Using Newer Interferon Gamma Release Assays in the Indian Health Service as Part of a Comprehensive Targeted Testing Program for Latent Tuberculosis Infection among American Indians & Alaskan Natives Classified as High-Risk for Progression to Active Stage TB Disease.

By

Jessica L. Damon

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Advisor Signature/Printed Name

Second Reader Signature/Printed Name

Date
Introduction

Latent tuberculosis infection (LTBI) is a silent threat to public health, nationwide, and addressing it remains a challenge. The Centers for Disease Control and Prevention (CDC) announced its Total TB Elimination Goal in 1989 with a target year of 2010 for the eradication of tuberculosis from the United States. Although TB rates have steadily declined over the last decade, the rate of decline is slowing every year (CDC, 2008). To reach this goal, all federal agencies will have to work together to design and implement effective screening programs. Improvements in the specificity of available testing methods hold one part of a national solution to TB elimination. Many state public health departments have already implemented TB programs which not only embrace these newer test methodologies, but also rely on targeted testing models for latent tuberculosis infection among special populations deemed to be at increased risk for the development of active TB disease. The Indian Health Service is lagging behind its peers in adequately addressing latent tuberculosis among Native Americans. By developing targeted screening programs for high-risk American Indians/Alaskan Natives which incorporate interferon gamma release assay methodologies for a more accurate diagnosis of infection, the disease disparity that exists for tuberculosis among AI/AN’s can be effectively reduced. The financial cost of running such programs would be offset by the health benefit of disease prevention among AI/AN’s and the associated reduction in health care expenditures to treat both infection and disease.

Although persons with LTBI cannot transmit TB disease to others, they harbor the etiologic agent of TB, *Mycobacterium tuberculosis*. In the report “Ending Neglect” (2000), the Institute of Medicine (IOM) stated that any individual with LTBI is at
increased risk for developing active TB disease and thereby entering an infectious state in which they can transmit the disease to others (p.16). Progression from LTBI to active disease carries a risk of 10% over the lifetime of the individual, with further increased risk found among immunocompromised groups (CDC, 2010b). Progression from latent infection to active disease is the result of a compromised immune system response to infection. Compromised immunity occurs through a variety of pathways including, but not limited to, the development of autoimmune diseases (i.e. rheumatoid arthritis, lupus erythematosis, scleroderma etc...); the onset of cancer (particularly lung and bronchus); HIV infection; pharmacologic immune suppression; health conditions such as diabetes mellitus and chronic renal failure; and health behaviors such as smoking and drug abuse (CDC, 2010a).

Native Americans form a unique high-risk group due in part to their ethnicity where there exists a higher genetic predisposition to the development of some immunocompromising diseases. Native Americans are also victim to many multifactoral health disparities which subsequently lead to increased rates of conditions and behaviors that weaken the immune system. Therefore, a new and more effective approach is required to adequately screen, accurately diagnose, and properly manage the treatment of American Indian and Alaskan Native (AI/AN) patients receiving care through Indian Health Service clinics nationwide. Utilizing newer Interferon Gamma Release Assays (IGRA), such as T. Spot TB and Quantiferon TB Gold In Tube, in Indian Health Service laboratories to target AI/AN's classified as “high risk” for progression of LTBI to active tuberculosis will increase patient compliance with testing, decrease the incidence of cross reactivity reactions, and more accurately identify
infection in immunocompromised AI/AN's. The cost savings over time is demonstrated to be significant thereby substantiating a transition to IGRA screening for Latent TB Infection at all federally funded facilities.

**Methods**

Research included a systematic review of topics using primary and secondary sources to demonstrate the importance of using highly specific test methods in a cost-effective LTBI screening program model designed to reach high-risk AI/AN's in the Indian Health System.

**Search Strategy:**

*Subject Search:* Three web browsers (Yahoo, MSN, and Google), two literature search engines (PubMed and Medline), and three online journal publications (*Archives of Internal Medicine, Chest, American Family Physician*)- were used to conduct searches of primary literature on the following subject list:

- Latent Tuberculosis Infection
- Targeted Tuberculosis Testing
- High-risk Groups for LTBI progression to TB
- Cost Effective Analysis of TB Testing Methods
- TB Testing Specificity and Sensitivity Studies.

*Organizational Web Pages:* In addition to subject searches, the organizational websites for Centers for Disease Control & Prevention, National Institute of Health, Cellestis,
Oxford Immunotec, and The National TB Center were used, in whole or in part, to access and review available tuberculosis data and statistics, including, but not limited to:

- TB Screening program materials
- Specific techniques and interpretations for TB screening methods
- Recommended guidelines for TB testing

The organizational websites for The National Kidney Foundation, The National Diabetes Information Clearing House, Indian Health Services, Office on Minority Health, Management of Science & Health, and Harvard School of Medicine were also culled to discern the specific health disparities which place AI/AN’s at increased risk for disease progression.

*State Health Departments*: State Departments of Health with TB prevention programs that included targeted testing protocols for latent TB infection were reviewed to construct potential program recommendations applicable to AI/AN’s receiving care in the Indian Health Service. The following states were chosen for review because they met the LTBI screening criterion and they were representative of a cross section of the United States: New York, Minnesota, California, Oklahoma, and Wisconsin.

*Technical Resources Employed*: Technical information regarding Mycobacterium tuberculosis and TB testing methods was derived from several different textbooks of microbiology and pathogenic microbiology, immunology/serology, anatomy/physiology and test package inserts for the manufacturers of the IGRA testing platforms.
**Conceptual Frameworks**: Sources for conceptual frameworks relating to health program development came from textbooks used in the University of North Carolina's Master's in Public Health Leadership Curriculum. These texts included concepts on population statistics, epidemiology, program planning, and leadership which were strategically incorporated into the conclusions and recommendations section of this research.

