncompliance (Mazurek et al., 2010).

### **Literature Review**

A review of literature was conducted for levels of evidence, quality, and summary to compare TST testing and a blood assay for mycobacterium tuberculosis screening of new hires for a healthcare system. Database searches included CINAHL, PubMed and Science Direct. Search terms included a combination of IGRA, Interferon gamma, tuberculosis screening, quantiferon, employee, healthcare worker, and tuberculosis. Search inclusion criteria included studies published in English conducted in low or medium TB incidence settings from 2005 to present with relevant information to IGRA testing in healthcare workers including QFT®, QFT®-TB Gold, QFT®-GIT, or T-SPOT®.TB. Studies were excluded that were conducted primarily in high TB incidence settings, did not include healthcare workers, were published in other languages, and those that involved only children or immune compromised patients. Articles were limited to the past 10 years. However, the Centers for Disease Control (CDC) study published in 2005

was included since it provides the guidance for landmark regulatory compliance for occupational health onboarding. Twenty-three studies were included in the final literature review. The John Hopkins nursing evidence-based practice model and guidelines were utilized to appraise the evidence. The search yielded There five level II studies, six level III, two level IV and ten level V. Eight studies were high quality, and fifteen studies were rated good. Low quality studies were excluded.

The literature analysis was organized into topics of the tuberculosis screening process, cost, accuracy, and conversions/reversions. Synthesis of the literature revealed a number of positive logistical factors that provided value for employee health offices including reduced number of visits for the new hire and reduced burden on employee health office staff time spent on tuberculosis clearance and follow-up while improving compliance (Cummings et al., 2009; Foster-Chang et al., 2014; Gonzalez & Conlon, 2013; Graban & Filby, 2015; Mazurek et al., 2010; Rangaka et al., 2012; Veerer, Smith, Handy, & Martin, 2007; Wrighton-Smith, Sneed, Humphreys, Tao, & Bernacki, 2012). Since QFT®-GITs are completed at one visit, new hire onboarding and tuberculosis clearance time was reduced (Cummings et al., 2009; Foster-Chang et al., 2014; Graban & Filby, 2015; Mazurek et al., 2010). Studies also found an enhanced convenience to the new hire using QFT®-GITs testing (Foster-Chang et al., 2014; Graban & Filby, 2015; Veerer et al., 2007). Cost analysis revealed that IGRAs are cost effective by reducing staff testing and follow-up time, reducing missed work time, and reducing treatment for false-positive results (dePerio, Tsevat, Roselle, Kralovic, & Eckman, 2009; Foster-Chang et



al., 2014; Graban & Filby, 2015; Nienhaus, 2013; Nienhaus, Schablon, Costa, & Diel, 2011).

The literature also demonstrated that the QFT®-GIT has high specificity but there are conflicting reports on sensitivity (Banaei, Gaur, & Pai, 2016; Cummings et al., 2009; Dorman et al., 2014; Loddenkemper, Diel, & Nienhaus, 2012; Schablon, Nienhaus, Ringshausen, Preisser, & Peters, 2014; Slater, Welland, Pai, Parsonnet, & Banaei, 2013; Weddle, Hamilton, Potthoff, Rivera, & Jackson, 2014; Zwerling et al., 2012).). Explanations offered were reductions in false-positives due to elimination of subjective reader interpretation and the lack of reaction of IGRAs to other non-mycobacterium tuberculosis (Dorman et al., 2014; Lamberti et al., 2015; Rangaka et al., 2012; Swindells et al., 2009) . However, sensitivity of the QFT®-GIT improves with consideration of patients with active tuberculosis (Mazurek et al., 2010). Some studies have shown that there can be issues with conversions and reversion and a borderline cutoff with retesting may be appropriate (Dorman et al., 2014; Loddenkemper et al., 2012; Mazurek et al., 2010; Schablon et al., 2014; Slater et al., 2013; Weddle et al., 2014; Zwerling et al., 2012). When interpreting results, the immunologic status of the patient should also be considered with indeterminate results (Cummings et al., 2009). Standardization of lab procedures can help overcome some of the variability in results (Banaei et al., 2016).

