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Grant Proposal for Tuberculosis Prevention through an Examination of Migration Patterns in Mexico, within the Border State of Tamaulipas

By

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Degree to be awarded: M.P.H.
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By

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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Abstract

Grant Proposal for Tuberculosis Prevention through an Examination of Migration Patterns in Mexico, within the Border State of Tamaulipas

By
Jennifer S. Curry

This project is in response to the National Institutes of Health (NIH) Funding Opportunity Announcement (FOA) PA-13-303, "NIH Exploratory/Developmental Research Grant Program (Parent R21)". The National Institute of Allergy and Infectious Disease (NIAID) is interested in supporting meritorious investigator-initiated research directed toward improving knowledge about tuberculosis (TB) and how it affects humans. As well, the NIAID is interested in supporting research to assess factors influencing the occurrence, distribution, and transmission of drug sensitive/resistant mycobacterium tuberculosis (Mtb). In support of these goals, the aim of this project is to conduct an uncontrolled cross-sectional cohort study that will investigate the contribution of population migration within Mexico to the prevalence of TB in the Mexican state of Tamaulipas. Tamaulipas borders the southernmost tip of Texas. The state of Tamaulipas was selected because it has one of the highest TB prevalence rates (30 per 100,000) versus Mexico's national average of 13.5 per 100,000, and the highest rate of multi-drug resistant TB (MDR-TB) cases in Mexico. While it is alluded that migration from the poorest states in Mexico may be responsible for a significant proportion of TB cases in the Mexican states bordering the U.S., this has never been systematically evaluated. In addition, the epidemiology of TB in the border regions of Tamaulipas, including: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure) will be evaluated. This fact along with the importance of TB prevention in Mexican border communities underscores a clear need for this research project. Additionally, the research findings will help inform the prevention of TB in communities throughout Mexico along both sides of the U.S./Mexico border.

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DEFINITION OF TERMS

Acid-fast bacilli (AFB) – mycobacteria that when stained, retain color even after they have been washed in an acid solution; may be detected under a microscope in a stained smear

Cavity – a hollow space within the lung, visible on a chest x-ray, that may contain many tubercle bacilli; often occurs in people with severe pulmonary TB disease

Directly Observed Therapy (DOT) – a strategy devised to help patients adhere to treatment; a designated person watches the TB patient swallow each dose of the prescribed drugs

Droplet nuclei – very small droplets (1 to 5 microns in diameter) containing *M. tuberculosis* that may be expelled when a person who has infectious TB coughs, sneezes, speaks, or sings; the droplets can remain suspended in the air for several hours, depending on the environment

Mycobacterium tuberculosis – the organism that causes TB in humans and is sometimes called the tubercle bacillus; belongs to a group of bacteria called mycobacteria

Pathogenesis – how an infection or disease develops in the body

Smear – a specimen that has been smeared onto a glass slide, stained, washed in an acid solution, and then placed under the microscope for examination; used to detect acid-fast bacilli in a specimen

Tuberculin skin test (TST) – a method of testing for TB infection; a needle and syringe are used to inject 0.1 ml of 5 tuberculin units of liquid tuberculin between the layers of the skin (intradermally), usually on the forearm; the reaction to this test, usually a small swollen area (induration), is measured 48 to 72 hours after the injection and is interpreted as positive or negative depending on the size of the reaction and the patient's risk factors for TB

Tubercle bacilli – another name for the *Mycobacterium tuberculosis* organisms that cause TB disease

Interferon-gamma release assays (IGRAs) – it is a type of blood test that measures an individual's immune reactivity to *M. tuberculosis*. In the U.S., there are currently two available IGRAs: QuantiFERON®-TB Gold and QuantiFERON®-TB Gold In-Tube

LIST OF ABBREVIATIONS

AFB – Acid-fast bacilli

CDC – Centers for Disease Control and Prevention

DOT – Directly Observed Therapy

FOA – Funding Opportunity Announcement

GFT-GIT – QuantiFERON-TB Gold In-Tube test

GWAS – Genome Wide Accelerated Study

IGRAs – Interferon-Gamma Release Assays

INEGI – Institute of Statistics, Geography, and Information

INH – Isoniazid

IOM – International Organization of Migration

IRB – Institutional Review Board

LRGV – Lower Rio Grande Valley

LTBI – Latent Tuberculosis Infection

MDGs – Millennium Development Goals

MDR-TB – Multidrug-Resistant Tuberculosis

NIAID – National Institute of Allergy and Infectious Diseases

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases

NIH – National Institutes of Health

OECD – Organization for Economic Co-operation and Development

PI – Principle Investigator

PPD – Purified Protein Derivative

PTB – Pulmonary Tuberculosis

RIF – Rifampin

RPG – Research Project Grant

SINAVE – Sistema Nacional de Vigilancia Epidemioloigca (English translation: National System of Epidemiological Surveillance)

SME – Subject Matter Expert

SSA – Secretaria de Salud de Tamaulipas

STIs – Sexually Transmitted Infections

TB – Tuberculosis

T-Spot – T-SPOT.TB

TST – Tuberculin Skin Test

USAID – United States Agency for International Development

UTHSC-SPH – University of Texas Health Science Center School of Public Health

UT-RGV – University of Texas Rio Grande Valley

CHAPTER 1: INTRODUCTION AND RATIONALE

INTRODUCTION

Recent outbreaks such as Ebola and Zika expose a predilection for reactionary responses toward disease control and prevention. By taking into account population migration movements, it may be possible to be proactive with regard to disease control and prevention rather than reactive. Though the overall incidence of tuberculosis (TB) and multidrug-resistant tuberculosis (MDR-TB) in the U.S. has declined in the last decade, the re-emergence of TB and MDR-TB as a rising concern in foreign-born individuals, particularly in communities along the U.S.-Mexico border, is cause to re-examine the association between population migration and TB incidence. A driving force behind this occurrence is the impact of globalization on intra- and inter-national migration, a key epidemiological determinant of TB. The six Mexican states (Baja California, Sonora, Chihuahua, Coahuila, Nuevo León, and Tamaulipas) that border the U.S. carry 34.3% of Mexico's TB burden. The purpose of this thesis is to draft a research grant that proposes to systematically quantify the contribution of population migration on TB prevalence in the Mexican state of Tamaulipas. Tamaulipas is one of two border-states that carry a high burden of TB, and because of its location it serves as a waypoint; it provides a unique opportunity to look at where TB is headed, and from where it has come as it directly affects communities on both sides of the U.S.-Mexico border.

PROBLEM STATEMENT

Although the incidence of TB has declined globally, its reputation remains affixed as one of the world's most highly infectious communicable diseases (World Health Organization, 2015a). Globally, one-third of the population carries the latent bacterium; however the disease will remain dormant in individuals with a healthy immune system. In

2014, active TB disease affected 9.6 million people globally (World Health Organization, 2015b), while in the U.S. the number of cases reported were 9,421 (Centers for Disease Control and Prevention, 2015). Most of the cases reported in the U.S. are attributed to foreign born individuals with Mexico contributing nearly 25% of the cases, and more than 65% in the communities along the U.S.-Mexico border. The economic burden of TB in the U.S. is $17,000 per TB case, while MDR-TB can reach upwards of $134,000 per patient.

The U.S.-Mexico border is a 2,000 mile corridor that comprises communities with heterogeneous behaviors and cultures that present challenges towards the prevention and control of TB, specifically poverty, overcrowding, and migration. Economic globalization is a driver of migration both within and between countries, and from rural to urban areas. For many Mexicans, economic insecurity along with the drug trafficking trade propagates migration movement in the hopes of better opportunities. Thus an interaction is occurring between globalization, the risk of TB infection, exposure to "obesogenic" urban communities (Young, Critchley, Johnston, & Unwin, 2009), and the allostatic load caused within the individual as they attempt to adapt to new environments. It is alluded from local observations that migration from the poorest regions and states in Mexico may be responsible for a significant proportion of TB cases in the Mexican states directly across the U.S. border. This has never been systemically evaluated, therefore understanding the epidemiology of the U.S.-Mexico border along with socio-demographics of the patients from this region is critical for TB prevention and control. It has been established that the most cost-effective method of detecting as well as preventing further TB transmission along a transient and porous border is dependent on

rapid diagnosis, evaluation of close contacts of active pulmonary TB, and effective treatment of cases, particularly among immigrants.

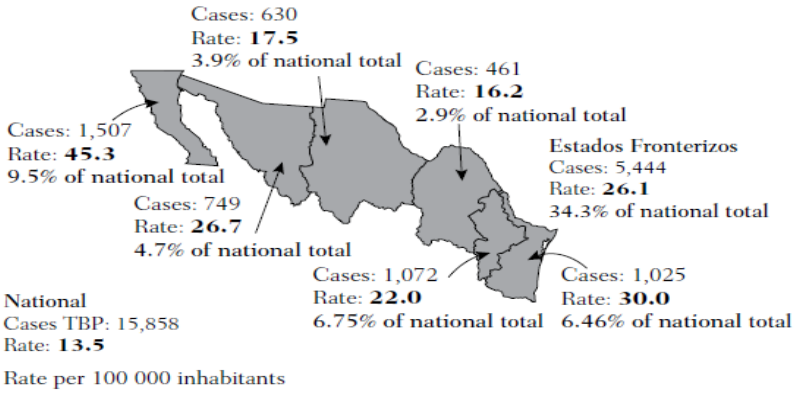
Considered as the most important corridor of migration in the world, Mexico serves as a country of origin, as a place of transit, and as a destination (United Nations Alliance of Civilizations, 2010). With over 41 million crossing the northbound border on foot, and an additional 122 million crossing over in personal vehicles in 2013 (U.S. Department of Transportation, 2013), it is not surprising that elimination of TB has not been possible. The state of Tamaulipas shares 348.6 miles of its northern border with the state of Texas (Figure 1.1) (Texas Department of Transportation, 2013) accounting for 17% of the total border shared.

Figure 1.1 - Map of U.S.-Mexico Border and State of Tamaulipas

Source: (Thornton, 2013)

Tamaulipas has a TB rate of 30 per 100,000 vs. Mexico's national average of 13.5 per 100,000 (Figure 1.2) (Joya, 2014). Second to Baja California, Tamaulipas has one of the highest incidence rates of TB and MDR-TB in Mexico (Joya, 2014).

Figure 1.2 - Incidence of Pulmonary TB in Mexican Border States, 2012



Source: (Joya, 2014)

Tamaulipas is a highly-dynamic state. Annually more than 50,000 individuals emigrate from Tamaulipas to settle in another Mexican state, e.g. Nuevo León, Veracruz, San Luis Potosí and Coahuila, and another 30,000 emigrate to the U.S (Secretaría de Salud, Gobierno del Estado de Tamaulipas, 2015). However, this loss is made up by a similar influx of 100,000 individuals coming into Tamaulipas in search of better job opportunities, principally from other Mexican states where the economy is depressed such as Veracruz, San Luis Potosí, Nuevo León and the State of Mexico. Given that poverty and TB go hand in hand, this human migration is likely to have a significant impact on the epidemiology of TB in Tamaulipas.

PURPOSE STATEMENT

TB has no boundaries, and now more than ever, it is critical to form an understanding of how demographic and population migration dynamics contribute to this public health concern. TB in Tamaulipas must be investigated with renewed interest in order to provide an increased understanding of how its TB burden contributes to disease prevalence along the U.S. border.

The purpose of this thesis is as follows:

- Determine the state of birth of the TB patients diagnosed in Tamaulipas,
- Establish their sociodemographic and medical characteristics,
- Determine if there are differences in sociodemographics or medical characteristics between patients born in Tamaulipas versus other Mexican states and Latin American countries, and
- Determine how these differences may help target efforts towards TB prevention in Mexican border states such as Tamaulipas to better inform at risk populations along both sides of the U.S.-Mexico border.

This will have implications for TB prevention and control in the U.S., particularly in border communities where at least 60% of the TB patients are born in Mexico.

PROJECT GOALS

1.) Determine the association between migration patterns and the incidence of TB in Tamaulipas,

- Identify the TB patient's place of birth,
- Identify the year TB patient left place of birth,
- Identify interim locations visited by TB patients en route to Tamaulipas,
- Identify the length of time TB patient has been in Tamaulipas,
- Compare the TB incidence between sanitary jurisdictions that border versus those that do not border with the state of Texas.

2.) Identify the characteristics that distinguish the TB patients in Tamaulipas that originate from border versus non-border states of Mexico with respect to: a) sociodemographics, b) medical characteristics, c) adverse TB outcomes (re-infection or treatment failure).

SIGNIFICANCE STATEMENT

Per the World Health Organization, the U.S. is categorized as a "low incidence" TB country with <20 cases per 100,000 population. Mexico, in particular the state of Tamaulipas, is not a low incidence TB area. However, TB is relevant to U.S.-Mexico border health as it has implications on the occurrence, surveillance, prevention and control of disease transmission. More importantly, the observations and knowledge gleaned along this corridor serve as a barometer and case study for low incidence TB countries (e.g. the United States) with neighboring high incidence TB countries (e.g. Mexico) and/or geographical areas. This area is a testament that low incidence TB countries are no longer immune to the complexities of TB control once experienced by high incidence countries.

In addition, there is an association with increased levels of TB with urban growth. This has implications for a state such as Tamaulipas especially along its northern border as three of its largest cities account for a floating population of over 2.5 million people with continued growth in sight. By exploring the socio-epidemiology of Tamaulipas, current and future studies can begin to assess the true burden of migration in these cities. In Tamaulipas, MDR-TB is the highest in the country, and here the primary spread of MDR-TB is set to become a significant threat to MDR-TB control which is exacerbated by poverty and population movement.

Finally, the turn of the 19th century provided great insight into infectious disease control in the U.S., but more importantly it taught us that destination communities are changed by immigrant populations therefore impacting the epidemiological landscape of the community. While the U.S.-Mexico border may seem homogenous, "the health

characteristics of migrant cohorts are influenced by the health environments and situations at their place of original residence, the environments through which they make the transition and their new destination" (Oppong, Denton, Moonan, & Weis, 2007, p. 2). Therefore, "knowledge of geographical trends is important for individual healthcare, public health and national infectious disease control or elimination programs" (Oppong, Denton, Moonan, & Weis, 2007, p. 2).

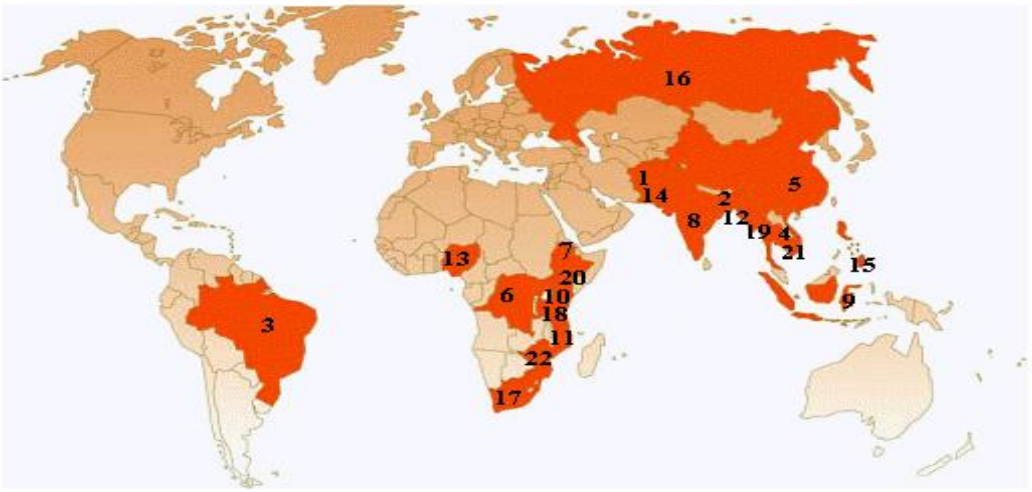
CHAPTER 2: REVIEW OF THE LITERATURE

Migration paths are tied to geo-political conflicts, and economic, cultural and environmental trends; furthermore they expose key links in disease diffusion and propagation that might have previously been missed by epidemiological methods. These are important contributing factors to the recent toll human migration has had on TB infection patterns (Tomas, et al., 2013). This chapter will discuss the burden of TB within the Americas down to its present state within the Mexican state of Tamaulipas, followed by an exploration of migration patterns in Mexico. Second, TB infection can be exacerbated by migration—this is examined in relation to TB pathogenesis. In addition, this chapter underscores the lack of studies that focus on TB prevention and control in Mexico, exposing a gap of knowledge in regard to Mexico's true sources of TB prevalence. Due to Tamaulipas sharing its northern border with the U.S., findings in the literature are highlighted that suggest cost effective and preventive measures occurring on non-U.S. soil are the best way of preventing and controlling TB in Mexico and the U.S. Finally, for the purpose of this review, the focus is on pulmonary TB (PTB) unless otherwise stated.

TB GLOBAL BURDEN

Although the incidence of TB has declined globally, TB still remains as the world's second-deadliest disease with1.5 million deaths in 2014 after HIV/AIDS (World Health Organization, 2015a). The global burden of individuals carrying active TB disease was 9.6 million in 2014, and 22 countries accounted for 83% of TB cases (Figure 2.1) (World Health Organization, 2015a).

Figure 2.1 - 22 High TB Burden Countries



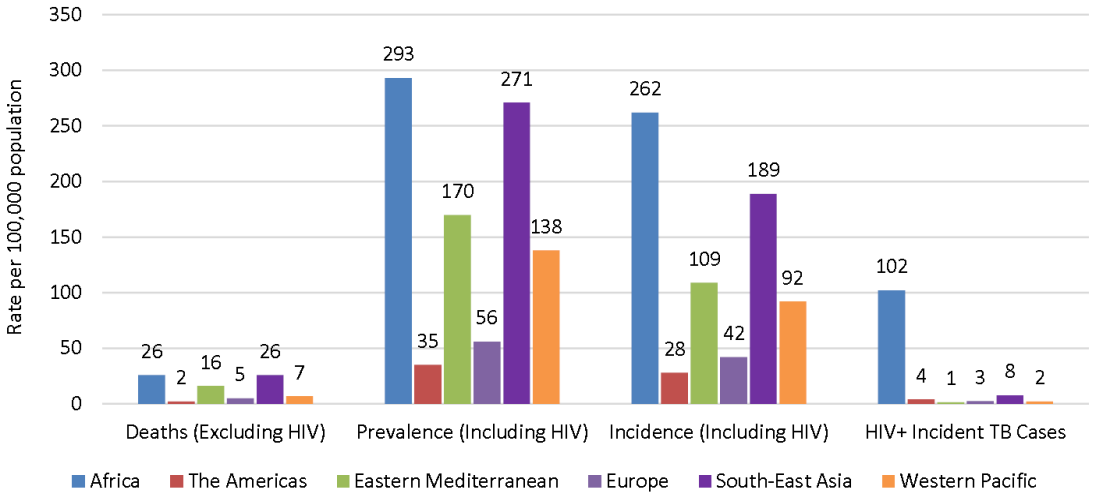
Source: (World Health Organization, 2015a)

Despite dramatic improvements made since the 1990s in providing access to high-quality TB services, along with the implementation of the Millennium Development Goals (MDGs) in 2000, many people with TB remain undiagnosed or are diagnosed only after long delays. The high burden of undiagnosed TB causes suffering, economic hardship, and sustains continued transmission of disease (World Health Organization, 2013).

TB IN THE AMERICAS

Figure 2.2 shows that the Americas have the lowest TB mortality and morbidity rates while Africa, Southeast Asia, and the Eastern Mediterranean have some of the highest. Even though the Americas maintain only one high-burden TB country (Brazil), it is a region plagued with disparate economic growth, which contributes to socio-economic conditions that impact population movement and transmission of disease.

Figure 2.2 - Burden of TB Worldwide, by Region, 2011



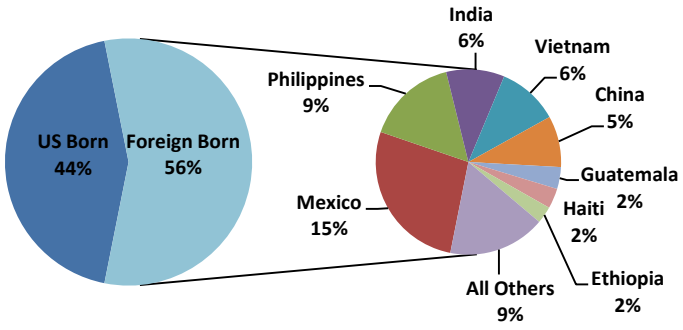
Source: (American Lung Association, 2013)

The statistics for the Americas are relatively low, and for the United States the decline is even lower with 9,421 TB cases reported in 2014 (Centers for Disease Control and Prevention, 2015). But, this decline has occurred disproportionately among the U.S.-born population, for whom the number of cases has decreased by 84% since the TB resurgence peak in 1993, while the number of TB cases among *foreign-born* persons in the United States *increased* (Centers for Disease Control and Prevention, 2014a). In foreign-born individuals the rate of TB is 13 times higher than U.S.-born individuals (Centers for Disease Control and Prevention, 2015). It has been noted the rate of TB disease among foreign-born persons has declined, but the rate has not declined as rapidly as the rate among U.S.-born persons, leading to the increasing disparity between U.S.-born and foreign-born persons. In 2014, 66% (6215) of all reported TB cases were among foreign-born persons (Figure 2.3) (Centers for Disease Control and Prevention, 2014a).

