Factors Affecting Uptake of, and Adherence to, Treatment for Latent Tuberculosis Infection in Ventanilla, Peru

Mariano Matias Iberico Lozada

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Wright State University
Acknowledgements

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### Acronyms

#### General

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>DOT</td>
<td>directly observed therapy</td>
</tr>
<tr>
<td>DOTS</td>
<td>directly observed therapy, short-course</td>
</tr>
<tr>
<td>IPT</td>
<td>isoniazid preventive therapy</td>
</tr>
<tr>
<td>LTBI</td>
<td>latent tuberculosis infection</td>
</tr>
<tr>
<td>NGO</td>
<td>non-governmental organization</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
</tbody>
</table>

#### Proper

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>IFHAD</td>
<td>Innovation for Health and Development</td>
</tr>
<tr>
<td>INEI</td>
<td>Instituto Nacional de Estadística e Información [Peruvian National Institute for Statistics and Information]</td>
</tr>
<tr>
<td>ISIAT</td>
<td>Innovative Socio-economic Interventions Against Tuberculosis</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goal</td>
</tr>
<tr>
<td>PLDP</td>
<td>Physician Leadership Development Program</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
<tr>
<td>UPCH</td>
<td>Universidad Peruana Cayetano Heredia</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Abstract

In Peru, treatment for latent tuberculosis infection (LTBI) with isoniazid is free for all people younger than 20 who have been in close contact with a person with active pulmonary tuberculosis (TB). Despite the availability of this drug therapy within the context of a TB control program that exceeds the international standards for TB care, very few children access, and even fewer complete a full course of treatment. This study was done in order to understand which factors contribute to latent tuberculosis infection treatment uptake and adherence, and whether a socio-economic intervention could improve uptake and adherence of treatment for latent tuberculosis infection. The research was based on data collected from 2007-2011 in a large periurban shantytown outside of Lima, Peru. The data were from a large cluster randomized controlled trial called Innovative Socio-economic Interventions Against Tuberculosis (ISIAT). First, a large database of TB treatment cards was analyzed for LTBI treatment uptake and utilization in individual contacts in the monitoring (control) group (n=3226). Age range of contact, crowding in household, index case place of origin, index case abandonment, and time established in Lima were all significant risk factors for uptake and adherence of LTBI treatment. Uptake and adherence were also analyzed with respect to the intervened (n=617) versus the control arm of the study. In the intervened areas, contacts were 1.74 times (95% CI [1.59, 1.87], p<0.001) as likely to start, and 2.64 times (95% CI [2.27, 3.07], p<0.001) as likely to complete LTBI treatment.

Keywords: latent tuberculosis, isoniazid, uptake, adherence, children, adolescents, Peru, South America
Factors Affecting Uptake of, and Adherence to, Treatment for Latent Tuberculosis Infection in Ventanilla, Peru

*Mycobacterium tuberculosis* is the single agent responsible for tuberculosis (TB) disease. *M. tuberculosis* is a slow-growing bacteria that is primarily transmitted via airborne droplet nuclei\(^1\), which can remain suspended in the air for hours (Riley, 1974). Due to this mechanism of transmission, TB is predominantly a disease of the lungs. Via dissemination through the blood and across tissue planes, however, TB can infect virtually any part of the body. For example, TB can infect the meninges in the brain, an especially devastating condition; the spinal column, called Pott’s disease; and the lymph nodes of the neck, called scrofula. Other species of the *Mycobacterium* genus may cause similar disease in humans, but none is as devastating or clinically important as *M. tuberculosis* and TB disease.

TB is a significant cause of morbidity and mortality in the world today. In 2011, there were a total of 8.7 million estimated cases of TB, with 0.5 million estimated cases in children aged less than fifteen years; and 1.4 million deaths from the disease, with 64,000 of those deaths in children aged less than fifteen years (World Health Organization [WHO], 2012). This was less than the previous World Health Organization (WHO) estimate of 8.8 million cases and 1.45 million deaths in 2010 and represents a continued trend of decreasing prevalence since 2006 and decreasing incidence rates since 2002 (WHO, 2011).

It is estimated that approximately two billion people, 29% of the world’s population, are infected with TB, but do not have any active disease. Some experts even put the number higher, at one third of the world’s population (Glaziou, Falzon, Floyd, & Raviglione, 2013). This infected state is called latent tuberculosis infection (LTBI). Most people with LTBI will never

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\(^1\) Droplet nuclei are microscopic particles that form after the fluid evaporates from droplets of respiratory secretions formed by sneezing, coughing, or spitting (Riley, 1974).
progress to active disease, but the large absolute number of people infected means that those who
do progress represent an enormous contribution to global incidence and prevalence rates (Barry
et al., 2009). It is notable that in high endemic settings LTBI prevalence has been calculated at
about 50% of those exposed (Whalen et al., 2011). This suggests that there is a heterogeneous
and inequitable global burden of latent disease.

In order to further reduce rates of TB disease worldwide, it is important to choose those
interventions that will most affect the incidence and prevalence. Currently, in the best
environment with high adherence, TB diagnosis and treatment can only hope to decrease the
incidence of TB by a maximum of 10% per year (Dye, 2011). In order to decrease the incidence
further, the vast number of people who are latently infected (and therefore represent a reservoir
for the disease) must be targeted. Isoniazid provides a convenient way to do this and could
possibly be the strongest biomedical intervention available.

Most TB control programs in the developing world, however, only focus on current
WHO recommendations: contacts less than five years old, and HIV positive individuals. Peru is
an exception to this, recommending treatment of LTBI for all child and adolescent close contacts
less than twenty years old, and giving physicians wide latitude in screening and treating other
special populations (Estrategia Sanitaria Nacional de Prevencion y Control de la Tuberculosis,
Ministerio de Salud Peru, Direccion General de Salud de las Personas, 2006).

Statement of Purpose

The purpose of this literature review is to understand the history of TB disease and
control, how LTBI plays an important role in TB disease and control, and how treating LTBI is
important for TB control efforts worldwide. The purpose of the original research conducted is to
understand the current state of LTBI treatment (uptake, adherence, barriers, facilitators, and
opportunities for change) in a Peruvian periurban shantytown, and to analyze the impact on LBTI treatment uptake and adherence of a cluster randomized controlled trial of a socioeconomic intervention called Innovative Socio-economic Interventions Against Tuberculosis (ISIAT). This paper, and the research presented herein, was conceived as a springboard for more in-depth analysis of the ISIAT data, as well as other avenues for research that might provide insights into how to improve tuberculosis control in Peru. The specific research questions addressed are:

1. What factors contribute to latent tuberculosis infection treatment uptake and adherence?
2. Does a socio-economic intervention improve uptake and adherence of treatment for latent tuberculosis infection?

**Literature Review**

**A Brief History of Tuberculosis Infection and Disease**

Tuberculosis is an ancient affliction. The Greek physician Hippocrates first described it in writing as *phthisis*, or wasting illness. In reference to its great destructive capacity, it has been variously called “The Captain among these men of death”, by 17th century English preacher John Bunyan when the incidence rate of active TB disease in London was 1000 per 100,000 persons per year (Zumla et al., 2009, p. 15), and “The Great White Plague” due to the pale appearance of the afflicted (Dubos & Dubos, 1987, p. 10). The oldest known record of genetically confirmed TB is in the fossil of a North American Bison dated to approximately 18,000 years ago (Rothschild et al., 2001). Evidence of TB has been demonstrated in a 9,000 year old Neolithic settlement (Hershkovitz et al., 2008), and the skull of a 500,000-year-old *Homo erectus* fossil (Kappelman et al., 2008).
Amrith (2002) described a first ‘wave’ of TB in the early 19th century, when populations began to congregate in cities. In the early periods of this demographic shift, new economic theories and practices emerged. This resulted in a growing class of urban poor, with the majority of the world’s population not feeling the economic benefits of the industrial revolution for some time. Due to increased crowding and deteriorating sanitation, TB prevalence in London and Paris during this period is estimated to have been near 100 percent, with English mortuary registers showing the preponderance of deaths at the lower end of the socioeconomic scale (Farmer, 2000; Gandy, 2003).

As global demographic shifts continued in the early 20th century, public health infrastructure, sanitation and clean water became more widely available, and were soon correlated with a rise in living standards and a drop in the incidence of TB disease. In 1943, streptomycin was isolated and shown to be an effective agent against TB. A decade later, in 1952, isoniazid was demonstrated as an effective anti-TB agent. Finally, the rifamycin drug class was discovered in 1959 (Bush, 2010; Daniel, 2005). Pyrazinamide and ethambutol, two other key drugs, were developed around the same time, and other second-line therapies soon followed. However, the decrease in TB incidence seen at the beginning of the 20th century happened well before the discovery of the first effective anti-TB drugs, and the impact of increasing prosperity, which led to improving nutrition, decreased crowding, increased education, and increased access to health care had the greatest impact on decreased incidence (McKeown, 2005). Improved public health measures occurring around this time, such as earlier identification and isolation of active cases, may also have had important effects on TB.

---

2 It was in the midst of these drug discoveries that the WHO was founded in 1948. In that same year it declared TB a priority (WHO, 1948) due to the “high prevalence and wide distribution of the problem throughout the world”, combined with the realistic possibility of mass vaccination campaigns (Raviglione & Pio, 2002, p. 775).
prevalence. Undoubtedly the new therapies for TB saved many lives, however, and the downward trend of TB incidence continued.

As tuberculosis faded from prominence in wealthy corners of the world, it soon became a disease of the poor—those with continued low access to health services, crowding, malnutrition, education, and other social determinants of health (Lonnroth et al., 2010). This also meant that TB got minimal attention in the developed world until it reemerged in the late 1970s through 1990s. A notable case from this period is New York City’s outbreak of tuberculosis in 1979, which has been attributed to HIV and discriminatory public policies that disproportionately affected poor black communities (Wallace, 2001). This resurgence brought the specter of TB back to the attention of the developed world, and highlighted the importance of improved LTBI treatment and other TB control activities (Wallace, 2001).

**Current Epidemiology**

Groups such as the United Nations and the WHO track TB epidemiology and have published goals for TB control (Table 1). Overall incidence rates of TB disease have been falling since 2002 and the estimated absolute number of TB cases has been falling slowly since 2006. In Latin America, in particular, incidence has been declining at a much greater rate of 3.2% (WHO, 2011). Except for sub-Saharan Africa, the world is now on track to meet the Stop TB Partnership’s goals for 2015 (WHO, 2012). Despite this accelerated decline, however, it will not be fast enough to meet the Stop TB Partnership goal of eliminating TB by 2050, even in Latin America (WHO, 2011).

---

3 The Stop TB Partnership is an alliance of over 1000 government, non-governmental and other international organizations administered by the World Health Organization. The partnership was established in the year 2000 with the express goal of eliminating tuberculosis.
Table 1
Goals, Targets, and Indicators for Global Tuberculosis Control

<table>
<thead>
<tr>
<th>United Nations Millennium Development Goals</th>
<th>Stop TB Partnership Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal 6</strong>: Combat HIV/AIDS, malaria and other diseases</td>
<td><strong>Goal</strong>: To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets</td>
</tr>
<tr>
<td><strong>Target 6c</strong>: Halt and begin to reverse the incidence of malaria and other major diseases by 2015</td>
<td><strong>By 2015</strong>: Reduce prevalence and death rates by 50%, compared with their levels in 1990</td>
</tr>
<tr>
<td><strong>Indicator 6.9</strong>: Incidence, prevalence and death rates associated with TB</td>
<td><strong>By 2050</strong>: Reduce the global incidence of active TB cases to &lt;1 case per 1 million population per year</td>
</tr>
<tr>
<td><strong>Indicator 6.10</strong>: Proportion of TB cases detected and cured under DOT</td>
<td></td>
</tr>
</tbody>
</table>

Source: Stop TB Partnership, 2006; United Nations [UN], 2008

Pathogenesis of *M. tuberculosis*

In order to understand LTBI and the rationale for policy measures concerning the treatment of LTBI, it is necessary to first understand TB pathogenesis and risk factors for TB disease. By understanding increased risk for TB disease it is possible to understand which groups are in greatest need of screening for and treatment of LTBI.