**Applied Analysis**: Statistics from these sources were used to demonstrate the cost effectiveness and cost-benefit of utilizing new Interferon Gamma Release Assays in the testing of high-risk Al/AN's in the Indian Health Service. Internal research by the Indian Health Service has not been conducted to date and is not part of the body of knowledge, therefore some program generalizations were employed in order to evaluate current practices in LTBI screening at IHS facilities.

**Literature Review & Objective Analysis**

*Latent TB Infection: A Population Perspective*

The Centers for Disease Control and Prevention (2010c) reports a third of the world's population to be infected with *Mycobacterium tuberculosis*. With the current world population at approximately 6,900,000,000 persons (US Census Bureau 2010a), nearly 2.3 billion people across the globe are infected with *M. tuberculosis*. Since infection with *M. tuberculosis* does not always result in the onset of TB disease, due to the unique immune status of the infected individual, understanding disease progression rates is crucial to comprehending the impact of LTBI on any given population and to the CDC's priority of TB elimination.
According to Dr. Charles Bryan, MD (2009), at the University of South Carolina Medical School, research designed to track and monitor sample sets of persons infected with TB demonstrated that approximately 5% of healthy individuals will develop TB disease in the first 24 months post infection, while the remaining 95% of individuals carry a 5% average lifetime progression risk of disease development from latent infection (Ch. 5, Section: Tuberculosis Overview. Causes, & Pathogenesis, 15). Certain high-risk groups demonstrated a rate much higher, upwards of 3% to 10% per year in HIV+ individuals co-infected with LTBI (Kawamura, 2006, Slide 15). Hence, of the 2.3 billion infected, a conservative estimate of 5% or 115 million people will progress from latent TB infection to active TB disease over the course of their lifetimes. Not only would these individuals become ill with classic manifestations of tuberculosis, including a cough lasting more than two weeks, weight loss, chills, night sweats and fever, they would become highly infectious and capable of spreading the disease to others. Therefore, these individuals who progress to active diseases become a force to be reckoned with in the fight to achieve total elimination of TB in the US.

The ability to accurately identify latent TB cases and effectively treat those who are most likely to develop active disease is a target of TB elimination programs worldwide. While active global case rates as well as United States active case rates are in decline, the number of individuals with LTBI continues to increase. Confounding progression rates for disease is the rapidly escalating number of individuals suffering from chronic illnesses. Many different chronic diseases and conditions weaken the immune system over time. In 2005, the CDC reported that 133 million Americans lived with at least one chronic disease, representing 45% of the American adult population (CDC, 2005a).
In the US, tuberculosis is a long-standing member of the nationally notifiable disease list due to the serious threat it poses to national public health. All fifty states have mandated reporting for TB and “confirmed cases” are entered into the Nationally Notifiable Disease Surveillance System (NNDSS) for statistical and epidemiological tracking purposes. In 2008, 12,904 cases of TB were reported into the NNDSS (CDC, 2009).

A multitude of variables prevents an accurate estimation of the number of citizens who were potentially infected with TB that same year but did not develop active TB disease. However, using the assumption that the 12,904 confirmed active TB cases represented a 5% progression rate from initial, then approximately 258,080 persons living in the US were potentially infected with TB that less than 24 months previously and a remaining 245,174 individuals are potentially latently infected. With a stabilizing rate of decline in TB cases in the US it is possible to presume that for every 12 to 24 months there is an increase of approximately 245,000 individuals who may be latently infected with tuberculosis. This increase compounds the estimated 10 to 15 million persons in the United States already currently estimated to be living with LTBI (Hauck, 2009, p.879).

With the ever increasing magnitude of latent tuberculosis infection it is essential to plan effective targeted testing programs using the most highly specific testing methodology for accurate LTBI case identification in order to combat the progression of latent infection to active disease. This can best be done by understanding the infectious process and the conditions which increase the risk of progression to TB disease.
Infection with Mycobacterium tuberculosis

To recognize the magnitude and severity of latent tuberculosis infection, it is essential to understand the etiologic agent, its predilection for lung tissue, its method of spread and its specific virulence factors that cause it to rank in the top ten leading causes of death worldwide. Human tuberculosis is an infectious bacterial disease caused by tubercle bacilli of the species *Mycobacterium tuberculosis*. Humans serve as the only known reservoir for this pathogenic microbe. The human host becomes infected with the bacterium through the inhalation of airborne particles, called droplet nuclei, formed primarily through the coughing of persons with an active TB infection. According to the Material Safety Data Sheet for *Mycobacterium tuberculosis* (MSDSonline, 2010), the infectious dose is extremely low, approximately 10 bacilli. Each droplet nuclei can contain up to 3 bacilli. Therefore 3 or 4 droplet nuclei, if inhaled, can readily transmit the disease. Todar (2009), in his online textbook of bacteriology, placed the transmissibility of tuberculosis infection into perspective when he explained that a single cough generates approximately 3000 droplet nuclei (p.3). The droplet nuclei containing the infectious bacilli spread easily from one human host to the next.

Infection begins when the droplet nuclei reach the alveoli, the tiny air sacs at the farthest ends of the host lungs. Alemuja Raja (2004), a resident in the Department of Immunology Tuberculosis Research Center, in Chennai, India said of the initial immune response to invasion:

*M. tuberculosis* is an obligate aerobe, requiring an environment rich in oxygen.

Therefore, this bacterium is well suited to infect lung tissue. Here, alveolar
macrophages phagocytize (ingest) the invading bacterium in a nonspecific immune response meant to act as the body’s natural barrier to dust and debris. Typically, phagocytized foreign invaders are degraded by the lytic properties of the phagosome that forms around them. But *M. tuberculosis* is resistant to this process allowing the bacteria to multiply unrestricted within the phagosome (p.214).