Even though the total contribution to the number of foreign-born individuals with TB in the U.S. is higher for individuals from other countries of origin, Mexico has the highest contribution for any single country followed by the Philippines, India, Vietnam

and China (Figure 2.3) (Centers for Disease Control and Prevention, 2014a). This highlights the problem along the U.S.-Mexico border, and the need to understand the dynamics of population movement and the social determinants' impact on TB disease and transmission on both sides of the border.

Figure 2.3 - Country of Origin of Foreign-Born TB Cases, 2014

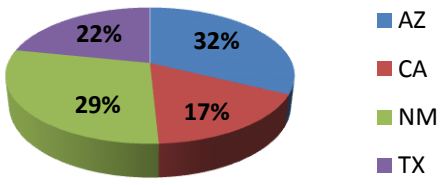


Source: Developed by the author with data from the CDC, 2014a

TB ALONG THE U.S.-MEXICO BORDER

Of TB cases among Mexican-born persons, 69% were reported from the four U.S. states bordering Mexico: California (448 cases), Texas (342 cases), Arizona (77 cases), and New Mexico (18 cases) (Centers for Disease Control and Prevention, 2014a). Figure 2.4 shows TB cases by border state for Mexican-born persons in 2014.

Figure 2.4 - Mexican-Born TB Cases by Border State, 2014



Source: Developed by the author with data from the CDC, 2014a

Underscoring a bi-national concern is that the reported prevalence of TB along the U.S.-Mexico border states is 9.2 versus the U.S. national rate of 2.96 (Texas Department of

State Health Services, 2015; Centers for Disease Control and Prevention, 2014a)versus Mexican border states at 34.3 versus Mexico's national rate of 13.5 (Pan American Health Organization, 2014; Secretaría de Salud, 2012). While this proposal looks specifically at the population in the state of Tamaulipas, it is paramount to also understand how its binational association affects the four U.S. counties of Starr, Hidalgo, Willacy, and Cameron—which make-up the Lower Rio Grande Valley (LRGV) of South Texas. Although Tamaulipas borders 17% of the state of Texas, 40% of its population (900,000) borders the LRGV. The LRGV population is young and medically underserved; however it comprises almost half of the entire U.S.-Mexican border population (Pan American Health Organization, 2012). Both sides of the border have at least a two times higher annual growth rate than national rates, and the diverse population and behaviors encountered present a challenge (Mier, et al., 2005).

The Texas/Mexico border is one of the busiest international boundaries in the world with an estimated population of 2.7 million residents (Texas Department of State Health Services, 2014). In 2014, Texas had 1,269 cases, and along the five Texas counties that flank the state of Tamaulipas, TB cases increased between 2013 and 2014 from 156 to 169 respectively (Table 2.1).

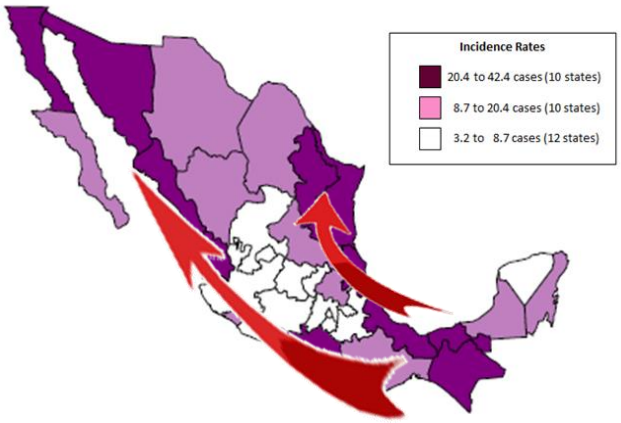
Table 2.1 - TB Cases in 5 Texas Counties along the Texas-Mexico Border

County	2013	2014
Webb	35	25
Zapata	0	1
Starr	4	6
Hidalgo	64	70
Cameron	53	67
Total	**156**	**169**

Source: Developed by the author with data from the (Texas Department of State Health Services, 2015)

In Tamaulipas the number of TB cases in 2012 was 1,025 with a prevalence rate of 30 per 100,000 inhabitants with over one-third of Mexico's TB patients (34.3%) concentrated along the U.S.-Mexico border (Joya, 2014). Additionally, it is observed that in the eastern corridor of Mexico the incidence of TB is consistently over 20.4 cases per 100,000 for the states of Tamaulipas, Veracruz, Tabasco, and Chiapas (Secretaría de Salud, 2012). However it is also known that another potential TB corridor in Mexico stems from Chiapas to Baja California (Figure 2.5). Herein lies a vital observation regarding the true burden of TB in Tamaulipas, and also within Mexico.

Figure 2.5 - TB Incidence in Mexico, 2010

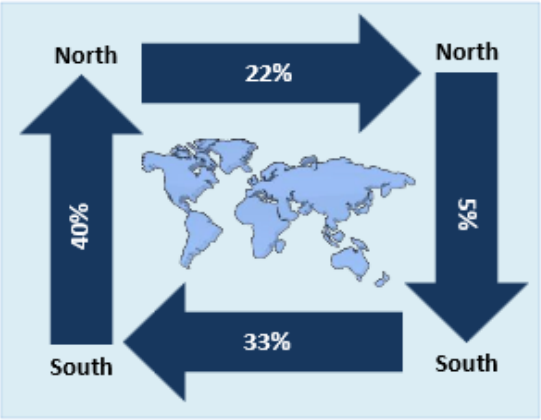


Source: (Secretaría de Salud, 2012). Arrows added by the author.

MIGRATION IN MEXICO

With a population of approximately 122 million, 55.3 million Mexicans live in poverty (National Council for the Evaluation of Social Development Policy, 2014). Since the 1960's, migration in Mexico has mainly been from rural to urban areas. However, over the past decade Mexico is once again experiencing another internal migration shift—one that is not being recognized internally and that is largely due to drug violence in certain areas. Because of this more and more Mexicans are living in states in which they were not born (Hernandez, 2011; American Immigration Council, 2011). Per longitudinal survey results from Mexico's National Institute of Statistics, Geography, and Information (INEGI), Martinez (2014) reports that roughly 20% of Mexicans live outside of their state of origin. A framework developed by the International Organization of Migration (IOM) posits that there are four migration pathways: North to South, South to South, South to North, and North to North (Figure 2.6). The most common migratory pathway experienced globally is from South to North with 40% of the total migrating population.

Figure 2.6 - International Migrants and the Four Migration Pathways



Source: (International Organization for Migration, 2013)

Mexico's internal migration from South to North follows global trends and this particular paradigm can also be applied to internal analysis of population shifts within each of Mexico's 31 states. The IOM framework feeds into the question of whether TB in Mexico stems mostly from its southern states, and is therefore increasing the prevalence of TB in northern states such as Tamaulipas; if so, would TB education and prevention control strategies be better served in states such as Chiapas and Oaxaca along its southern border? Or should greater emphasis be placed along the northern border or even the eastern Gulf Coast which seems to be a corridor of further exploration? Infectious diseases can be prevented at a variety of points, however determining a best "specific point" that reduces transmission in an resource challenged country such as Mexico which is marred by constant migration makes it all the more important.

Mexico's National Epidemiological Surveillance System (SINAVE) divides the country into three different regions: the northern zone, the central zone and the southern zone (Najera Ortiz & Nunez Medina, 2015). The following is a breakdown of the states in each of the three zones (Table 2.2).

Table 2.2 - SINAVE Epidemiological Regions

Northern Zone	Central Zone	Southern Zone
Baja California	Aguascalientes	Chiapas
Sonora	Colima	Guerrero
Chihuahua	Distrito Federal	Veracruz
Coahuila	Querétaro	Oaxaca
Nuevo León	Guanajuato	Puebla
Tamaulipas	Michoacán	Tabasco
	Taxcala	
	Estado de México	

Source: (Najera Ortiz & Nunez Medina, 2015)

The epidemiological categorization that SINAVE provides brings to light an interesting juxtaposition regarding what is known of key social risk factor of TB. In essence, SINAVE stipulates that the northern zone is considered to be the most developed in Mexico; however a close examination of all of Mexico's northern states highlights the fact that its northern border has the highest prevalence rates of TB in the country. Whereas the central zone is densely populated with metropolitan areas such as Mexico City, yet it carries the lowest TB prevalence rates in the country, yet its residents have the highest frequency of contact with individuals from states with high TB prevalence. Mexico seems to be a conundrum as once held stark presuppositions of TB disease may no longer fit the mold. Mexico is therefore an ideal candidate for a longer and more in-depth longitudinal study that delves further into the complexity of its TB disease.

TRANSMISSION AND PATHOGENESIS OF TB

Mycobacterium tuberculosis (Mtb) Transmission

It is an infectious bacterial disease caused by *Mtb,* which affects the lungs in 90% of cases (Centers for Disease Control and Prevention, 2008) due to its proclivity of growing best in tissues with high oxygen content (Lawn & Zumla, 2011), but it can also affect other organs of the body (National Institute of Allergy and Infectious Diseases, 2012). Transmission of TB is spread from person-to-person through the air via droplet nuclei containing tubercle bacilli that have been expelled from the throat and lungs of an individual with the active respiratory disease (Centers for Disease Control and Prevention, 2008) and replicates itself every 15 to 20 hours (Lawn & Zumla, 2011). Depending on the environment, each droplet containing the nuclei can remain suspended in the air for several hours (Centers for Disease Control and Prevention, 2008).

Per the Centers for Disease Control and Prevention (2008) transmission is dependent on several factors: innate immunity, susceptibility, duration of exposure, and virulence. Each year an individual with untreated, active TB can infect 10-15 additional people who are usually close personal contacts of the infected person (World Health Organization, 2015b; Achkar, Sherpa, Cohen, & Holzman, 2008). Once inhaled, the larger droplets containing bacilli become lodged in the upper respiratory tract while some continue a migratory path into the smaller air sacs of the lung (Centers for Disease Control and Prevention, 2008). The immunological response begins within 2 to 8 weeks with the production of immune cells called macrophages that can engulf and kill the bacilli halting multiplication and spread of the disease (Centers for Disease Control and Prevention, 2008; Fogel, 2015). During this initial interaction, if the bacilli are not killed, they can proliferate rapidly signaling the production of an inflammatory response (Fogel, 2015). However, TB is considered to have entered a latent state of infection when cells form a barrier against the bacilli, halting multiplication and further spread of the disease (Centers for Disease Control and Prevention, 2008). It is the varied immunological response in individuals to *Mtb* that remains an enigma, but that ultimately determines disease outcome. Variations between *Mtb* strains are also possible, but this needs further study.

Latent TB Infection (LTBI)

Due to the aerosolized nature in which individuals are exposed, about one-third or approximately 2 billion people in the world are infected with TB; however in healthy people it will remain dormant due to the body's immune response in keeping the bacteria under control and asymptomatic (Centers for Disease Control and Prevention, 2008).

Although LTBI individuals carry the tubercle bacilli in their body they are not infectious and cannot spread the infection to other individuals. However, 5% to 10% of LTBI individuals will progress from infection to an *active* TB state (Fogel, 2015) with the risk of conversion being the highest within the first 2 years after infection (Lawn & Zumla, 2011). As a result of the burden of individuals with LTBI, the development of cost effective diagnostic and screening tools that provide greater specificity and sensitivity are necessary in order to detect and control the disease. Unlike the U.S. where LTBI screening is done using the tuberculin skin test (TST), in Mexico, little TB screening is performed rendering an unknown prevalence of LTBI, and a reservoir of disease (Garfein, et al., 2010).

Presently, the most common diagnostic methods for LTBI is to measure the memory response of T cells to *Mtb* antigens using either commercially-available Interferon-gamma release assays (IGRAs) or the Mantoux tuberculin skin test (TST) (Fogel, 2015). Albeit more expensive and technical, IGRAs are more specific since blood is drawn in order to measure a person's immune reactivity to *Mtb* (Fogel, 2015). The two Food and Drug Administration approved IGRA tests are the QuantiFERON -TB Gold In-Tube test (GFT-GIT) and the T-SPOT.TB (T-Spot) (Centers for Disease Control and Prevention, 2014b). The second type of test is the TST, which uses intradermal injection of the purified protein derivative (PPD)-of *Mtb*; it is the most cost effective test and entails injecting PPD intradermally into a person (Fogel, 2015). These tests only indicate infection with the bacteria, but do not distinguish between LTBI or active TB disease (Centers for Disease Control and Prevention, 2014b).

As TB incidence has decreased in the U.S., the Centers for Disease Control and Prevention (CDC) has placed most emphasis on TB prevention. As a prophylaxis to prevent active TB disease, treatment can be given to individuals with LTBI depending on their TB risk (Centers for Disease Control and Prevention, 2008; Fogel, 2015). The preferred regimen is isoniazid (INH) given daily for 9 months. Alternative regimens for LTBI treatment is rifampin (RIF) given daily for 4 months (Centers for Disease Control and Prevention, 2008).

Risk Factors for Progression of LTBI to TB

Multiple clinical conditions are associated with increased risk for progression from LTBI to TB disease. The strongest known is HIV infection, but other risk factors such as age, gender, immune status, malnutrition, poverty, and lack of access to health care put individuals at risk. Particularly, type 2 diabetes, which is an underappreciated association, is gaining traction due to its high global prevalence. This particular risk factor is singled out and is cause for concern in Mexico where 14% of adults have diabetes (Barquera, et al., 2013), and 1 in 3 Mexicans are obese (Organization for Economic Co-operation and Developement, 2014). There are studies that present conflicting information regarding diabetes as a link between LTBI and TB. The most notable analysis comes from Dooley & Chaisson (2009) which discuss the effect of diabetes on the clinical characteristics of TB. Others have also reported that cavitary legions in the lungs of diabetic patients with TB are more common (Baghaei , Marjani, Javanmard, Tabarsi, & Reza Masjedi, 2013). Therefore, patients with cavitary pulmonary TB are more likely than those without pulmonary cavities to be sputum AFB smear–positive which signifies an active infection (Yoder, Lamichhane, & Bishai, 2004; Saeed, 2012). This is important because patients with cavitary pulmonary disease have a greater

frequency of cough and greater potential to transmit TB due to a higher bacillary load of disease in their lungs. So the three causal factors for infectivity are a combination of cavitary pulmonary disease, a positive sputum AFB smear, and a higher occurrence of cough. AFB smear–negative patients with TB can also transmit TB, but with lower potential than smear-positive patients (Yoder, Lamichhane, & Bishai, 2004). This particular aspect of TB pathogenesis underscores the dynamics of disease transmission to population mobility.

This point is emphasized in Achkar, Sherpa, Cohen, & Holzman (2008). In 2005, Achkar and colleagues conducted a cross-sectional study by reviewing medical records of 194 subjects with confirmed PTB from a public hospital in New York City. They looked at three groups of patients with PTB: U.S.-born, foreign-born with documents, and undocumented. The results indicated that undocumented foreign-born subjects presented with significantly higher frequencies of cough and blood in their cough (Achkar, Sherpa, Cohen, & Holzman, 2008). In addition, the undocumented foreign-born subjects had longer median symptom duration (8 weeks) versus U.S.-born (4 weeks). The limitation of this study is that the hospital chosen in New York was located near homeless shelter facilities in Chinatown near midtown Manhattan, NY; therefore the population sample had a larger Asian cohort. Adjusting to control for confounding factors Achkar, *et al.*, conclude that the results can be generalized towards other urban areas with large undocumented immigrant populations. Achkar *et al.*'s study, along with others, emphasize that individuals with smear-positive cavitary disease transmit TB more frequently. Achkar *et al.*'s findings emphasize the need for larger, population-based studies. While their study was primarily focused on finding ways to reduce barriers for

undocumented immigrants in order to improve TB control and stigma in the community, this study is of significance in that it was the first in the U.S. that looked and compared documented and undocumented foreign-born and U.S.-born persons with PTB and provided an insight into their clinical presentation. This was also followed by same findings in Europe (Fortun, et al., 2011).

POPULATION MOBILITY CAN SHAPE TB TRANSMISSION DYNAMICS

The introduction of a high-risk population into a low-incidence area can alter the dynamics of the area's TB burden by increasing the number of TB cases and by perpetuating TB in the immigrant population (Lobato, Mohamed, & Hadler, 2008). Patterns of immigration change the face of TB. Studies chronicling the change are not only seen in the U.S. starting in the mid-2000s, but particularly through Europe and Asia as well. Analysis of retrospective surveillance data from Connecticut between 1996 through 2005 by Lobato, *et al.*, set out to determine if immigration impacted Connecticut's TB burden. Lobato and colleagues chose Connecticut for their study because of its high proportion of foreign-born patients. Almost half of the foreign-born persons were from six countries: India, Ecuador, Haiti, the Philippines, Peru and Vietnam. During the 10 year time period of this study, TB case rates in Connecticut declined in U.S. born persons, but the proportion of TB cases among foreign-born persons increased from 50% to 66.3%. This study highlights that most patients were found to have TB during the first 5 years after arrival in the U.S. and the capacity for reactivation of TB persisted for more than a decade after emigration. The data suggests that a high incidence of TB occurs within the first 5 years among people emigrating from high-incidence areas and may persist for more than a decade after emigration. Cain, *et al.*

(2008) mention that foreign-born cases in the U.S. are primarily a reactivation of LTBI and therefore attempts at prevention should focus on pre-screening individuals before arriving in the U.S. TB risk factors among foreign-born persons reflect the epidemiology in their countries of origin. As such, conventional TB risk factors in the U.S., i.e., non-injecting and injecting drug use, excessive alcohol use, homelessness, HIV infection, are less common in foreign-born persons than in U.S.-born persons with TB (Lobato, Mohamed, & Hadler, 2008).

As is the case in the United States, European countries are also experiencing a decreasing trend in TB rates; however this is masked by the fact that the rates in their foreign-born populations are increasing. Also, there are migration variations between each country. In Gilbert, *et al.* (2009) a descriptive analysis of 21 European Organization for Economic Co-operation and Development (OECD) member countries set out to compare data between the U.K. and other European countries to determine if the increase in TB cases was related to immigration. Results from the study concluded that different patterns of migration may explain, in part, the differing TB trends. Although TB notification rates increased in the U.K. (Norway and Sweden, notwithstanding), TB rates in the U.K. had the highest significant increase due to the influx of foreign-born immigrants between 1996 and 2005. This was followed by Portugal, Spain and Germany. Therefore, the proportion of cases that occur in foreign-born populations affect TB rates in a particular country (Gilbert, French, Abubakar, Watson, & Jones, 2009).

There are conflicting molecular epidemiological studies such as (Goldblatt, et al., 2014), in Israel and a systematic review of the European Union and European Economic Area by (Sandgren, et al., 2014), that purport that increased migration of a population

into a new area does not increase transmission to native-born persons. However, there is evidence to the contrary. Several studies provide evidence of recent transmission from a migrating population to a native population in Almeria, Spain (Martinez-Lirola, et al., 2008) and in Madrid, Spain (Alonso Rodriguez, et al., 2009). Spain is unique from other European countries. Spain receives immigrants from Africa and other European countries, but interestingly it has become the second destination after the U.S. for foreign-born individuals from Latin America. There is a long standing assumption that TB in the migrating population is mainly the result of reactivation of infection acquired in the country of origin, and efforts to analyze recent transmission patterns of the immigrant population in the host country are minimal (Martinez-Lirola, et al., 2008; Alonso Rodriguez, et al., 2009). However, Alonso Rodriguez, *et al.* conclude that the reason Spain has greater transmission permeability between immigrant and host cases is because of similar cultural and linguistic backgrounds shared between the two.

LIMITED NUMBER OF TB STUDIES IN MEXICO

Presently, low incidence TB countries with high levels of immigration purport that the best mechanism for minimizing and controlling transmission in immigrant populations are achieved through early detection, adherence to treatment for individuals who have the active infection, detection, and prophylactic treatment of latent asymptomatic infections. While Tomas, *et al.* (2013) acknowledge that TB screening programs for immigrants are different for each country, and are based on the country's screening location and financial autonomy, there is a rudimentary, if not naïve, perception that migration follows a strict set of rules, and that all individuals migrating follow non-tangential paths towards new opportunities in a foreign lands. This

perspective may be changing. The idea that all immigration/migration flows one-way (and legally) into a country is giving way to a more realistic, complicated understanding of how migration and TB are related. To this end, Tomas, *et al.* mention that there are challenges brought on by the changing patterns of TB in low-incidence countries, and the stressful effects that migration places on TB control. They embark on a systematic review of qualitative studies that examine the perceptions of immigrants regarding TB and TB control programs; however, of the thirty studies included, only six focused on Latin America, and of those six, only three were from Mexico. This highlights a gross deficiency in TB control studies in Mexico and Tamaulipas, in particular.

Several additional studies have stemmed from this area of northern Mexico. Unfortunately, they do not provide enough information to make general conclusions about transmission permeability within Mexican host communities, although two studies have come close. An epidemiological study by Moser, *et al*. (1996) by local health departments in Arizona, California, New Mexico, and Texas set out to characterize patterns of immigration and migration among foreign-born Hispanic patients with TB in 8 U.S. counties along the border. They looked at 164 with 154 being born in Mexico and 10 born in Central America. Of the 154 patients, 76 or 46% of patients were born in non-border states. Of the 76 patients, 43 immigrated directly from their respective state of birth and 33 moved to a border town and then immigrated to the U.S. Of the 154 patients born in Mexico, 93 or 60% of them had been living in a border town in Mexico before immigrating to the U.S. and of the 93, 51 patients who were not born in Mexican border towns had lived in that border town for greater than or equal to 2 years. Although the study was small, it findings showed that 40% of TB patients had immigrated from non-

border communities suggesting that efforts were needed in non-border regions of Mexico (Moser, et al., 1996).