The life cycle of *M. tuberculosis* in the context of TB disease has four main phases: infection, latency, disease and transmission (Figure 1). Most models of TB disease identify these phases as they relate to individuals: susceptible to infection, latent infected, infectious with active disease, and recovered (Blower et al., 1995; Murray, Oxlade, & Lin, 2011). Murray, Oxlade, and Lin (2011) further divides latency into fast latency, where individuals may rapidly progress into an active disease (infectious) state; and slow latency, where individuals are much less likely to convert to an active disease state after five years of infection. As discussed previously, the *M. tuberculosis* bacillus is most easily transmitted via droplet nuclei in the air. Additionally *M. tuberculosis* is an oxygen-loving bacterium, so it preferentially infects the lungs.
FACTORS AFFECTING LATENT TUBERCULOSIS TREATMENT

It is commonly assumed that approximately 30% of healthy individuals exposed to *M. tuberculosis* will develop latent TB infection. The data for this assumption was taken from several large studies done before treatment for LTBI was widely available and published in a recommendation by the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America [ATS/CDC/IDSA] (2000). Additionally, about 5-10% of infected individuals will progress to active disease in their lifetime depending on risk factors. 

*Some percentage of these individuals will progress to active disease quite rapidly. These individuals are typically children under the age of five, or immune compromised individuals. (American Thoracic Society, Centers for Disease Control and Prevention, Diseases Society of America, 2000)*

**Varies by risk factors:**
- 5-10% overall risk in healthy adult (Horsburgh, 2004)
- 20% in children <5 years old (Brailey, 1940; Dheda, Smit, Badri, & Pai, 2009)
- 30% in HIV + (Selwyn et al., 1989)
- 40% in children <2 years old (Brailey, 1940; Dheda, Smit, Badri, & Pai, 2009)

---

*Figure 1. Tuberculosis pathogenesis*

Modified with permission from the American College of Chest Physicians (S. K. Sharma, Mohanan, & Sharma, 2012)

- *Some percentage of these individuals will progress to active disease quite rapidly. These individuals are typically children under the age of five, or immune compromised individuals.*
- **Varies by risk factors:**
  - 5-10% overall risk in healthy adult (Horsburgh, 2004)
  - 20% in children <5 years old (Brailey, 1940; Dheda, Smit, Badri, & Pai, 2009)
  - 30% in HIV + (Selwyn et al., 1989)
  - 40% in children <2 years old (Brailey, 1940; Dheda, Smit, Badri, & Pai, 2009)
factors present (Horsburgh, 2004). The risk of progression decreases the farther away a person gets from the time of infection (Mack, Migliori, Sester, & Rieder, 2009). These assumptions have been reinforced by more recent mathematical modeling, which has contributed to contemporary WHO estimates (Dye & Williams, 2008). It takes about three years to self-cure or die from active TB, with 30% of smear positive cases self-curing and 80% of culture positive, smear negative cases self-curing (Tiemersma, van der Werf, Borgdorff, Williams, & Nagelkerke, 2011). It can therefore be assumed that a certain percentage of persons with LTBI will eliminate the infection without treatment (Styblo, 1980), but adequate studies on this aspect have not been done due to the ethics of allowing a TB infection to progress naturally. In the United States of America, an example of a very low endemic tuberculosis country, it is estimated that 80% of tuberculosis cases are due to reactivation of LTBI, and most of these cases are in foreign-born persons (ATS/CDC/IDSA, 2000; Geng et al., 2002). In order to prevent the spread of TB, the United States has a very inclusive LTBI screening and treatment policy.

**Risk Factors**

**Risk factors for tuberculosis disease.**

In 1994 the American Thoracic Society defined risk categories for progression of TB disease (Table 2) (Bass et al., 1994). Typically treatment of LTBI is recommended for the second and third categories. Out of all risk factors on an individual level, young age and HIV greatly increase risk for TB progression and for severe or disseminated disease; young age and HIV infection also form part of WHO targeted recommendations for LTBI treatment (Nelson & Wells, 2004; Swaminathan & Rekha, 2010).
Table 2

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 0</td>
<td>No history of TB exposure, negative TST</td>
</tr>
<tr>
<td>Category 1</td>
<td>There is a history of exposure but TST is negative</td>
</tr>
<tr>
<td>Category 2</td>
<td>TST +, no TB symptoms, no radiological, or bacteriological evidence of disease</td>
</tr>
<tr>
<td>Category 3</td>
<td>TB infection with signs and symptoms of disease</td>
</tr>
</tbody>
</table>

Note: TST=tuberculin skin test; TB=tuberculosis

A recent study in Kampala, Uganda estimated an attack rate\(^4\) for close contacts of persons with active tuberculosis disease in an endemic setting and without the benefit of treatment for LTBI. In the study area, 47.4% of the members of a household had LTBI, and 6.3% of those (4.6% in all persons older than five) developed active TB within the span of twenty-four months (Whalen et al., 2011). The risk in young children was significantly higher with a 10.1% risk of progression in children five and under, and 1.4% and 5.8% respectively in individuals six to fifteen and sixteen to twenty five years old (Whalen et al., 2011).

Poverty, HIV, and young age are considered the major risk factors for progression of TB disease (Boccia et al., 2009; Swaminathan & Rekha, 2010). A very recent comprehensive review has highlighted malnutrition, diabetes, HIV/AIDS, aging, and smoking as major contributors to impaired immunology in the TB context (Fox & Menzies, 2013). Another recent paper focusing on socioeconomic determinants identified and categorized similar risk factors, and listed well-studied and less well-studied risk factors (Murray et al., 2011). Most of the social factors were included in the less well-studied group (Table 3).

\(^4\) An attack rate is the cumulative incidence over a certain period of time in a population. When the population is the close contacts of a person with some communicable disease, as in this case, this number is referred to as the secondary attack rate.
Table 3
Risk Factors Contributing to Tuberculosis Infection and Disease

<table>
<thead>
<tr>
<th>Well-studied</th>
<th>Less well-studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Crowding</td>
</tr>
<tr>
<td>Smoking</td>
<td>Housing conditions</td>
</tr>
<tr>
<td>Indoor air pollution</td>
<td>Migration</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Aging</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>Economic trends</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Host genetics</td>
</tr>
<tr>
<td>Young age</td>
<td>Poverty</td>
</tr>
</tbody>
</table>

Note: HIV=human immunodeficiency virus
Source: Murray et al., 2011

Malnutrition has a detrimental effect on biological defenses against TB and increases risk of progression to active disease (Schaible & Kaufmann, 2007). When combined with other common situations in the setting of poverty, especially crowding, one can see why TB is considered a disease of poverty.

Considering children specifically, it is well established that the risk of developing active disease in those infected before two years of age is approximately 20-50% and that most of these children will develop milliary or meningeal disease (Marais et al., 2004). By the age of five, children revert to the average population risk, but by the time they are adolescents, children once again show an increased rate of progression to active disease, although in the absence of increased risk for serious extra-pulmonary manifestations (Marais et al., 2004). Other studies have also reported children under five, and, to a greater degree, children under two as groups with high risk of progression (Brailey, 1940; Dheda & Migliori, 2011).

Risk factors for latent tuberculosis infection.

Studies of LTBI have shown a high prevalence among high-exposure groups in low- and middle-income countries—79% in the Ivory Coast and 63% in Peru (Joshi, Reingold, Menzies,
& Pai, 2006). Other studies have also established the risk for LTBI associated with being a close contact (Menzies & Doherty, 2006; Morrison, Pai, & Hopewell, 2008). Risk of infection associated with being a close contact is further modified by the level of infectivity of, physical proximity to, and time in contact with the index case (Singh & Patra, 2011). In addition to being a close contact, there are some complex biochemical interactions that can put the immune compromised at greater risk of community acquired infection, and, therefore, at a proportionately higher risk for TB progression (Flynn & Chan, 2001; Gupta, Kaul, Tsolaki, Kishore, & Bhakta, 2012).

**Diagnosis of Latent Tuberculosis Infection**

Before administering LTBI treatment it is important to exclude a possible diagnosis of (active) TB disease so as not to cause drug resistance via inappropriate therapy. Active pulmonary TB has multiple diagnostic modalities. Typically, it is diagnosed with sputum smear microscopy, but a definitive positive or negative result can only be delivered via culture, which can take up to sixty days (Harries & Dye, 2006; Marais, 2008). Other tests include: a solid media color test (Toit et al., 2012), the Microscopically Observed Drug Susceptibility (MODS) test (Mendoza et al., 2011; Moore et al., 2006), and an automated PCR system called GeneXpert (Chen, Chen, Chen, Chien, & Chen, 2013). Children, however, often have paucibacillary disease, or are incapable of producing a good sputum sample, and so will often be negative on sputum smear or culture, despite having active disease. Furthermore, disease in children is often extrapulmonary, complicating early diagnosis. In Peru, the standard diagnostic tool for TB in the LTBI assessment algorithm for children (see Appendix A) is the Stegen & Toledo criteria. This criteria utilizes signs and symptoms, including a tuberculin skin test, to assign a person a score and categorize their risk of active disease (Montenegro et al., 2003).
The next step is ideally a positive diagnosis of LTBI. Unfortunately there is no gold standard for diagnosis of LTBI (Vernon, 2013). The best modalities available are the TST and the interferon gamma release assay (IGRA). Neither, however, distinguishes LTBI from active disease (Marais, 2008). Benefits of IGRA are that it is not affected by Bacille de Calmette et Guérin (BCG) vaccination and that it may more reliably differentiate a lack of reaction due to a weak immune system from a true negative. The benefit of TST is that it is much less expensive and requires little infrastructure. For this reason, TST is more easily applied in developing world contexts. Beyond the mentioned differences, both TST and IGRA can be interpreted equivalently (Trajman, Steffen, & Menzies, 2013), and most guidelines state that therapeutic decisions should always be aided by appropriate clinical judgment. Because of the complications with interpreting IGRA and TST, guidelines in Peru state that exclusion of active TB disease is the only necessary component for starting LTBI treatment (Estrategia Sanitaria Nacional de Prevencion y Control de la Tuberculosis et al., 2006).

**Biomedical Treatment of Latent Tuberculosis Infections**

Individuals who are infected with *M. tuberculosis*, but do not immediately convert to active disease represent an important reservoir for disease. Because LTBI and active TB disease are different manifestations of the same infectious agent, it was logical to borrow from the modalities of active TB disease treatment to treat LTBI, especially when considering drug resistant LTBI.

Treatment of TB has been simplified, standardized and promoted by the WHO as Directly Observed Therapy – Short Course, better known as DOTS⁵, since the early 1990s (Bayer &

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⁵ The full DOTS strategy includes five components: (1) Secure political commitment, with adequate and sustained financing, (2) Ensure early case detection, and diagnosis through quality-assured bacteriology, (3) Provide standardized treatment with supervision, and patient support (4) Ensure effective drug supply and management (5) Monitor and evaluate performance and impact
Wilkinson, 1995; Comstock, Baum, & Snider, 1979; WHO, 1999). The chemotherapeutic regimen that underlies DOTS includes four first-line drugs: isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB). Even before this standardization of TB treatment occurred, it became clear that, for LTBI, isoniazid was perhaps the most effective biomedical intervention in the fight to control and eradicate tuberculosis.

There is some confusion about the terminology utilized for the treatment of latent TB, which is done to prevent the development of active disease. The terms isoniazid preventive therapy (IPT), and tuberculosis preventive therapy (TBPT), both commonly used in the literature, imply primary prevention, but in actuality indicate secondary prevention. This is due to the fact that for latent TB infection, the person being treated to prevent active disease is already infected. In the case of non-infected persons being administered the medication, it will not prevent an infection, but may eliminate any infection that might occur in its most incipient phases. For this reason, it is preferable to use the term latent tuberculosis infection (LTBI) treatment because it states exactly what is intended with pharmacological prophylaxis, and is also more general, allowing for regimens other than isoniazid monotherapy.

The dosage of isoniazid is 5 mg/kg in children up to 300 mg/day, which is the maximum adult dose. The drug has high efficacy, is inexpensive, widely available, and has few adverse effects (Cohn & El-Sadr, 2006; Enarson, Rieder, Arnadottir, & Trébucq, 2000; Stop TB Partnership Childhood TB Subgroup, 2007). Studies amongst Canadian Yupik Eskimos in the 1970s showed that isoniazid can reduce incidence rate of TB by nearly 100%, and reported 19 years of protection after LTBI treatment (Bayer & Wilkinson, 1995; Comstock et al., 1979; WHO, 1999). Then, in the 1980s a large 30-year study in children demonstrated isoniazid’s

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6 Prevention may be primary (before infection has occurred), secondary (after infection has occurred, but before symptoms are apparent), or tertiary (after illness has occurred and in an effort to minimize morbidity and mortality).
unequivocal effectiveness in curing latent infection and preventing reactivation, even going so far as to suggest a permanent cure (Bayer & Wilkinson, 1995; Comstock et al., 1979; Franke et al., 2013; Hsu, 1984; WHO, 1999). Drug trials in Bethel, Alaska in the 1960s and 1970s provided the first strong evidence that the drug was effective for the prevention of active disease in individuals with LTBI (Comstock, 1962; Comstock et al., 1979). The Bethel isoniazid studies also shifted recommended length of treatment for LTBI from twelve months to 6-9 months. More recently combined regimens have been used including rifamycin class antibiotics, ethambutol, and pyrazinamide in various combinations. Currently the WHO recommends targeting children under five years old who are close contacts\(^7\) of individuals\(^8\) with pulmonary TB, and HIV positive individuals. In the USA and Canada all close contacts are screened for LTBI and treated if necessary.