Raja also stated “The protective and pathologic response of (the) host to *M. tuberculosis* is complex and multifaceted involving many components of the immune system” (p.224) At this point in the infectious process, the fate of the human host is dependent upon a highly complex cell-mediated immune (CMI) response that develops over a two- to six-week period.

*The Role of the Immune System in Latent TB Infection*

The complexity of human immunity and TB infection far exceeds the scope of this work. Nonetheless, some key concepts require exploration in order to better understand infection with *M. tuberculosis* and the risk for progression of latent infection to an active disease state in certain high-risk groups.

Initially, infection with *M. tuberculosis* is mitigated by the host’s *innate* immunity. The Merck manual (2008) describes innate immunity as being “present at birth…non-specific…treating all foreign invaders the same”. Thus, the innate response to invading tubercle bacilli is physiologic and not mediated by chemicals produced at a cellular level. Instead, the response is produced by specialized cells in the human respiratory tract which work to destroy the pathogen on contact. Complete and total destruction of
the infectious bacilli is one possible immune system response to infection with *M. tuberculosis*. This response is most likely when the exposure rate to TB is low, the exposure episode was brief and/or the individual is in excellent health. If the bacilli make their way into the tiny air sacs of the lung, then they are ingested (endocytized) and digested (phagocytized) by alveolar macrophages. While other cells in the lungs, including the alveolar epithelium, will also ingest the tubercle bacilli, the alveolar macrophage is most often the cell to perform this task.

This innate immune response is nonspecific but is also mediated through receptors on the surface of the alveolar macrophage which allow for binding to the tubercle bacillus. Because there exists an array of receptor types that promote binding and endocytosis, van Crevel (2002) wrote that “distinct routes of entry of *M. tuberculosis* may lead to differences in signal transduction, immune activation, and intracellular survival of *M. tuberculosis*” (p.297). Van Crevel and his colleagues stated that the role of variable routes for entry into the alveolar macrophage remains unclear but is strongly suggestive of immune evasion on the part of the bacteria as certain receptors are more favorable to the bacterium survival *in vivo*.

*M. tuberculosis* is well equipped for innate immune system evasion. As such, the second step in the immune response process is to call for reinforcements in the form of cells directed to the site of invasion by cytokines (inflammatory response chemicals). These “additional troops” will assist in recognition by the host’s immune system of the bacteria or its constituents and products. A very complicated interaction of cellular chemotaxis allows for other macrophages and T cell lymphocytes to be routed to the area of invasion. (A key point to remember, is that this cell-mediated process will form
the basis for the newer testing methodologies discussed later.) When these cells migrate to the site of infection and work to stop the growth of the bacilli, they “encapsulate” the organism inside a granulomatous lesion. Here the tubercle bacilli will remain dormant, held in a state of suspended animation for as long as the host’s immune system can keep the granuloma intact. This is the potential immune system response that results in latent TB infection.

The third immune response is the development of disease which occurs due to a failure of the host’s immune system to destroy or sequester the bacteria. In active TB disease, cases can range from a strict pulmonary infection (confined to the lungs) to a more aggressive, disseminated infection sometimes referred to as miliary or disseminated TB. Miliary TB spreads throughout the body creating lesions on a wide variety of tissues. Active cases of TB are most frequently seen in the socioeconomically challenged due to dietary impact on immune system strength, genetically susceptible populations like African Americans, and the severely immunocompromised such as HIV/AIDS patients. Lastly, the fourth type of immune response to *Mycobacterium tuberculosis* is one about which there is growing concern in the scientific and medical communities. This outcome occurs when changing immune system strength due to chronic disease states leads to the breakdown of the granulomas harboring the dormant bacteria in the latently infected and progression to active TB disease occurs. Progression is a possible outcome for all latently infected persons, though research has demonstrated many factors that increase this risk in certain groups.
LTBI and High-risk Groups

According to the CDC’s Guidelines for Targeted Testing and Treatment of LTBI, those with increased risk for progression to active disease can be separated into two groups. The first group of individuals is at increased risk due to a recent TB exposure with progression rates being highest in the first two years post exposure. This group includes:

- Close contacts of a person with infectious TB
- Recent TST converters (persons with baseline testing results who have an increase of 10 mm or more in the size of the TST reaction within a 2-year period)
- Persons who have immigrated from TB-endemic regions of the world
- Children ≤ 5 years of age who have a positive TST result
- Persons who work or reside in facilities or institutions with people who are at high-risk for TB, such as hospitals, homeless shelters, correctional facilities, nursing homes, or residential facilities for patients with AIDS (CDC, 2005b).

The second group is comprised of individuals who are compromised by health conditions that alter the strength of their immune system and lead to the breakdown of the protective capsules containing the dormant Mycobacterium tuberculosis. This group includes:

- Persons with HIV Infection
- Persons with HIV infection
- Injection drug users
• Radiographic evidence of prior healed TB

• Persons with a low body weight (≥ 10% below ideal)

• Individuals with other medical conditions, such as silicosis, diabetes mellitus, chronic renal failure or on hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant, head and neck cancer, and other conditions that require prolonged use of prednisone or other immunosuppressive agents such as TNF-α antagonists (CDC, 2005b).

The CDC concludes that there is evidence to support the targeted testing and treatment of individuals who fall into either the first or the second group in an effective TB eradication program. However, the CDC recommends against the wasting of resources to perform widespread testing and treatment of individuals with a low risk.