A second epidemiological study by Chittoor, *et al.* (2013) in the state of Chihuahua set out to identify if there were genetic variants that influenced the progression of LTBI to TB. This study recruited 150 individuals (75 cases and 75 controls), and was particularly interested in finding environmental risk factors; however, what proved to be a significant finding in this study was that a majority of the cases compared to controls were originally from states other than the state of Chihuahua. Unfortunately, Chittoor, *et al.* do not provide a list of the non-Chihuahua states to glean any further insight.

TB PREVENTION AND CONTROL IN MEXICO

The effectiveness of screening is limited by administrative problems and poor adherence to treatment. It is not possible to screen every undocumented migrant and visitor, but as previous studies have alluded, it is important to move beyond our border in order to prevent TB mortality and morbidity. A key study done by Schwartzman, *et al.* (2005) concluded that economic investment by expanding the directly observed therapy (DOT) program in key countries that are the source of migrants would reduce TB mortality and morbidity among individuals migrating to the U.S., and produce net cost savings for the U.S. They evaluated three strategies: current radiographic screening and TB control in Mexico, radiographic screening plus expansion of DOT program in Mexico, and radiographic screening with a TB skin test. They looked at the three strategies over a projected 20 year period among Mexican born migrants to the U.S. Migrants were defined as legal immigrants (persons applying for entry from abroad or

within the U.S., refugees, asylum seekers, and short-term laborers), undocumented migrants, or temporary visitors. Three source countries were considered: Mexico for the primary analysis, and Haiti and the Dominican Republic for secondary analysis. Over the 20-year period of analysis, they projected 35.4 million migrants will enter the U.S. from Mexico. In a first scenario, they estimated that there would be 47,610 cases of TB and 5245 deaths related to TB in this population, resulting in direct and indirect costs of $1.96 billion and $632 million, respectively. They claimed that if the U.S. government invested $34.9 million to expand the DOT program in Mexico without changing screening or control programs in the U.S., there would be 2591 fewer cases of TB and 349 fewer deaths related to TB in the U.S. These numbers reflect the projected reduction in LTBI infection, particularly recent infection, among newly arrived migrants owing to the reduction in incidence after the expansion of the DOT program in Mexico (Schwartzman, et al., 2005). In a second scenario, they simply added a TB skin test to radiographic screening, which would result in 401 fewer cases of TB in the U.S., and would cost an additional $329 million. Schwartzman's study was instrumental and continues to be a landmark study in emphasizing the importance of moving beyond borders to prevent TB. Somewhat contrary to the predictions of Schwartzman, *et al.*, even after 16 million dollars have been poured into Mexico for DOT therapy and laboratory infrastructure between 2000 and 2012 by the United States Agency for International Development (USAID) (PATH, 2012), there continues to be a steady, but increased, rate of TB in Mexico. This is not to say Schwartzman *et al.*'s prescriptions were incorrect, only that some other factor is contributing to a continued, albeit slow, increase in TB. Delgado-

Sanchez, *et al.* (2015) explain that the increase may be attributed to complex biological, environmental, and social determinants.

Woodruff, Winston, & Miramontes (2013) set out to understand the importance of TB trends in order to guide U.S. TB control and program planning. Their study aimed at predicting the number of future TB cases in the U.S. among foreign-born individuals through the year 2020. Using data acquired through the National Tuberculosis Surveillance System (NTSS) from January 1, 2000 through December 31, 2010, they looked at U.S.-born, foreign-born and foreign-born persons from Mexico, Philippines, India, Vietnam and China. Data was examined using joinpoint models which detect significant changes in trend. The results from the joinpoint model analysis predicted declining trends for all sub-groups; however a significant observation was detected for Mexico, which showed that change in TB cases from foreign-born individuals from Mexico preceded changes in trends in all foreign-born TB cases by three years. After completing the joinpoint analysis Woodruff, *et al*. hypothesized that changing the number of cases among persons from Mexico, which account for one-fourth of all foreign-born TB cases in the U.S., decreases the trend in *all* foreign-born persons in the U.S. The hypothesis was put to the test, and by removing Mexico from the foreign-born group Woodruff, *et al*. found that trends for foreign-born people from Mexico preceded a similar decreasing trend in the foreign-born population by 1 year. Mexico therefore serves as a predictor of trends, influences the year of changes in trend, and has a crucial role to play in the western hemisphere (Woodruff, Winston, & Miramontes, 2013).

While the U.S. has spent the past decade analyzing data that solidifies its top countries of foreign-born contributors, it must move beyond its borders to understand the

unique challenges that these countries face within their TB prevention and control programs. A final observation made in Woodruff, *et al*. is that between 2006 and 2010, there was a 60% decline in the number of individuals emigrating from Mexico to the U.S.; however the decline had little impact, if any, on the number of foreign-born TB cases attributed to individuals from Mexico (Woodruff, Winston, & Miramontes, 2013). Woodruff, *et al.* conclude that immigration and its patterns must be considered as these factors have the potential to alter case count predictions. U.S. agencies such as the CDC along with the USAID have spent millions in DOT for the treatment of TB along the U.S.-Mexico border; continued resurgence along this area should remind public health professionals that prevention of disease is not a stop-and-go fluctuation of the foot on a gas pedal. It should be continuous, precise and unmarred by the ethnic make-up of the population in question.

CONCLUSION

The results will provide novel information on the epidemiology of newly-diagnosed TB patients in Tamaulipas in relation to their migratory history within Mexico or other Central American countries. This information will help guide the implementation of strategies for targeting TB prevention in Tamaulipas. The goal is to provide a strategy to target the individuals at highest risk for TB development based on their combined sociodemographic and migratory history. The contribution of co-morbidities such as diabetes will be of particular interest given the high prevalence of this disease in Mexico, and the reported prevalence of up to 36% in the northern border of Tamaulipas. Our findings should be complemented with the recent recommendations for shorter LTBI treatments which are now part of the standard of care in the U.S., and can be used in

Mexico as well. In addition, what happens in Mexico does not stay in Mexico, and therefore we anticipate that TB prevention in Tamaulipas will have an impact on TB control across the south Texas border.

CHAPTER 3: METHODOLOGY OF THE REVIEW PROCESS

DESCRIPTION OF GRANT ANNOUNCEMENT

This project is in response to the National Institutes of Health (NIH) Funding Opportunity Announcement (FOA) PA-13-303, "NIH Exploratory/Developmental Research Grant Program (Parent R21)" (Appendix A). The purpose of the NIH R21 FOA is to support the development of new research activities within the specific NIH Institute categorical program areas. Projects that are in early or conceptual stages are often considered to be high risk endeavors due to the inherent uncertainty of the outcome or value of the future product. This can create difficulty in securing funding for such a project, especially during times when budget constraints are paramount. However, it is understood that the "novel techniques, agents, methodologies, models, or applications" that can arise from such high risk research is worth the investment. This FOA supports research project proposals for up to a two years' duration and a combined total direct costs' budget of $275,000 during the project period. Therefore, projects proposed under this mechanism must prove feasible within the two-year time period.

The grant process at NIH and many other federal funding organizations rely on an external peer review. To arrive at the overall impact/priority score, the following criteria are considered by reviewers: *Significance, Investigator(s), Innovation, Approach,* and *Environment*. The proposal is responsive to each of the five criteria as follows:

1. **Significance** – This is significant because this part of the border is porous and is a waypoint for the migration of both individuals and TB. Examining what happens with TB in Tamaulipas will help us to better understand how population migration influences TB not just in Mexico but along the greater border region. Additionally,

this is significant because lessons from Tamaulipas might provide insights into migration influences for other infectious diseases.

2. **Investigator(s)** – The following individuals will serve as investigators:
    a. *Jennifer Curry (Principle Investigator),* is a graduate student in the Executive MPH program in the Rollins School of Public Health at Emory University who has a distinct interest in health disparities and prevention of diseases in underrepresented and vulnerable populations.
    b. *Blanca Restrepo, Ph.D.(Co-investigator),* is a Professor at the University of Texas Health Science Center School of Public Health (UTHSC-SPH) Brownsville, in South Texas, and leads a TB-DM2 research program devoted to understanding the epidemiology and the biological basis for the re-emerging importance of DM2 as a risk factor for TB. She has conducted research in TB in South Texas for over 20 years.
    c. *Bassent Abdelbary, MBChB, MPH (Co-investigator),* is an Assistant Clinical Professor at the University of Texas Rio Grande Valley (UT-RGV) Edinburg. Her areas of expertise are in infectious and cardiovascular disease, evidence-based medicine, health disparities within the Hispanic community, and preventive and community health along the U.S.-border.
3. **Innovation** – The relationship between population migration and TB has been previously examined, however to date investigations have focused primarily on populations in Europe. The novel approach of this proposal is to investigate the relationship between population migration and TB in Tamaulipas, Mexico, which will provide a first look at the effects of population migration on TB in the Americas.

Additionally, studying population migration and TB in Tamaulipas may be understood as gaining knowledge about the whole iceberg from looking at the tip; that is, Tamaulipas a gauge for understanding how population migration affects TB incidence in a wider region.

4. **Approach** – A TB dataset from the state of Tamaulipas will be used as a primary source of information for an uncontrolled cross-sectional cohort study, which aims to determine whether there is a difference in TB prevalence between those who have migrated to Tamaulipas and those who are from Tamaulipas, as well as determine the contribution of immigration to the incidence of TB in border versus non-border regions of Tamaulipas. Additionally a descriptive analysis will identify the characteristics that distinguish migrant versus non-migrant TB patients in Tamaulipas with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure).
5. **Environment** – Research will be conducted at the UTHSC-SPH, Brownsville. UTHSC-SPH is a premier research Institution in the region and is specifically well-suited to the exploration of border health issues, as its location places it at the crossroads of Mexico and the United States. Research will primarily consist of data analysis on an existing dataset, and will not require the collection of new data or the employment of specialized laboratory equipment.

REVIEW OF FUNDING AGENCY

The National Institutes of Health (NIH) is composed of 27 different Institutes and Centers and within the NIH community, and the National Institute of Allergy and Infectious Diseases (NIAID) is tasked with supporting and finding new ways to

understand, diagnose, treat and prevent TB in the global community. The NIAID is the second largest Institute at NIH with an annual budget of over $4.7 billion. The NIAID not only supports basic research, but they also support research to assess what factors influence the occurrence, distribution, and transmission of disease in the human host. Another organization that funds TB research and development is the Bill and Melinda Gates Foundation. The rationale for selecting the NIAID as the funding agency to support such research ideas stems from their board purview of TB, the continuous allocation of funds, and their commitment to exploring novel ideas.

GRANT REVIEW PROCESS

NIH Review Process

The grant process at NIH and many other funding organizations rely on an external peer review. The NIH assigned reviewers use the above mentioned criteria of Significance, Investigator, Innovation, Approach, and Environment to arrive at the grantee's overall impact/priority score. However, the impact/priority score does not represent a mathematical sum, rather it is an overarching composition of the reviewers scientific judgment of the projects impact on public health. As NIH puts simply, the impact/priority score is a "gestalt – an integrated whole that cannot be derived from the sum of its parts". The impact/priority score and funding percentile ultimately becomes the basis by which an individual/Institution receives funding from the NIH. In reviewing an application, reviewers want to see an application that is capable of making a strong impact within its field.

The significance criterion gauges the importance of the proposed research and its likelihood of advancing clinical, scientific, and/or technical capability, but does not take

into account the ability of the researcher to complete the proposed work. A researcher may have their score reduced if it seems unlikely that they will be unable to complete the work, but this will not affect the overall significance score. The approach criterion is perhaps the second most important after the significance. While the significance can be seen to determine whether the proposed work is worth beginning at all, the approach tells the reviewer whether the steps to be taken will logically lead to successful completion. The innovation criterion judges whether the proposed work is novel in either its approach to a problem or otherwise brings novel instrumentation, methodologies, or concepts to bear on the problem, but it is not necessary that a project be innovative in order to be significant. The investigator and environment criteria provide reviewers with further evidence as to whether the researchers have the necessary expertise and resources to complete the proposed research in a timely, competent, and efficient manner.

Role of the Review Criteria

Each of the five review criteria receives a score of 1 to 9 with 1 being exceptional with no flaws, five being acceptable but with a least one flaw of worthy of consideration, and 9 being poor quality with major, possibly disqualifying flaws. Both usage of all criteria and adherence to the criteria will vary with each committee member, and each member may score based on their own interpretation of the scientific merit of the proposed work. As mentioned, reviewers may find a particular proposal to be exceptional, even though it is not innovative, if it serves to advance the science of a field, and an effort with high significance will receive a high score even though it may be deficient in other criteria.

Table 3.1 - Scoring Table for Research Grants

Impact	Impact/Priority Score	Descriptor	Additional Guidance on Strengths/Weaknesses
High	1	Exceptional	Exceptionally strong with essentially no weaknesses
	2	Outstanding	Extremely strong with negligible weaknesses
	3	Excellent	Very strong with only some minor weaknesses
Moderate	4	Very Good	Strong but with numerous minor weaknesses
	5	Good	Strong but with at least one moderate weakness
	6	Satisfactory	Some strengths but also some moderate weaknesses
Low	7	Fair	Some strengths but with at least one major weakness
	8	Marginal	A few strengths and a few major weaknesses
	9	Poor	Very few strengths and numerous major weaknesses
Definitions			
Minor: easily addressable weakness that does not substantially lessen the impact of the project. Moderate: weakness that lessens the impact of the project. Major: weakness that severely limits the impact of the project.			

Source: (National Institute of Allergy and Infectious Diseases, 2014)

Impact Is a Function of Importance and Likelihood

However, as mentioned, it is important to remember that the proposal is scored as a combination of all the individual scores and the final result is an overall *impact/priority* score, which sums up the reviewer's assessment of the both the **likelihood** of success of meeting the stated objectives, and the **importance** of the outcome to the advancement of knowledge in the field. Each peer reviewer assigns an individual final impact/priority score from 1 to 9 for the grant application. The application's final impact/priority score is the arithmetic mean of the individual final impact/priority scores multiplied by ten (10), and rounded to the nearest whole integer.

Review Process for Current Proposal

The reviewers for this proposal were sent emails requesting their participation to serve as a reviewer starting in March 2016 through May 2016. They were informed that

they would be reviewing a research grant proposal that would fulfill the master's thesis requirement for the author who is seeking the degree of a Master in Public Health (MPH) from the Emory Rollins School of Public Health in their Executive MPH Program. Two reviewers from Emory University, two reviewers from the NIAID, and one reviewer from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) were selected. The reviewers were told that they would have two weeks to review the proposal, they were provided with a fillable template that is used by the NIH for reviews of R21 grants. They were instructed to use the NIH review criteria that focus on Significance, Investigator, Innovation, Approach, Environment, and Overall Impact (Appendix B). Further, each review criteria is then broken down into strengths and weaknesses. The reviews of each reviewer were not shared with each other and reviewers were instructed to provide the author with their individual review as comments to the grant proposal with a final overall impact/priority score.

GRANT PROPOSAL REVIEWERS

Reviewers were selected from the Rollins School of Public Health at Emory University, the NIAID and the NIDDK at the NIH. The five reviewers are as follows:

1. **Linelle Blais, Ph.D.** – Dr. Blais is the Director of the Emory Centers for Training and Technical Assistance. She also serves as Associate Professor at the Rollins School of Public Health at Emory University. As a health psychologist and certified professional facilitator, her professional interests include individual and organizational change, program development and evaluation, and translation of science to practice. Prior to joining Emory, Dr. Blais worked at the American Cancer Society's National Home Office where she directed applied research and evaluation

projects and led nationwide capacity-building initiatives as a National Vice President in Field Operations and Talent Strategy. With the Cancer Prevention Research Center at the University of Rhode Island, she conducted health behavior change research and theory testing. Dr. Blais also worked at Brown University's Center for Gerontology and Health Care Research.

Reason for selection: Dr. Blais serves as the author's chair and her work in her in understanding the translation of science to practice and its effect on population health.

2. **Kathleen Miner, Ph.D. –** Dr. Miner is a tenured professor in Behavioral Sciences and Health Education and Associate Dean for Applied Public Health at the Rollins School of Public Health at Emory University, and serves as the principal investigator for the Region IV Public Health Training Center (PHTC) Program. She is a leader, manager and educator in the public health field with over 35 years of experience during which time she has been the PI on training grants in excess of $48 million. Dr. Miner has been instrumental in the development of numerous professional competencies sets and is a recognized expert in competency-based adult education development and delivery. She is an active member of both local and national professional associations, including GASOPHE, National SOPHE, GPHA, and APHA. She took the lead on funding and being one of the guest editors on the special issue of Health Promotion Practice dedicated to the work of the PHTCs.

   Reason for selection: Dr. Miner's experience as a PI, her vast knowledge of public health and her awareness of the issues that South Texans face make her an ideal choice as a reviewer.

3. **Christine Sizemore, Ph.D.** – Dr. Christine F. Sizemore is the Chief of the Tuberculosis, Leprosy and other Mycobacterial Diseases Section at the NIAID. In this capacity, she is responsible for the scientific direction, oversight, and management of a large part of NIAID's extramural research program in mycobacterial diseases. This program includes fundamental, translational and clinical science, product development for drugs, vaccines and diagnostics, and clinical evaluation for product candidates. Dr. Sizemore serves as NIAID's liaison and subject matter expert with national and international bodies involved in tuberculosis research, as with advocacy groups, and often represent NIAID on all aspects of fundamental, translational and clinical research in mycobacteria that are within the mission of NIAID. Dr. Sizemore holds a Ph.D. in bacterial genetics and microbiology and a Master's Degree in Biology from the Friedrich Alexander University in Erlangen, Germany. Prior to joining NIAID in 2000, Dr. Sizemore spent 8 years in the pharmaceutical industry in anti-infective development.

   Reason for selection: Dr. Sizemore was selected as reviewer since all TB grant proposals are funded by NIAID at NIH and through her department.

4. **Karen Lacourciere, Ph.D.** – Dr. Karen Lacourciere is the Program Officer in the Tuberculosis and other Mycobacterial Diseases Section, Respiratory Disease Branch at the National Institute of Allergy and Infectious Diseases.

   Reason for selection: Dr. Lacourciere was similarly chosen since she serves as a Program Officer at NIAID and is responsible with various TB grant portfolios.

5. **Ken Wilkins, Ph.D. –** Dr. Wilkins is a mathematical statistician serving in the biostatistics program at the NIDDK, which provides advice to both extramural and

intramural NIDDK staff on the design and feasibility of proposed research studies and the conduct of ongoing studies. Having taught courses at Harvard School of Public Health and Uniformed Services University of the Health Sciences, Dr. Wilkins adds to the biostatistics program's capacity by conducting educational seminars. He also performs research on statistical methods, focusing on causal inference from longitudinal or multilevel studies and handling incomplete data, among other topics relevant to NIDDK research. Dr. Wilkins actively consults and collaborates on research projects, whether developed from the extramural program (such as issues faced by Data and Safety Monitoring Boards) or by intramural investigators, contributing to the design/analysis of NIDDK-sponsored biomedical research. Dr. Wilkins earned his Ph.D. in biostatistics from Harvard University, and his master's degree from the University of Virginia. Prior to joining the NIDDK, he served as a senior biostatistician for the Infectious Disease Clinical Research Program. His duties ranged from scientific review of proposed research to development and implementation of multicenter protocols, helping to develop its worldwide research network which was sponsored jointly by the National Institute of Allergy and Infectious Diseases and the Uniformed Services University within the Department of Defense.

Reason for selection: Dr. Wilkins' knowledge in infectious disease and working with datasets is the reason for his selection as a reviewer.

PROTECTION OF HUMAN SUBJECTS

This study involves Human Subjects (as defined in 45CFR46.102(f), however an exemption from IRB Oversight under 45CFR46.101(b)(4), will be requested. While this

proposal will not be submitted, the protection of human subjects must be considered if the proposal were to be funded in the following manner. It is understood that only the Institutional Review Board (IRB) can determine and authorize exemption under one of the six categories of exemption specified in 45CFR46 (Department of Health and Human Services, 2009).

However, it is expected that the work proposed will be exempted under category four:

> **Existing Data, Documents, Records, Specimens**
>
> "Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects" (Emory Institutional Review Board, 2016).

Human Subjects Research:

A. Risks to the Subjects:

A.1 Human subjects' involvement and characteristics:

The data used for the proposed research analysis is obtained from an administrative dataset derived from Mexico's Sistema Nacional de Vigilancia Epidemioloigca (SINAVE). SINAVE is an epidemiological data collection platform for infectious disease information for patients in Mexico. The information is entered by doctors, clinicians, and other public health officials and only information from patients diagnosed and confirmed to have TB are entered into SINAVE. It is the information from the SINAVE-derived dataset that this research proposal will use for analysis. The

information includes basic demographic information (e.g., age, gender, etc.), date of diagnosis, co-morbid conditions, date of diagnosis with TB, TB status as MDR-TB or non-MDR-TB, city/state of birth.

A.2 Potential Risks

The potential risks to the individual human subjects are no more than minimal risk. The research proposal does not include the prospective collection of any data through physical procedure or manipulation of the subject or the subject's environment. As the data has previously been collected, there will be no prospective interaction between investigator and research subject. Additional data contained within the SINAVE dataset has been de-identified, and no linkage between the identifying codes and the individual subjects will be available to the investigator. The major potential risk to individuals whose information occurs in the dataset is the breach of confidentiality that may occur. However, as noted, due to the absence of access by the investigator to the identifier information, this is highly unlikely.