One limitation of the review was the lack of Level I studies. In conclusion, the literature review showed that utilization of the QFT®-GIT has potential to improve tuberculosis screening processes, reduce costs, reduce false-positive results with

improved specificity, and has the potential to contribute to reduced tuberculosis screening time and improve compliance (Banaei et al., 2016; Cummings et al., 2009; Dorman et al., 2014; Foster-Chang et al., 2014; Graban & Filby, 2015; Loddenkemper et al., 2012; Nienhaus, 2013; Nienhaus et al., 2011; Schablon et al., 2014; Slater et al., 2013; Veesser et al., 2007, 2007; Weddle et al., 2014; Wrighton-Smith et al., 2012; Zwerling et al., 2012).

### **Purpose**

Historically, the healthcare system completed two-step tuberculosis skin testing for new hire employees. With the increase volume of new hires, hiring managers and Corporate Administration requested that Employee Health expedite onboarding time for new hires. Hiring managers expressed frustration with delays in onboarding times for new hires, especially for TST screening processes. Thus, Corporate Administration directed Employee Health to investigate new processes for onboarding new hires and develop recommendations. In the Fall of 2015, the Employee Health Manager convened a new hire committee to review all onboarding processes and to recommend changes to streamline processes. Information regarding the benefits of implementation of QFT®-GITs for new hire tuberculosis screening was presented to the new hire committee, the Vice-President of Human Resources, and Employee Health staff. Support was obtained, and Employee Health staff initiated a new procedure, specifically QFT®-GIT testing for new hires. Employee Health staff received training for policies and procedures for implementing the QFT®-GIT. The internal lab and an outside vendor lab was advised of the changes and capacity for incubation was determined. The state regulatory agency was

contacted to ensure that the blood test would be accepted and further guidance was sought for retesting borderline positive results of less than 1 was obtained. In February of 2016, the healthcare system began QFT®-GITs for tuberculosis screening of all new hire employees. At the time of formation of the new hire committee, the Employee Health office completed 100-125 pre-placement visits per month. By July of 2016, the Employee Health office completed 187 pre-placement visits in one month.

## **Methods**

### **Setting**

The setting for the quality improvement project was a major southeast healthcare system comprising of 6,800 employees and consisting of 2 acute care hospitals, a post-acute facility, hospice facility, home health agency, multiple outpatient offices, and other specialty healthcare services. The healthcare system is identified as a TB low risk facility per CDC guidelines. The healthcare system contracts with a local lab vendor to complete QFT®-GIT at a negotiated price of \$53 per QFT®-GIT. Since CDC recommendations do not have a preference of QFT versus T-spot®, the QFT®-GIT was selected for the project (Mazureck et al., 2010).

### **Data Collection**

Data was collected by the primary author retrospectively through electronic medical record review, new hire spreadsheets, and the human resources database. All data was stored in a password protected excel spreadsheet with all personal identifiers removed that could be traced back to the new hire. Data points collected included

tuberculosis screening time (TB clear days), either total number of days to complete two step TST placement and readings or number of days for results of the QFT®-GIT. If any testing by TST or QFT®-GIT was positive, then time for completion of symptom review and chest x-ray was included in tuberculosis screening time. Overall onboarding time (clear days) included placement and reading of at least one TST, QFT®-GIT result and/or symptom assessment, drug screen results, lab results, and if required chest x-ray, fit for duty examination, pre-work screens, or personal provider work notes.

### **Sample**

The initial sample included 537 subjects who had pre-placement assessments at the healthcare system's Employee Health department in April and May of 2015 and 2016. Subjects were excluded from the study included volunteers (n=40), new hire subjects with positive drug screens (n=6), subjects who failed to report for employment (n=4) or failed fit for duty examination (n=1), subjects who failed pre-work screen (n=1) or did not show for pre-work screen (n=1). The final sample size included 484 new hire employees comprising 81.4% female subjects (see Table 1). The three most frequently hired age groups included ages 21, 25, and 27 years. The mean age for the sample was 35.08 (n=484) (see Table 1). There were 323 Caucasian subjects (66.73), 112 African American (Black) (23.14), 13 Hispanic (2.69), 12 Asian (2.48), and 24 other (4.96). The most frequent job title for the sample was registered nurses (n=111), followed by nursing support (n =62). Of the sample, 227 had TST testing and 257 had QFT Testing.