**Testing for LTBI: Limitations and Technological Advancements**

The oldest method for TB testing, and still the most widely used, is the tuberculin skin test. Although newer IGRA methodologies emerged nearly a decade ago, there was limited clinical data and evaluation on their sensitivity and specificity for *M. tuberculosis*. However, on June 25th, 2010 the CDC released “Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis*”. These new guidelines were developed by a panel of experts who reviewed the available body of scientific literature (152 journal articles) to determine the advantages, disadvantages and limitations of the tuberculin skin test (TST), the Interferon Gamma Release Assays Quantiferon Gold in Tube (QFT-IT) and T. Spot TB (CDC, 2010d).
The Tuberculin Skin Test (Mantoux method): Developed in 1907 by Robert Koch, this method relies on the use of a purified protein derivative (PPD) made from sterile culture filtrates of Mycobacterium bovis. In the tuberculin skin test method, a dose of 0.5ml's is administered intradermally, on the underside of the forearm. All resultant reactions should be read and measured by a trained healthcare professional between 48 and 72 hours after administration. The reaction is read in millimeters measuring the site of induration (the hard raised reaction produced from a delayed-type hypersensitivity reaction to the PPD) across the long axis of the forearm with no induration being 0mm, and significant cutoff points being set at 5mm, 10mm, and 15mm based upon medical and exposure history.

In the CDC’s 2004 Interactive Core Curriculum on Tuberculosis for physicians, the variable cutoff point applications are outlined in the section entitled Testing for Latent Tuberculosis Infection/Testing Methods and reproduced here as follows for reference:

- A TST reaction of ≥ 5 mm of induration is interpreted as a positive result in the following groups: HIV-infected persons, recent contacts of a known TB case, persons with fibrotic changes on chest radiograph consistent with old healed TB, and patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/day of prednisone for ≥ 1 month). (CDC 2004, Slide 19)

- A TST reaction of ≥ 10 mm of induration is interpreted as a positive result in persons who do not meet the preceding criteria but who have other risk factors for TB. These include recent arrivals to the U.S. (< 5 years) from high-prevalence
countries, injection drug users, residents and employees of high-risk congregate settings, mycobacteriology laboratory personnel, persons with medical conditions that place them at high risk, children < 4 years of age, and children and adolescents exposed to adults in high-risk categories. (CDC 2004, Slide 20)

- A TST reaction of $\geq 15$ mm of induration is interpreted as a positive result in persons with no known risk factors for TB who except for certain screening programs required by local law or regulation would otherwise not be tested. (CDC 2004, Slide 21)

When variable cutoff interpretations are used in the reading of tuberculin skin tests the specificity of the test method increases. However, a review of pooled data from numerous studies demonstrated only 85% accuracy in the detection of infection with Mycobacterium tuberculosis when this testing method is used (CDC 2005b, p. 3)

Although implementation of the variable cutoffs almost eliminates false negatives in high-risk groups, this method still produces a high rate of false positives leading to treatment measures that are not necessary in 15% of detected infection cases. False positive reactions occur due to the nature of the tuberculin itself which does not allow for the differentiation between reactions caused by Mycobacterium tuberculosis, and those produced by other environmental Mycobacterium species or undocumented vaccination with BCG.

**T. Spot TB Test (ELISpot method):** The T. Spot TB test is based upon a testing method called ELISpot (enzyme-linked immunospot), which was developed in 1983. Modified and marketed in 2005 for TB testing, this method directly measures the number of
effector T cell lymphocytes responding to the antigens used in the testing platform. According to test literature published by the test manufacturer, Oxford Immunotec (2010b) effector T cells are part of the host’s cell-mediated immune response.

These cells form part of the immune system’s response to current invasion and are designed to actively engage and destroy a pathogen when it is encountered. The presence of effector T cells sensitized to M. tuberculosis antigens means that M. tuberculosis is currently being fought off by the body’s immune defense. This is the case in both active and latent TB disease. (Oxford Immunotec 2010b, T Cell Immunology, ¶4)

All T cells secrete a cytokine called Interferon Gamma (IFN-γ). Cytokines help cells to move toward and bind to other cells, tissues and foreign invaders. In this case, the cytokine, interferon Gamma, will be released by the effector T cell when exposed to the ESAT-6 and CFP-10 M tuberculosis antigens embedded in the solid phase of the test platform. IFN-γ promotes the binding of the effector T cell to the antigens. At each site where cell-to-antigen binding occurs there is the formation of a colored spot. The spots are quantified and compared against an internal negative test control (Nil) to determine a test result of positive, equivocal or negative.

The package insert for the test platform (Oxford Immunotec, 2010a) gives the following guidance for result interpretation:

Results for the T. SpotTB test are interpreted by subtracting the spot count in the Nil control well from the spot count in each of the panels, according to the following algorithm:
• The test result is Positive if (Panel A-Nil) and/or (Panel B-Nil) ≥ 8 spots.

• The test result is Negative if both (Panel A-Nil) and (Panel B-Nil) ≤ 4 spots. This includes values less than zero.

• Results where the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6 or 7 spots should be considered Borderline (equivocal) and retesting by collecting another patient specimen is recommended (Oxford Immunotec 2010a, p.12).

In comparison to the tuberculin skin test, one strength of the T Spot. TB is the utilization of the ESAT-6 and CFP10 antigens. Derived from a gene sequence not found in the BCG vaccine matrix or the purified protein derivative used in the Mantoux method, these antigens are highly specific to M. tuberculosis. Positive results from the test will not occur in reaction to BCG vaccine status or to other commonly encountered environmental mycobacterial species. Pooled specificity for the T. Spot TB test was 88% compared to the TST specificity of 85% (CDC 2010b, p. 3). Hence, a significant decrease in the rate of false positives occurs with this testing method. A false positive result can result in the treatment of patients for LTBI who are not actually infected with M. tuberculosis. Therefore, although the T. Spot TB test costs more to perform, the expense of treating false positive cases is reduced by use of this IGRA.