B. Adequacy of Protection Against Risks:

B.1 Protection of Confidentiality

The dataset to be used is an existing dataset, and, as such, risks involving recruitment, informed consent and protection against risk are not applicable; however protection of confidentiality is of paramount importance. In the event that personally identifiable information (PII) is present in the data, a unique identifier will be assigned to identify personal health information. The dataset to be used must first be cleaned in order to ensure consistency and reliability of the information, and avoid redundancy in reporting. Then, a master file allowing linkage of the specific participant and the coded

identifier will be recorded in an encrypted, password protected file on removable media, and accessible only to the principle investigator, co-investigators, and study staff. Additionally, all research staff will be trained in the principles of human subjects protection and maintenance of confidentiality.

C. Potential Benefits of the Proposed Research to Human Subjects and Others:

C.1 Potential Benefits

Since this research proposal does not involve the collection of new data, there will be no obvious or immediate benefit to the patients whose data was recorded in SINAVE.

C.2 Why Risks Are Reasonable in Relation to Benefits

The use of the data in this research presents no more than minimal risk to those whose data was collected, and the results of the research may serve to provide largescale guidance and direction to future disease prevention efforts.

D. Importance of the Knowledge to be Gained:

The quantification of the contribution of population migration on TB prevalence in the Mexican state of Tamaulipas may lead to a new proactive approach to disease control and prevention rather than one which is reactive. In reality, the two approaches will likely be complimentary, but being able to predict future disease incidents and trends has obvious benefits to at risk populations.

E. Inclusion of Women and Minorities:

E.1 Inclusion of Women

There is no basis for the exclusion of dataset information by gender in this proposal, and thus both females and males will be included.

E.2 Inclusion of Minorities

The individuals whose data is recorded in the dataset are primarily of Mexican or Central American birth, and residence; however there is no basis for the exclusion of dataset information by race or ethnicity in this proposal.

E.3 Planned Enrollment Table

E.4. Inclusion of Children

While TB infection rates in children (age <18) is much less than in adults, children do develop TB infection and are included in the SINAVE database. As the database does not have a pre-specified age range for inclusion, it is likely that children will be included in this database. As such, the proposed research will include children.

The investigator does not possess specific expertise for working with children. However, as the database contains retrospective data collected on persons in Tamaulipas, Mexico who are diagnosed with TB infection, and there is no direct interaction between the investigator and the research subjects, the absence of pediatric expertise does not raise any safety concerns for the proposed research plan.

CHAPTER 4: REVIEWER COMMENTS

The author would like to thank each of the five reviewers who took the time to review the proposal and provide constructive feedback towards a project that has potential merit towards understanding TB in Mexico, but also along the U.S. side of the border. The final analysis of such a proposal would provide the state of Tamaulipas and Mexico with key data to develop strategic and targeted prevention policies and educational campaigns in key areas of the state and country.

The following chapter presents comments made by each of the five reviewers to the grant proposal. The comments from each reviewer are listed according to the NIH review criteria of Significance, Investigator, Innovation, Approach, Environment, along with the Overall Impact. In addition, each review criteria is broken down further by reviewing the strengths and weaknesses of the proposal. Below each reviewer comment is the author's response to the comment. Table 4.1, at the end of this chapter lists the scores for each reviewer per review criteria and final overall impact score. The reviewer comments, if applicable, are incorporated into the final grant proposal (see Chapter 5). The reviews from each of the five reviewers are not in the order as their names appear in Chapter 3. Comments from the reviewers are included as direct quotes.

The comments from the reviewers along with the author's response are as follows:

REVIEWER 1 COMMENTS

SIGNIFICANCE

COMMENT 1: The reviewer states the following as strengths: "The authors make a strong case for examining the TB cases within Tamaulipas, Mexico and their relationships with the TB cases in communities near the U.S. border in Brownsville,

Texas. The migration patterns and the prevalence of TB can result in better understanding of the disease socio-demographic patterns, medical disease effects, and TB reinfections or treatment failure. These outcomes could lead to additional insight for TB patterns in other border US/Mexico communities."

RESPONSE TO COMMENT 1: No response required.

COMMENT 2: The reviewer states the following as weaknesses: "The authors do not mention anything about the economic cost of TB within these communities nor how TB compares with other medical/health care concerns within these communities."

RESPONSE TO COMMENT 2: Per the World Health Organization Country Profile for Mexico, Mexico's TB budget in 2015 was equivalent to $17 U.S. million dollars. When compared to the U.S., the U.S. domestic TB budget in 2015 was $142 million (World Health Organization, 2016). This is alarming since Mexico has twice the number of TB patients as the U.S. with only 1/10 of the budget to help combat the disease. In addition, when compared to other health care concerns within Mexico, Mexico spent over 15 Billion USD in 2008 to manage diabetes and its complications (Sosa-Rubi, Galarraga, & Lopez-Ridaura, 2009). However, even though knowing an economic cost would be important, it is premature to conclude that the hypotheses are correct and that resources should/need to be deployed to curb TB infection.

INVESTIGATOR(S)

COMMENT 3: The reviewer states the following as strengths: "Both senior investigators have backgrounds in infectious disease, including TB. Their backgrounds include laboratory science and epidemiology investigations. They have experience near the Mexican border. They are well published. The junior investigator has community

development experience with nonprofits and international experience in the Peace Corps."

RESPONSE TO COMMENT 3: No response required.

COMMENT 4: The reviewer states the following as weaknesses: "There is minimal evidence that the personnel in this proposal have experience in conducting the type of research. The narrative needs to highlight their experience in performing this type of research. It would be wise to highlight a publication or to that confirms this expertise."

RESPONSE TO COMMENT 4: The biosketches of both Dr. Restrepo and the PI have been augmented to highlight their expertise. In particular, Dr. Restrepo's published work from 2007 and 2011 (publication number 33 and 41 in her biosketch) regarding her analysis of 6 years of retrospective data to explore the association of diabetes and tuberculosis in South Texas and Tamaulipas is highlighted. The PI's data entry and analysis work on a longitudinal study on the Natural History Study of Rheumatoid Arthritis for the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the NIH is highlighted in her biosketch. The PI's recent coursework experience in statistics, biostatistics, and epidemiology, along with practicum work in TB along the U.S. border, have also been included. The PI's work as the Project Officer at the NIDDK for one of the Institute's new Initiatives that focus on developing the biomedical pipeline with young Hispanic research investigators has been added. The PI's duties with the new $325,000, five year Initiative, are to manage all programmatic aspects of the project from recruitment to evaluation. Dr. Abdelbary's expertise in data analysis, including analysis for the state of Tamaulipas with Dr. Restrepo, is highlighted in her biosketch.

INNOVATION

COMMENT 5: The reviewer states the following as strengths: "The authors describe the global TB patterns and briefly describe the TB prevalence/patterns throughout areas within Mexico with some references to migration patterns. The narrative cites only a few citations that describe the specific TB migration patterns specific to the east gulf coast of Mexico, where the study population resides. They make the case that there is a dearth of data to detail the TB migration patterns in this population. They postulate that by clarifying the migration patterns of persons with TB from the south to the north, these data will provide insight to alter health patterns in U.S border communities."

RESPONSE TO COMMENT 5: No response required.

COMMENT 6: The reviewer states the following as weaknesses: "Their narrative does not link their intended health outcomes with their data outputs. This not to say that there is not a link. It is not well described. For example, the using iceberg figure, while well intended, leads to nothing gained. Linking co-morbidities with TB is an important concept in this population, i.e., diabetes. Yet, there could be others both infectious and not, such as, STIs, heart disease, malnutrition, etc. The point is describing the migratory population may have more than one concern. The research has to account for these or intentionally describe how they are not."

RESPONSE TO COMMENT 6: The occurrence of STIs or heart disease have not been linked with risk of TB. They are co-morbidities that are likely to also impact the migratory population, but this is outside the scope of this study.

APPROACH

COMMENT 7: The reviewer states the following as strengths: **"**Collaborating with the Tamaulipas Department of Health is likely to be the best source of the data. Of course, this may require negotiation which takes time. It would be wise to have some of these processes in hand prior to submitting this proposal. The data processes are standard and they are fine."

RESPONSE TO COMMENT 7: The author has edited the proposal to indicate that Dr. Restrepo has been collaborating for more than 10 years with the Tamaulipas Department of Health, and this proposal will be an extension of this partnership.

COMMENT 8: The reviewer states the following as weaknesses: "There needs to be a clear statement of how the researchers will ensure that the data will be protected. The IRB process will expect this. IRB will expect the data to be protected throughout the study. The data processes for data protection should be listed with the initial steps of the data processes and throughout the data use or contact with anyone who was subject in the study. Your response to human subjects is fine. This part is all about the individual patients and their data, etc. Be sure that during data collection you outline your steps for securing data, as well."

RESPONSE TO COMMENT 8: This has been stated in the section on 'Protection of Human Subjects,' paragraphs A.2 and B.1. Specifically, it is indicated that the data comes from an existing dataset which has been de-identified so there will be no availability of linkage to patient information by the PI or team, which is how the proposed study would be eligible for exemption from IRB oversight.

ENVIRONMENT

COMMENT 9: The reviewer states the following as strengths: "The location for this research is in need of information that could inform public health professionals to improve services to populations on both sides of the US border. It is likely to lead to new insights and interventions for the migratory populations with TB and other morbidities."

RESPONSE TO COMMENT 9: No response required.

COMMENT 10: The reviewer states the following as weaknesses: "The researchers have established relationships with border communities. What is not clear is how much research intervention using this proposed methodology. It can be surmised from the vitae. It would be helpful for some specific examples."

RESPONSE TO COMMENT 10: An intervention will not be conducted in the proposed study. The findings provide the basis to design a future intervention study aimed at reducing TB incidence among immigrants in Tamaulipas. This has been clarified in the 'Resolution of Challenges' section, subsection c.

OVERALL IMPACT

"This proposal proposes to describe the migratory patterns of persons with TB in the eastern Gulf of Mexico and U.S border communities. These migratory patterns tend to follow from the southern communities to the northern border of the U.S. These are unserved regions of both the countries. In addition many of these and many of these migratory persons have both TB and other co-morbidities. The data that are collected will enable to improve the public health services provided in both countries.

A couple of observations:

1.) Data: is a plural word. Thus is writing a proposal it would data are, these data, etc.

RESPONSE: The author's understanding is that data is both singular and plural.

See: http://www.oxforddictionaries.com/us/definition/american_english/data

2.) In the paragraphs where you cite the same author throughout the entire paragraph. You only have to cite the author at the end of the paragraph. Moser, et al is an example. You have a couple of other ones.

RESPONSE: The author has changed the instances of multiple citations to single citation in the 'Significance' section, subsection b, paragraphs 3 and 4, and subsection c, paragraph 1.

3.) Be careful with leaps of faith. Look at page 14 under c. paragraph last sentence. This evidence… I would suggest that you reword—while I agree—there is no fact.

RESPONSE: In the 'Significance' section, the last sentence in the paragraph in sub-section c, has been changed from "This evidence points to the fact…" to "This evidence can suggest that…"

4.) Figure 3. As I have said below drop the iceberg. And in the paragraph better explain the map graphic. It is not easy to see—I get what you mean. Remember that the viewers will not like something they cannot see or get right away.

RESPONSE: The graphic depicting the 'iceberg' has been removed from the 'Innovation' section, and the author has opted for a more detailed written description of corresponding Figure 3, as suggested by the reviewer.

5.) Most grant proposals avoid using first person. See if you can rewrite without the we, us, etc.

RESPONSE: All first person references have been removed from the final proposal.

6.) Page 13. Last sentence under b first paragraph. Why the italics?—this would not go over well.

RESPONSE: It is the author's experience that PIs frequently use bold and italics in grant applications to highlight concepts. However, in response to the reviewer's comment, the author has changed from italics to non-italics the sentence in the 'Significance' section, subsection b, the last sentence in paragraph 1, "The most common migratory pathway experienced globally is from South to North representing 40% of total global migratory movement."

7.) Page 3. Under facilities you mention Mexican students—you might to explain a bit more—as in do they came from the area in which are using in the proposal? Do the cross the border every day? Get some benefit out of this? Would they get involved in the research?"

RESPONSE: Under the 'Facilities and Other Resources' section, mentioning that the UTHSC-SPH in Brownsville serves as an Institution of higher learning for many young Mexican students is meant merely to highlight the fact that the Institution meets the technical and logistical requirements, and has a general educational climate that has insight to the needs of Hispanic and border communities in general. The reference was not meant to be a statement pertaining to students being involved in the proposed study or the study population. The author has decided to leave wording as it is.

REVIEWER 2 COMMENTS:

SIGNIFICANCE

COMMENT 1: The reviewer states the following as strengths: "**1)** Important area of research to demonstrate the impact of migration within northern Mexican states on the

incidence and prevalence of TB in the border state of Tamaulipas. **2)** Data from the study have the potential to inform where educational and case ascertainment efforts could be conducted to lower the number of TB patients in border countries. **3)** Data appear readily available for assessment."

RESPONSE TO COMMENT 1: No response required.

COMMENT 2: The reviewer states the following as weaknesses: "While it is clearly articulated in the introduction that finding appropriate points of intervention to reduce cross border TB rates, the application is sparse on details about the actual study and hence, significance can only be inferred."

RESPONSE TO COMMENT 2: There is difficulty in accessing illegal/undocumented immigrant's medical information from Mexico to the U.S., so it can only be inferred that addressing TB prevalence on the Mexico side of the border will impact the prevalence in the U.S. along the border states. Since an administrative database is being used, direct causality cannot be shown. However, it can be inferred from CDC data pertaining to TB rates along the contiguous U.S. border, whether or not the TB rates in the contiguous Mexican states have an impact. Thus, if the Mexican rates decline, we can monitor the U.S. rates, and the percentage of incident cases that are Mexican, and make a determination.

INVESTIGATOR(S)

COMMENT 3: The reviewer states the following as strengths: "Co-investigators are highly experienced in conducting the proposed work."

RESPONSE TO COMMENT 3: No response required.

COMMENT 4: The reviewer states the following as weaknesses: "Responsibilities of key personnel not clear from the application."

RESPONSE TO COMMENT 4: The following information on key personnel responsibilities have been incorporated as a second paragraph into the 'Multidisciplinary Team' section on page 85: "The PI will be responsible for translating the variables in the SINAVE dataset into English, removing duplicate data, data entry into SAS database, statistical analysis, and data reporting. Dr. Restrepo (Co-PI) will provide project oversight, arrange the transfer of the dataset, confirm translation, and provide oversight of the analysis plan. Dr. Abdelbary (Co-PI) will duplicate data entry for confirmation of correct data entry, and duplicate analysis, along with providing assistance with statistical analysis."

INNOVATION

COMMENT 5: The reviewer states the following as strengths: "Straight forward analysis but this also means that it is not very innovative."

RESPONSE TO COMMENT 5: The author concurs that the analysis is straightforward, however disagrees that the proposed work is not innovative. The northern states are considered to be the most developed in Mexico; however a close examination of all of Mexico's northern states highlights the fact that its northern border has the highest prevalence rates of TB in the country. Whereas the central zone is densely populated with metropolitan areas such as Mexico City, yet it carries the lowest TB prevalence rates in the country, and its residents have the highest frequency of contact with individuals from states with high TB prevalence. This highlights that once-held presuppositions of TB disease may no longer fit the mold, which is cause for further investigation.

COMMENT 6: The reviewer states the following as weaknesses: "See above"

RESPONSE TO COMMENT 6: Please see response to comment 5.

APPROACH

COMMENT 7: The reviewer states the following as strengths: "Straightforward data analysis in principle."

RESPONSE TO COMMENT 7: No response required.

COMMENT 8: The reviewer states the following as weaknesses: "**1)** Key variables that will be assessed as part of data mining are not provided. **2)** Not clear what data are currently available in the public health database. **3)** Not clear what variables will be compared to confirm/dispute stated hypotheses. **4)** No letter of support provided from the Mexican Health Authorities making it difficult to assess the feasibility of the study. **5)** Not clear why persons with relapse TB or persons who have not completed therapy are excluded – one would think these individuals contribute to the prevalence and hence the continued spread of TB in the border state. **6)** Limited data provided on how persons are diagnosed for TB and whether this diagnosis is consistent across the data in the public health database. **7)** Not clear who will de-identify the public health records. If done by the Public Health officials, letters of support will be critical. If done by the PI, then non-anonymized data are available for the study and extra safeguards need to be in place to protect confidentiality. **8)** Introduction states that the project will be cost effective for public health, but no cost effectiveness assessment is proposed."

RESPONSE TO COMMENT 8: 1) The author has modified the 'Approach' section in the grant to include new subsections b and c: 'Outcome Variable' and 'Independent Variables' listing all of the variables to be used from the de-identified information from

the SINAVE dataset. **2)** The variables now listed under the new 'independent variables' section contain all of the information necessary to conduct the described analyses. **3)** To test the first hypothesis that the prevalence of TB among those who are from Tamaulipas is different from those who are not from Tamaulipas, the following variables will be used: state of residence, state of birth, initial date of signs of symptoms, diagnostic method, date of diagnosis, contact made with person with TB, and state where contact was made. Using this information, two comparison groups will be identified to test the hypothesis: those with TB who have migrated to Tamaulipas and currently reside there, and those who are from Tamaulipas and reside there. To test the hypothesis in Aim 2, similar variables and comparisons will be made except the additional variables of residential jurisdictions, municipalities and locations for Tamaulipas will be used (these are analogous to county, city, and neighborhood). This has been clarified in the proposal. **4)** A previous dataset (1998-2003) has been obtained by the Co-PI Dr. Restrepo for previous published studies. The current dataset is an updated version, thus the procedures and obstacles to obtaining it are known, and it is not anticipated that obtaining a properly de-identified data set will be problematic. This has been clarified in the proposal. **5)** 'Approach' section, subsection b; the text has been edited to clarify that persons who have not completed therapy have been included in the inclusion group, but relapsed persons have been kept out because the author considers this to be of concern for possible double counting of occurrences. **6)** How people are diagnosed with TB will be determined through the variable 'diagnostic method' which is included as part of the information requested by health officials in Mexico when TB patient data is entered into SINAVE. This diagnostic method is consistent across all 31 Mexican states and the

District of Mexico, and recorded in SINAVE. **7)** The data will be de-identified by the Mexican Health Authority and a letter of support has been requested. **8)** In the 'Approach' section, the last sentence in subsection e, it is stated that "The cross-sectional design is used…because it is simple, inexpensive, ethically safe, allows for quick data collection, and attrition is not likely because the administrative dataset is defined." The proposed study is cost effective *due* to the study design being employed.

ENVIRONMENT

COMMENT 9: The reviewer states the following as strengths: "Study location and location of the PIs and key personnel are appropriate and well suited to conduct this project."

RESPONSE TO COMMENT 9: No response required.

COMMENT 10: The reviewer states the following as weaknesses: "None"

RESPONSE TO COMMENT 10: No response required.

OVERALL IMPACT

"This is an interesting proposal to determine to what extent immigration of persons with TB may impact incidence and prevalence rates of TB in northern Mexican Border regions and whether, based on demographic and other factors, points of intervention can be defined. The study has the potential to produce important data but insufficient detail regarding the actual study design are provided. This puts the feasibility of the study in question and lowers the potential impact assessment. The PI is greatly encouraged to revise this application and resubmit."

REVIEWER 3 COMMENTS:

SIGNIFICANCE

COMMENT 1: The reviewer states the following as strengths: "**1)** Well motivates the unique opportunities afforded by Tamaulipas' population for studying association of migration with TB incidence, to inform effectiveness of prevention efforts. **2)** Leverages ideas of precision medicine at a population level, motivating how sub-populations at greater risk may be identified, a key strategy to mitigate infectious diseases."

RESPONSE TO COMMENT 1: No response required.

COMMENT 2: The reviewer states the following as weaknesses: "No elaboration on clear implications of anticipated study findings: informing follow-on studies' design(s) to emphasize epidemiology / treatment uptake of migratory subgroups."

RESPONSE TO COMMENT 2: In the 'Innovation' section, in the second to last sentence in the paragraph, the author states that "Findings from the proposed study should be complemented with the recent recommendations for shorter LTBI treatments, which are now part of the standard of care in the U.S., and can be used in Mexico as well. In addition, what happens in Mexico does not stay in Mexico, and therefore it is anticipated that TB prevention in Tamaulipas will have an impact on TB control across the south Texas border." Additionally, in the 'Approach section, subsection e, paragraph 'Data Analysis', the author states in the last sentence of the paragraph that "Our findings will help guide what is the best use of limited resources for TB control in Tamaulipas, and provide insight for the design of future prospective studies."

INVESTIGATOR(S)

COMMENT 3: The reviewer states the following as strengths: "Investigative team with a diversity of experience and skill sets, as needed for proposal."

RESPONSE TO COMMENT 3: No response required.

COMMENT 4: The reviewer states the following as weaknesses: "The proposal does not explicitly acknowledge how Dr. Restrepo's expertise in diabetes contribution to TB risk might inform how its potential as a confounder will be handled."

RESPONSE TO COMMENT 4: The personal statement in Dr. Restrepo's biosketch has been edited to indicate her expertise in how diabetes contributes to TB risk. Dr. Restrepo's extensive list of publications in this area is well-attested, especially articles numbered 30, 32, 33, 34, 40, and 41 under Dr. Restrepo's list of publications located in her biosketch. In addition, Dr. Restrepo is currently a Co-PI on an R01 grant that looks at the altered immune-endocrine axis in type 2 diabetes and tuberculosis diabetes patients.

INNOVATION

COMMENT 5: The reviewer states the following as strengths: "Identifies an un(der)studied resource in gleaning data to quantify how proactive prevention efforts targeting potential sub-population(s) at greater TB risk may warrant further study."