Worldwide, most tuberculosis control programs indicate six months of LTBI treatment, as recommended by the WHO. For example, in the Western South America region, both Chile and Ecuador follow the six-month policy. The USA changed their policy to nine months in light of the Bethel isoniazid studies, which showed a small benefit of nine months over six months, and noted that longer than nine to twelve months adds marginal benefit (Comstock, 1999; Farmer & Kim, 1998). No programs recommend longer than nine months of treatment outside the context of HIV infected individuals.

Due to its effectiveness, the WHO and the International Union Against Tuberculosis and Lung Disease recommend that LTBI treatment be given to all contacts of pulmonary TB cases who are either HIV positive, or less than five years of age without active disease (Cohn & El-

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\(^7\) The term ‘close contact’ indicates a person who has spent significant amounts of time with the TB patient. In Peruvian TB policy this term is not further defined, but there is a distinction made between intra and extradomiciliary contacts, both of who are considered.

\(^8\) This individual is the index case, or the initial identified person with TB disease from whom all those secondarily affected are supposed to have acquired the infection.
Sadr, 2006; Enarson et al., 2000; Stop TB Partnership Childhood TB Subgroup, 2007). Children and HIV positive individuals not only represent a large reservoir of *M. tuberculosis* infection, but are also more susceptible to developing active disease than healthy adults (Marais et al., 2004). The WHO focuses on these groups mainly because they are relatively small, easily targeted, and high risk; therefore they are more cost effective to target than other high-risk groups.

Additionally, LTBI treatment has generally been considered cost-ineffective at the population level in low- and middle-income (and more often than not, high prevalence) countries (Dye & Floyd, 2006). In a more recent investigation, treatment for LTBI was reported to be synergistic with DOTS, and, if it is applied more broadly, may make possible the 2050 goal of TB elimination (Dye & Williams, 2008). The major limitation of studies concerning LTBI treatment in low- and middle-income countries, where the burden of disease is highest, is that there have not been very many of them, and many of their underlying assumptions are unreliable (Vernon, 2013). It is notable that, without making it a recommendation, the WHO has stated that it is desirable to treat all persons with LTBI (Stop TB Partnership Childhood TB Subgroup, 2007).

One concern with using isoniazid monotherapy to treat LTBI is the possibility of increasing drug resistance. A 2006 systematic review of 13 studies determined that the summary relative risk of developing resistance was 1.45, but the results were not significant (Balcells, Thomas, Godfrey-Faussett, & Grant, 2006). A recent review on treatment of LTBI summarizes the current expert opinion, stating that due to “limited reports of INH resistance in cases occurring after prophylaxis,” and the prevailing understanding of LTBI as a slow growing, paucibacillary infection, the probability of spontaneous mutations conferring resistance is very low (Vernon, 2013, p. 76). The main concern with regards to treatment of LTBI and resistance
is the treatment of individuals with active TB disease that is not recognized. This is especially problematic in children, due to the difficulties diagnosing active disease.

**Current recommendations.**

Typically, the recommendation in the USA is for nine months of self-administered isoniazid, or, if twelve years old or greater, twelve weekly directly observed doses of rifapentine and isoniazid (Centers for Disease Control and Prevention [CDC], 2011). In low- and middle-income countries, including Peru, six months of isoniazid monotherapy is the standard practice (Estrategia Sanitaria Nacional de Prevencion y Control de la Tuberculosis et al., 2006).

**Alternative regimens.**

Various shortened and combined regimens to treat LTBI have been studied (LoBue & Menzies, 2010; Martinson et al., 2011; van Zyl et al., 2006). One of the most commonly cited is a once weekly isoniazid/rifampicin combination administered for three months (Balcells et al., 2006; Bright-Thomas, Nandwani, Smith, Morris, & Ormerod, 2010). Additionally, intermittent directly observed twice weekly treatment with either isoniazid or a rifamycin group agent, has been tried with high adherence rates (Cruz & Starke, 2013; Vernon, 2013). A twelve-dose once weekly directly observed regimen with rifapentine and isoniazid combined was also shown to be highly effective (100% adherence in trial group) (LoBue & Menzies, 2010; Martinson et al., 2011; Sterling et al., 2011; van Zyl et al., 2006). Officially, in the USA and Canada, rifamycin group agent monotherapy for four months is considered an acceptable alternative treatment, while a combination isoniazid/rifampicin regimen is acceptable in the United Kingdom (Leung, Rieder, Lange, & Yew, 2011).
Treatment of close contacts of mono-resistant, MDR and XDR TB cases.

Early on clinicians noticed that *M. tuberculosis* would develop resistance to streptomycin therapy, a problem which continued with the development of new drugs (Keshavjee & Farmer, 2013). The problem was exacerbated by incomplete treatment⁹ and continued to expand until the end of the 20th century, when multiple-drug resistant (MDR) TB¹⁰ was recognized as a real threat arising from improperly administered TB therapy. This was thanks in part to the MDR TB outbreaks in the USA of the late 1980s and early 1990s (CDC, 2010). The CDC and the WHO reported extensively drug resistant (XDR) TB¹¹ as a threat in March of 2006.

Common sense would dictate that LTBI contracted from an MDR or XDR TB patient would also be resistant to at least isoniazid and rifampin. Unfortunately, to date no acceptable study has confirmed this, or determined what a suitable treatment might be. In general, recommendations for MDR LTBI are to monitor clinically, and possibly treat high-risk contacts with combined regimens containing agents active against the resistant strain (CDC/ATS/IDSA, 2000). In the 2000 revision of the joint CDC, American Thoracic Society, and Infectious Diseases Society of America guidelines, a two-month combined regimen of rifampin and pyrazinamide, or a four-month regimen of rifampin was recommended for treatment of a suspected isoniazid mono-resistant LTBI (CDC/ATS/IDSA, 2000).

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⁹ DOTS is the five component WHO recommended TB treatment strategy. Initially it was focused on treating drug susceptible TB only, and was often misapplied, and has therefore been implicated in the rise of MDR TB. For more details see pathogenesis section below and Smith Nonini’s excellent account of MDR TB in Peru (Smith-Nonini, 2005).

¹⁰ MDR TB is TB that is resistant to at least isoniazid and rifampicin, the two most powerful first line drugs used to treat the disease. For more information see the excellent chapter on the subject in *Challenges in Infectious Diseases* by Ignatius Fong (Fong, 2013).

¹¹ XDR TB is TB that is resistant to isoniazid, rifampicin, at least one member of the quinolone family and at least one of the following second-line drugs: amikacin, kanamycin, or capreomycin (World Health Organization [WHO], 2007).
Latent Tuberculosis Infection Treatment Uptake and Adherence

There is still much discussion over the cost effectiveness of LTBI treatment, and few low- and middle-income countries have followed Peru’s lead in broadening the target population. A reason cited for not expanding use of LTBI therapy is low uptake and adherence, which has been demonstrated globally, and which further decreases cost-effectiveness. It can be seen that higher-income countries with lower prevalence of LTBI generally have higher adherence rates, but even in the best of cases, rates often are not above 50%.

South Africa.

Van Zyl et al. (2006) found low completion rates in children who were close contacts of individuals with pulmonary TB in South Africa, showing that completion of a six month isoniazid regimen was only 28%, compared to 67% completion of a three month regimen of combined isoniazid and rifampicin. In a similar study in Cape Town, South Africa, Marais et al. (2006) found that only 20% of children completed at least five months of isoniazid monotherapy for LTBI. A mixed methods study of LTBI treatment for HIV positive patients in South Africa demonstrated that 47% of patients starting a six-month course of LTBI treatment completed it (Rowe et al., 2005).

Eastern Africa.

In 2006, a study of TB patients in Malawi evaluated attendance at a hospital-based screening service for child contacts. Only 7.7% of 1438 adult source cases brought their child contacts to the clinic, and uptake was significantly lower for male (4.5%) vs. female (12%) patients (Nyirenda, Sinfield, Haves, Molyneux, & Graham, 2006). A study comparing passive and active LTBI case finding in Malawi in 2003, found that uptake of treatment was 17% and
22% respectively, with economics being cited as the main reason for not starting (Zachariah et al., 2003).

**Pacific Islands.**

A study in Indonesia showed overall good adherence rates (greater than or equal to four months of isoniazid) for only 25.6% (95% CI 16.6–36.4) (Rutherford et al., 2012).

**Middle East.**

A recent study in Iran demonstrated very high completion rates in children less than six years old (87% uptake and 100% completion), but had a very low sample size (n=15) (Aminzadeh & Asl, 2011). In a very large study of child contacts in Israel, only 28% of eligible contacts started treatment, and only 16% finished (Bibi et al., 2002).

**USA.**

In a US study from 2002, 89% of persons recommended to start treatment did, and 51% completed six months of treatment; however, 20% of those treated underwent directly observed therapy, which may have skewed the results considering that directly observed treatment for LTBI is not standard practice (Reichler et al., 2002). In a large study in New York City from 2002-2004, a total of 15,035 patients started and 6788 (45.2%) completed treatment for LTBI (Li, Munsiff, Tarantino, & Dorsinville, 2010). A large systematic review of LTBI treatment adherence in the USA and Canada, published in 2008, showed adherence rates ranging from 19% to 96% but noted that overall adherence in high risk groups was low (Hirsch-Moverman, Daftary, Franks, & Colson, 2008).

**South America.**

A study in Lima, Peru highlighted variable adherence rates depending on whether WHO definitions (i.e. missed doses are acceptable), or the research site’s more stringent
recommendations were used: 53% and 19% respectively (Salazar-López, Arévalo-Abanto, & Ticona-Chávez, 2010). Published abstracts of results from Callao, Peru have shown very low completion rates of 12% and 22% in two different studies (Iberico et al., 2011a; Iberico et al., 2011b).

Risk Factors for Non-Adherence to LTBI Treatment

The majority of research on risk factors has been completed in the USA and Canada. Some studies have also been completed in high HIV and TB incidence areas such as Brazil and South Africa. Only one applicable study was found in Peru. This may have been due to limitations in indexing of Latin American journals, but more likely reflects a limited quantity of research having been done on the subject. Additionally, most studies are retrospective.

Age.

The only significant factor associated with low adherence in a Peruvian study at the national hospital Dos de Mayo was age; patients over forty years of age had lower adherence to treatment (Salazar-López et al., 2010). Another study in New York City showed decreased adherence in adults older than thirty-five (Li et al., 2010). A study specifically targeting Latino adolescents in San Diego showed worse adherence in older adolescents, with age analyzed as a continuous independent variable in the range of twelve to nineteen years (Hovell et al., 2003b). A study in Brazil showed no significant relationship between any age group and adherence (Machado et al., 2009). One paper noted that studies on age and its relationship to LTBI treatment adherence have shown variable results, and there is ambiguity about what age means (Goswami et al., 2012). A large retrospective survey of LTBI treatment in the USA and Canada showed age greater than fifteen to be significantly associated with failure to complete treatment (Horsburgh et al., 2010).
**Gender.**

In most reviewed studies gender was not significantly related to uptake, or completion of treatment (Rutherford et al., 2012; Salazar-López et al., 2010; Sebastian & Bothamley, 2000; Trajman et al., 2010). A prospective study in the late 1990s in Indonesia did show females to be three times as likely to be highly adherent to treatment for LTBI (Ngamvithayapong, Uthaivoravit, Yanai, Akarasewi, & Sawanpanyalert, 1997).

**Ethnicity/race/place of origin.**

A large multicenter study of risk factors for completion of LTBI treatment in Canada, Saudi Arabia and Brazil showed that patients in Brazil had overall lower completion rates. The authors are undertaking studies on health beliefs, culture, and socioeconomic factors to further explore this finding (Trajman et al., 2010). Studies in the USA, have consistently shown that non-US born persons have higher completion rates (LoBue & Moser, 2003; Parsyan, Saakkonen, Barry, Sharnprapai, & Horsburgh, 2007).

**Costs/poverty.**

A study in Indonesia identified high transport costs and medication costs as significantly associated with poor adherence (Rutherford et al., 2012). A study in Brazil showed that close contacts needing to take more than one bus to the health center were much less likely to complete treatment, and that bus fares represented a significant cost to the low-income families involved in the study (Machado et al., 2009). A lower education level has been associated with decreased adherence in Hispanics in the United States (Zuñiga, 2012). Unstable housing is another related factor (Hirsch-Moverman et al., 2008). The quantitative portion of a mixed methods study of children taking LTBI treatment in Indonesia reported that, from an extensive list of possible risk factors, only cost of transportation and cost of medications had a significant
correlation with low adherence rates (Rutherford et al., 2012). The qualitative portion of the same study demonstrated a preponderance of cost-related themes related to adherence (Rutherford et al., 2012).