In addition to increased specificity, another distinct difference between the TST and T. Spot TB method, is that the T. Spot TB is a laboratory test which requires trained medical laboratory professionals to perform and for which there are standardized readings thereby decreasing the subjectivity of test results. An additional benefit of using the T. Spot TB platform is that it requires only a single patient interaction for the
initial blood draw with no subsequent follow-up visit to read the patient test result. This greatly increases patient compliance with testing, particularly in the homeless, the socioeconomically challenged, geographically challenged and drug addicted where return rates for TST reading are among the lowest.

QuantiFERON TB Gold in Tube (QFT-GIT): Cellestis released QuantiFERON TB in 2003 and produced this modified version, QuantiFERON TB Gold in 2005. In 2007, they further expanded the stability and performance of the platform with the introduction of the “in tube” method. Another IGRA assay, the QFT-GIT method is similar to the T. Spot TB in that it is performed in a laboratory using blood drawn from the patient in a single patient visit, has standardized interpretations, and is reliant upon the cytokine interferon gamma (IFN-γ). However, the performing technique is not the same.

In this testing platform, enzyme-linked immunosorbant assay (ELISA) is utilized to measure the quantity of the IFN-γ released into the plasma portion of the blood in response to TB antigen exposure. As with T. Spot TB, this platform utilizes the same highly specific antigens from the M. tuberculosis genome but adds yet a third antigen TB7.7 (Cellestis 2006, p.4). Unlike the T. Spot TB which uses a single lithium heparin tube found in most laboratory phlebotomy sites, the QFT-GIT requires three special collection tubes marketed by the manufacturer. All three tubes are required for test performance.

The grey topped NIL tube is drawn first, and contains only the anticoagulant heparin and no antigens. Thus it serves as the negative control for the test procedure. The red topped tube is collected next and contains the anticoagulant heparin along with the TB
antigens which heavily coat the inner plastic surface of the tube. It is thought that the immediate exposure of circulating effector T cells to the test antigens inside this tube promotes the release of IFN-γ. The purple topped tube is collected last and also contains the anticoagulant heparin like the previous tubes. However, in the purple tube, there are no TB antigens, only a “mitogen”. A mitogen is a protein that stimulates cell division. In this method the mitogen acts as a positive control, validating the test subject’s ability to produce a sufficiently strong immune response. Its purpose is to validate that the platform works in subjects with a compromised immune status, thereby eliminating false negatives, something the T. Spot TB is not equipped to do, making the QFT-GIT method more appropriate in immune-suppressed high-risk patients.

An additional test benefit to using the QFT-GIT method is the availability of test interpretation software from the manufacturer, Cellestis. Cellestis' package insert for QuantiFERON TB Gold In Tube Method claims that the software “performs a Quality Control assessment of the assay, generates a standard curve and provides a test result for each subject, as detailed in the Interpretation of Results section” (Cellestis, 2006, p.16). Manual test interpretation can be performed by the laboratory professional if software is not used. Interpretation tables are available in the package insert. In general, test interpretation begins with measurement of the negative control tube (Nil). Results of IFN-γ values must measure less than 8.0 IU/ml or test results will be considered indeterminate. In test populations, 8.0 IU/ml or higher circulating levels of IFN-γ occurred in only 0.25% of test subjects (Cellestis, 2006, p. 19). Positive results occur when the difference between the IFN-γ levels in the Nil tube and the TB Antigen coated is >0.35 IU/ml and >25% of the Nil value (Cellestis, 2006, p.17) The QFT-IT
method increases the specificity of TB testing for M. tuberculosis while decreasing the rate of both false negative and false positive results which makes the QFT-GIT method the superior test for targeted LTBI testing programs.

American Indian/Alaskan Native's as a Unique High-Risk Group

Unfortunately, health disparities due to a complex interaction of behavioral, socioeconomic, and genetic factors, place AI/AN’s at significantly higher risk for progression of LTBI to active disease. In addition to an increased risk for disease progression there is also an increased risk of mortality from active stage disease. According to the Provider's Guide to Quality & Culture, a collaborative project of the Management Sciences for Health (2008), American Indians have a "disproportionately high rate of mortality" from tuberculosis in comparison to other Americans (p.1). In fact, the age-adjusted mortality rate is quoted as being 500% higher than the general U.S. population (p.3). Effective targeted testing of AI/AN’s at high-risk begins by recognizing the health conditions and behaviors that contribute to this increased risk.

In a recent article for American Family Physician, Hauck (2009) wrote that an increased risk of progression occurs most significantly in the first two years after infection is acquired, and that this risk is further increased by any decrease in the immune competence of the host. The conditions listed in the article which threaten to compromise host immunity included HIV infection, diabetes mellitus, chronic renal failure and end-stage renal disease, and those persons with “disorders requiring long term use of corticosteroids or other immunosuppressant medications (tumor necrosis factor alpha antagonists)(p.880). With the exception of HIV, these chronic health
conditions are notoriously endemic to the Native American population. In the publication entitled *National Diabetes Statistics, 2007*, the National Diabetes Information Clearinghouse (2008) reported a rate of 16.5% for diabetes in AI/AN's, more than twice the national average of 7.8%. Hand in hand with this increase, the National Kidney Foundation (2002) reported in the *Diabetes & Chronic Kidney Disease Guide for American Indians and Alaskan Natives* brochure, a three-fold increase for kidney failure in AI/AN's over white Americans directly resulting from the impact of diabetes mellitus on kidney health and function (p.3). In addition, the observed increase is not uniform, as end-stage renal disease (ESRD), the last stage of chronic kidney disease, occurs in AI/AN's at a rate of six times that of non-Native Americans (Davita.com, 2006, ¶2). It is clear that diabetes mellitus poses a significant threat to immune system health in Native American populations thereby indicating that all AI/AN's with diabetes should be routinely screened for the presence of LTBI so that immediate treatment can be offered to prevent progression to active stage tuberculosis.