RESPONSE TO COMMENT 5: No response required.

COMMENT 6: The reviewer states the following as weaknesses: "Fails to recognize capacity for generalizing findings beyond Tamaulipas (e.g., use of direct/indirect standardization coupled with aggregate data for other border areas)."

RESPONSE TO COMMENT 6: The author agrees with this assessment and has added this wording to the paragraph in the 'Innovation' section.

APPROACH

COMMENT 7: The reviewer states the following as strengths: "Well-delineated population that represents an un(der)studied opportunity for obtaining initial estimates of TB association with migration patterns for eastern Mexico border area. Employs a design well-suited both to leveraging unique data source and informing the knowledge gap in prevention efforts targeting high-incidence border area populations"

RESPONSE TO COMMENT 7: No response required.

COMMENT 8: The reviewer states the following as weaknesses: "**1)** Proposal lacks adequate specification of how findings will be quantified: sample size is large yet little-studied hypotheses warrant power analysis, tied to explicit model/test plan. **2)** Lack of prespecified definition of migratory subgroups from known available data; inadequate caveats concerning recall bias, potential missing/unmeasured confounders."

RESPONSE TO COMMENT 8: 1) Specifying a power analysis without knowledge of the results is unwarranted in this scenario because it is not known **a priori** what the difference in prevalence between the two study groups (migrated versus did not migrate) is. This can be done post-hoc—once the prevalence rates are known, one could use the sample size and verify a power for the difference between the two. **2)** While the descriptive analysis (Aim 3) will explore the originating states/areas and related sociodemographics of different migratory 'subgroups', The hypotheses to be tested in Aims 1 and 2 simply distinguish between those patients 'from' Tamaulipas and those 'not from' Tamaulipas, and thus further subcategorization is not necessary.

ENVIRONMENT

COMMENT 9: The reviewer states the following as strengths: "Multi-institution environment, diversity of relationships to national public health agencies NIH-funded institution embedded within border communities most closely associated with population of interest, institutional review board experienced in cross-border epidemiology."

RESPONSE TO COMMENT 9: No response required.

COMMENT 10: The reviewer states the following as weaknesses: "No explicitly cited resource for preparing and curating individually-identifiable study data in a manner that adheres to NIH data sharing policy without risk to persons"

RESPONSE TO COMMENT 10: The dataset will be de-identified by the Mexican Health Authority prior to being obtained by the PI and team, so preparing and curating individually-identifiable study data will not be necessary. A statement pertaining to this has been added in the 'Approach' section, subsection a, last sentence of the paragraph. In addition, per the NIH Data Sharing Policy, the results from the proposed research is not generating a novel organism, it is not conducting a Genome Wide Accelerated Study (GWAS), and it is not seeking more than $500,000 or more per year in research funds, therefore a resource sharing policy is not needed (U.S. Department of Health and Human Services, 2015). Finally, the results of the proposed research can be shared through publications, but the research team cannot share the data with another Institution since it belongs to the Mexican Health Authority.

OVERALL IMPACT

Strengths

"High potential impact study leveraging access to a unique population-level resource, led by investigators familiar with the comorbidities, social context, and localities of TB+ population

Innovative evaluation of apparently understudied role of migratory patterns' association with TB incidence for the eastern US-Mexico border area, to inform how subsequent study is done. Well-grounded in both available literature on study's aims and capacities of design, data & PIs."

Weaknesses

"Does not quantify the proposed studies' capacity to detect a discernible difference in proportions for each of Aims 1 & 2, whether in terms of precision or statistical power (despite specifying null hypotheses to test for significance); a range of scenarios should be explored. While R21s do not require preliminary data, some consideration could be given to marginal proportions of TB cases that may fall in each Aim 1-2 subgroup (as done for sex; some allowance for proportions of CureTB/TBnet referred cases-cited by Joya-should be employed)."

RESPONSE TO COMMENT: It is unclear to the author what the relationship of the CureTB/TBnet cases is in relation to the Tamaulipas population. In looking at the Cure/TB cases, these cases stem from southern California and from the Mexican state of Baja California, and it is known that HIV/AIDS in this part of both the U.S. and Mexico is increasing the incidence cases of TB. In addition, California also has a high Asian population. Second, TBnet cases stem from a network of European countries

participating in TB research. Therefore, in looking at both CureTB/TBnet, these cases appear to comprise populations with somewhat different epidemiologies.

REVIEWER 4 COMMENTS:

SIGNIFICANCE

COMMENT 1: The reviewer states the following as strengths: "**1)** This will be a novel study in an important area of the world and may provide input into how tuberculosis control programs can be more effectively applied to preventing transmission of TB. **2)** Although the study will only be applied in one state of Mexico, it could have applications throughout the country and implications for control of TB along the Border States of the United States. **3)** This is will be the first rigorous study of this kind in Mexico."

RESPONSE TO COMMENT 1: No response required.

COMMENT 2: The reviewer states the following as weaknesses: "**1)** The analysis planned lacks detail. **2)** The research plan is very descriptive and the hypotheses that will be explored are not well articulated. **3)** Significance is diminished because it is unclear what specific questions will be answered by this study.

RESPONSE TO COMMENT 2: **1)** In response to reviewer #3, the author has provided further detail on the variables to be analyzed. **2)** The author believes that the hypotheses are now more clear given that the variables have been specified. It is possible the reviewer had difficulty figuring out which groups were going to be compared, especially given that the variables in the SINAVE dataset were not explicitly stated. The author has made the variables explicit, and made reference to them in the 'Approach' section, subsection b and c, and in the descriptions of Aims 1 and 2, in the 'Approach' section, subsection e. **3)** The questions answered will be those stated in the 'Approach' section,

under subsection e, Aims 1, 2, and 3. Specifically, it will be determined whether there is a difference in TB prevalence between those who have migrated to Tamaulipas from elsewhere (Aim 1), and those who are from Tamaulipas. Aim 2 will determine whether there is a difference in TB incidence among TB patients from border regions of Tamaulipas versus non-border regions of Tamaulipas. Aim 3 is descriptive, and while not designed to answer a specific question, will provide valuable information regarding 'characteristics that distinguish migrant versus non-migrant TB patients in Tamaulipas with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or recurrent TB within 2 years of treatment, or treatment failure where TB patient does not clear M. tuberculosis within the first 3 months of treatment.'

INVESTIGATOR(S)

COMMENT 3: The reviewer states the following as strengths: "**1)** The identified investigators have the right expertise to complete the aims of the project. **2)** Although the PI is a young investigator, she has support from two very experienced researchers**. 3)** Having two investigators fluent in Spanish is a positive.

RESPONSE TO COMMENT 3: No response required.

COMMENT 4: The reviewer states the following as weaknesses: **1)** "There is no one identified in Mexico associated with the project, but this would seem to be important to include. **2)** The PI is a young investigator and will benefit from collaborating with two experienced investigators. The PI, however, is at Emory and her collaborators are in Texas. It would be beneficial for the PI to have a mentor at Emory that she could rely on for day to day issues that she may encounter."

RESPONSE TO COMMENT 4: **1)** A statement has been added to the proposal in the 'Approach' section, subsection d, under 'data acquisition' stating that the project has a collaborator in Mexico to assist in obtaining the necessary data and to answer any questions regarding the dataset. **2)** The PI is originally from the Rio Grande Valley of South Texas, and travels to this region on a regular basis. Given the ease of communication via Skype and email, among others, we do not anticipate that being at Emory will be a limitation. The author has edited the proposal under the 'Work Plan' section to specify this means of communication between the PI and collaborators.

INNOVATION

COMMENT 5: The reviewer states the following as strengths: "This is innovative in being the first study of this kind to be conducted in Mexico."

RESPONSE TO COMMENT 5: No response required.

COMMENT 6: The reviewer states the following as weaknesses: "The lack of a clear set of hypotheses diminishes the innovation, as it is not clear what specific questions are being addressed and what the specific outcomes will be from the analysis."

RESPONSE TO COMMENT 6: The clarity of the hypothesis, and the questions being addressed are discussed in the response to reviewer 4, comment 2.

APPROACH

COMMENT 7: The reviewer states the following as strengths: "The data from Sistema Nacional de Vigilancia Epidemiologica (SINAVE) in Mexico is a great resource."

RESPONSE TO COMMENT 7: No response required.

COMMENT 8: The reviewer states the following as weaknesses: "**1)** The proposal lacks details on what data is available in the SINAVE database. **2)** It is unclear how the

analysis will account for many variables. There are not enough details regarding the analysis. **3)** There is no letter of support to confirm that the investigator will have access to the data in the database, nor are there any investigators in Mexico collaborating on the project. **4)** The initial plan includes meeting with the Tamaulipas Department of Health and requesting access to the database, however, there is no back up plan in the event that the investigators cannot get access to the database."

RESPONSE TO COMMENT 8: 1) The author has added explicit reference to variables used from the SINAVE dataset. This is in response to reviewer 2, comment 8. **2)** This comment is addressed in the response to reviewer 4, comment 2. **3)** This is addressed in response to reviewer 2, comment 8. **4)** This is in response to reviewer 2, comment 8.

ENVIRONMENT

COMMENT 9: The reviewer states the following as strengths: "Both University of Texas School of Public Health, Brownsville (UT-SPH) in South Texas and the Rollins School of Public Health at Emory University provide a supportive environment for the research"

RESPONSE TO COMMENT 9: No response required.

COMMENT 10: The reviewer states the following as weaknesses: "**1)** There is not a clear connection to the SINAVE database. **2)** It is unclear how the PI and her two collaborators will work together when they are geographically separated. A strong communication plan would be essential."

RESPONSE TO COMMENT 10: 1) Please see 'Approach' section, subsection a, on page 86-87, specifying that that the SINAVE database contains the variables/information used for analysis in the proposed study. **2)** The 'Work Plan' section, subsection b, has

been created to delineate the team's communication plan. Communication will be facilitated by email, Skype, WebEx, the phone, and other shared information networks such as cloud based storage. Weekly teleconferences will be established at the outset with clear parameters defining the most convenient modes of communication between all collaborators.

OVERALL IMPACT

"This is a new submission from a promising young investigator, backed by a strong, multi-disciplinary team to conduct a retrospective cross-sectional cohort study to investigate the contribution of population migration within Mexico to the prevalence to of TB to the Mexican state of Tamaulipas. The significance of the proposal lies with the potential to understand the patterns of Tuberculosis transmission as they relate to migration patterns in Mexico. The outcome may allow public health officials to understand to most effectively utilize resources for treating and preventing the transmission of Tuberculosis."

REVIEWER 5 COMMENTS:

SIGNIFICANCE

COMMENT 1: The reviewer states the following as strengths: "**1)** Adds to gap in literature about impact of population migration generally and on TB prevalence in the Mexican state of Tamaulipas, specifically. **2)** Provides a necessary first step prior to future prospective work. **3)** Implications have relevance to strategic design of future prevention strategies — where to intervene for greatest impact. **4)** Timeliness of focus

area given the threat of emerging and re-emerging infectious diseases such as Zika, Ebola as well as TB, especially within the political context of population migration.

RESPONSE TO COMMENT 1: No response required.

COMMENT 2: The reviewer states the following as weaknesses: "None"

RESPONSE TO COMMENT 2: No response required.

INVESTIGATOR(S)

COMMENT 3: The reviewer states the following as strengths: "**1)** Senior collaborators identified to work with new researcher. **2)** Dr. Restrepo has over 15 years of extensive SME and research experience in TB and has a laboratory adjacent to the Mexican border; has experience mentoring junior investigators. **3)** Dr. Abdelbary brings subject matter expertise in infectious disease and data analysis expertise. **4)** Jennifer Curry brings experience in relationship building and communications with international communities."

RESPONSE TO COMMENT 3: No response required.

COMMENT 4: The reviewer states the following as weaknesses: "**1)** Personal statement needs to more strongly indicate level of experience, if any, in working in or leading a research project, basic project management skills, and/or data analysis experience indicated. **2)** Specific role on project needs to be better described in personal statement."

RESPONSE TO COMMENT 4: To address the first concern, the biosketches of the PI and Dr. Restrepo have been updated to reflect the necessary experience and expertise. Please see the response to reviewer 1, comment 4. To address the second concern, specific roles and responsibilities of each team member have been described in the 'Multidisciplinary Team' section, paragraph 2, rather than in the personal statements located in the biosketch section of each team member.

INNOVATION

COMMENT 5: The reviewer states the following as strengths: "**1)** Migration from the poorest states in Mexico may be responsible for a significant proportion of TB cases in the Mexican states bordering the U.S., and this has never been systematically evaluated. **2)** Necessary, if not novel, initial work to better understand the association between migration patterns and the prevalence of TB in Tamaulipas, Mexico, and to identify the characteristics that distinguish TB patients who originate from border versus those who are from non-border states of Mexico. **3)** A first look at population migration and impact on TB in Mexican state of Tamaulipas that will inform future prospective research."

RESPONSE TO COMMENT 5: No response required.

COMMENT 6: The reviewer states the following as weaknesses: "None"

RESPONSE TO COMMENT 6: No Response required.

APPROACH

COMMENT 7: The reviewer states the following as strengths: "**1)** Cross-sectional cohort design is appropriate. **2)** Access to the 12,000 TB patients through state SINAVE. **3)** Extensive data cleaning planned and well outlined."

RESPONSE TO COMMENT 7: No response required.

COMMENT 8: The reviewer states the following as weaknesses: "**1)** Limited analysis to the data elements collected for inquiry; discuss this more. **2)** Data quality/accuracy dependent on data entry on SINVAE forms by multiple people which is then transferred to a state database – all not within investigator control. **3)** Uncontrolled study so other confounding explanations possible and other disease states, such as Diabetes, and its contribution not discussed. **4)** Not necessarily generalizable beyond Tamaulipas."

RESPONSE TO COMMENT 8: 1) Since the two hypotheses to be tested in Aims 1 and 2 are meant to show simple differences in prevalence and incidence of TB in those not from Tamaulipas versus those from Tamaulipas, and in those from Tamaulipas border regions versus those not from Tamaulipas border regions, simple two-sided hypothesis testing seems to be the most straight forward methods. However, in future studies that could potentially include other border states and how migration affects TB prevalence and incidence across all border states, then an analysis of variance could be used to handle multiple variable comparisons. **2)** It is true that data is entered by multiple people, and not under investigator control, but since this is an administrative database there are limitations, which are assumed from the outset. The outcomes from the analyses in the proposal are intended to spur further, possibly prospective studies designed to be more free of inherent ambiguity. The proposal has been edited under the section 'Resolution of Challenges' subpart c. that recognized this potential limitation. However, an advantage of using these surveillance datasets is the sample size and coverage of nearly all the TB patients in the state of Tamaulipas. **3)** It is true that diabetes can be a major confounding factor, and one way to deal with this is to exclude patients with diabetes from the population under study, even if this means a reduction in the sample size. In addition, while diabetes (or other host factors) could be potential confounders, two options will be considered in the data analysis: stratification of analysis by diabetes, or multivariable models where diabetes is controlled. This has been included in the section 'Resolution of Challenges' under subpart b. **4)** Many border states are experiencing similar migration issues, but the proposed data being analyzed only pertains to Tamaulipas. SINAVE is a national database that houses all TB epidemiological information for all of Mexico,

therefore, future studies can go back and look at each individual state. The following was added to the 'Resolution of Challenges' section as subsection c. "The results of this analysis may provide a way of creating a dialogue in the state of Tamaulipas and Mexico by 1) helping to identify whether other specific variables are needed within the SINAVE database, therefore providing the opportunity to improve the SINAVE database and TB surveillance, 2) highlighting and ensuring the consistency of diagnostics throughout all of Mexico, 3) improving treatment protocols, and 4) allowing the comparison of results with other states along the northern Mexican border, for example, Tamaulipas versus Baja California, to determine if there are similarities and/or other outcomes than need further analysis."

ENVIRONMENT

COMMENT 9: The reviewer states the following as strengths: "**1)** Demonstration of support from experienced Investigators and mentorship. **2)** Database availability and access. **3)** Effective history of collaboration across investigators with other research entities."

RESPONSE TO COMMENT 9: No response required.

COMMENT 10: The reviewer states the following as weaknesses: "Any potential limitations or challenges to use of SINAVE anticipated?"

RESPONSE TO COMMENT 10: The primary challenge to the SINAVE database is that, as mentioned, it is an administrative database, and as such, the data is not subject to the rigorous controls of data collected in a prospective study or other type of study where the investigator controls the collection of data. However, there is very little data at all in Mexico on this topic, and in this instance using an administrative database such as this in

order to answer simple questions designed to spur further research is considered to be helpful and perhaps necessary as mentioned in the response to comment 8 and in the section ‘Resolution of Challenges’.

In conclusion, Table 4.1 lists the final review scores per each of the NIH scorable criteria for this grant proposal.

Table 4.1 - Review Score Per Criteria

Reviewer	Significance	Investigator(s)	Innovation	Approach	Environment	Overall Impact Score
1	3	4	4	5	2	3
2	4	3	6	6	3	5
3	3	4	1	2	3	2
4	3	3	4	7	3	4
5	2	3	4	5	3	3

CHAPTER 5: FINAL VERSION OF THE PROPOSAL

The final version of the grant proposal follows on the next page. The font and font size, along with margin changes, are different from the rest of document in order to abide by NIH grant proposal requirements. However, the references listed within the grant proposal are included in the final reference section of this Thesis. Reviewer comments from Chapter 4 have been addressed and incorporated, if applicable, into the final version of the grant proposal.

COVER LETTER

Clayton Huntley, Ph.D.

Division of Microbiology and Infectious Diseases (DMID)

National Institute of Allergy and Infectious Diseases (NIAID)

National Institutes of Health

BG 5601FL RM 7E38

5601 Fishers Lane

Rockville, MD 20852

Dear Dr. Huntley:

Please accept this investigator-initiated application in response to the Funding Opportunity Announcement (FOA) PA-13-303, “NIH Exploratory/Developmental Research Grant Program (Parent R21)”. My proposal is entitled *“Tuberculosis Prevention: An Examination of Migration Patterns in Mexico, within the Border State of Tamaulipas.”*

I would like to request primary assignment for review to the following Institute/Center:

National Institute of Allergy and Infectious Diseases

Additionally, I would like to request primary review assignment to the following Center for Scientific Review Study Section:

Infectious, Reproductive, Asthma and Pulmonary Conditions Study Section [IRAP]

The Key/Senior Personnel for this research plan are:

Jennifer Curry: Emory University; Role: PD/PI

Blanca Restrepo, PhD: University of Texas Health Science Center School of Public Health, Brownsville, TX; Role: Co-Investigator

Bassent Abdelbary, MBChB: University of Texas Health Science Center School of Public Health, Brownsville, TX; Role: Co-Investigator

The central goal of this project is to determine the association between migration patterns and the prevalence of TB in Tamaulipas, Mexico, and to identify the characteristics that distinguish TB patients in Tamaulipas who originate from border versus those who are from non-border states of Mexico with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure).

Sincerely,

Jennifer Curry

PROJECT SUMMARY

This project is in response to the National Institutes of Health (NIH) Funding Opportunity Announcement (FOA) PA-13-303, “NIH Exploratory/Developmental Research Grant Program (Parent R21)”. The National Institute of Allergy and Infectious Disease (NIAID) is interested in supporting meritorious investigator-initiated research directed toward improving knowledge about tuberculosis (TB) and how it affects humans. As well, the NIAID is interested in supporting research to assess factors influencing the occurrence, distribution, and transmission of drug sensitive/resistant mycobacterium tuberculosis (Mtb). In support of these goals, the aim of this project is to conduct an uncontrolled cross-sectional cohort study that will investigate the contribution of population migration within Mexico to the prevalence of TB in the Mexican state of Tamaulipas. Tamaulipas borders the southernmost tip of Texas. The state of Tamaulipas was selected because it has one of the highest TB prevalence rates and the highest rate of multi-drug resistant TB (MDR-TB) cases in Mexico. This has implications for TB prevention and control, not only in Tamaulipas, but also in communities on the U.S. side of the border and mainland. While it is alluded that migration from the poorest states in Mexico may be responsible for a significant proportion of TB cases in the Mexican states bordering the U.S., this has never been systematically evaluated. In addition, the epidemiology of TB in the border regions of Tamaulipas, including: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure) will be evaluated. This fact along with the importance of TB prevention in Mexican border communities underscores a clear need for this research project. Additionally, the research findings will help inform the prevention of TB in communities throughout Mexico along both sides of the U.S./Mexico border.

PROJECT NARRATIVE

The central goal of this project is to determine the association between migration patterns and the prevalence of TB in Tamaulipas, Mexico, and to identify the characteristics that distinguish TB patients in Tamaulipas who originate from border versus those who are from non-border states of Mexico with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure).

FACILITIES AND OTHER RESOURCES

The primary research components and data analysis will be carried out at the University of Texas Health Science Center School of Public Health (UTHSC-SPH), Brownsville located in southernmost tip of Texas. Its proximity to the Mexican border provides researchers and students with a deep understanding of the values that make-up border culture. In addition, the University is committed to enhancing the well-being of the communities that constitute the Rio Grande Valley of South Texas. It serves as an institution of higher learning for many young Mexican-American students, which provides a foundation for international learning and cooperation. The University has a substantial commitment to the success of research within the community and to this research project. There are ample resources for the necessary technology and professional workspace required for the project.

Equipment – The University has standard equipment available such as computers and office supplies necessary for data collection and analysis. The software on the computer is maintained with the latest updates. Each computer is set with an individual password, ensuring privacy and confidentiality regarding patient information. They also are equipped with standard software such as Microsoft Office that is kept updated. The computer designated for data analysis will have data analysis software, SAS, installed.