## **Results**

The mean number of days for completing all onboarding requirements to begin orientation was 6.40 days. The mean number of days to complete tuberculosis screening by TST was 8.06, ranging from 0-36 days. One hundred twenty-four subjects supplied documentation of at least one previous TST, thereby reducing the number of days required for subsequent testing. Seven subjects required repeated TST's due to failure to follow up for TST reading. TB clear days included the amount of time required for tuberculosis screening and was 5.92 mean days for the TST and the QFT groups. However, Quantiferon® testing yielded an average 4.11 days to complete testing with a range of 1 to 10 days. There were four positive QFT® results with 3 of those being borderline less than 1.0. The mean number of days for drug screen results was 2.71 days with a maximum of 19 days resulting from subjects who had 2 dilute drug screens, necessitating a hair drug screen. Thirty-six employees were required to have pre-work screen tests, averaging 5.68 days to complete. Six subjects were required to bring documentation from their personal health care provider regarding work status (see Table 2).

### **Question 1. Will implementation of QFT®-GIT reduce the number of days to complete tuberculosis screening for new hires?**

There was a statistically significant difference in number of mean days to complete tuberculosis screening for the QFT® group in comparison to the TST group ( $p < .0001$ ) (see Table 3). The average mean number of days to clear tuberculosis screening was 8.03 for TST and 4.11 for the QFT®. When comparing mean age between

the two groups for testing completion days, there was no statistically significant difference ( $p=0.0849$ ) (see Table 3).

**Question 2. Will implementation of QFT®-GIT for new hires reduce the overall number of days to complete onboarding?**

Findings indicated a statistically significant difference in the overall number of mean days to complete Employee Health screening for the QFT®-GIT in comparison to the TST group ( $p<.0001$ ) even when adding in other new hire screening requirements. A reduction in number of days was demonstrated for onboarding days when using the QFT method from 7.92 (TST group) to 5.07 (QFT® group) ( $p<.0001$ ). There was no statistically significant difference between the TST and the QFT® groups in the number of mean days to complete drug screens ( $p=0.8009$ ), fit for duties ( $p=0.8009$ ), or pre-work screens ( $p=0.1265$ ) (see Table 4).

Data was further analyzed to determine if there was a correlation between onboarding clearance time and age, TST clear days, QFT®-GIT clear days, drug screen days, fit for duty days, pre-work screen days, or PCP note days. A weak but positive correlation was demonstrated between overall onboarding time and age ( $r=0.10094$ ,  $p=0.0268$ ) (see Table 5). However, findings showed a statistically significant stronger positive relationship between overall onboarding time and number of days to complete TST screening ( $r=0.71838$ ,  $p<.0001$ ) and number of days for clearance by QFT® ( $r=0.62275$ ,  $p<.0001$ ). A positive relationship was also found between onboarding clearance time with number of days to complete drug screens ( $r=0.30298$ ,  $p<.0001$ ). There was also a positive relationship between the number of days and fit for duties

( $r=0.76433$ ,  $p<.0001$ ), however, only 36 subjects were required to complete the examination. For onboarding time with the number of days to complete pre-work screens, a positive correlation was found among six subjects ( $r=0.68600$ ,  $p<.0001$ ) but none was found between onboarding clearance time and the number of days to bring documentation clearance from the PCP ( $r=0.40584$ ,  $p=0.4247$ ) (see Table 5).

**Question 3. Will implementation of QFT®-GIT for new employees improve compliance with completion of tuberculosis screening within 10 days of orientation?**

Analyses showed a statistically significant improvement in compliance with the QFT® group in comparison to the TST group ( $p<.0001$ ) (see Table 6). Overall, the compliance rate for completing the tuberculosis screening was 99.29% in the TST group and 100% the QFT group. There was no statistical difference for tuberculosis screening compliance between races. However, there was a statistically significant difference in compliance between genders with an increase in compliance among female employees (97.96%;  $p=.0010$ ) (see Table 6). Three employees failed to complete two step TSTs. Ten employees failed to have at least one TST with a final reading prior to orientation. Sixteen employees in the TST group failed to complete tuberculosis screening within 10 days of orientation. No QFT group subjects failed to complete screening within 10 days of hire date.