Autoimmune diseases are also found in higher rates among Native American females than in the general US population. According to the National Institute of Health's (NIH, 2009) September 2009 podcast transcript on *Autoimmune Diseases and Their Impact on Women*, “Autoimmune diseases are a category of disorders that can affect just about every organ system in the body — from hair to toenails — and are often chronic diseases that can go on for a lifetime” (¶1). Autoimmune disease occurs when the body begins to recognize normal healthy tissue as being a foreign invader. When this happens, the defense mechanisms normally used to trap and kill pathogens, like viruses and bacteria, are used to attack and destroy the body’s own cells. Tissue destruction
leads to a wide array of symptoms and in some extreme cases the process can even be fatal. Autoimmune disorders are commonly categorized as either isolated or systemic. In AI/AN females, systemic autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are encountered with greater frequency than in non-native females. While the increased incidence of SLE is approximately three fold (US DHHS Office of Minority Health, 2008), for RA there is a 5 times greater likelihood of development in AI/AN females over their Caucasian counterparts (Smith, 2010). Drugs commonly used to treat autoimmune disease include the Tumor Necrosis Factor (TNF) blockers - Enbrel, Remecade and Humira. These drugs are useful in moderating patient symptoms, particularly in patients for whom Methotrexate and Sulfanizole have failed to work. However, use of TNF blockers place these individuals at significantly greater risk of LTBI progression to active TB.

The high prevalence of diabetes mellitus, RA and SLE place further emphasis on the cruciality of effective screening programs in the Indian Health Services. All Native Americans with diagnoses which place them at increased risk should be screened annually with a test method that offers the highest degree of sensitivity and specificity for Mycobacterium tuberculosis as part of a comprehensive LTBI screening program. All positives must be investigated and individuals encouraged to complete drug treatment regimens to prevent progression of latent infection to TB disease.

Conclusions:

Current Approaches to LTBI Screening in Indian Health Service Are Insufficient
There are approximately 3.2 million American Indians and Alaskan Natives living in the United States (Census Bureau, 2007). The Indian Health Service (2006) estimated, in the publication *Facts on Indian Health Disparities*, that more than half the AI/AN's living in the US accessed health care services at the 49 hospitals and more than 600 clinics operated by the Indian Health Service, Tribes, and Alaskan Native corporations. This represents approximately 1.8 million AI/AN’s from 562 different tribes. It is, therefore, a responsibility of the Indian Health Service to adequately address LTBI through the targeted testing of those AI/AN’s who are at increased risk for progression to active disease. However, health care finance plays a key role in any effort to reduce or eliminate tuberculosis in AI/AN’s.

In a Symposium on Native American Health Disparities held in November 2007 at Harvard, the Chief Information Officer of IHS, Theresa Cullen, stated that, though historically underfunded and understaffed, the Indian Health Service is asked by Congress to provide this care with inadequate resources (Harvard Science, 2007). In his 2009 lecture entitled “Indian Healthcare Challenges in Leadership”, Dr. Vincent Berkley, Chief Medical Officer for the Phoenix Area of IHS, stated that the United States government spends more money on each individual in its prison system than it does on AI/AN citizens for basic health care. Therefore, health disparities remain and so does TB.

The 2010 Indian Health Recovery Act placed funding into facilities, equipment and programs in an effort to reduce and eliminate the severity of health disparities among AI/AN’s. However, it is paramount to recognize that even with the Congressional appropriation of over 4 billion dollars to fund healthcare for Native Americans, and an
estimated $9 million in third-party payer collections, this amounts to approximately $2690 per capita health expenditure on each AI/AN for the 2010 budget year. The per capita expenditure on healthcare for the general US population is $6826 (IHS, 2010). Thus, it is anticipated that the added cost of Interferon Gamma Release Assay testing methods for LTBI is likely to present the greatest barrier to adoption and implementation of an effective LTBI targeted testing program in the Indian Health Service. To this end, demonstrating the increased cost-benefit ratio both to the agency as a healthcare provider and to the AI/AN patient as the healthcare consumer is paramount to the adoption of new screening protocols.

Exploring the Cost-Benefit Ration for IGRA Use Demonstrates Appropriate Management of IHS Resources

Due to the introduction of new testing platforms with an increased specificity to detect tuberculosis infection, several cost analysis studies, independent of the test manufacturers, have begun to emerge. Utilizing knowledge from these studies, the Indian Health Service can better extrapolate the cost-benefit ratio of implementing IGRA testing platforms for the detection of LTBI in high-risk groups. A 2009 study, lead by researchers from the University of Cincinnati and the Veterans Affairs Office of Infectious Diseases in Washington DC and published in the Archives of Internal Medicine, sought to examine the cost effectiveness of using IGRAs to screen health care workers (HCW), who, like American Indian/Alaskan Natives, also form a unique high-risk group due to HCW's increased risk of repeated TB exposure. Lead researcher, Marie A. De Perio, MD (2009), concluded that "QFT-GIT strategies are more effective and less costly than the TST method" regardless of previous vaccination status with
BCG (p.185, ¶2). Dr. de Perio and her research team further stated that sensitivity analysis for IGRA testing demonstrated that the newer test platforms were "clinically and economically worthwhile" (p.185, ¶2). One cautionary statement emerged from the study commentary that "batch testing" helps to keep associated costs (such as lab personnel time involved to perform the analysis) moderated. Due to the increased stability of the new QFT-GIT method, performing laboratories are electing to save patient isolates for testing one day a week in low volume laboratories. This is an important consideration for the Indian Health Service as many health clinics are located in rural areas and serve smaller populations than their urban counterparts. In these settings, adjustments to scheduling may be required to keep incurred costs to a minimum.