Office Space – The University has standard office space suitable for the proposed tasks.

SINAVE Database – Infectious disease information, such as TB, for patients in Mexico is entered by a public health official into a platform called the Sistema Nacional de Vigilancia Epidemiologica (SINAVE) that collects epidemiological data. Data from SINAVE will be compiled into an administrative dataset by the Tamaulipas Department of Public Health in Ciudad Victoria, Mexico which will be used in the proposed research.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH – JENNIFER CURRY

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: CURRY, JENNIFER

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: GRADUATE STUDENT

EDUCATION/TRAINING ***(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)***

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Baylor University, Waco, TX	B.A.	2000	Political Science & Int'l Studies
Emory University, Atlanta, GA	M.P.H.	2016	Prevention Science

A. Personal Statement

Between 2003 to 2005, I worked on a longitudinal study on the Natural History Study of Rheumatoid Arthritis for the National Institute of Arthritis and Musculoskeletal and Skin Diseases at the NIH. As part of my responsibilities, I was involved with data entry and analysis using Epi Info and Microsoft Access. I currently serve as the Project Officer at the National Institute of Diabetes and Digestive and Kidney Diseases for one the Institute's new Initiatives that focus on developing the biomedical pipeline with young Hispanic research investigators. My duties with the new Initiative are to manage all programmatic aspects of the project from recruitment to evaluation. The project is currently budgeted at $325,000 for the next five year. In addition to this experience and expertise, my recent coursework in statistics, biostatistics, and epidemiology, along with my practicum work in TB along the U.S. border provide me with the necessary skills to

complete the project. I have specific training and expertise in working in an international setting and in establishing strong ties with communities and community providers. As a result of these previous experiences, I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget.

B. Positions and Honors

Positions and Employment

2000 – 2001	Staff Assistant, United States House of Representatives, U.S., Congressman Rubén Hinojosa (TX-15), McAllen, TX
2001 – 2001	Peace Corps Training, U.S. Peace Corps, Mityana, Uganda
2001 – 2003	Primary School Teacher Trainer, U.S. Peace Corps, Uganda
2003 – 2005	Health Educator, Office of Communications and Public Liaison, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD
2005 – present	Program Specialist, Office of Minority Health Research Coordination, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Awards and Fellowships

2001	Travel Grant, International Conference on HIV/AIDS, Jinja, Uganda

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH – BLANCA RESTREPO

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: RESTREPO, BLANCA

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Associate Professor of Epidemiology

EDUCATION/TRAINING ***(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)***

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Colegio Mayor de Antioquia, Medllín, Colombia	B.S.	1986	Medical Technology
University of Texas Health Science Center, San Antonio, Texas	Ph.D.	1994	Microbiology

A. Personal Statement

For over two decades I have focused my research on the dysfunctional immunity of TB in diabetes patients, and the role of hormones (immune-endocrine axis) in these defects. Some of these studies are being conducted with collaborators in South Africa. I also participate in field studies to evaluate novel point-of-care diagnostics for TB. My laboratory is in South Texas, adjacent to the Mexican border. This region is one of the poorest in the U.S., and has one of the highest obesity and type 2 diabetes prevalence rates in the world. Tuberculosis is also higher in this community when compared to the rest of the U.S. Specifically my, expertise is highlighted in two publications in 2007 and 2011. From 1998 – 2003, I analyzed 6 years of retrospective data to explore the association of diabetes and tuberculosis in South Texas and Tamaulipas. The results of

this analysis were published in 2007, and in 2011 results from a prospective study conducted between 2006 and 2008 were published in the World Health Organization Bulletin. Additionally, I have mentored students for over a decade and therefore I am well qualified to serve as a subject matter expert on tuberculosis and data analysis and contribute to the proposed studies.

B. Positions and Honors

Positions and Employment

1986 – 1987	**Social Service Year on Research**: Corporación para Investigaciones Biológicas, CIB., Division of Medical Mycology, Medellín, Colombia Audie L. Murphy Veterans Administration Hospital, San Antonio, TX.
1994 – 1997	**Post-doctoral fellow**, Department of Microbiology, Dr. Judy M. Teale's laboratory
1997 – 2001	**Head, Molecular Parasitology Lab**, Corporación para Investigaciones Biológicas, CIB, Medellín, Colombia
2002 – 2003	**Post-doctoral fellow**, University of Texas Health Science Center Houston-School of Public Health (UT-SPH), Brownsville Campus
2003 – 2007	**Assistant Professor of Epidemiology, NTR** UT-SPH Brownsville Campus
2007 – 2010	**Assistant Professor of Epidemiology, Tenure track** UT-SPH Brownsville Campus
2012 – 2015	**Adjunct Associate Professor of Microbiology**, UT Health Science Center San Antonio, Edinburg RAHC campus

2010 – present **Associate Professor of Epidemiology, Tenured** UTHSC-SPH Brownsville Campus

C. Peer-Reviewed Publications

1. Restrepo BI, McEwen JG, Salazar ME, Restrepo A. Morphological development of the conidia produced by Paracoccidioides brasiliensis mycelial form. J Med.Vet.Mycol. 1986 Aug; 24(4):337-9

2. McEwen JG, **Restrepo** BI, Salazar ME, Restrepo A. Nuclear staining of Paracoccidioides brasiliensis conidia. J Med.Vet.Mycol. 1987 Oct; 25(5):343-5

3. Restrepo BI, Barbour AG. Cloning of 18S and 25S rDNAs from the pathogenic fungus Cryptococcus neoformans. J Bacteriol. 1989 Oct; 171(10):5596-600. PMCID or free URL: PMC210402

4. Restrepo BI, Ahrens J, Graybill JR. Efficacy of SCH39304 in murine cryptococcosis. Antimicrob.Agents Chemother. 1989 Aug; 33(8):1242-6. PMCID or free URL: PMC172633

5. Burman N, Bergstrom S, **Restrepo** BI, Barbour AG. The variable antigens Vmp7 and Vmp21 of the relapsing fever bacterium Borrelia hermsii are structurally analogous to the VSG proteins of the African trypanosome. Mol.Microbiol. 1990 Oct; 4(10):1715-26

6. **Restrepo** BI, Kitten T, Carter CJ, Infante D, Barbour AG. Subtelomeric expression regions of Borrelia hermsii linear plasmids are highly polymorphic. Mol.Microbiol. 1992 Nov; 6(22):3299-311

7. Wilske B, Barbour AG, Bergstrom S, Burman N, **Restrepo** BI, Rosa PA, Schwan T, Soutschek E, Wallich R. Antigenic variation and strain heterogeneity in Borrelia spp. Res.Microbiol. 1992 Jul; 143(6):583-96

8. Restrepo BI, Barbour AG. Antigen diversity in the bacterium B. hermsii through "somatic" mutations in rearranged vmp genes. Cell 1994 Sep 9; 78(5):867-76

9. Restrepo BI, Carter CJ, Barbour AG. Activation of a vmp pseudogene in Borrelia hermsii: an alternate mechanism of antigenic variation during relapsing fever. Mol.Microbiol. 1994 Jul; 13(2):287-99

10. Hinnebusch BJ, Barbour AG, **Restrepo** BI, Schwan TG. Population structure of the relapsing fever spirochete Borrelia hermsii as indicated by polymorphism of two multigene families that encode immunogenic outer surface lipoproteins. Infect.Immun. 1998 Feb; 66(2):432-40. PMCID or free URL: PMC107923

11. Restrepo BI, Llaguno P, Sandoval MA, Enciso JA, Teale JM. Analysis of immune lesions in neurocysticercosis patients: central nervous system response to helminth appears Th1-like instead of Th2. J Neuroimmunol. 1998 Aug 14; 89(1-2):64-72

12. Cardona AE, **Restrepo** BI, Jaramillo JM, Teale JM. Development of an animal model for neurocysticercosis: immune response in the central nervous system is characterized by a predominance of gamma delta T cells. J Immunol. 1999 Jan 15; 162(2):995-1002

13. Barbour AG, **Restrepo** BI. Antigenic variation in vector-borne pathogens. Emerg.Infect.Dis. 2000 Sep; 6(5):449-57. PMCID or free URL: PMC2627965

14. Restrepo BI, Obregon-Henao A, Mesa M, Gil DL, Ortiz BL, Mejia JS, Villota GE, Sanzon F, Teale JM. Characterisation of the carbohydrate components of Taenia solium metacestode glycoprotein antigens. Int J Parasitol. 2000 May; 30(6):689-96

15. Melby PC, Tabares A, **Restrepo** BI, Cardona AE, McGuff HS, Teale JM. Leishmania donovani: evolution and architecture of the splenic cellular immune response related to control of infection. Exp.Parasitol. 2001 Sep; 99(1):17-25

16. Obregon-Henao A, Gil DL, Gomez DI, Sanzon F, Teale JM, **Restrepo** BI. The role of N-linked carbohydrates in the antigenicity of Taenia solium metacestode glycoproteins of 12, 16 and 18 kD. Mol.Biochem.Parasitol. 2001 May; 114(2):209-15

17. Restrepo BI, Alvarez JI, Castano JA, Arias LF, **Restrepo** M, Trujillo J, Colegial CH, Teale JM. Brain granulomas in neurocysticercosis patients are associated with a Th1 and Th2 profile. Infect.Immun. 2001 Jul; 69(7):4554-60. PMCID or free URL: PMC98532

18. Restrepo BI, Aguilar MI, Melby PC, Teale JM. Analysis of the peripheral immune response in patients with neurocysticercosis: evidence for T cell reactivity to parasite glycoprotein and vesicular fluid antigens. Am J Trop.Med.Hyg. 2001 Oct; 65(4):366-70

19. Alvarez JI, Colegial CH, Castano CA, Trujillo J, Teale JM, **Restrepo** BI. The human nervous tissue in proximity to granulomatous lesions induced by Taenia solium metacestodes displays an active response. J Neuroimmunol. 2002 Jun; 127(1-2):139-44

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49. Jenny Pang, Larry D Teeter, Dolly Katz, Amy L Davidow, Wilson Miranda, Kirsten Wall, Smita Ghosh, Trudy Stein-Hart, Blanca I **Restrepo**, Randall Reves, Edward A Graviss, on behalf of the Tuberculosis Epidemiology Studies Consortium. The Impact of Global Immigration on Tuberculosis in Children Younger than 5 Years of Age within the United States. Pediatrics (*in press*)

50. Medrano B, Salinas G, Sanchez C, Miramontes R, **Restrepo** BI, Haddad MB, Lambert LA. A Missed case of tuberculosis resulting in hospital transmission. Infection Control and Hospital Epidemiology (*in press*)

D. Research Support

R01 US-South Africa Collaboration | Restrepo (co-PI) Dec 2014 – 2019

Study Title: Altered immune-endocrine axis in type 2 diabetes and tuberculosis diabetes patients

Purpose: To evalutate the impact of type 2 diabetes on alterations to the hypothalamus-Pituitary-Adrenal axis (HPA axis) that in turn compromise immunity to Mycobacterium tuberculosis

Role: Co-PI with Dr. Katharina Ronacher (South African PI)

Environment: University of Texas Health Science Center Brownsville, Brownsville, Texas

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH – BASSENT ABDELBARY

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: ABDELBARY, BASSENT

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: ASSISTANT CLINICAL PROFESSOR

EDUCATION/TRAINING ***(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)***

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
UT Health Science Center School of Public Health, Edinburg, TX	Ph.D.	2016	Epidemiology
UT Health Science Center School of Public Health, Brownsville, TX	M.P.H.	2012	Maternal &Child Health
University of Alexandria, Alexandria, Egypt	MBChB	1998	

A. Personal Statement

I have the expertise, leadership, training and motivation necessary to successfully carry out the proposed research project. I have a broad background in infectious disease, cardiovascular disease, maternal child health, evidence based medicine, health disparities, and preventive and community health. I am serving as a subject matter and data analysis expert. The current application builds logically on my prior work.

B. Positions and Honors

Positions and Employment

2015 – Present	Assistant Clinical Professor, University of Texas Rio Grande Valley, TX
2015 – Present	Editorial board member, Journal of Family Medicine and Disease Prevention
2011 – 2014	Teaching Assistant, UT Health Science Center School of Public Health, TX
2009 – 2015	Graduate Research Assistant, UT Health Science Center School of Public Health, TX
2008 – 2009	Volunteer/ Observer, Valley Baptist Brownsville, TX
2004 – 2015	Clinical Controller, Monzer H. Yazji and Associates, TX
2001 – 2003	Volunteer, Monzer H. Yazji and Associates, TX
2000	General Family Physician, Ministry of Health, Egypt

C. Peer-Reviewed Publications

1. Salinas J, Abdelbary B, Rocha E, Al Snih S "Contextualizing the burden of chronic disease: Diabetes, mortality and disability in Older Mexicans." Book chapter *Health and Health Care Policy Challenges for Aging Latinos: The Mexican-Origin Population*.

2. Salinas J, Abdelbary B, Wilson J, Hossain M, Fisher-Hoch S, McCormick J “Using the Framingham Risk Score to Evaluate Immigrant Effect on Cardiovascular Disease Risk in Mexican Americans.” Journal of Health Care for the Poor and Underserved 2012;23(2):666-77.

3. Salinas J, Abdelbary B, Rocha E, Gay J, Sexton K. “Impact of Hispanic Ethnic Concentration and Socioeconomic Status on Obesity Prevalence in Texas Counties”

International Journal of Environmental Research and Public Health 2012, 9(4), 1201-1215.

4. Salinas JJ, Shah M , Abdelbary B, Gay JL, Sexton K “Application of a Novel Method for Assessing Cumulative Risk Burden by County” International Journal of Environmental Research and Public Health 2012, 9(5), 1820-1835.

5. Salinas J, Abdelbary B, Brinkworth J, Hossain M, Rocha E, Fisher-Hoch S, Rentfro A, McCormick J, Wilson JG "Mexican Cultural Neighborhood Environment and Diabetes Risk in Mexican Americans." Hispanic Health Care International 2012, 10(3), 146-153.

6. Salinas J, Abdelbary B, Castellanos, Rentfro A, Fisher-Hoch S, McCormick JB. “Region of Birth and CVD in Mexican American living in the Texas-Mexico Border” Hispanic Health Care International 2013; 11(1).

7. Salinas J, Abdelbary B, Rentfro A, Fisher-Hoch S, McCormick J. “Cardiovascular Disease Risk Among the Mexican American Population in the Texas-Mexico Border Region, by Age and Length of Residence in United States.” Preventing Chronic Disease 2014, 11(4): E58.

8. Salinas JJ, Abdelbary B, Klaas K, Sexton K, Socioeconomic context and the food landscape in Texas: Results from hotspot analysis and border/non-border comparison of unhealthy food environments. American Journal of Preventive Medicine 2014, 11(6), 5640-5650.

D. Research Support

PI: Restrepo 2014 – 2015

HSC-SPH-12-0037

Study Title: Diabetes and Tuberculosis Research Program in South Texas Impact of type 2 diabetes on monocyte responses to Mycobacterium tuberculosis

Purpose: To evaluate altered immunological response in diabetics that can play an important role in TB outcomes.

Role: Graduate Research Assistant

Environment: University of Texas Health Science Center Houston, Houston, Texas

PI: Parra-Medina 2013 – 2014

National Heart Lung and Blood Institute (NHLBI) 1 R01 HL111718-01A1

Study Title: ENLACE: A Promotora-Led Physical Activity Intervention Trial for Latinas in Texas

Purpose: To evaluate the use of a promatora model to increase physical activity among Mexican origin women living in South Carolina and South Texas.

Role: Graduate Research Assistant

Environment: University of Texas Health Science Center Houston, Houston, Texas/ University of Texas Health Science Center San Antonio, San Antonio, Texas

PI: Salinas 2010 – 2012

American Heart Association Beginning Grant-in-Aid 10BGIA3080006

Study Title: Cardiovascular disease in Mexican Americans living in South Texas: Prevalence and risk factors

Purpose: To examine the prevalence of cardiovascular disease in Mexican Americans living in the US Mexico border region.

Role: Graduate Research Assistant

Environment: University of Texas Health Science Center Houston, Houston, Texas

SPECIFIC AIMS

An uncontrolled cross-sectional cohort study is proposed that will examine the contribution of population migration within Mexico to the prevalence and epidemiology of tuberculosis (TB) in the Mexican state of Tamaulipas. This type of study is deemed appropriate because the available dataset for analysis will provide data on more than 12,000 TB patients diagnosed in Tamaulipas between 2005 – 2013. Our research study will be cost-effective and its findings will guide the design of future prospective cohort studies.

The primary source of infectious disease information, such as TB, for patients in Mexico, and which will be used in this program, is entered by a public health official into a platform called the Sistema Nacional de Vigilancia Epidemiologica (SINAVE) that collects epidemiological data. Data from SINAVE will be compiled into an administrative dataset by the Tamaulipas Department of Public Health in Ciudad Victoria, Mexico which will be used in the proposed research.

The specific aims detailed below will serve to achieve the overall goal, which is to determine the association between migration patterns and the prevalence of TB in Tamaulipas, Mexico, and to identify the characteristics that distinguish the TB patients in Tamaulipas that originate from border versus non-border states of Mexico with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure).

Aim 1: Determine if there is a difference in TB prevalence between those who have migrated to Tamaulipas and those who are from Tamaulipas between 2005 – 2013. The hypothesis that there is an association between migrating to Tamaulipas and an increased prevalence of TB will be tested, where P_{NT} is the prevalence of TB among

patients not from Tamaulipas and P_T is the prevalence of TB among patients from Tamaulipas:

$$H_A: P_{NT} \neq P_T$$

$$H_O: P_{NT} = P_T$$

Aim 2: Determine the contribution of immigration to the incidence of TB in border versus non-border regions within Tamaulipas. For this the proportion of TB patients who were born in a region different from the place of TB diagnosis will be determined. Then the hypothesis that there is a difference in migration among TB patients from border (versus non-border) regions of Tamaulipas, where M_{BP} is Migration among TB patients from a border region and N_{BP} is migration among TB patients from a non-border region will be tested.

$$H_A: M_{BP} \neq M_{NBP}$$

$$H_O: M_{BP} = M_{NBP}$$

Aim 3: Identify the characteristics that distinguish migrant versus non-migrant TB patients in Tamaulipas with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or treatment failure).

RESEARCH STRATEGY

1. SIGNIFICANCE

a. Burden of Disease

Figure 1 - Map of U.S.-Mexico Border and State of Tamaulipas

Source: (Thornton, 2013)

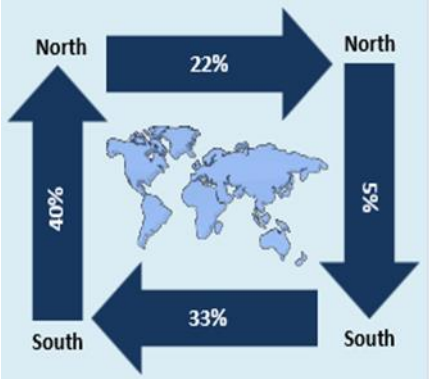
Although the incidence of TB has declined globally, it is still the world's second-deadliest disease with1.5 million attributed deaths in 2014 after HIV/AIDS (World Health Organization, 2015a). The global burden of individuals carrying active TB disease was 9.6 million in 2014, and 22 countries accounted for 83% of TB cases (World Health Organization, 2015a). Even though the total contribution to the number of foreign-born individuals with TB in the U.S. is higher for individuals from other countries of origin, Mexico has the highest contribution for any single country followed by the Philippines, India, Vietnam and China (Centers for Disease Control and Prevention, 2014a). This highlights the problem along the U.S.-Mexico border, and the need to understand the dynamics of population movement, and the social determinants' impact on TB disease and transmission on both sides of the border. Tamaulipas **(Figure 1)** has a TB prevalence rate of 30 per 100,000 vs. Mexico's national average of 13.5 per 100,000 (Joya, 2014). Second to Baja California, Tamaulipas has one of the highest incidence rates of TB and MDR-TB in Mexico (Joya, 2014). In Tamaulipas the number of TB cases in 2012 was 1,025 with over one-third of Mexico's TB patients (34.3%) concentrated along the U.S.-Mexico border (Joya, 2014). An additional observation is the eastern corridor of Mexico where the incidence of TB is consistently over 20.4 cases per 100,000 for the states of Tamaulipas, Veracruz, Tabasco, and Chiapas (Secretaría de Salud, 2012). However it is also known that another potential TB corridor in Mexico stems from Chiapas to Baja California. Herein

lies a vital observation regarding the true burden of TB in Tamaulipas, but also within Mexico.

b. Relevant Literature on TB and Migration

With a population of approximately 122 million, 55.3 million Mexicans live in poverty (National Council for the Evaluation of Social Development Policy, 2014). Since the 1960's, migration in Mexico has mainly been from rural to urban areas. However, over the past decade Mexico is once again experiencing another migration shift—one that is not being recognized internally—which is that more Mexicans are increasingly living in states in which they were not born. Longitudinal survey results from Mexico's National Institute of Statistics, Geography, and Information (INEGI), (Martinez, 2014) report that roughly 20% of Mexicans live outside of their state of origin. A framework developed by the International Organization of Migration (IOM) **(Figure 2)** posits that there are four migration pathways: North to South, South to South, South to North, and North to North. The most common migratory pathway experienced globally is from South to North representing 40% of total global migratory movement.