**Q4. Will implementation of QFT®-GIT be cost-effective?**

The average cost for a two-step TST in Employee Health was estimated at \$87.87

per person and for QFT® \$101.66 (cost of lab test, supplies, staff time for review of results). At initial glance, the QFT®-GITs appears to cost more per person (\$13.79). However, further consideration is warranted when factoring other variables. Seven subjects failed to have at least one TST read and had to be replaced which required a second TST at an additional cost of \$30.01- \$37.76 per person (total costs of \$210.07). Sixteen subjects failed to complete screening within 10 days of orientation which resulted in an increase in Corporate cost to allocate Employee Health staff time recalling these new hired employees (\$25 per hour x 8 hours per week used for recalls = \$200.00 per week). Corporate could have been forced to contract with a staffing agency for 16 locum tenens nurses while onboarding new hire employees to replace those who failed to comply with initial testing resulting in an additional cost of \$76,800 per month (\$30/hr for each locum tenens for full time x 160 hours in month = \$4,800 x 16 employees = \$76,800). Four subjects in the TST group did not complete both steps of the two-step tuberculin skin test within the specified time frame, which potentially placed the system at risk for DHEC penalties ranging from \$12,675 to \$126,749 each for violations (S.C.Department of Health and Environmental Control, 2015). Occupational Health Safety Administration (OSHA, 2017). Fortunately, Employee Health staff were vigilant in their efforts to complete the testing later but again allocating staff time was costly to Corporate.

## **Conclusions**

The utilization of the QFT®-GIT for tuberculosis screening of new hire healthcare employees in comparison to the TST testing significantly reduced tuberculosis screening and onboarding time while improving compliance with tuberculosis screening



within 10 days of hire date ( $p < .0001$ ; TST = 8.03 days, 4.11 days = QFT group).

Anecdotal feedback back from hiring managers and senior management indicated an improvement in satisfaction with the Employee Health new hire process. They fully appreciated the decrease in onboarding time, quicker start dates for new hires, less delays in orientation, and an increase in volume of new hire visits. Employee Health manager admits to receiving less complaints regarding appointment availability for screening processes and orientation start dates for new hires. Streamlining processes has also facilitated regulatory site visits with the QFT®-GIT because data is more easily retrievable and accurate. Clearly, the cost of QFT®-GIT can be more as a single test but agencies should account for other variables in the cost analyses including, staffing costs, lab testing, and locum tenens use. Streamlining processes and improved efficiency are critical to Corporate overhead costs and compliance.

### **Implications for Practice and Future Research**

Organizations should consider implementation of an IGRA to streamline processes for onboarding new hires. Of course, new processes require negotiations between hospital departments and lab vendors, changes in policy and procedures, and Employee Health staff development for IGRA testing procedures to facilitate new hires onboarding.

Future research should include discrete cost analyses comparing screening with TST versus QFT®-GITs for both new hires and annual testing. A pilot study could provide foundation for future research to compare annual screening with QFT®-GIT and TST. Analyses could include measurements of process improvement, screening time, and

employee satisfaction surveys for onboarding.

### **Manuscript References**

Banaei, N., Gaur, R. L., & Pai, M. (2016). Interferon Gamma Release Assays for Latent Tuberculosis: What Are the Sources of Variability? *Journal of Clinical Microbiology*, 54(4), 845–850. <https://doi.org/10.1128/JCM.02803-15>

Cummings, K. J., Smith, T. S., Shogren, E. S., Khakoo, R., Nanda, S., Bunner, L., ... Weissman, D. N. (2009). Prospective comparison of tuberculin skin test and QuantiFERON-TB Gold In-Tube assay for the detection of latent tuberculosis infection among healthcare workers in a low-incidence setting. *Infection Control & Hospital Epidemiology*, 30(11), 1123–1126. <https://doi.org/10.1086/644754>

dePerio, M. A., Tsevat, J., Roselle, G. A., Kralovic, S. M., & Eckman, M. H. (2009). Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in health care workers. *Archives of Internal Medicine*, 169(2), 179–187. <https://doi.org/10.1001/archinternmed.2008.524>