**Index case related factors.**

A study in southeast Asia found that TB patient index cases with high perceived susceptibility to TB disease were three times as likely to bring in their close contacts aged less than fifteen in for evaluation, but found no significant relationship to age, education, socioeconomic status, or relationship to index case (Tornee et al., 2005). Additionally, TB patients with high stated intention and who resided near the health center were more likely to bring their close contacts in for evaluation (Tornee et al., 2005). These data are important because screening is the first step towards uptake of LTBI treatment.

**Duration of treatment.**

Generally, shorter regimens and directly observed treatment regimens have high completion rates. The Trajan et al. (2010) multicenter study of risk factors considered a shorter regimen the strongest indicator for completion.

**Other factors.**

The Trajman et al. 2010 study also found that “early adherence, measured by regularity of treatment and percentage of doses taken, was predictive of final completion of treatment” (p. 557). Side effects of medication used in LTBI treatment was cited as a significant determinant of non-completion in a study in Brazil (Machado et al., 2009). A study of Latino adolescents in San Diego considered engagement in risky behavior as a negative predictor of adherence (Hovell, et al., 2003a). In a study of risk factors in primarily foreign born persons (19% African, 20% Latin American) with LTBI living in the USA, factors positively correlated to completion
included being a close contact to an infectious TB case (RR 2.5), and having regular primary care (RR 1.4) (Goswami et al., 2012). Goswami et al. (2012) also categorized people with LTBI into risk categories and demonstrated that higher risk for progression of TB disease was correlated with a higher likelihood of treatment uptake, but not completion.

Operational factors have also been cited in the literature. One study in HIV positive individuals in South Africa highlighted that misunderstanding of how to diagnose LTBI and the importance of treating LTBI contributed to an uptake of zero because no patients were even aware that LTBI treatment was an option (Lester et al., 2010).

**Tuberculosis Infection and Disease in Urban Peru**

**Demographics and geography.**

Peru is a developing country with one of the strongest economic growth rates in South America, ranking third in terms of real GDP growth rate. The World Bank (n.d.) rates Peru as an upper middle-income country and reported the GNI per capita in Peru was 4,710 USD in 2010, increasing to 5,150 USD in 2011. Despite a strong economy, the country continues to have high rates of rural poverty and disparities between poor and rich in more developed urban settings such as the capital city of Lima. In 2010, 12.7% of the population lived on less than 2 international dollars per day, adjusted for purchasing power parity (PPP), and approximately 30% lived below the official poverty line (World Bank, n.d.) (Table 4).

The 2007 Peruvian census placed the national population at 28.5 million people (Instituto Nacional de Estadística e Informatica [INEI], n.d.) and a later document, by the Dirección Tecnica de Demografía e Indicadores Sociales of the INEI of Peru, in conjunction with the United Nations (UN), estimated that in 2012 the population would have grown to 30.1 million people (2009) (Table 4).
Table 4

Social Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2007 (last census)</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population, Peru *</td>
<td>28,481,901</td>
<td>30,135,875 ††</td>
</tr>
<tr>
<td>Population in Lima Metropolitan Area *</td>
<td>8,482,619</td>
<td>10,364,319 ††</td>
</tr>
<tr>
<td>Population in Ventanilla *</td>
<td>280,511</td>
<td>370,517 ††</td>
</tr>
<tr>
<td>Uninsured (public or private) in Peru **</td>
<td>15,813,459 (56%)</td>
<td>-</td>
</tr>
<tr>
<td>Uninsured in Ventanilla (2007) **</td>
<td>167,101 (60%)</td>
<td>-</td>
</tr>
<tr>
<td>Average life expectancy, national **</td>
<td>69</td>
<td>-</td>
</tr>
<tr>
<td>Infant mortality rate, national</td>
<td>31/1,000 live births **</td>
<td>14/1,000 live births ††</td>
</tr>
<tr>
<td>Gross national index per capita, PPP †</td>
<td>$7,160</td>
<td>$9,440 ††</td>
</tr>
<tr>
<td>Population under national poverty line†</td>
<td>42.4%</td>
<td>27.8% ††</td>
</tr>
<tr>
<td>Tuberculosis incidence, national **</td>
<td>108/100,000</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: Chart modified from Shin et al., 2008; PPP=purchasing power parity
*(Instituto Nacional de Estadistica e Informatica [INEI], 2009)
**(Instituto Nacional de Estadistica e Informatica, n.d.)
† World Bank, n.d.
†† 2011 World Bank projection

Geographically, Peru is comprised of 25 administrative regions, each of which contains various provinces divided into districts. Lima, the capital city, comprises a district in the province of Lima. Despite this geographical distinction, politically the city of Lima is considered to comprise the entire province of Lima, which functions autonomously from the larger Lima regional government due to its status as national capital. Additionally, the province of Lima completely surrounds the costal region of Callao, which is made up entirely of the Constitutional Province of Callao and considered part of the Lima greater metropolitan area. The Lima metropolitan area is a densely populated area with about 30% of the country’s population, while the city of Lima occupies less than 0.5% of the total land area of the country (INEI, n.d.).

Ventanilla (see Appendix C for images) is the largest human ‘asentamiento,’ or squatter settlement, in Peru with an INEI estimated population of about 0.4 million people in 2012 (Table
4). Ventanilla is comprised of Peruvians who have migrated from the mountains (*sierra*) and the jungle (*selva*) and other poor rural areas looking for a better life in Lima. Its population features a mix of income levels, but the majority of its inhabitants are below the national poverty line. About 5% of the population of Ventanilla lives in improvised shacks or is squatting on land that is not meant for human settlement. About 93% live in sturdier independent dwellings, often made of recycled wood walls with corrugated roofs, and another 2% of the population live in more permanent apartment buildings (e.g. cement or cinder block), connected housing, or other accommodations (INEI, n.d.) (Figure 2).

![Figure 2. Housing type in Ventanilla in 2007 (INEI, n.d.)](image)

**Tuberculosis control program.**

The Peruvian ministry of health operates sixteen TB program offices, which diagnose and manage care for affected individuals and families in the district of Ventanilla. Officially, the sixteen offices are part of the Ventanilla health network. Fifteen are housed in Ministry of
Health centers and one is in a hospital, which is an independent collaborator with the Ministry of Health.

All centers rely primarily on passive case finding. The Ministry of Health uses public health education campaigns, a web site, public service announcements and posters in the health centers and hospital to encourage all individuals experiencing more than two weeks of coughing to go to the health center and submit sputum samples for smear microscopy. If diagnosed with TB, patients are asked to list their close contacts irrespective of whether they live in the same house.

The TB control program in Peru is called The National Sanitary Strategy for the Prevention and Control of Tuberculosis, or Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis (ESN-PCT). In the 1990s the WHO considered Peru’s program a model program for DOTS because of high treatment rates and early adoption. The Peruvian strategy is more inclusive than other plans in the region, such as Chile and Ecuador, and its consideration of social determinants is unmatched. Since 1991, the Ministry of Health has indicated that contacts younger than fifteen should be evaluated for active TB and, in its absence, be administered six months of LTBI treatment. In April 2006, the policy was updated to include contacts up to nineteen years old (Estrategia Sanitaria Nacional de Prevencion y Control de la Tuberculosis et al., 2006). Additionally, contacts are advised to seek consultation if they experience cough of more than two weeks, and/or fever and night sweats. The policy also gives physicians wide latitude in decision making, and allows administration of LTBI outside of the recommendations for a series of conditions that may make an adult immune compromised (Estrategia Sanitaria Nacional de Prevencion y Control de la Tuberculosis et al., 2006). These elements make it the most inclusive LTBI treatment strategy in South America.
Latent tuberculosis infection control.

Despite the existence of a model TB program that goes beyond international guidelines, there is low uptake of, and adherence to, LTBI treatment in Peru. The Peruvian government indicates in their national tuberculosis program policy that LTBI treatment should be given to all contacts less than twenty years old who do not have active TB (Estrategia Sanitaria Nacional de Prevencion y Control de la Tuberculosis et al., 2006). Before isoniazid is prescribed, however, contacts must complete medical assessments. This requires questioning by health center nurse, identification by index case, and several health center visits, which are free for those with social security, but may involve costs for the uninsured and always involve indirect costs such as transport. All these may be barriers for poor families (See Appendix A for flow-chart of process).

The ISIAT project (Rocha et al., 2011) studied the equity of adherence between Peruvian families with income in the bottom quartile and families with income in the top quartile of their sample population, and showed that despite the increased equity and increased completion, the rates of completion were still very low across the board (Iberico et al., 2011a).

The importance of LTBI treatment, coupled with the poor levels of uptake and completion globally and in Peru, prompted this study’s examination of factors affecting uptake and completion, derived from information contained in index case treatment cards.

Other than the studies done by the ISIAT group, little to no research has been done on factors affecting uptake of, and adherence to, LTBI treatment in Peru. Globally there has been some research, but only a small amount of it has been done on LTBI treatment for HIV negative individuals.
Description of Innovative Socio-economic Interventions Against Tuberculosis

In 2007 a research project began in Ventanilla, a district of the Peruvian city Callao (Figure 3) to investigate the impact of socioeconomic interventions on TB control. The project was called: *Innovative Socio-economic Interventions Against Tuberculosis* (ISIAT). The research team for ISIAT works in conjunction with Innovation for Health and Development (IFHAD, a British non-governmental organization (NGO)), PRISMA (a Peruvian NGO), and the Peruvian Ministry of Health.

![Figure 3. Map of Lima and Callao](http://en.wikipedia.org/wiki/Callao_District)

Despite a focused biomedical approach to controlling TB via DOTS, recurrence and transmission of the disease continues in the shantytowns where the research is occurring to a greater degree than in the country as a whole (Figure 4). As a response, the ISIAT project takes a three-pronged biosocial approach to controlling TB: rights (education & advocacy), social
interventions (microcredit, training, and microenterprise activities), and biomedical interventions (development and implementation of appropriate sustainable diagnostics). Social interventions target poverty, while the rights approach leads to improved TB care via improved case-finding, prophylactic treatment of close contacts, and better adherence to treatment. The social aspects of ISIAT make it unique. This biosocial approach has already shown promising results in leading to an increase of pediatric TB diagnosis (Rocha et al., 2011).

Figure 4. Tuberculosis incidence per 100,000 people in Peru
Peru starts DOTS in 1990 and achieves increased case finding in 1991. ISIAT begins in 2007. Peru data is from the Instituto Nacional de Estadística e Información (INEI). Ventanilla data is from an unpublished dataset incorporating INEI census data.

The ISIAT study has so far been described in one operational assessment done in 2011 (Rocha et al., 2011). The study was designed to evaluate a group of socio-economic interventions for the impact they might have on strengthening TB control. Specifically, the study aimed to measure uptake of TB care and prevention services, as defined in Peruvian health
policy, in interventions and monitoring (control) groups made up of randomly allocated health centers. The TB care and prevention services included LTBI treatment. Before beginning the intervention, the ISIAT team identified barriers to TB control by interviewing TB-affected families using both quantitative and qualitative methodology (Onifade et al., 2010). Data from previous studies utilizing randomly selected population control households, which had been collected starting in 2003, were also used. Based on these findings, knowledge of the literature, and contextual knowledge, the ISIAT team then offered four categories of activities to reduce these barriers: (1) household visits (health knowledge and gender rights) (2) community workshops (community mobilization and advocacy), (3) psychosocial support (community mobilization, advocacy, recruitment, and continued participation), (4) microenterprise, microcredit, vocational training, food transfers, and cash transfers (poverty mitigation and income generation). Categories one through three were intended to affect health seeking, time to diagnosis, contact screening, treatment uptake (TB and LTBI), treatment completion (TB and LTBI), sustained cure, and prevention behaviors. Category four was intended to directly combat poverty, with the aim of indirectly affecting poverty-associated risk factors. These factors included housing quality, crowding, and nutrition; all of which can affect the spread of LTBI and incidence of TB disease. This last category included vocational training in animal husbandry and other productive activities, loans for startup costs of a business, and food and cash transfers tied to TB control goals, such as attending DOTS.

Built in to all of the interventions were ‘crosscutting outputs,’ i.e. outputs that were designed to affect both poverty (i.e. fundamental determinants of health) and health promotion, in a more traditional public health sense. The main interventions falling under this definition
were: (a) empowerment (mostly category 2, as discussed above, as well as daily encouragement and facilitation of any empowerment activities undertaken by TB affected families), (b) advocacy (research team members actively attempting to influence health care policies), and (c) equity (purposeful targeting of the poorest and most vulnerable members of the intervention group).