Figure 2 - International Migrants and the Four Migration Pathways



Source: (International Organization for Migration, 2013)

It is not surprising then that Mexico's internal migration from South to North follows global trends, and this particular paradigm can also be applied to internal analysis of population shifts within each of Mexico's 31 states. The IOM framework therefore feeds into the question of whether TB in Mexico stems mostly from its southern states, and is therefore increasing the prevalence of TB in northern states such as Tamaulipas; if so, would TB education and prevention control strategies be better served in states such as Chiapas and Oaxaca along its southern border? Or should greater

emphasis be placed along the northern border or even the eastern Gulf Coast which seems to be a corridor of further exploration? Infectious diseases can be prevented at a variety of points, however determining a “specific point” that reduces transmission in a resource challenged country such as Mexico which is marred by constant migration makes it all the more difficult.

Several studies have stemmed from this area of northern Mexico. Unfortunately, they do not provide enough information to make general conclusions about transmission permeability within Mexican host communities. Two studies have come close. An epidemiological study by Moser, et al. at the local health departments in Arizona, California, New Mexico, and Texas set out to characterize patterns of immigration and migration among foreign-born Hispanic patients with TB in 8 U.S. counties along the border. They looked at 164 patients, with 154 being born in Mexico, and 10 born in Central America. Of the 154 Mexican-born patients, 76 (46%) were born in non-border states. Of the 76 patients, 43 emigrated directly from their respective state of birth and 33 moved to a border town and then immigrated to the U.S. Of the 154 patients born in Mexico, 93 (60%) of them had been living in a border town in Mexico before immigrating to the U.S. and of the 93, 51 patients who were not born in Mexican border towns had lived in that border town for 2 or more years. Although the study was small, these findings showed that 40% of TB patients had immigrated from non-border communities suggesting that efforts were needed in non-border regions of Mexico (Moser, et al., 1996).

A second epidemiological study in 2013 by Chittoor, et al. in the state of Chihuahua set out to identify if there were genetic variants that influenced the progression of latent TB infection (LTBI) to TB. This study recruited 150 individuals (75 cases and 75 controls), and was particularly interested in finding environmental risk factors; however what proved to be a significant finding in this study is that when the

controls were compared to the cases, a majority of the cases were originally from states other than the state of Chihuahua. Unfortunately, these authors did not provide a list of the non-Chihuahua states to glean any further insight (Chittoor, et al.).

c. Ramifications of Uncontrolled TB in Tamaulipas, Mexico

The introduction of a high-risk population into a low-incidence area can alter the dynamics of the area's TB burden by increasing the number of TB cases, and by perpetuating TB in the immigrant population. Patterns of immigration change the face of TB. Studies chronicling the change are not only seen in the U.S. starting in the mid-2000s, but particularly through Europe and Asia as well. Analysis of retrospective surveillance data from Connecticut between 1996 through 2005 by Lobato, Mohamed and Hadler, set out to determine if immigration impacted Connecticut's TB burden. Lobato and colleagues chose Connecticut for their study because of its high proportion of foreign-born patients. Almost half of the foreign-born persons were from six countries: India, Ecuador, Haiti, the Philippines, Peru and Vietnam. During the 10 year time period of this study, TB case rates in Connecticut declined in U.S. born persons, but the proportion of TB cases among foreign-born persons increased from 50% to 66.3%. This study highlights that most patients were found to have TB during the first 5 years after arrival in the U.S., and reactivation of TB persisted for more than a decade after emigration. The data suggests that a high incidence of TB occurs within the first 5 years among people emigrating from high-incidence areas, and may persist for more than a decade after emigration. This evidence can suggest that an increase in TB in Tamaulipas has the potential to have long-term effects in U.S. border communities and beyond (Lobato, Mohamed, & Hadler, 2008).

2. MULTIDISCIPLINARY TEAM

The research team is from the University of Texas Health Science Center School of Public Health (UTHSC-SPH), Brownsville in South Texas and the Rollins School of Public Health at Emory University. Our multidisciplinary team has expertise in TB disease and epidemiology (**Blanca Restrepo, Ph.D**—Associate Professor at the UTHSC-SPH, and leads a TB-DM2 research program devoted to understanding the epidemiology and biological basis for the re-emerging importance of DM2 as a risk factor for TB. She has conducted research in TB in South Texas for over 20 years); and conducts data analysis using SPSS, SAS, and STATA (**Bassent Abdelbary, MBChB, MPH**—Assistant Clinical Professor at UT-RGV. Her areas of expertise are in infectious and cardiovascular disease, evidence-based medicine, and preventive and community health); and knowledge of health disparities within the Hispanic community (**Jennifer Curry**—graduate student in the Rollins School of Public Health at Emory University). Cumulatively, the team has 40 years of experience working with underrepresented and vulnerable populations. In addition, two team members are fluent in Spanish (Dr. Restrepo and Ms. Curry) which will help with translation, interpretation, and further communication if necessary with the Tamaulipas Department of Health. All members of the team also have extensive experience working collaboratively on projects with Mexico and/or other federal agencies.

The PI will be responsible for translating the variables in the SINAVE dataset into English, removing duplicate data, data entry into SAS database, statistical analysis, and data reporting. Dr. Restrepo (Co-PI) will provide project oversight, arrange the transfer of the dataset, confirm translation, and provide oversight of the analysis plan. Dr. Abdelbary (Co-PI) will duplicate data entry for confirmation of correct data entry, and duplicate analysis, along with providing assistance with statistical analysis.

3. INNOVATION

The relationship between population migration and TB has been previously examined; however, to date, investigations have focused primarily on populations in Europe, India, and China. The novel approach of this proposal is to investigate the relationship between population migration and TB in Tamaulipas, Mexico, which will provide a first look at the effects of population migration on TB in the Americas. Additionally, studying population migration and TB in Tamaulipas may be understood as gaining knowledge about the whole iceberg from looking at the tip; that is, Tamaulipas can be seen as a gauge for understanding how population migration affects TB incidence in a wider region **(Figure 3)**. The results will provide new information on the epidemiology of newly-diagnosed TB patients in Tamaulipas in relation to their migratory history within Mexico or other Central American countries. This information will help guide the implementation of strategies for targeting TB prevention in Tamaulipas. The goal is to provide a strategy to target the individuals at highest risk for TB development based on their combined sociodemographic and migratory history. Additionally, the findings may potentially be generalized beyond Tamaulipas through direct/indirect standardization coupled with aggregate data for other border areas. The contribution of co-morbidities such as diabetes will be of particular interest given the high prevalence of this disease in Mexico, and the reported prevalence of up to 36% in the northern border of Tamaulipas. Findings from the proposed study should be complemented with the recent recommendations for shorter LTBI treatments, which are

Figure 3 - Map of Mexico Showing Border States as the Tip of an 'Iceberg' with Regard to TB Incidence in a Wider Region

Source: Adapted from (Córdova & Zamorano, 2004)

now part of the standard of care in the U.S., and can be used in Mexico as well. In addition, what happens in Mexico does not stay in Mexico, and therefore it is anticipated that TB prevention in Tamaulipas will have an impact on TB control across the south Texas border.

4. APPROACH

a. Study Population and Sources

This study will use data from the SINAVE database. The data to be analyzed contains all pulmonary and extrapulmonary TB patients information reported to the Secretaria de Salud from the state of Tamaulipas, Mexico between 2005 – 2013. Tamaulipas is a northern Mexican state that is directly across the south Texas border. In Mexico, TB patients identified at public and private institutions are reported to the appropriate sanitary jurisdictions. Patient data is electronically entered into the state SINAVE form at each local sanitary jurisdiction, and then submitted to the central state Tuberculosis Program Control office in Ciudad Victoria, as part of the State of Tamaulipas database. The database contains over 12,000 entries, and will be de-identified by the Mexican Health Authority prior to use by the PI and team.

b. Outcome Variable

The primary outcome variable is TB disease in Tamaulipas. Inclusion criteria for patients with the outcome include those with confirmed diagnosis of pulmonary TB, and those who have abandoned treatment. Exclusions include those with extrapulmonary TB, re-entries and relapses.

c. Independent Variables

Independent variables from de-identified data will include current state of residence (including jurisdiction, municipality, location) previous state(s) of residence, previous state(s) visited, date of visitation to previous states, date of birth, state of birth,

age, sex, education, occupation, initial date of signs, diagnostic method, date of diagnosis, year of treatment, contact made with person with TB, state where contact was made, place of detection, and previous TB occurrence.

d. Dataset acquisition, coding and cleaning

The total project including all activities will last 2 years as described in the work plan. The following are the major activities that will need to be completed to accomplish the overall goal:

1. Set-up a meeting with the Director of the Tamaulipas Department of Health (who will serve as the Mexican collaborator for the project) to discuss the proposed research, significance of the research, and permission to acquire and use de-identified information from the database.
2. Official request of variables and dataset will be sent to the public health officials at the Tamaulipas Department of Health in Mexico.
3. Submission of the research protocol for review by the Institutional Review Boards (IRB) of Emory University, UT-SPH, and the Secretaria de Salud de Tamaulipas (SSA), in order to ensure compliance with all necessary rules and regulations. Once IRB approval is obtained, study activities will commence.
4. Upon receiving the variable library and dataset, all variables will need to be translated from Spanish to English. If there is a question regarding the variable meaning, the research team will reach out to the health officials in Tamaulipas for further clarification and explanation.
5. After all variables are translated, variables will be reviewed, combined, and renamed (if needed), and coded. Coding each variable will allow the analyzer to identify the variable/question during the data analysis process.
6. A manual of operations and/or standard operating procedures must be developed to ensure that all personnel on the grant are abiding by common standards to properly

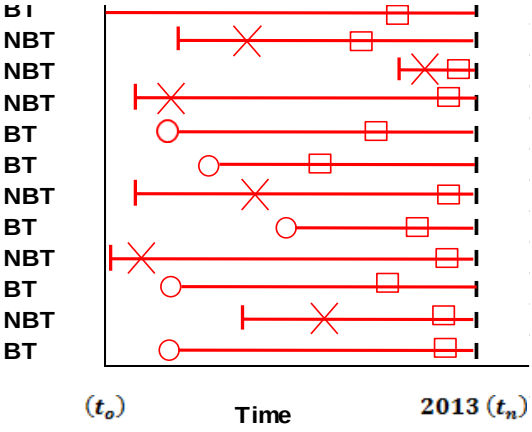
document the dataset. In addition, a codebook will be developed to keep track of what is coded, how each variable is coded, and what each variable means.

7. Clean the data file by removing any elements that the research team does not want to leave in the dataset, such as duplicate entries, to ensure a clean set of raw data.
8. Process the data. Before data analysis takes place it may be necessary to parse, recode, or otherwise reformat the data.
9. Create an analysis-ready copy of the data so that the data can be imported into a statistics package.
10. Development of databases in Microsoft Access and SAS will be needed to analyze data. Microsoft Access is a software tool used to create databases. Access can create tables of data, run queries about the data, create forms to view data, and generate printable reports. Access also can compare data using relationships between the data stored in the individual tables. Access's ability to support a wide variety of data file types allows for importing and exporting of data from other files and programs. SAS has the ability to provide descriptive statistics, bivariate statistics, predictions for numerical outcomes and predictions for identifying groups.
11. Document the data so that the actions on the data are clear when the file is revisited by the research team at a later date.

e. Study Design and Data Analysis

Study design. The proposed research strategy is a cross-sectional, cohort study. This type of study assesses the timing of exposures and outcomes retrospectively (Hudson, Pope, Jr., & Glynn, 2005). Cross-sectional study looks at data that is collected from a population, or a representative subset, at a specific point in time. In addition, the relationships between their characteristics are considered. These studies are useful for establishing associations rather than causality and for determining prevalence, rather than incidence. The cross-sectional design is used here because it is simple,

Figure 4 - Graphical Depiction of Study Design



Source: Adapted from (Hudson, Pope, Jr., & Glynn, 2005)

inexpensive, ethically safe, allows for quick data collection, and attrition is not likely because the administrative dataset is defined.

The cross-sectional cohort "design involves cross-sectional sampling to obtain a study cohort, and then retrospective assessment of the history of exposures and outcomes in the members of that cohort" (Hudson, Pope, Jr., & Glynn, 2005). In the proposed work, the study cohort will consist of all individuals who are available at an initial time t_o, and who still exist in the study at t_n, where t_o is the earliest year the first person entered the period of risk, and t_n is the last year of the dataset (i.e. 2013). This means the study cohort is the group of all people in Tamaulipas with TB as determined from the cleaned dataset. **Figure 4** above (adapted from (Hudson, Pope, Jr., & Glynn, 2005)) graphically depicts the cross-sectional cohort design with 12 hypothetical individuals from the cohort. It begins at time t_o. The vertical bars represent the time of onset of the period of risk, which is when they left their home state. The x's represent the time they entered Tamaulipas, and the boxes represent the time of diagnosis. If the person has always lived in Tamaulipas, the circles represent when they were born.

Data Analysis. The dataset is anticipated to contain data on 12,000 TB patients. Descriptive statistics will be provided, and all statistical analysis will be performed in SAS. Differences between study groups will be established by a chi-square test for discrete variables, and *t*-test for continuous variables. To determine the independent association between the exposure and outcome variables of interest, a secondary data analysis will be conducted. Analysis will consist of two-sided hypothesis testing using a

small significance level ($\alpha = 0.05$), to reduce the chance of rejecting a true null hypothesis. It is determined that the predictor variable is 'migration to Tamaulipas' and the outcome variable is TB disease. Our findings will help guide what is the best use of limited resources for TB control in Tamaulipas, and provide insight for the design of future prospective studies.

Aim 1: Determine if there is a difference in TB prevalence between those who have migrated to Tamaulipas and those who are from Tamaulipas between 2005 – 2013. Relevant information used to make this determination will include TB patients place of birth, year TB patient left place of birth, interim locations visited by TB patients en route to Tamaulipas, and time TB patient has been in Tamaulipas prior to TB diagnosis. Using this information, two comparison groups will be identified to test the hypothesis: those with TB who have migrated to Tamaulipas and currently reside there, and those who are from Tamaulipas and reside there. The hypothesis that there is an association between migrating to Tamaulipas and an increased prevalence of TB where P_{NT} is the prevalence of TB among patients not from Tamaulipas and P_T is the prevalence of TB among patients from Tamaulipas will be tested. The null hypothesis is that there is no difference between the two.

$$H_A: P_{NT} \neq P_T$$

$$H_O: P_{NT} = P_T$$

Aim 2: Determine the contribution of immigration to the incidence of TB in border versus non-border regions of Tamaulipas. For this the proportion of TB patients who were born in a region different from the place of TB diagnosis will be determined. Then the hypothesis that there is a difference in migration among TB patients from border (versus non-border) regions of Tamaulipas, where MBP is Migration among TB patients from a

border region and NBP is migration among TB patients from a non-border region will be tested. To test this, similar variables as in Aim 1 will be used, except the additional variables of residential jurisdictions, municipalities and locations for Tamaulipas will be used. Primary exposure: Immigrant (born in city or region different from the one where TB is diagnosed). Outcome: TB diagnosis in the border or non-border region of Tamaulipas.

$$H_A: M_{BP} \neq M_{NBP}$$

$$H_O: M_{BP} = M_{NBP}$$

Aim 3: Identify the characteristics that distinguish migrant versus non-migrant TB patients in Tamaulipas with respect to: a) sociodemographics, b) medical characteristics, and c) adverse TB outcomes (re-infection or recurrent TB within 2 years of treatment, or treatment failure where TB patient does not clear M. tuberculosis within the first 3 months of treatment).

5. WORK PLAN

a. Timeline of events

Task	Month																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Preliminary Activities	◄	─	─	─	─	─	─	─	─	─	─	─►												
Purchase Supplies	x	x																						
Request dataset	x	x	x	x	x	x	x	x																
Submit IRB							x	x	x															
Review and Code Vars.									x	x	x													
Clean and Process Data									x	x	x	x												
Document Process							x	x	x	x	x	x												
Aim 1													◄	─	─	─►								
Statistical Analysis													x	x	x	x								
Document													x	x	x	x								

Process																						
Aim 2																						
Statistical Analysis													x	x	x	x						
Document Process													x	x	x	x						
Aim 3																						
Descriptive Analysis																x	x	x				
Document Process																x	x	x				
Reporting																						
Interpret Data																			x	x	x	
Write Paper																			x	x	x	

b. Communication Plan

Communication will be facilitated by email, Skype, WebEx, and other shared information networks such as cloud based storage. Weekly teleconferences will be established at the outset with clear parameters defining the most convenient modes of communication between all collaborators.

6. RESOLUTION OF CHALLENGES

a. Study Population

A challenge presented by this dataset is that it only looks at patients who were diagnosed with TB in the state of Tamaulipas. Therefore, generalizing to other border states should be done with caution, taking into account there may be differences in the epidemiology, however this is not to suggest that future analysis cannot be done in other Mexican states.

b. Data Analysis

Uncontrolled studies, such as this one, lend itself to confounding variables. For instance, there could be other plausible explanations for the outcome than the particular exposure identified such as diabetes. Therefore, two options for this will be considered in the data analysis: 1) stratification of analysis by diabetes, or 2) multivariable models where we control for diabetes status. Additionally, there may be bias in the recording of

data (for example co-morbid conditions) between sanitary jurisdictions. Also, there may be a bias in missing data between border and non-border regions of the state.

c. Future Directions

The results of this analysis may provide a way of creating a dialogue in the state of Tamaulipas and Mexico by 1) helping to identify whether other specific variables are needed within the SINAVE database, therefore providing the opportunity to improve the SINAVE database and TB surveillance, 2) highlighting and ensuring the consistency of diagnostics throughout all of Mexico, 3) improving treatment protocols, and 4) allowing the comparison of results with other states along the northern Mexican border, for example, Tamaulipas versus Baja California, to determine if there are similarities and/or other outcomes that need further analysis.

BUDGET AND BUDGET JUSTIFICATION
BUDGET

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001

Budget Period: 1

Start Date 4/1/2017 End Date: 3/31/2018

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	**$150,000**
Consortium F&A	**$0**
* Total Direct Costs	**$150,000**

B. Indirect Costs

Indirect Cost Type	Indirect Co Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
	55.5%	$150,000	**$83,250**
	0%		$0
	0%		$0
	0%		$0

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date

Total Indirect Costs **$83,250**

C. Total Direct and Indirect Costs (A + B) Funds Requested ($) **$233,250**

Budget Period: 2

Start Date 4/1/2018 End Date: 3/31/2019

A. Direct Costs

	* Funds Requested ($)
* Direct Cost less Consortium F&A	**$125,000**
Consortium F&A	**$0**
* Total Direct Costs	**$125,000**

B. Indirect Costs

Indirect Cost Type	Indirect Co Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
	55.5%	$125,000	**$69,375**
	0%		$0
	0%		$0
	0%		$0

Cognizant Agency (Agency Name, POC Name and Phone Number)

Indirect Cost Rate Agreement Date 5/10/2013 Total Indirect Costs **$69,375**

C. Total Direct and Indirect Costs (A + B) Funds Requested ($) **$194,375**

BUDGET JUSTIFICATION

This proposal is requesting total cost in the amount of $427,625. Per the R21 funding mechanism, the research proposal should not exceed a combined total of $275,000 for direct costs for Y1 and Y2, per this proposal; total direct costs are $275,000. Personnel on this grant along with the number of person-months devoted to this project are as follows: Jennifer Curry (PD/PI), 12 person-month effort; Blanca Restrepo, Ph.D., 12 person-month effort, and Bassent Abdelbary, MBChB, 5.5 person-month effort (effort is expressed per year of the budget, as the budget, as the NIH only makes for one year at a time. There are no consortium fees to include. In addition, there are no requests for variations in the number of modules requested annually.

PROTECTION OF HUMAN SUBJECTS

A. Risks to the Subjects:

Data collected from human subjects will be involved in the proposed research plan. This human subjects research falls under exemption 4 and will be submitted to Emory University, University of Texas Health Science Center School of Public Health, Brownsville, and SSA IRBs for confirmation. This research qualifies for exemption in that collection of existing data, documents and records are de-identified and coded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects.

A.1 Human subjects' involvement and characteristics:

The data used for the proposed research analysis is obtained from an administrative dataset derived from Mexico's Sistema Nacional de Vigilancia Epidemioloigca (SINAVE). SINAVE is an epidemiological data collection platform for infectious disease information for patients in Mexico. The information is entered by doctors, clinicians, and other public health officials, and only information from patients diagnosed and confirmed to have TB are entered into SINAVE. It is the information from the SINAVE-derived dataset that this research proposal will use for analysis. The information includes basic demographic information (e.g., age, gender, etc.), date of diagnosis, co-morbid conditions, date of diagnosis with TB, TB status as MDR-TB or non-MDR-TB, city/state of birth.

A.2 Potential Risks

The potential risks to the individual human subjects are no more than minimal risk. The research proposal does not include the prospective collection of any data through physical procedure or manipulation of the subject or the subject's environment. As the data has previously been collected, there will be no prospective interaction between investigator and research subject. Additional data contained within the SINAVE

dataset has been de-identified, and no linkage between the identifying codes and the individual subjects will be available to the investigator. The major potential risk to

individuals whose information occurs in the dataset is the breach of confidentiality that may occur. However, as noted, due to the absence of access by the investigator to any identifier information, this is highly unlikely.

B. Adequacy of Protection Against Risks:

B.1 Protection of Confidentiality

The dataset to be used is an existing dataset, and, as such, risks involving recruitment, informed consent and protection against risk are not applicable; however protection of confidentiality is of paramount importance. In the event that personally identifiable information (PII) is present in the data, a unique identifier will be assigned to identify personal health information. The dataset to be used must first be cleaned in order to ensure consistency and reliability of the information, and avoid redundancy in reporting. Additionally, all research staff will be trained in the principles of human subjects protection and maintenance of confidentiality.