Dorman, S. E., Belknap, R., Graviss, E. A., Reves, R., Schluger, N., Weinfurter, P., ... Daley, C. L. (2014). Interferon-[gamma] Release Assays and Tuberculin Skin Testing for Diagnosis of Latent Tuberculosis Infection in Healthcare Workers in the United States. *American Journal of Respiratory & Critical Care Medicine*, 189(1), 77–87. <https://doi.org/10.1164/rccm.201302-0365OC>

Foster-Chang, S. A., Manning, M. L., & Chandler, L. (2014). Tuberculosis Screening of New Hospital Employees: Compliance, Clearance to Work Time, and Cost Using

- Tuberculin Skin Test and Interferon-Gamma Release Assays. *Workplace Health & Safety*, 62(11), 460–467. <https://doi.org/10.3928/21650799-20140902-02>
- Gonzalez, M., & Conlon, H. A. (2013). Updating a Tuberculosis Surveillance Program Considering All of the Variables. *Workplace Health & Safety*, 61(6), 271–278. <https://doi.org/10.1177/216507991306100606>
- Grabau, M., & Filby, D. (2015). Lean-the-new-Hire-Onboarding-Process-for-Healthcare-Workers - QIAGEN. Retrieved April 22, 2016, from <https://www.qiagen.com/us/resources/resourcedetail?id=a17784e8-d734-434e-a26a-4e39945aa55d&lang=en>
- Lamberti, M., Uccello, R., Monaco, M. G. L., Muoio, M., Feola, D., Sannolo, N., ... Chiodini, P. (2015). Tuberculin skin test and Quantiferon test agreement and influencing factors in tuberculosis screening of healthcare workers: a systematic review and meta-analysis. *Journal of Occupational Medicine & Toxicology*, 10(1), 1–13. <https://doi.org/10.1186/s12995-015-0044-y>
- Loddenkemper, R., Diel, R., & Nienhaus, A. (2012). To Repeat or Not to Repeat-That Is the Question!: Serial Testing of Health-care Workers for TB Infection. *CHEST*, 142(1), 10–11. <https://doi.org/10.1378/chest.12-0045>
- Mazurek, G. H., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., & Castro, K. (2010). Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection -- United States, 2010. *MMWR Recommendations & Reports*, 59(RR-5), 1–26.
- Nienhaus, A. (2013). Clinical review of literature pertaining to the use of interferon-gamma release assays for tuberculosis screening in healthcare workers: Evidence

- base and clinical experience with QuantiFERON-TB Gold (QFT). *Qiagen Clinical Review*. <https://doi.org/QM31635290A>
- Nienhaus, A., Schablon, A., Costa, J. T., & Diel, R. (2011). Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Services Research, 11*(1), 247–247.
- Rangaka, M. X., Wilkinson, K. A., Glynn, J. R., Ling, D., Menzies, D., Mwansa-Kambafwile, J., ... Pai, M. (2012). Predictive value of interferon-[gamma] release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infectious Diseases, 12*(1), 45–55.
- S.C.Department of Health and Environmental Control. (2015). R.61-16, Minimum Standards for Licensing Hospitals and Institutional General Infirmaries. Retrieved from <https://www.scdhec.gov/Agency/docs/health-regs/61-16.pdf>
- Schablon, A., Nienhaus, A., Ringshausen, F. C., Preisser, A. M., & Peters, C. (2014). Occupational Screening for Tuberculosis and the Use of a Borderline Zone for Interpretation of the IGRA in German Healthcare Workers. *PLOS ONE, 9*(12), 1–16. <https://doi.org/10.1371/journal.pone.0115322>
- Slater, M. L., Welland, G., Pai, M., Parsonnet, J., & Banaei, N. (2013). Challenges with QuantiFERON-TB Gold Assay for Large-Scale, Routine Screening of U.S. Healthcare Workers. *American Journal of Respiratory & Critical Care Medicine, 188*(8), 1005–1010. <https://doi.org/10.1164/rccm.201305-0831OC>
- Swindells, J. E., Aliyu, S. H., Enoch, D. A., & Abubakar, I. (2009). Role of interferon-gamma release assays in healthcare workers. *Journal of Hospital Infection, 73*(2), 101–108. <https://doi.org/10.1016/j.jhin.2009.05.005>