The monitoring group received the standard of care provided by the health system as well as some educational benefit from the visit of ISIAT team members in an initial interview when the index case was identified. Due to ethical concerns, community workers were not given any specific indications on withholding information on TB treatment, LTBI treatment, and/or health rights, or from helping families find requested information.

Methods

For this study of LTBI treatment in Ventanilla, a quantitative descriptive analysis of TB treatment data was conducted. The purpose of this study was to identify factors that were associated with high or low adherence with LTBI treatment by children and adolescents.

Study Cohort

The cohort in this study was identified through health center registries of TB-affected families in the health network of Ventanilla, Peru. Most index cases were discovered via passive case finding, some were found in active case finding campaigns by the TB program, or through contact evaluation. Aggregate data were available for all child contacts listed on a TB patient’s treatment card (see Appendix B for example) by age group. The data were de-aggregated using Stata®11 (StataCorp, LP, College Station, TX, USA), which involved creating new rows of data representing individual contacts registered on the index case treatment card. All data in new rows were duplicated from the household, or index case data, except the data on LTBI treatment.
Dummy variables were created indicating age range and number of months of treatment completed for each contact listed. Three and four weeks of treatment dispensed were considered one month of LTBI treatment for the purposes of this study.

The unit of analysis was individual contacts. Inclusion criteria were treatment cards of TB cases indicating TB treatment between June 1st 2006 and Dec 31st 2010 in one of 16 catchment areas in Ventanilla. Cases could not be MDR and had to have at least one registered contact younger than twenty years old. This date range was chosen because the TB control policy changed in April 2006 to include adolescents from the ages of fifteen to nineteen in the LTBI treatment recommendations. This gave a leeway of three months for health centers to adopt the new policy. December 2010 was the last date for which the dataset contained reliable information. The data had been previously collected for an ongoing project dating back to 2002 by the NGOs: Innovations For Health And Development (IFHAD) and Asociación Benéfica Prism (PRISMA) in conjunction with the Universidad Peruana Cayetano Heredia (UPCH). IRB approval was obtained through Wright State University (Appendix D).

Data Collection

For this study TB patients were referred to as index cases. All contacts identified by the index case at time of registration at the health center, and/or at time of domiciliary visit by health center staff, were called close contacts. If a household had more than one case of TB disease, the first case was denoted the index case and subsequent cases were considered secondary cases. For the purposes of this paper, all cases of TB disease with contacts were considered index cases, unless otherwise noted (see methods section for more explanation).

LTBI treatment prescription records were generated prospectively at the point of patient care by health center staff, at the time of patient registration. Records were de-identified and
digitized prospectively by the IFHAD research team as they were generated, and previous to this author’s arrival. The research team also prospectively visited all the households and enrolled them in the IFHAD study in order to register demographic information, socioeconomic information and other variables for ongoing studies. Specific variables used for this study from the treatment card were: date of first pill of TB treatment taken by the index patient, number of contacts listed on the treatment card by age grouping (0-14 and 15-19), number of contacts completing each month of treatment by age grouping, and status of treated patient (completed treatment, cured, abandoned treatment, etc.). This information was analyzed with ISIAT study variables: date intervened in IFHAD study, study group (monitoring or intervention), monthly income of household, census of contacts, level of education of patient, patient drug use, time household had been living in Ventanilla and geographic place of birth (sierra, jungle, Lima, or the coast other than Lima). Contacts who were lost to follow up during treatment were reclassified as having abandoned treatment, and the number of weeks of LTBI treatment dispensed were recorded and included in the analysis.

**Variable Selection**

Due to the enormity of data present on the TB treatment cards and household surveys, and the limited scope of the research questions being addressed, key variables were chosen for analysis. These variables best aligned with previously studied adherence factors, and with the research team’s understanding of the context of Ventanilla and LTBI treatment (See Table 5).
Table 5

<table>
<thead>
<tr>
<th>Variable</th>
<th>Operational Definition</th>
<th>Range of Possible Scores/Coding</th>
<th>Type of Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Contact characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range</td>
<td>Contact’s age range as present in de-identified dataset</td>
<td>0-15 = 0, 16-21 = 1</td>
<td>categorical</td>
</tr>
<tr>
<td>Is a close contact of a secondary case</td>
<td>Whether individual is a close contact of an index case in a household or a secondary case</td>
<td>yes = 1, no = 0</td>
<td>categorical</td>
</tr>
<tr>
<td>Experimental group</td>
<td>Whether individual was registered on a card from an intervened or a monitoring household</td>
<td>monitoring = 1, intervention = 0</td>
<td>categorical</td>
</tr>
<tr>
<td><strong>Index case characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education completed high school</td>
<td>Whether, or not index case had completed high school, if appropriate.</td>
<td>yes = 1, no = 0</td>
<td>categorical</td>
</tr>
<tr>
<td>Place of birth</td>
<td>Place of birth</td>
<td></td>
<td>categorical</td>
</tr>
<tr>
<td>Drug use</td>
<td>Any illicit drug use by index case</td>
<td>yes = 1, no = 0</td>
<td>categorical</td>
</tr>
<tr>
<td>Abandoned DOTS</td>
<td>Treatment card abandoned status vs. finished, or cured</td>
<td>yes = 1, no = 0</td>
<td>categorical</td>
</tr>
<tr>
<td>Time lived in Lima</td>
<td>Time lived in Lima Metropolitan Area necessary to be well settled</td>
<td>&lt;2 years = 1, ≥2 years = 0</td>
<td>categorical</td>
</tr>
<tr>
<td><strong>Poverty proxies/household characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crowding</td>
<td>≥75th percentile crowding, which was nine persons</td>
<td>crowded = 1, less crowded = 0</td>
<td>categorical</td>
</tr>
<tr>
<td>Income per person</td>
<td>Two income groups were defined using below the median as lower-income group</td>
<td>lower-income = 1, higher-income = 0</td>
<td>categorical</td>
</tr>
<tr>
<td><strong>Dependent variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTBI treatment uptake</td>
<td>Whether or not contact was dispensed any LTBI treatment doses</td>
<td>&lt;2 weeks = 1, ≥2 weeks = 0</td>
<td>categorical</td>
</tr>
<tr>
<td>LTBI treatment adherence</td>
<td>Whether or not there was poor adherence to LTBI treatment or good adherence</td>
<td>&lt;22 weeks = 1, ≥22 weeks = 0</td>
<td>categorical</td>
</tr>
</tbody>
</table>
Analyses

The research questions considered in this study concerned factors contributing to LTBI treatment uptake and adherence and whether or not ISIAT improved uptake and adherence of LTBI treatment.

Two separate analyses were done. First, a descriptive analysis utilized treatment card data linked to households in the ISIAT monitoring group. This analysis examined uptake and completion of LTBI treatment to answer the first research question. The second analysis compared uptake and completion of LTBI treatment between the interventions and monitoring groups of ISIAT in order to answer the second research question. An additional sub-analysis of LTBI uptake and adherence among contacts of secondary cases enrolled in this cluster randomized controlled trial was part of this second analysis.

Data were analyzed in Stata®. Treatment card data were merged with IFHAD study data using unique identifiers for each household and treatment card. Aggregate data for LTBI treatment adherence were then expanded, based on the number of contacts listed on the card by age group. This enabled the unit of analysis to be individuals clustered in households. Simple 2 x 2 tables were made for all binomial variables, and relative risks were calculated. Dichotomous variables were created from continuous variables using the median as an arbitrary cutoff rate, except in some special instances where the literature suggested different cutoff points, which are discussed in more detail below. Significance was evaluated with Fisher’s exact test. The alpha level was 0.05, and p-values from 2-tailed tests less than or equal to this value were considered to be unlikely to be explained by chance.

In order to simplify the analysis, several variables were converted from continuous or categorical to binomial. Income per person was used as the primary socioeconomic indicator
and was defined by median income. For crowding, 75th percentile (9 persons in a household) and above was used as the cutoff point, as this has been shown to be a more strongly associated with TB disease than using the median as a cutoff point (Boccia et al., 2009). Length of residence in the Lima metro area was used as an indicator of how established a household was likely to be within their community, and was also included with the idea that more established households would have more community support and more knowledge about services available. The median time (seven years) seemed to be too high to differentiate established households vs. less established households; therefore a more intuitive cutoff of two years was arbitrarily selected and used in all analyses. Income was converted to US dollars using an exchange rate of 2.85 PEN\textsuperscript{12} = 1 USD.

For all analyses, two dependent variables were considered: LTBI treatment uptake and good adherence. Medication for contacts was dispensed weekly to index cases during DOTS. The LTBI treatment data were originally recorded in a weekly format by health center staff on the treatment cards; in the ISIAT database, however, the data were reported in a monthly format, where a month was defined as two or more weeks of treatment. Thus one week of treatment was counted as zero months, two to five weeks were counted as one month, six to nine weeks as two months, and so on. Practically this meant that, for this study, uptake was defined as treatment dispensed to a child contact for at least two weeks, and good adherence was defined as 22 or more weeks of treatment dispensed.

**Results**

For the study period, there were 2427 index and secondary TB patient cases in the IFHAD database. Of these, 110 had missing treatment cards, 170 received MDR-TB treatment, 12 PEN = Peruvian Nuevo Sol, the unit of currency in Peru.
and 642 had no contacts younger than 20 years old so were excluded. The remaining 1505 treatment cards were utilized in this study.

**Descriptive Results for the Entire Study Population**

There were 1267 treatment cards including 3226 contacts in the monitoring group in the ISIAT study. There were 238 treatment cards including 617 contacts in the interventions group. Participants in the monitoring and interventions groups had similar baseline characteristics for the independent variables studied (See Table 6).

**Descriptive Results for the Monitoring (Control) Group**

This section presents analysis of the data for the monitoring group only; this was done so as to eliminate any effect the intervention may have had on the population. Of the close contacts, 1102 (34.2%, 95% CI [32.5, 35.8]) initiated treatment for LTBI and 378 (11.7%, 95%CI [10.6, 12.8]) had good adherence. Most of the close contacts (77.5%) were older than fourteen years old. The median per capita income was equivalent to 1.12 USD (inter-quartile range 1.90 to 4.94) per day and assuming 30 days to a month. The median number of household residents was 7 (inter-quartile range 5 to 9). The proportion of contacts residing in lower-income houses (below the median) was 48.7%, and the proportion of contacts residing in crowded houses (25th percentile) was 29.7%. Close contacts of secondary cases were the minority at 7.5% of all contacts.
Table 6