C. Potential Benefits of the Proposed Research to Human Subjects and Others:

C.1 Potential Benefits

Since this research proposal does not involve the collection of new data, there will be no obvious or immediate benefit to the patients whose data was recorded in SINAVE.

C.2 Why Risks Are Reasonable in Relation to Benefits

The use of the data in this research presents no more than minimal risk to those whose data was collected, and the results of the research may serve to provide largescale guidance and direction to future disease prevention efforts.

D. Importance of the Knowledge to be Gained:

The quantification of the contribution of population migration on TB prevalence in the Mexican state of Tamaulipas may lead to a new proactive approach to disease control and prevention rather than one which is reactive. In reality, the two approaches will likely be complimentary, but being able to predict future disease incidents and trends has obvious benefits to at risk populations. The threat of emerging or re-emerging infectious diseases, i.e., Zika, TB, Ebola, has taught us that when governments abandon prevention programs the price is policy failure and an unnecessary toll to human life.

E. Inclusion of Women and Minorities:

E.1 Inclusion of Women

There is no basis for the exclusion of dataset information by gender in this proposal, and thus both females and males will be included.

E.2 Inclusion of Minorities

The individuals whose data is recorded in the dataset are primarily of Mexican or Central American birth, and residence; however there is no basis for the exclusion of dataset information by race or ethnicity in this proposal.

E.3 Planned Enrollment Table

See Inclusion Enrollment Report under Targeted/Planned Enrollment Table

E.4. Inclusion of Children

While TB infection rates in children (age <18) is much less than in adults, children do develop TB infection and are included in the SINAVE database. As the database does not have a pre-specified age range for inclusion, it is likely that children will be included in this database. As such, the proposed research will include children.

The investigator does not possess specific expertise for working with children. However, as the database contains retrospective data collected on persons in Tamaulipas, Mexico who are diagnosed with TB infection, and there is no direct

interaction between the investigator and the research subjects, the absence of pediatric expertise does not raise any safety concerns for the proposed research plan.

TARGETED/PLANNED ENROLLMENT TABLE

The aforementioned distribution by gender, race and ethnicity were used to calculate the following planned enrollment table for the individuals in this study.

Inclusion Enrollment Report

This report format should NOT be used for data collection from study

Study Title: Tuberculosis Prevention: An Examination of Migration Patterns in Mexico, within the Border State of Tamaulipas

Total 12,000 **Protocol** N/A

Grant Number: N/A

PART A. TOTAL ENROLLMENT REPORT:			**Number of Subjects Enrolled to Date (Cumulative)**	
Ethnic Category	**Females**	**Males**	**Sex/Gender Unknown or**	**Total**
Hispanic or Latino	4,800	7,20		12,000 **
Not Hispanic or Latino				
Unknown (individuals not reporting				
Ethnic Category: Total of All	4,800	7,20		12,000 *
Racial Categories				
American Indian/Alaska Native				
Asian				
Native Hawaiian or Other Pacific				
Black or African American				
White				
More Than One Race				
Unknown or Not Reported	4,800	7,20		12,000
Racial Categories: Total of All	4,800	7,20		12,000 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)				
Racial Categories	**Females**	**Males**	**Sex/Gender Unknown or**	**Total**
American Indian or Alaska Native				
Asian				
Native Hawaiian or Other Pacific				
Black or African American				
White				
More Than One Race				
Unknown or Not Reported	4,800	7,20		12,000
Racial Categories: Total of	4,800	7,20		12,000 **

* These totals must agree.
** These totals must agree.

RESOURCE SHARING

At the conclusion of the study, and after manuscripts have been published, in accordance with NIH rules, the results will be publicly available. Implementation manuals will be shared with the public, as appropriate, per NIH rules. No new resources will be developed as part of this proposed research and so a Resource Sharing Plan does not apply.

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APPENDICES

Appendix A: Developmental Research Grant Program (Parent R21)

Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Eye Institute (NEI) National Human Genome Research Institute (NHGRI) National Institute on Aging (NIA) National Institute on Alcohol Abuse and Alcoholism (NIAAA) National Institute of Allergy and Infectious Diseases (NIAID) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) National Institute of Biomedical Imaging and Bioengineering (NIBIB) *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) National Institute on Deafness and Other Communication Disorders (NIDCD) National Institute of Dental and Craniofacial Research (NIDCR) National Institute on Drug Abuse (NIDA) National Institute of Environmental Health Sciences (NIEHS) National Institute of Mental Health (NIMH) National Institute on Minority Health and Health Disparities (NIMHD) National Institute of Neurological Disorders and Stroke (NINDS) National Institute of Nursing Research (NINR) National Library of Medicine (NLM) National Center for Complementary and Integrative Health (NCCIH formerly NCCAM)
Funding Opportunity Title	**NIH Exploratory/Developmental Research Grant Program (Parent R21)**
Activity Code	R21 Exploratory/Developmental Research Grant
Announcement Type	Reissue of PA-11-261

Related Notices	March 31, 2016 - This PA has been reissued as PA-16-161. January 7, 2016 - Notice of National Institute on Minority Health and Health Disparities (NIMHD) Participation in PA-13-303. See Notice NOT-MD-16-002. NOT-OD-16-004 - NIH & AHRQ Announce Upcoming Changes to Policies, Instructions and Forms for 2016 Grant Applications (November 18, 2015) NOT-OD-16-006 - Simplification of the Vertebrate Animals Section of NIH Grant Applications and Contract Proposals (November 18, 2015) NOT-OD-16-011 - Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications (November 18, 2015) April 16, 2015 - Notice of Information: NIMH High-Priority Areas for Research on Women's Mental Health During Pregnancy and the Postpartum Period . See Notice NOT-MH-15-013. March 6, 2015 - NCCIH Policy for Submission of R21 Applications Containing Clinical Trials . See Notice NOT-AT-15-004. September 25, 2014 - See Notice NOT-MH-14-033. Notice of Information on High-Priority Research Areas to Understand and Reduce Mental Health Disparities. August 06, 2014 - See Notice NOT-MH-14-007. Notice of change to application requirements. June 10, 2014 - Notice of NICHD's Interest in Supporting Research on Contraception, Long-Term Outcomes of Assisted Reproductive Technologies, and Intrauterine Assessment of Placental and Fetal Function. See Notice NOT-HD-14-020. June 4, 2014 - Notice NOT-14-074 supersedes instructions in Section III.3 regarding applications that are essentially the same. August 21, 2013: Removed reference to ASSIST in section IV.3, since ASSIST is currently only available for multi-project applications. August 7, 2013 - Use this funding opportunity announcement for due dates of September 25, 2013 and beyond.
Funding Opportunity Announcement (FOA) Number	**PA-13-303**
Companion Funding Opportunity	None
Number of Applications	See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)	93.361; 93.113; 93.273; 93.879; 93.286; 93.173; 93.866; 93.853; 93.856; 93.855; 93.121; 93.172; 93.867; 93.213; 93.242; 93.846; 93.865; 93.279; 93.307
Funding Opportunity Purpose	The National Institutes of Health (NIH) Exploratory/Developmental Grant (R21) funding opportunity supports the development of new research activities in categorical program areas. The R21 activity code is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research.

Key Dates

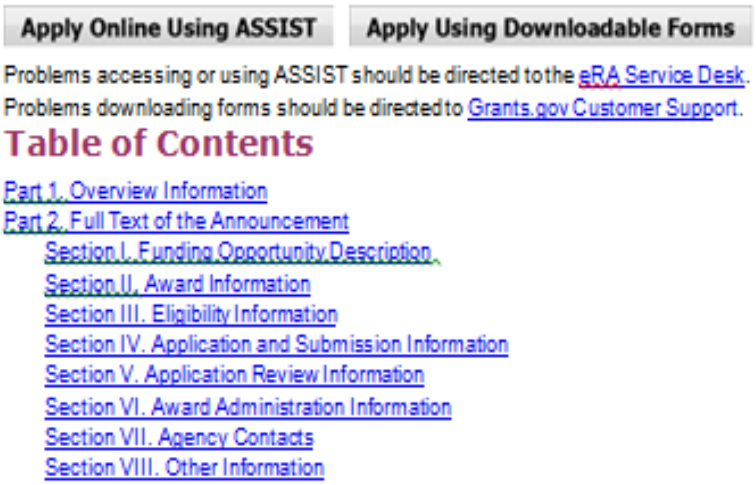
Posted Date	August 2, 2013
Open Date (Earliest Submission Date)	August 7, 2013
Letter of Intent Due Date(s)	Not Applicable
Application Due Date(s)	Standard dates apply, by 5:00 PM local time of applicant organization.
AIDS Application Due Date(s)	Standard AIDS dates apply, by 5:00 PM local time of applicant organization.
Scientific Merit Review	Standard dates apply
Advisory Council Review	Standard dates apply
Earliest Start Date	Standard dates apply
Expiration Date	**New Date** May 10, 2016 per issuance of PA-16-161. (Original Expiration Date: September 8, 2016)
Due Dates for E.O. 12372	Not Applicable

Required Application Instructions

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide, except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide*

for Grants and Contracts). Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options to submit your application to the agency through Grants.gov. You can use the ASSIST system to prepare, submit and track your application online. You can download an application package from Grants.gov, complete the forms offline, submit the completed forms to Grants.gov and track your application in eRA Commons. Or, you can use other institutional system- to-system solutions to prepare and submit your application to Grants.gov and track your application in eRA Commons. Learn more.



Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

The evolution and vitality of the biomedical sciences require a constant infusion of new ideas, techniques, and points of view. These may differ substantially from current thinking or practice and may not yet be supported by substantial preliminary data. By using the R21 activity code, the NIH seeks to foster the introduction of novel scientific ideas, model systems, tools, agents, targets, and technologies that have the potential to substantially advance biomedical research.

The R21 activity code is intended to encourage new exploratory and developmental research projects. For example, such projects could assess the feasibility of a novel area of investigation or a new experimental system that has the potential to enhance

health-related research. Another example could include the unique and innovative use of an existing methodology to explore a new scientific area. These studies may involve considerable risk but may lead to a breakthrough in a particular area, or to the development of novel techniques, agents, methodologies, models, or applications that could have a major impact on a field of biomedical, behavioral, or clinical research.

Applications for R21 awards should describe projects distinct from those supported through the traditional R01 activity code. For example, long-term projects, or projects designed to increase knowledge in a well-established area, will not be considered for R21 awards. Applications submitted to this FOA should be exploratory and novel. These studies should break new ground or extend previous discoveries toward new directions or applications. Projects of limited cost or scope that use widely accepted approaches and methods within well-established fields are better suited for the R03 small grant activity code. Information on the R03 program can be found at http://grants.nih.gov/grants/funding/r03.htm.

Section II. Award Information

Funding Instrument	Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.
Application Types Allowed	New Resubmisson Revision The OER Glossary and the SF424 (R&R) Application Guide provide details on these application types.
Funds Available and Anticipated Number of Awards	The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.
Award Budget	The combined budget for direct costs for the two year project period may not exceed $275,000. No more than $200,000 may be requested in any single year. Applicants may request direct costs in $25,000 modules, up to the total direct costs limitation of $275,000 for the combined two-year award period.
Award Project Period	The total project period may not exceed 2 years.

NIH grants policies as described in the NIH Grants Policy Statement will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Eligible Organizations

Higher Education Institutions

- *Public/State Controlled Institutions of Higher Education*
- *Private Institutions of Higher Education*

The following types of Higher Education Institutions are always encouraged to apply for NIH support as

- *Public of Private Institutions of Higher Education*
- *Hispanic-Serving Instructions*
- *Historically Black Colleges and Universities (HBCUS)*
- *Tribally Controlled Colleges and Universities (TCCUS), Alaska Native and Native Hawaiian Serving Institutions*
- *Asian American Native American Pacific Islander Serving Institutions (AANAPISIS)*

Nonprofits Other Than Institutions of Higher Education

- *Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)*
- *Nonprofits without 501(c)(3) Status (Other than Institutions of Higher Education)*

For-Profit Organizations

- *Small Businesses*
- *For-Profit Organizations (Other than Small Businesses)*

Governments

- *State Governments*
- *County Governments*
- *City of Township Governments*
- *Special District Governments*
- *Indian/Native America Tribal Governments (Federally Recognized)*
- *Indian/Native American Tribal governments (other than Federally Recognized)*
- *Eligible Agencies of the Federal Government*
- *U.s Territory or Possession*

Other

- *Independent School Districts*
- *Public Housing Authorities/Indian Housing Authorities*
- *Native American Tribal Organizations (other than Federally recognized tribal governments)*
- *Faith-based or Community-based Organizations*
- *Regional Organizations*
- *Non-domestic (non-U.S.) Entities (Foreign Institutions)*

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.
Non-domestic (non-U.S.) components of U.S.

Organizations **are** eligible to apply. Foreign

components, as defined in the *NIH Grants Policy*

Statement, **are** allowed.

Required Registrations

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Late Submission of Grant Applications states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (formerly CCR) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
- NATO Commercial and Government Entity (NCAGE) Code – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.
- Grants.gov – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account and should work with their organizational officials to either create a new account or to affiliate an existing account with the applicant organization's eRA Commons account. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Eligible Individuals (Program Director/Principal Investigator)

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

1. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

2. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

NIH will not accept any application that is essentially the same as one already reviewed within the past thirty-seven months (as described in the *NIH Grants Policy Statement*), except for submission:

- To an RFA of an application that was submitted previously as an investigator-initiated application but not paid;
- Of an investigator-initiated application that was originally submitted to an RFA but not paid; or
- Of an application with a changed grant activity code.

Section IV. Application and Submission Information

1. Requesting an Application Package

Applicants must download the SF424 (R&R) application package associated with this

funding opportunity using the “Apply for Grant Electronically” button in this FOA or following the directions provided at Grants.gov.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide, except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

For information on Application Submission and Receipt, visit Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications.

Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits must be followed.

Required and Optional Components

The forms package associated with this FOA includes all applicable components, required and optional. Please note that some components marked optional in the application package are required for submission of applications for this FOA. Follow all instructions in the SF424 (R&R) Application Guide to ensure you complete all appropriate “optional” components.

Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

SF424(R&R) Cover

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Project/Performance Site Locations

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Senior/Key Person Profile

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R or Modular Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans (Data Sharing Plan, Sharing Model Organisms, and Genome Wide Association Studies (GWAS)) as provided in the SF424 (R&R) Application Guide.

Appendix: Do not use the Appendix to circumvent page limits. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

Planned Enrollment Report

When conducting clinical research, follow all instructions for completing Planned Enrollment Reports as described in the SF424 (R&R) Application Guide.

PHS 398 Cumulative Inclusion Enrollment Report

When conducting clinical research, follow all instructions for completing Cumulative Inclusion Enrollment Report as described in the SF424 (R&R) Application Guide.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the *NIH Grants Policy Statement*, and procedures for foreign institutions described throughout the SF424 (R&R) Application Guide.

3. Submission Dates and Times

Part I. Overview Information contains information about Key Dates. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission.

Organizations must submit applications to Grants.gov, the online portal to find and apply for grants across all Federal agencies. Applicants must then complete the submission process by tracking the status of the application in the eRA Commons, NIH's electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date. If a Changed/Corrected application is submitted after the deadline, the application will be considered late.

Applicants are responsible for viewing their application before the due date in the

eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

4. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement*. Pre-award costs are allowable only as described in the *NIH Grants Policy Statement*.

Other Submission Requirements and

Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted. **Applicants must complete all required registrations before the application due date.** Section III. Eligibility Information contains information about registration. For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically.

Important reminders:

All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH. See Section III of this FOA for information on registration requirements.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.

See more tips for avoiding common errors.

Upon receipt, applications will be evaluated for completeness by the Center for Scientific Review, NIH. Applications that are incomplete will not be reviewed.

Post-Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in NOT-OD-13-030.

Section V. Application Review Information

Important Update: See NOT-OD-16-006 and NOT-OD-16-011 for updated review language for applications for due dates on or after January 25, 2016.

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

For this particular announcement, note the following:

The R21 exploratory/developmental grant supports investigation of novel scientific ideas or new model systems, tools, or technologies that have the potential for significant impact on biomedical or biobehavioral research. An R21 grant application need not have extensive background material or preliminary information. Accordingly, reviewers will focus their evaluation on the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. Preliminary data are not required for R21 applications; however, they may be included if available.

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi- PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?

If the project involves humans subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks and 2) the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children justified in terms of the scientific goals and research strategy proposed?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional

items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information, see the Human Subjects Protections Guidelines.

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information, see the Human Subjects Inclusion Guidelines.

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewals

Not Applicable

Revisions

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for

appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by the Center for Scientific Review, in accordance with NIH peer review policy and procedures, using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications. Following initial peer review, recommended applications will receive a second level of review by the appropriate national Advisory Council or Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review
- Availability of funds
- Relevance of the proposed project to program priorities

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons. Information

regarding the disposition of applications is available in the *NIH Grants Policy Statement*.

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement*.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to the DUNS, SAM Registration, and Transparency Act requirements as noted on the Award Conditions and Information for NIH Grants website.

1. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities. More information is provided at Award Conditions and Information for NIH Grants.

Cooperative Agreement Terms and Conditions of Award

Not Applicable

2. Reporting

When multiple years are involved, awardees will be required to submit the annual Non-Competing Progress Report (PHS 2590 or RPPR) and financial statements as required in the *NIH Grants Policy Statement*.

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000. See the *NIH Grants Policy Statement* for additional information on this reporting requirement.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)
Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Web ticketing system: https://public.era.nih.gov/commonshelp
TTY: 301-451-5939
Email: commons@od.nih.gov

Grants.gov Customer Support (Questions regarding Grants.gov registration and submission, downloading forms and application packages) Contact Center Telephone: 800-518-4726

Web ticketing system: https://grants-portal.psc.gov/ContactUs.aspx
Email: support@grants.gov

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)

Telephone: 301-435-0714
TTY: 301-451-5936
Email: GrantsInfo@nih.gov

Scientific/Research Contact(s)

Participating ICs and their contacts are listed at http://grants.nih.gov/grants/guide/contacts/parent_R21.html

Peer Review Contact(s)

Examine your eRA Commons account for review assignment and contact information (information appears two weeks after the submission due date).

Financial/Grants Management Contact(s)

Participating ICs and their contacts are listed at
http://grants.nih.gov/grants/guide/contacts/parent_R21.html

Section VIII. Other Information

Recently issued trans-NIH policy notices may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts*. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement.

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Parts 74 and 92.

Appendix B: RPG Critique Template

RPG/X01/R01/R03/R21/R33/R34 Review

If you cannot access the hyperlinks below,
visit http://grants.nih.gov/grants/peer/critiques/rpg_D.htm.

Application #:

Principal Investigator(s):

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five scored review criteria, and additional review criteria. An application does not need to be strong in all categories to be judged likely to have major scientific impact.

Overall Impact *Write a paragraph summarizing the factors that informed your Overall Impact score.*

Scored Review Criteria

Reviewers will consider each of the five review criteria below in the determination of scientific and technical merit, and give a separate score for each.

1. Significance
Strengths • **Weaknesses** •

2. Investigator(s)

Strengths • **Weaknesses** •

3. Innovation
Strengths • **Weaknesses** •

4. Approach
Strengths • **Weaknesses** •

5. Environment
Strengths • **Weaknesses** •

Additional Review Criteria

As applicable for the project proposed, reviewers will consider **the following additional items in the determination of scientific and technical merit, but will not give separate scores for these items.**

— Responses for Protections for Human Subjects, Vertebrate Animals, and Biohazards **are required from reviewers for all applications**.

— A response for Inclusion of Women, Minorities and Children **is required from reviewers** for applications proposing Human Subjects Research.

Protections for Human Subjects

Click Here to Select

Comments (Required Unless Not Applicable):

-

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Click Here to Select

Comments (Required Unless Not Applicable):

-

Inclusion of Women, Minorities and Children **Applicable Only for Human Subjects research and not IRB Exemption #4.**

- Sex/Gender: Click Here to Select
- Race/Ethnicity: Click Here to Select
- For NIH-Defined Phase III trials, Plans for valid design and analysis: Click Here to Select
- Inclusion/Exclusion of Children under 18: Click Here to Select

Comments (Required Unless Not Applicable):

-

Vertebrate Animals

Is the proposed research involving vertebrate animals scientifically appropriate, including the justification for animal usage and protections for research animals described in the Vertebrate Animal section?

Click Here to Select

Comments (Required Unless Not Applicable):

-

Biohazards

Click Here to Select

Comments (Required Unless Not Applicable):

-

Resubmission
Comments (if applicable): •

Renewal
Comments (if applicable): •

Revision
Comments (if applicable): •

Additional Review Considerations

As applicable for the project proposed, reviewers will address each of the following items, but will not give scores for these items and should not consider them in providing an overall impact/priority score.

Applications from Foreign Organizations
Click Here to Select Comments (Required Unless Not Applicable): •

Select Agents
Click Here to Select Comments (Required if Unacceptable): •

Resource Sharing Plans
Click Here to Select Comments (Required if Unacceptable):

•

Authentication of Key Biological and/or Chemical Resources
Click Here to Select Comments (Required if Unacceptable): •

Budget and Period of Support
Click Here to Select Recommended budget modifications or possible overlap identified: •

Additional Comments to Applicant

Reviewers may provide guidance to the applicant or recommend against resubmission without fundamental revision.

Additional Comments to Applicant (Optional)
•