Another important criterion for consideration in the cost benefit ratio is the tradeoff between test sensitivity and test specificity. Sensitivity describes a test's ability to detect positive cases of disease. In a test method with "high" sensitivity few positives are missed but the tradeoff is frequently in the specificity of the test. Test specificity refers to the ability of a test method to detect true disease (aka "true" positives). In latent tuberculosis infection screening, increased test specificity generates a cost savings. This results from the fact that all positives, whether real or false, require further testing and evaluation to rule out active disease, including chest x-rays, subsequent IGRA testing, and additional physical exams by a physician. Also, drug treatment must be provided to any presumed positives among the latently infected at high-risk for disease progression. By preventing false positives, valuable resources can be saved, allowing
the more costly but most specific test platform to essentially pay for itself over the
duration of its use.

**Great Waste Can Be Avoided by Changing Test Methods & Implementing Targeted Testing for LTB**

When change is imminent, leaders emerge at the forefront. According to Rowitz (2003), a professor in the School of Public Health at the University of Illinois, "If public health leaders are oriented to change and want to become catalysts for change, they need to develop program scenarios for possible futures" (pg. 59). One such leadership example in IHS is the combined efforts of Medical Officer, Suzanne Gnaegy, MD, and Public Health Nurse, Elizabeth Sullivan, RN, who collaborated on a project to fund IGRA testing for latent tuberculosis infection for patients served at the Colville Indian Health Center, a clinic located in the Portland Area of IHS. Colville IHC is located on the Colville Reservation which spans 1.4 million acres of land and is home to twelve tribes and one band. Colville Indian Health Center serves 9600 AI/AN's from a 40,000 square-foot family practice facility recently constructed in 2007.

Staying abreast of the latest research and recognizing the advantages of utilizing the newer testing methodology, in August 2007 Dr. Gnaegy and Ms. Sullivan applied for a grant to use the QuantiFERON TB Gold test to screen all tribal members. As emphasized by Rowitz (2003) in Public Health Leadership: Putting Principles into Practice, "leaders of local public health agencies have the responsibility to ... make sure the agencies are viewed as providers of high-quality programs and services" (p. 65). Dr. Gnaegy's and Ms. Sullivan's promotion of integrating Interferon Gamma Release
Assays into TB testing, based upon strong scientific evidence in the current body of literature, demonstrates their commitment as a healthcare team to ensuring the highest quality of care for their patient population. Together their foundational statistics quoted in their grant application paves the way for other IHS clinics to follow in their footsteps.

In the application for this grant, they cited a 25% no show rate on tuberculin skin test reads among their patients which is mirrored at other clinics throughout the nation. In part, this is due to transportation and economic barriers for patients (Gnaegy. S and Sullivan, E., 2007). Unfortunately, this 25% represents a significant number of patients who remain unscreened. For those among them who would have produced a positive TST reaction, these individuals remain untreated and at risk for progression. They also provided cost estimates of $739 - $1,311 per patient for treatment of positive TST's. By utilizing their statistics and the national estimate of 1.8 million AI/AN's served through IHS facilities nationwide, the financial impact of screening all AI/AN's annually with a method having poor specificity and minimal compliance rates can be extrapolated.

Of the 1.8 million screened with TST, 450,000 will be lost to follow up. Of the 1.35 million who receive the follow up result reading in the appropriate window, only 85% will generate an accurate result. Fifteen percent, or 202,500, will be falsely positive and require treatment at a total cost to IHS of approximately $150 to $266 million dollars. In the 2007 presentation at the IGRA Symposium, entitled IGRA's in Public Health Practice: Economic Issues, Dr. Kawamura (2007) cited results of a cost analysis study that demonstrated incurred lab costs of $302,000 per year per 10,000 tests for the QFT-GIT method (Slide 8). If this cost is analyzed across 1.8 million AI/AN's receiving care through IHS, with the high specificity of 99% of disease detection and the 100%
compliance with testing, then the costs of screening all AI/AN's in the system can be estimated to be approximately $54.5 million. Of these, there will be an approximate 1% false positive rate incurring wasted treatment costs approximating $1.3 to $2.3 million. Thereby the savings to the federal government in waste associated costs with the currently used tuberculin skin test is estimated to be in the hundreds of millions of dollars. It is likely that the concurrent development and implementation of targeted testing models in IHS, using CDC recommendations, could further reduce the cost of testing.

Recommendations

Leadership Driven Change is Required to Execute More Effective LTBI Screening Programs in IHS

Because services are strongly tied to already inadequate funding in the Indian Health Service, both tribal and federal leadership will be required to secure policy changes which ensure the development of effective screening programs for latent tuberculosis infection among American Indians and Alaskan Natives. To chart the agencies pathway towards an effective transformation in the Indian Health Service approach to LTBI screening, it is beneficial to consider all recommendations in relation to the core functions and essential services model of Public Health.

In 1988, the institute of Medicine (IOM) identified three core functions of public health-. Subsequently, in 1994, the IOM, CDC, American Public Health Association and National Association of County & City Health Officials, formed the Public Health Functions committee. This committee strove to identify the essential services that were embodied
by the IOM's core functions. From this collaborative effort, a representative model was established to define Public Health. Reprinted below for reference, the model is comprised of several concentric layers (Public Health Functions Committee, 1994). The outer ring of the model, featured in black arrows, represents the core functions while the inner colored pie pieces represent the essential services these functions embody. Embedded in each essential service are a multitude of leadership activities not depicted by the model but expounded upon by the American Public Health Association. Residing at the core of the model is research. Research is thusly depicted as impetus that drives the all essential services. Therefore, in the case of tuberculosis screening, current research should create the underlying driver for change.