Descriptive Variables by Monitoring and Intervention Groups

<table>
<thead>
<tr>
<th>Characteristic Variables</th>
<th>Monitoring n (%)</th>
<th>Intervened n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEPENDENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>2500 (77.5)</td>
<td>481 (78)</td>
<td>2981 (77.6)</td>
</tr>
<tr>
<td>0-14</td>
<td>726 (22.5)</td>
<td>136 (22)</td>
<td>862 (22.4)</td>
</tr>
<tr>
<td>Lower-income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>1222 (48.7)</td>
<td>312 (52.4)</td>
<td>1534 (49.4)</td>
</tr>
<tr>
<td>no</td>
<td>1287 (51.3)</td>
<td>283 (47.6)</td>
<td>1570 (50.6)</td>
</tr>
<tr>
<td>Crowded</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>2267 (70.3)</td>
<td>404 (65.5)</td>
<td>2671 (69.5)</td>
</tr>
<tr>
<td>yes</td>
<td>959 (29.7)</td>
<td>213 (34.5)</td>
<td>1172 (30.5)</td>
</tr>
<tr>
<td>Education past high school</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>1466 (55.9)</td>
<td>351 (58.4)</td>
<td>1817 (69.1)</td>
</tr>
<tr>
<td>yes</td>
<td>1156 (44.1)</td>
<td>250 (41.6)</td>
<td>1406 (30.9)</td>
</tr>
<tr>
<td>Index case place of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventanilla</td>
<td>120 (5.8)</td>
<td>27 (4.5)</td>
<td>147 (5.5)</td>
</tr>
<tr>
<td>Other Lima Metro Area</td>
<td>899 (43.7)</td>
<td>229 (38.5)</td>
<td>1128 (42.6)</td>
</tr>
<tr>
<td>Coast</td>
<td>268 (13.0)</td>
<td>77 (12.9)</td>
<td>345 (13.0)</td>
</tr>
<tr>
<td>Central</td>
<td>597 (29.1)</td>
<td>167 (28.1)</td>
<td>764 (28.8)</td>
</tr>
<tr>
<td>Jungle</td>
<td>171 (8.3)</td>
<td>95 (16.0)</td>
<td>266 (10.0)</td>
</tr>
<tr>
<td>Index case drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>196 (6.1)</td>
<td>31 (5.0)</td>
<td>227 (5.9)</td>
</tr>
<tr>
<td>No</td>
<td>3030 (93.9)</td>
<td>586 (95)</td>
<td>3616 (94.1)</td>
</tr>
<tr>
<td>Index case abandoned DOTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>379 (14.3)</td>
<td>53 (11.3)</td>
<td>432 (13.9)</td>
</tr>
<tr>
<td>No</td>
<td>2272 (85.7)</td>
<td>414 (88.7)</td>
<td>2686 (86.1)</td>
</tr>
<tr>
<td>Index case time in Lima</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>737 (36.4)</td>
<td>224 (38.1)</td>
<td>961 (36.8)</td>
</tr>
<tr>
<td>≥2 years</td>
<td>1289 (63.6)</td>
<td>364 (61.9)</td>
<td>1653 (63.2)</td>
</tr>
<tr>
<td>Is close contact of a secondary case</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>229 (7.5)</td>
<td>26 (4.5)</td>
<td>255 (7.0)</td>
</tr>
<tr>
<td>no</td>
<td>2833 (92.5)</td>
<td>558 (95.5)</td>
<td>3391 (93.0)</td>
</tr>
<tr>
<td><strong>DEPENDENT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTBI treatment uptake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 weeks</td>
<td>2124 (65.84)</td>
<td>251 (40.68)</td>
<td>2375 (61.8)</td>
</tr>
<tr>
<td>≥2 weeks</td>
<td>1102 (34.16)</td>
<td>366 (59.32)</td>
<td>1468 (38.2)</td>
</tr>
<tr>
<td>Adherence to LTBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22 weeks</td>
<td>2848 (88.3)</td>
<td>426 (69.0)</td>
<td>3274 (85.2)</td>
</tr>
<tr>
<td>≥22 weeks</td>
<td>378 (11.7)</td>
<td>191 (31.0)</td>
<td>569 (14.8)</td>
</tr>
</tbody>
</table>
Considering index case factors, 44.1% were educated at least to the high school, or appropriate level. Although 49.5% had been born in Lima Metropolitan Area, only 5.8% had been born in Ventanilla. Sixty three percent of index cases had resided in Lima for more than two years. Among index cases, 6.1% admitted to having used some illicit substance in the past, and 14.3% were noted to have abandoned their course of DOTS before completion.

**Risk Factor Analysis for the Monitoring (Control) Group**

**Uptake.**

Fisher tests for non-uptake of LTBI treatment (Table 7) showed that close contacts in the fifteen-to-nineteen year old age group were more likely to fail to initiate treatment (RR 1.29, 95% CI [1.23, 1.35], p<0.001). Close contacts living in a lower-income household (RR 1.06, 95% CI [1.00, 1.13], p=0.05), or in a crowded household (RR 1.10, 95% CI [1.04, 1.16], p=0.003) were slightly more likely to fail to initiate treatment than those living in a less crowded household. Birthplace of index cases was in some cases correlated with failing to initiate treatment; those contacts associated with index cases who had been born in any district of Lima or Callao (except Ventanilla) had an increased risk of failing to initiate treatment (RR 1.08, 95% CI [1.01, 1.15], p=0.04). Having an index case born in the central highlands of Peru was a protective factor for uptake (RR 0.86, 95% CI [0.79, 0.93], p<0.001). If the index case associated with a contact abandoned DOTS, there was an increased risk that the contact would fail to initiate treatment (RR 1.34, 95% CI [1.26, 1.42], p<0.001). Less than two years of a family being established in Lima was also associated with a contact failing to initiate treatment (RR 1.15, 95% CI [1.08, 1.23], p<0.001). Finally, there was also an increased risk of failure to initiate treatment if the TB-affected individual associated with the contact was considered a secondary case (RR 1.16, 95% CI [1.07, 1.25], p<0.001).
Table 7
Risk Factors for Latent Tuberculosis Infection Treatment Uptake and Adherence

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>No uptake* n (%)</th>
<th>RR [95%CI]</th>
<th>p value</th>
<th>Poor adherence** n (%)</th>
<th>RR [95%CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-19</td>
<td>579 (79.8)</td>
<td>1.29</td>
<td>1.23-1.35</td>
<td>&lt;0.001</td>
<td>690 (95.0)</td>
<td>1.10</td>
</tr>
<tr>
<td>0-14</td>
<td>1545 (61.8)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2158 (86.3)</td>
<td>1</td>
</tr>
<tr>
<td>Income †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>791 (64.7)</td>
<td>1.06</td>
<td>1.00-1.13</td>
<td>0.052</td>
<td>1078 (88.2)</td>
<td>1.02</td>
</tr>
<tr>
<td>Higher</td>
<td>784 (60.9)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1115 (87.6)</td>
<td>1</td>
</tr>
<tr>
<td>Crowded ††</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>451 (70.9)</td>
<td>1.10</td>
<td>1.04-1.16</td>
<td>0.003</td>
<td>588 (92.5)</td>
<td>1.06</td>
</tr>
<tr>
<td>no</td>
<td>1673 (64.6)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2260 (87.3)</td>
<td>1</td>
</tr>
<tr>
<td>IC education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS or less</td>
<td>1148 (63.3)</td>
<td>0.97</td>
<td>0.91-1.03</td>
<td>0.336</td>
<td>1574 (86.8)</td>
<td>1.03</td>
</tr>
<tr>
<td>Past HS</td>
<td>496 (61.3)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>722 (89.2)</td>
<td>1</td>
</tr>
<tr>
<td>IC place of birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventanilla</td>
<td>83 (69.2)</td>
<td>1.12</td>
<td>0.99-1.27</td>
<td>0.121</td>
<td>104 (86.7)</td>
<td>0.99</td>
</tr>
<tr>
<td>Other Lima ‡</td>
<td>583 (64.8)</td>
<td>1.08</td>
<td>1.01-1.15</td>
<td>0.035</td>
<td>827 (92.0)</td>
<td>1.10</td>
</tr>
<tr>
<td>Coast</td>
<td>176 (65.7)</td>
<td>1.06</td>
<td>0.97-1.17</td>
<td>0.224</td>
<td>228 (85.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>Central</td>
<td>333 (55.8)</td>
<td>0.86</td>
<td>0.79-0.93</td>
<td>&lt;0.001</td>
<td>483 (80.9)</td>
<td>0.90</td>
</tr>
<tr>
<td>Jungle</td>
<td>104 (60.8)</td>
<td>0.98</td>
<td>0.86-1.11</td>
<td>0.681</td>
<td>149 (87.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>IC drug use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>139 (70.9)</td>
<td>1.08</td>
<td>0.99-1.19</td>
<td>0.140</td>
<td>178 (90.8)</td>
<td>1.03</td>
</tr>
<tr>
<td>No</td>
<td>1985 (65.5)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2670 (88.1)</td>
<td>1</td>
</tr>
<tr>
<td>IC abandoned DOTS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>308 (81.3)</td>
<td>1.34</td>
<td>1.26-1.42</td>
<td>&lt;0.001</td>
<td>366 (96.6)</td>
<td>1.13</td>
</tr>
<tr>
<td>No</td>
<td>1380 (52.1)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1938 (85.3)</td>
<td>1</td>
</tr>
<tr>
<td>IC time in Lima</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>498 (67.6)</td>
<td>1.15</td>
<td>1.08-1.23</td>
<td>&lt;0.001</td>
<td>668 (90.6)</td>
<td>1.07</td>
</tr>
<tr>
<td>≥2 years</td>
<td>757 (58.7)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1094 (84.9)</td>
<td>1</td>
</tr>
<tr>
<td>Close contact of SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>173 (75.6)</td>
<td>1.16</td>
<td>1.07-1.25</td>
<td>0.001</td>
<td>197 (86.0)</td>
<td>0.97</td>
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<tr>
<td>no</td>
<td>1951 (65.1)</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2651 (88.5)</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: CI = confidence interval; HS = high school; IC = index case; LTBI = latent tuberculosis infection; RR = relative risk; SC = secondary case

* No uptake defined as less than two weeks of treatment recorded as dispensed
** Poor adherence defined as less than 22 weeks of treatment recorded as dispensed
† Lower-income defines as less than median income per person (33.68 USD per month)
‡ Crowded defined as nine or more people in one household
‡‡ Refers to Lima Metropolitan Area, which includes both Callao and Lima
Education level of index case, and any illicit drug use were not significantly associated with close contacts failing to initiate treatment. There was no significant association found if the index case related to the close contact had been born in Ventanilla, coastal region or the jungle region.

**Adherence.**

Fisher tests examining poor adherence to LTBI treatment (Table 7) showed that being in the fifteen-to-nineteen year old age group was associated with poor adherence (RR 1.10, 95% CI [1.08, 1.13], p<0.001). Close contacts living in a crowded household (RR 1.06, 95% CI [1.03, 1.09], p<0.001) were more likely to have poor adherence than those living in a less crowded household. Birthplace of index case was also correlated with poor adherence, if birthplace was Other Lima Metropolitan (RR 1.10, 95% CI [1.07, 1.14], p<0.001). If birthplace was central highlands, however, contacts were more likely to have good adherence (RR 0.90, 95% CI [0.86, 0.94], p<0.001). If the contacts associated with the index case had abandoned DOTS, there was an increased rate of poor adherence (RR 1.13, 95% CI [1.10, 1.16], p<0.001). Finally, if the contact’s family had been established in Lima for less than two years, the contact was more likely to have poor adherence (RR 1.07, 95% CI [1.03, 1.10], p<0.001).

Lower-income, education level of index case, birth place of index case in Ventanilla, coast or jungle, any illicit drug use, and being the close contact of a secondary case were not significantly associated with poor adherence.

**ISIAT Latent TB Infection Treatment Uptake and Adherence Analysis**

**All contacts uptake.**

Of those in the monitoring group, 34.2% started LTBI treatment, defined as having had two or more weeks of treatment dispensed. In the interventions group, 59.3% of contacts started
LTBI treatment. Contacts in the monitoring group had 1.62 (RR 95% CI [1.47, 1.79], p<0.001) times the risk of not starting when compared to the interventions group. The contacts in the interventions group were 1.74 times more likely to start LTBI treatment than those in the monitoring group (RR 95% CI [1.60, 1.88], p<0.001) (Table 8).

Table 8
Impact of ISIAT on Uptake and Completion of LTBI Treatment

<table>
<thead>
<tr>
<th>Uptake* (%)</th>
<th>RR [95%CI]</th>
<th>Fisher p value</th>
<th>Good adherence** (%)</th>
<th>RR [95%CI]</th>
<th>Fisher p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All contacts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervened</td>
<td>366 (59.3)</td>
<td>1.74</td>
<td>1.60-1.88</td>
<td>191 (31.0)</td>
<td>2.64</td>
</tr>
<tr>
<td>Monitored</td>
<td>1102 (34.2)</td>
<td></td>
<td></td>
<td>378 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Contacts of ICs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervened</td>
<td>355 (60.1)</td>
<td>1.72</td>
<td>1.59-1.87</td>
<td>190 (32.2)</td>
<td>2.78</td>
</tr>
<tr>
<td>Monitored</td>
<td>1046 (34.9)</td>
<td>1</td>
<td></td>
<td>346 (11.5)</td>
<td>1</td>
</tr>
<tr>
<td>Contacts of SC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervened</td>
<td>11 (42.3)</td>
<td>1.73</td>
<td>1.05-2.86</td>
<td>1 (3.85)</td>
<td>0.28</td>
</tr>
<tr>
<td>Monitored</td>
<td>56 (24.5)</td>
<td></td>
<td></td>
<td>32 (14.0)</td>
<td></td>
</tr>
</tbody>
</table>

Note: CI = confidence interval; IC = index case; LTBI = latent tuberculosis infection; RR = relative risk; SC = secondary case
* Uptake defined as greater than or equal to two weeks of treatment recorded as dispensed
** Good adherence defined as greater than or equal to 22 weeks of treatment recorded as dispensed

Contacts of index cases uptake.

The results for this group were nearly identical to the all contacts group, with 65.1% of those in monitoring having poor adherence (RR 1.63, 95% CI [1.47, 1.81], p<0.001). Contacts in interventions were 1.74 times more likely to start treatment (95% CI [1.59, 1.87], p<0.001).

Contacts of secondary cases uptake.

The results for this group were non-significant for uptake (RR 1.73, 95% CI [1.05, 2.86], p=0.061).
All contacts adherence.