- Veesser, P. I., Smith, P. K., Handy, B., & Martin, S. (2007). Tuberculosis screening on a health science campus: use of quantiFERON-TB Gold test for students and employees. *Journal of American College Health, 56*(2), 175–180.
- Weddle, G., Hamilton, M., Potthoff, D., Rivera, D., & Jackson, M. A. (2014). QuantiFERON-TB Gold In-Tube Testing for Tuberculosis in Healthcare Professionals. *Laboratory Medicine, 45*(3), 207–210.  
<https://doi.org/10.1309/LMLSJ4BVXS66WJHS>
- Wrighton-Smith, P., Sneed, L., Humphreys, F., Tao, X., & Bernacki, E. (2012). Screening Health Care Workers With Interferon- $\gamma$  Release Assay Versus Tuberculin Skin Test. *Journal of Occupational & Environmental Medicine, 54*(7), 806–815. <https://doi.org/10.1097/JOM.ObO>
- Zwerling, A., van den Hof, Scholten, J., Cobelens, F., Menzies, D., & Pai, M. (2012). Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review. *Thorax, 67*(1), 62–70.

## Manuscript Tables

Table H.1  
*Frequency distribution for demographic variables*

| <b>Sample demographic variables</b> | <b>N</b> | <b>%</b> |
|-------------------------------------|----------|----------|
| <b>Gender</b>                       |          |          |
| Male                                | 90       | 18.60    |
| Female                              | 394      | 81.40    |
| <b>Age: Most frequently hired</b>   |          |          |
| 25 yrs.                             | 24       | 4.96     |
| 27 yrs.                             | 24       | 4.96     |
| 21 yrs.                             | 23       | 4.75     |
| Other                               | 413      | 85.33    |
| <b>Race</b>                         |          |          |
| White                               | 323      | 66.73    |
| Black                               | 112      | 23.14    |
| Hispanic                            | 13       | 2.69     |
| Asian                               | 12       | 2.48     |
| Other                               | 24       | 4.96     |
| <b>Job</b>                          |          |          |
| RN                                  | 111      | 23.03    |
| Nursing Support                     | 62       | 12.86    |
| EMS/Transport                       | 32       | 6.4      |
| Resident physicians                 | 15       | 3.11     |
| Epic/IS                             | 14       | 6.64     |
| Other                               | 245      | 47.96    |

Table H.2

*N, means, standard deviation, minimum, maximum for select variables*

| <b>Variable</b> | <b>Label</b>      | <b>N</b> | <b>Mean</b> | <b>Std Dev</b> | <b>Minimum</b> | <b>Maximum</b> |
|-----------------|-------------------|----------|-------------|----------------|----------------|----------------|
| age             | Age               | 484      | 35.08       | 11.54          | 18.00          | 67.00          |
| cldy            | Clear days        | 481      | 6.40        | 5.08           | 1.00           | 30.00          |
| tstcldy         | TST clear days    | 223      | 8.06        | 7.16           | 0.00           | 36.00          |
| tbclrd          | TB clear days     | 481      | 5.92        | 5.35           | 0.00           | 36.00          |
| qftdy           | # days result QFT | 255      | 4.11        | 1.26           | 1.00           | 10.00          |
| dsdy            | d/s days          | 481      | 2.71        | 2.27           | 1.00           | 19.00          |
| ffddy           | FFD days          | 36       | 7.94        | 4.26           | 2.00           | 18.00          |
| pwsdy           | PWS days          | 31       | 5.68        | 4.77           | 0.00           | 21.00          |
| pcpndy          | PCP note days     | 6        | 7.17        | 8.57           | 1.00           | 24.00          |