Fig. 1 Courtesy of the Public Health Functions Committee, Fall 1994

Assessment: What is learned through research is often conveyed to the Public Health workforce via statistics. For example, statistics demonstrate that Al/AN's are disproportionately affected by the incidence of tuberculosis as well as by health conditions which increase their risk of latent TB Infection progression to active disease. Armed with this knowledge, the Indian Health Service must explore the cause of
increased rates of TB in this population. A failure to effectively diagnose and treat LTBI cases among AI/AN's forms a significant contribution to this disparity.

Through the essential service of Evaluation, IHS can use internally collected information to better Educate and Empower it's leaders to improved latent tuberculosis screening. Cost-benefit analyses are one useful assessment tool that can successfully drive policy development while leading to quality assurance in the form of improved patient care. In the CDC tutorial on Cost Analysis, a part of the Economic Evaluation of Public Health Preparedness and Response lecture series, the appropriate use of cost analysis is described to be when the following criteria are met:

- A single program (i.e. Tuberculosis Screening) is being assessed
- Information about the program's "effectiveness" is unavailable (i.e. IHS does not have adequate capture of effectiveness although the ongoing disparity in TB incidence among AI/AN's is indicative of poor program performance)
- Interventions to be assessed or compared are equally effective (in the case of TB screening, the CDC states that IGRA methods are employable in all instances where TST methodology is currently being used.)

Since it is debatable that the two interventions, TST and IGRA, can be considered "equally effective", in light of the rapidly increasing evidence supporting the greater sensitivity of IGRA's and the increased patient compliance when this method is employed, it then becomes necessary to consider broadening the scope of the cost analysis to include a cost-benefit analysis on each individual method.
A cost-benefit analysis works to identify and quantify, in monetary terms, all of the benefits (deemed to be the pro’s or benefits for using the method) and the costs (the con’s or the costs of using the method). The total “cost” is subtracted from the total “benefit” to show the “profit” for employing each method. The most “profitable method” should be the method of choice. For programmatic evaluations, costs and benefits can be somewhat elusive – such as money saved in decreased physician/nurse contact with patient or the cost of patient progressing to active TB due to failed ability to identify disease. However, a skilled team possessing a statistician and epidemiologist can often achieve accurate estimates. A recommended approach to performing a cost-benefit analysis would be to “run the numbers” on all three methods – TST, T. Spot TB, and QFT-GIT for the entire population. Then to repeat the analysis on only those AI/AN’s deemed to be at-risk for progression.

Assurance: Use of the newer and more specific Interferon Gamma Release Assays to perform targeted LTBI screening on those AI/AN’s with chronic diseases, such as diabetes mellitus and autoimmune disease, must be separately considered from routine screening. Therefore, these high-risk groups present a different concern to the agency. Evidence-based practice is a call to treat all patients with the highest quality of care based upon the current body of knowledge. As this knowledge is rapidly increasing for high-risk LTBI groups, the Indian Health Service must consider the evidence in its approach to TB screening program development and funding.

One way to assure that TB screening programs are compliant with evidenced based practices is to evaluate the cost effectiveness and utility of using IGRA technology in these high risk populations first. By, performing a cost-benefit analysis using statistical
data representative of only those patients who comprise these high-risk groups, it may be discovered that targeted testing in these individuals with IGRA is a funding priority over routine screening with IGRA. Some studies have shown this to be an effective patient management approach within generalized TB screening programs. In Turnock’s book, *Public Health: What It Is and How It Works*, he emphasizes that “At the heart of public health interventions for improving the quality of life and reducing preventable mortality and morbidity are scientifically sound strategies and approaches” (p.260).

Leadership in the Indian Health Service has a responsibility to stay current on the latest research affecting TB screening and to work toward embracing this knowledge and incorporating it into the design, structure and function of its approach to reducing TB incidence and mortality among Native Americans. Clinical preventative services, which include screening, counseling, immunizations, and chemoprevention, are monitored by the US Preventative Services Task Force for their ability to truly improve clinical outcomes. Each time the task force convenes it publishes a list of recommended services based upon the evidence that these services improve outcomes. TB screening remains on this list and as such any improvement in the effectiveness of screening can be assumed to correlate with improvement in health outcomes.

**Policy Development:** In the case of TB testing the Indian Health Service needs to review the “bottom line”, or profit, in light of both agency funding as well as a patient quality of care. IHS leadership must internally demonstrate that federal funding streams can be more effectively utilized with IGRA implementation as these platforms demonstrate a significant cost savings over the currently used tuberculin skin test. Tribal leadership can help to augment screening programs through tribal grants therefore assuring
greater success in eliminating the health disparity of TB disease among AI/AN's. Goal three of the Indian Health Service's strategic plan for 2006 through 2011 is the fostering of collaboration and innovation across the Indian health network. Objective 3.1 is to expand coalitions and partnerships across the network through innovative partnerships. If funding issues create a barrier to redesigning the Tuberculosis screening programs across the Indian Health Service then local service units should attempt to collaborate with tribes to generate funding for incorporating IGRA. The more data that can be generated at the local service unit level, the more leverage the agency can use to access funding for these improvements. This provides a wonderful opportunity for local federal facilities and their associated tribes to work together.

Through collaboration with the tribal governments, adequate assessment, better policy development and increased assurance of quality health care can be achieved. The combination of increased test specificity, increased testing compliance, and the proactive treatment of individuals in high-risk groups for LTBI progression has the potential to significantly impact rates of tuberculosis morbidity and mortality among all AI/AN's and will serve to align the Indian Health Service with the strategic TB elimination goals of the Centers for Disease Control and Prevention.
References