There were 3226 contacts in the monitoring group and 617 in the interventions group included in this study. Of those in the monitoring group, 11.7% finished LTBI treatment, and 88.3% had poor adherence, previously defined in the analysis section as less than 22 weeks of treatment dispensed. In the interventions group, 31.0% of contacts finished LTBI treatment, and 69% had poor adherence. Contacts in the monitoring group had 1.28 times the risk of having poor adherence when compared to the interventions group (95% CI [1.21, 1.35], p<0.001). Contacts in interventions were 2.64 times more likely to complete LTBI treatment than those in the monitoring group (95% CI [2.27, 3.07], p<0.001).

Contacts of index cases adherence.

When secondary cases were removed from consideration there were 2997 monitoring and 591 interventions contacts. The results for this group were nearly identical to the all contacts group, with 88.5% of those in monitoring having poor adherence (RR 1.30, 95% CI [1.23, 1.38], p<0.001) and interventions being 2.78 times more likely to have good adherence than those in monitoring (95% CI [2.39, 3.25], p<0.001).

Contacts of secondary cases adherence.

The results for this group were also non-significant adherence (p=0.218).

Discussion

The purpose of this study was to understand the factors that contribute to poor uptake and adherence of LTBI treatment in Ventanilla, Peru. This involved an analysis of data abstracted from treatment cards of TB patients, and analysis data from a cluster randomized controlled trial of a complex socioeconomic intervention with respect to uptake and adherence on LTBI treatment in the same community.
Descriptive Statistics and Analysis of Risk Factors

The descriptive statistics showed that 34.2% of monitoring contacts initiated treatment for LTBI, but that only 11.7% had good adherence, reflecting a significant need for understanding the factors contributing to low uptake and adherence. This also closely reflects previous findings in Peru of 19% good adherence in a different urban setting (Salazar-López et al., 2010) and previously published abstracts of preliminary results from Ventanilla; 12% and 22% adherent in two different studies (Iberico et al., 2011a; Iberico et al., 2011b). These results reflect similar findings of very poor adherence in Malawi (uptake 22% with active case finding) (Zachariah et al., 2003) and Israel (28% uptake, 16% completion) (Bibi et al., 2002), indicating that this is not an isolated problem. Studies in the developed economies of the US and Canada show significantly higher rates, but do not go above 50%.

In the analysis of risk factors it was clear that barriers to completion of LTBI treatment, just like risk factors for increased TB disease, are related to social factors. A simple cross tabulation demonstrated a slight, but significant, relationship of crowding and low per capita income on LTBI treatment adherence rates. There are several reasons why poverty might contribute to decreased uptake of, and adherence to, LTBI treatment. A previous study in the same population showed that there were many hidden costs to TB therapy such as the cost of taking time off work and costs associated with transportation (Gavino et al., 2010). Although these costs were specific to TB treatment, socio-economic incentives and enablers may be required for the poorest members of communities to access even free TB control interventions such as LTBI treatment. One can easily appreciate the complexity of the contact screening process in Peru by viewing the simplified flowchart in Appendix A. Examples of possible incentives include conditional items such as food baskets that are simply given to TB affected
persons when they show up for DOTS, and cash transfers in exchange for the completion of various LTBI treatment goals. Conditional cash transfers have been demonstrated by the Juntos program in exchange for meeting educational and other preventive health goals (Cotlear, 2006; Perova & Vakis, 2009).

Considering how close of an association TB disease and poverty have, it was somewhat surprising that the socio-economic variables used in this study showed a small magnitude of association to LTBI treatment uptake and adherence. This may be related to the fact that the vast majority of residents in Ventanilla have very low monetary income, resulting in a skewed distribution, and a small magnitude of difference between families above and below the median income level. It is notable, however, that this finding is not in contradiction with some current studies. Boccia et al. (2013) reports that her own study in Zambia, as well as multiple other prevalence surveys, had not found associations between single socio-economic indicators and prevalent TB. A more sophisticated treatment of poverty analysis might yield different results in future studies.

This study, because of the way the data were obtained, provided little demographic information about the close contacts. The author, however, was able to analyze differences in uptake and adherence between the two aggregate age groups (0-14 years old and 15-19 years old), which yielded interesting results. Contacts in the older age group were much less likely to start treatment (79.8%, RR 1.29) when compared to the younger age group (61.8%). The same pattern held for adherence, but the magnitude of risk was lower (95%, RR 1.10). This reflects results from a survey of LTBI treatment in the USA and Canada showing adolescents older than fifteen to be less likely to complete treatment (Horsburgh et al., 2010), and indicates that this group of adolescents should be specifically targeted.
The factor contributing the largest magnitude of risk in this study was that of the index case failing to complete treatment (RR 1.34 uptake, RR 1.13 adherence). LTBI treatment is closely tied to DOTS and TB treatment of the index case. Once every week when the index case goes to clinic for DOTS, the nurse will dispense the LTBI treatment doses for all contacts younger than 20 years old who have gone through the contact evaluation process and been determined not to have active TB disease. If the index case abandons DOTS then there is no mechanism set up to continue to dispense LTBI treatment to contacts. In some cases it has been reported that mothers will take the extra initiative to visit the health center to collect the LTBI treatment for their children, but this is not common.

Concerning index case abandonment, it was surprising that adherence did not have a higher relative risk compared to uptake. One would assume that index case abandonment of DOTS would have little to do with uptake and more to do with adherence. This is because LTBI treatment is tied to DOTS, and if an index case does not show up for directly observed therapy then there is no one to receive the LTBI treatment dose for the contacts. Since abandonment typically occurs more frequently after a few months of DOTS, contacts should already have initiated treatment. It is possible that those individuals more likely to abandon DOTS were also less likely to report accurately about close contacts, or have them evaluated appropriately. This issue merits further research.

**Analysis of ISIAT Impact on Uptake and Adherence**

In the analysis of ISIAT’s impact on uptake and adherence, it was clear that this complex intervention was more protective with regards to uptake and adherence than any of the other factors in the study. It is significant to note that the interventions group only increased from 11.7% LTBI treatment adherence to 31% treatment adherence. Although a large and important
increase, it is still far below levels that would be considered adequate. Significant operational barriers exist, such as drug stock-outs, use of untrained students versus program staff in data collection, and pressures to fulfill quotas. The issue of quotas often drives nursing staff to devote more time to higher turnover areas, such as vaccine campaigns and general services (e.g. general medicine, or pediatrics), and less time to contact census verification, home visits, index case education, etc. If the operational barriers that most affect LTBI treatment are identified and eliminated or improved, then these numbers might be expected to increase accordingly.

In this study it was not possible to differentiate contacts that had been listed twice from new contacts on the secondary case card. In order to make sure that this was not affecting the all contacts results, the sub-analysis of index case contacts was performed. In this sub-analysis the results were not significant. If differences between index and secondary case contacts do exist more in-depth research is necessary to understand those differences. One possibility is that there could be operational differences (i.e. the health center staff considers secondary case contacts less important since they have been previously assessed, and either doesn’t list them, or doesn't give them priority for LTBI treatment).

Strengths

The major strength of this study was its large sample size, which allowed the calculation of relatively narrow confidence intervals, and increased the probability that these results are generalizable to other urban contexts in Peru and the world. Further, the examination of index case characteristics is not common within the limited existing literature. The analysis of index case specific variable is especially interesting because LTBI treatment uptake is contingent on index case reporting of contacts and receiving doses of LTBI to take to contacts. LTBI treatment adherence is similarly linked to index case DOTS adherence.
Limitations

During the data cleaning process missing variables came to light, and many were not recoverable. This did not allow for the most robust analysis of barriers and facilitators. Data were missing due to mistakes made in the field as well as mistakes of omission made in the TB control office, refusal to answer on the part of study participants, or incorrectly placed dates that proved irretrievable. The large sample size served to mitigate this effect, but non-response bias may still have affected the outcomes. Another issue was that of contacts lost to follow up, which were classified as not having completed treatment. For those individuals the length of treatment completed up to that point was utilized for analysis. The majority of these contacts were truly non-completers, as verified by subsequent ISIAT household visits, but a minority may have moved to another health system and continued treatment there.

The aggregate nature of the anonymized data made it impossible to analyze age as a continuous variable, or to look at the sex or education level of individual contacts. This was partly due to the surveys and the treatment cards not being specifically designed for analysis of factors contributing to uptake of, and adherence to, LTBI treatment. Also, as the IRB granted to this project prohibited direct questioning of children under the age of eighteen, the only data available directly concerning children was their age range and number of weeks of treatment administered by the health center. All other data was household data or index patient data. At a future time it would be worth going back to examine the original health center data, and to question children about what facilitates or impedes starting and/or finishing treatment.

Defining and analyzing poverty and social class is notoriously complicated (Krieger, Williams, & Moss, 1997). This study used simple indicators such as income, crowding and education as proxies for poverty. Various studies have shown that both simple indicators and
different complex calculations of socio-economic status have various effects on the results of analysis (Bollen, Glanville, & Stecklov, 2002; Houweling, Kunst, & Mackenbach, 2003). Income especially can be misleading due to its volatility, especially in poor populations such as the one in Ventanilla where a shift in tens of dollars per month would make a disproportionate impact. In economics this is known as a decreased income elasticity of demand. In other words, ten dollars per month would make a proportionately smaller impact on the demand for goods (including health services) in a wealthier population when compared to a poorer one. In Ventanilla this could mean that using a simple indicator (income) that is highly volatile might not give a realistic image of a family’s true socioeconomic standing. Unfortunately, the dataset did not, in its current state, allow for more complex analysis. This makes a compelling case for utilization of more complex methods, such as principal component analysis, to look at the data that ISIAT has collected on various indicators of economic well-being, including housing materials, domestic appliance ownership, and diet.

**Future Study**

This author did not conduct multivariate analysis, and this should be done in future work to more clearly identify true facilitators and barriers. Use of a poverty score, such as that based on debt, housing quality, or appliance ownership, may also have a role in future work. Already ISIAT questionnaires are closely aligned with the Grameen Foundation’s Progress out of Poverty Index (PPI) for Peru, and could provide a source for a more accurate analysis of poverty.

There remains much additional research to be done in the area of LTBI treatment. Looking at child contacts in more detail, and considering variables such as: continuous age, gender of contacts, relationship to index case, caretaker information, etc. will be important in future work. Studies examining operational barriers are also important. Looking with more
detail at the process of contact evaluation, and, specifically, how far each contact makes it in the LTBI process and what reasons there might be for not starting, dropping out at certain points, or not completing the final physician evaluation after completion of LTBI treatment are key points to consider further. There is also a difference between uptake and adherence reported on treatment cards (i.e. how much medication was dispensed) and the reality—what made it home and how many doses child and adolescent contacts actually took, which would provide an interesting area to apply urine tests and other methods to examine true adherence.

**Impact on Practice**

This study opened up various possible considerations in terms of targeted interventions. Known issues within the ESN-PCT such as poor contact census practices, poor follow up on contacts, LTBI treatment administering policies varying from health center to health center are all likely contributing factors and seem to be more likely important factors than individual patient factors. From the process of mapping the TB policy (see Appendix A), it was apparent that the Peruvian TB health policy document must be clarified. Additionally, the factors identified in this study that may put a contact at highest risk of non-uptake and completion should be prioritized. These include socioeconomic status, age greater than fourteen, and index case abandonment. Changes should be made considering the context and everyday job requirements of healthcare professionals in Ventanilla and other similar communities in Peru. Being a physician, nurse, or healthcare worker in these poor communities is difficult work due to long distances, low pay and high demands. Interventions must be efficient and not complicate existing duties.

One interesting area for possible change is in the structure of the contact census and isoniazid dispensing register. In India it has been recognized that LTBI treatment uptake is often
dependent on health care worker adherence to the TB control policy, and that the use of separate LTBI treatment registry cards for contacts can increase uptake of treatment significantly (Rekha et al., 2013). In Peru it has been a longstanding policy to include these registration details on the back of the TB index case treatment card, unlike in the previously cited study, so the impact of a similar reform is unclear. It very well could clarify the role of the census process with regards to LTBI treatment, and could highlight the importance of this process. It would, however, create a significant increase in storage space needed for contact LTBI treatment cards.

Treatment of LTBI for high exposure individuals should be a positive right. At the very least, expanding current policy to other high risk groups such as adolescents and the elderly, who often have limited control of their environments, should be considered (Stop TB Partnership Childhood TB Subgroup, 2007). In a back and forth correspondence between a medical student and the head of the TB control program in Peru in 2010, it is clear that the ministry of health considers it cost effective to treat LTBI in a broad range of high risk groups; including adults with diabetes, silicosis, gastrectomy, hematological malignancies, immunosuppressive treatment for another illness, terminal renal failure and renal transplants, prolonged corticosteroid therapy, and wasting illnesses (Jave & Llanos-Tejada, 2010; Maquera-Afaray, 2010). Furthermore, influential researchers in the global tuberculosis control community have stated that DOTS for TB disease and LTBI treatment are synergistic, and, if used together, could lead to elimination of TB by 2050 (Dye & Williams, 2008). This certainly merits a reexamination of current global policy with regards to treatment for LTBI in high exposure groups.