Table H.3

*N, mean, standard deviation for select variables by group*

| <b>Variable</b>                   | <b>TST group</b> |             |             | <b>QFT group</b> |             |             |
|-----------------------------------|------------------|-------------|-------------|------------------|-------------|-------------|
|                                   | <b>N</b>         | <b>Mean</b> | <b>Std.</b> | <b>N</b>         | <b>Mean</b> | <b>Std.</b> |
| Age <sup>a</sup>                  | 227              | 34.11       | 11.78       | 257              | 35.93       | 11.27       |
| TB screen clear days <sup>b</sup> | 224              | 8.03        | 7.16        | 257              | 4.08        | 1.29        |
| QFT complete days                 | 0                | .           | .           | 255              | 4.11        | 1.26        |
| TST complete days                 | 223              | 8.06        | 7.16        | 0                |             |             |

a. t-test p=0.0849

b. t-test p<.0001

Table H.4

*N, mean, standard deviation for select onboarding variables by group*

| Variable                          | TST group |       |      | QFT group |      |      |
|-----------------------------------|-----------|-------|------|-----------|------|------|
|                                   | N         | Mean  | Std. | N         | Mean | Std. |
| Clear days <sup>a</sup>           | 223       | 7.92  | 6.54 | 256       | 5.07 | 2.68 |
| Drug screen days <sup>b</sup>     | 225       | 2.74  | 2.84 | 256       | 2.68 | 1.61 |
| Fit for duty days <sup>c</sup>    | 11        | 10.18 | 5.10 | 25        | 6.96 | 3.52 |
| Pre-work screen days <sup>d</sup> | 20        | 6.6   | 5.0  | 11        | 4.00 | 4.00 |
| PCP note days                     | 6         | 7.17  | 8.57 | 0         | .    | .    |

a. t-test  $p < .0001$

b. t-test  $p = 0.8009$

c. t-test  $p = 0.0768$

d. t-test  $p = 0.1265$

Table H.5

*Spearman Correlation of selected variables for onboarding clearance days*

| Variable                          | Onboarding Clear Days |             |
|-----------------------------------|-----------------------|-------------|
|                                   | N                     | Correlation |
| Age <sup>a</sup>                  | 481                   | 0.10094     |
| TST clear days <sup>b</sup>       | 223                   | 0.71838     |
| QFT days <sup>b</sup>             | 255                   | 0.62275     |
| Drug screen days <sup>b</sup>     | 479                   | 0.30298     |
| Fit for duty days <sup>b</sup>    | 36                    | 0.76433     |
| Pre-work screen days <sup>b</sup> | 31                    | 0.68600     |
| PCP note days <sup>c</sup>        | 6                     | 0.40584     |

a.  $p = 0.0268$

b.  $p < .0001$

c.  $p = 0.4247$



Table H.6  
*Frequency distribution for clear within 10 days*

| Variables                 | Yes |       | No |      |
|---------------------------|-----|-------|----|------|
|                           | N   | %     | N  | %    |
| <b>Gender<sup>a</sup></b> |     |       |    |      |
| Female                    | 385 | 97.96 | 8  | 2.04 |
| Male                      | 82  | 91.11 | 8  | 8.89 |
| <b>Race<sup>b</sup></b>   |     |       |    |      |
| White                     | 309 | 95.96 | 13 | 4.04 |
| Black                     | 109 | 97.32 | 3  | 2.68 |
| Other                     | 49  | 100   | 0  | 0    |
| <b>Group<sup>c</sup></b>  |     |       |    |      |
| TST                       | 210 | 92.92 | 16 | 7.08 |
| QFT                       | 257 | 100   | 0  | 0    |

- d. Fisher exact test p value = .0010
- e. Fisher exact test p value = .3092
- f. Fisher exact test p value <.0001

**Permission to Publish Manuscript in Dissertation for ProQuest**

Email 3/9/17 from the AOHP Journal Editor

We will definitely grant that permission...just site that the article was “originally published in AOHP Journal..and the issue”

Kim Stanchfield, RN COHN-S