**Conclusion**

This study has shown that in Peru, risk factors such as age, crowding, place of origin, index case abandonment, and establishment in Lima are significant risk factors for uptake and
adherence of LTBI treatment (summarized in Table 9). Additionally, this study has shown that a relatively inexpensive panel of socio-economic interventions designed for TB-affected households living in impoverished periurban shantytowns was associated with a marked increase in uptake of, and adherence to, LTBI treatment, resulting in strengthened TB control (Table 8).

Table 9
Summary of Risk Factors ($p<0.05$)

<table>
<thead>
<tr>
<th></th>
<th>No Uptake</th>
<th>RR</th>
<th>Poor Adherence</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 15-19</td>
<td>79.0%</td>
<td>1.29</td>
<td>95%</td>
<td>1.10</td>
</tr>
<tr>
<td>Crowded *</td>
<td>70.9%</td>
<td>1.10</td>
<td>92.5%</td>
<td>1.06</td>
</tr>
<tr>
<td><strong>IC Born in:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Lima Metro **</td>
<td>64.8%</td>
<td>1.08</td>
<td>92.0%</td>
<td>1.10</td>
</tr>
<tr>
<td>Central</td>
<td>55.8%</td>
<td>0.86</td>
<td>80.9%</td>
<td>0.90</td>
</tr>
<tr>
<td>IC abandoned DOTS</td>
<td>81.3%</td>
<td>1.34</td>
<td>96.6%</td>
<td>1.13</td>
</tr>
<tr>
<td>IC lived in Lima &lt;2 years</td>
<td>67.6%</td>
<td>1.15</td>
<td>90.6%</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Note: DOTS = directly observed therapy short course; IC = index case; RR = relative risk
* Crowded defined as nine or more people in one household
** Refers to Lima Metropolitan Area, which includes both Callao and Lima
References


FACTORS AFFECTING LATENT TUBERCULOSIS TREATMENT

Estadística e Informática. Retrieved from
http://www.inei.gob.pe/biblioineipub/bancopub/Est/Lib0842/


FACTORS AFFECTING LATENT TUBERCULOSIS TREATMENT


doi:10.1002/ppul.20787


doi:10.1056/NEJMoal005136


Peruvian children by use of a heminested IS6110 polymerase chain reaction assay.

*Clinical Infectious Diseases, 36*(1), 16-23. doi:10.1086/344900


doi:10.1056/NEJMoa055524

close contacts of people with pulmonary tuberculosis in low-income and middle-income
countries: A systematic review and meta-analysis. *The Lancet Infectious Diseases, 8*(6),
359-368. doi:10.1016/S1473-3099(08)70071-9

determinants of tuberculosis. *The International Journal of Tuberculosis and Lung
Disease, 15*(6), 64-70. doi:10.5588/ijtld.10.0535

International Journal of Tuberculosis and Lung Disease, 8*(5), 636-647.

Adherence to tuberculosis preventive therapy among HIV-infected persons in Chiang

attendance at a child TB contact clinic in Malawi. *The International Journal of
Tuberculosis and Lung Disease, 10*(5), 585-587.


dated 17,000 years before the present. *Clinical Infectious Diseases, 33*(3), 305-311.
doi:10.1086/321886

Rowe, K. A., Makhubele, B., Hargreaves, J. R., Porter, J. D., Hausler, H. P., & Pronyk, P. M.
(2005). Adherence to TB preventive therapy for HIV-positive patients in rural South
Africa: Implications for antiretroviral delivery in resource-poor settings? *The
International Journal of Tuberculosis and Lung Disease, 9*(3), 263-269.

Rutherford, M. E., Ruslami, R., Maharani, W., Yulita, I., Lovell, S., van Crevel, R., . . . Hill, P.
C. (2012). Adherence to isoniazid preventive therapy in Indonesian children: A
quantitative and qualitative investigation. *BMC Research Notes, 5*. 7. doi:10.1186/1756-
0500-5-7

quimioprofilaxis con isoniaicida y factores asociados en pacientes infectados con el VIH

and global impacts. *PLoS Medicine, 4*(5), 806-812. doi:10.1371/journal.pmed.0040115

Sebastian, M. S., & Bothamley, G. H. (2000). Tuberculosis preventive therapy: Perspective from
a multi-ethnic community. *Respiratory Medicine, 94*(7), 648-653.

intravenous drug users with human immunodeficiency virus infection. *The New England
Journal of Medicine, 320*(9), 545-550. doi:10.1056/NEJM198903023200901


APPENDIX A: TB Control Policy: Simplified Contact Assessment Flow-Chart

Close Contacts ≤19 years old

<15 years old

PPD
Chest X-Ray
Microscopy

15-19 years old

Microscopy #1 (day of initial evaluation)
Microscopy #2 (day after initial evaluation)
Symptomatic only:
Chest X-Ray
Sputum Culture

Results
Doctor Consult #1

Stegen and Toledo
≤2 Points
3-4 Points
≥5 Points

Possible Specialist Medical Consult

Active TB: DOTS

No TB Disease: LTBIT pathway

Begin LTBIT

Continue
drug reaction

Contra-indication
Stop LTBIT

Reevaluate contact at start of DOTS, DOTS phase change, and end of DOTS
### Record of LTBI treatment weekly dose dispensing

<table>
<thead>
<tr>
<th>Nº de Consulta</th>
<th>Consulta Médica (fechas)</th>
<th>Entrevista de Enfermería (fechas)</th>
<th>Entrevista de Servicio Social (fechas)</th>
<th>Visitas domiciliarias</th>
<th>Charles Educativas (fechas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nº de Control</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nº Orden</td>
<td>Edad</td>
<td>Peso</td>
<td>Dosis</td>
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</tr>
<tr>
<td></td>
<td>M</td>
<td>F</td>
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<td>130.00</td>
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</table>

### Control de Contactos

<table>
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<tr>
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<th>Apellidos y Nombres</th>
<th>EDAD</th>
<th>RELACION CASE</th>
<th>BCG</th>
<th>HPC</th>
<th>DOSIS</th>
<th>PRIMER CONTROL</th>
<th>SEGUNDO CONTROL</th>
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<td>6º</td>
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</tbody>
</table>

### FACTORS AFFECTING LATENT TUBERCULOSIS TREATMENT

The image contains data related to patients with latent tuberculosis infection (LTBI) treatment, including weekly dose dispensing and control of contacts. The information includes patient identifiers, ages, and treatment details.
This is a view of Ventanilla from the highway that shows a mix of construction types. The dwellings on the hill, for instance, are mostly dirt floor, repurposed wood walled, corrugated metal roofed and have no electricity or running water. Many of the dwellings in the foreground have electricity, although running water is more irregular.

This image shows the contrast of some of the simpler shack like dwellings often found on the hillsides, far from any paved road, and more developed cinder block and brick buildings in the background. It can take ten years or more for a squatter settlement to get electricity and running water.

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View inside a home in Ventanilla.
APPENDIX D: IRB Approval

RESEARCH INVOLVING HUMAN SUBJECTS
SC # 4216

ACTION OF THE WRIGHT STATE UNIVERSITY
EXPEDITED REVIEW
Assurance Number: FWA00002427

Title: ‘Exploring Factors Affecting Access and Utilization of Tuberculosis Health Systems in Peru’

Principal Investigator: Mariano M. Iberico Lozado, M.D., Doc. Student
Cristina Redko, Ph.D., Fac. Advisor

Department: Public Health Program

Expeditied Category: 7

The Institutional Review Board has approved the use of human subjects on this proposed project.

REMININDER: FDA regulations require prompt reporting to the IRB of any changes in research activity, changes in approved research during the approval period may not be initiated without IRB review (submission of an amendment), and prompt reporting of any unanticipated problems (adverse events).

Signed Chair, WSU-IRB

Expedited Review Date: June 04, 2010
IRB Meeting Date: June 21, 2010

This approval is effective only through: June 4, 2011
To continue the activities approved under this protocol you should receive the appropriate form (s) from Research and Sponsored Programs (RSP) two to three months prior to the required due date. If you do not receive this notification, please contact RSP at 775-2425.
### APPENDIX E: List of Tier 1 Core Public Health Competencies Met

<table>
<thead>
<tr>
<th>Domain #1: Analytic/Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify the health status of populations and their related determinants of health and illness (e.g., factors contributing to health promotion and disease prevention, the quality, availability and use of health services)</td>
</tr>
<tr>
<td>Describe the characteristics of a population-based health problem (e.g., equity, social determinants, environment)</td>
</tr>
<tr>
<td>Use variables that measure public health conditions</td>
</tr>
<tr>
<td>Use methods and instruments for collecting valid and reliable quantitative and qualitative data</td>
</tr>
<tr>
<td>Identify sources of public health data and information</td>
</tr>
<tr>
<td>Recognize the integrity and comparability of data</td>
</tr>
<tr>
<td>Identify gaps in data sources</td>
</tr>
<tr>
<td>Adhere to ethical principles in the collection, maintenance, use, and dissemination of data and information</td>
</tr>
<tr>
<td>Describe the public health applications of quantitative and qualitative data</td>
</tr>
<tr>
<td>Collect quantitative and qualitative community data (e.g., risks and benefits to the community, health and resource needs)</td>
</tr>
<tr>
<td>Use information technology to collect, store, and retrieve data</td>
</tr>
<tr>
<td>Describe how data are used to address scientific, political, ethical, and social public health issues</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Domain #2: Policy Development and Program Planning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gather information relevant to specific public health policy issues</td>
</tr>
<tr>
<td>Describe how policy options can influence public health programs</td>
</tr>
<tr>
<td>Gather information that will inform policy decisions (e.g., health, fiscal, administrative, legal, ethical, social, political)</td>
</tr>
<tr>
<td>Participate in program planning processes</td>
</tr>
<tr>
<td>Identify mechanisms to monitor and evaluate programs for their effectiveness and quality</td>
</tr>
<tr>
<td>Apply strategies for continuous quality improvement</td>
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<tr>
<th>Domain #3: Communication</th>
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<tbody>
<tr>
<td>Identify the health literacy of populations served</td>
</tr>
<tr>
<td>Communicate in writing and orally, in person, and through electronic means, with linguistic and cultural proficiency</td>
</tr>
<tr>
<td>Solicit community-based input from individuals and organizations</td>
</tr>
<tr>
<td>Participate in the development of demographic, statistical, programmatic and scientific presentations</td>
</tr>
<tr>
<td>Apply communication and group dynamic strategies (e.g., principled negotiation, conflict resolution, active listening, risk communication) in interactions with individuals and groups</td>
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<tr>
<th>Domain #4: Cultural Competency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporate strategies for interacting with persons from diverse backgrounds (e.g., cultural, socioeconomic, educational, racial, gender, age, ethnic, sexual orientation, professional, religious affiliation, mental and physical capabilities)</td>
</tr>
<tr>
<td>Recognize the role of cultural, social, and behavioral factors in the accessibility, availability, acceptability and delivery of public health services</td>
</tr>
<tr>
<td>Respond to diverse needs that are the result of cultural differences</td>
</tr>
<tr>
<td>Describe the dynamic forces that contribute to cultural diversity</td>
</tr>
<tr>
<td>Describe the need for a diverse public health workforce</td>
</tr>
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<tr>
<th>Domain #5: Community Dimensions of Practice</th>
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</thead>
<tbody>
<tr>
<td>Recognize community linkages and relationships among multiple factors (or determinants) affecting health (e.g., The Socio-Ecological Model)</td>
</tr>
<tr>
<td>Identify stakeholders</td>
</tr>
<tr>
<td>Collaborate with community partners to promote the health of the population</td>
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<tr>
<td>Maintain partnerships with key stakeholders</td>
</tr>
<tr>
<td>Use group processes to advance community involvement</td>
</tr>
<tr>
<td>Describe the role of governmental and non-governmental organizations in the delivery of community health services</td>
</tr>
<tr>
<td>Gather input from the community to inform the development of public health policy and programs</td>
</tr>
<tr>
<td>Inform the public about policies, programs, and resources</td>
</tr>
<tr>
<td><strong>Domain #6: Public Health Sciences</strong></td>
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<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Describe the scientific foundation of the field of public health</td>
</tr>
<tr>
<td>Identify prominent events in the history of the public health profession</td>
</tr>
<tr>
<td>Identify the basic public health sciences (including, but not limited to biostatistics, epidemiology, environmental health sciences, health services administration, and social and behavioral health sciences)</td>
</tr>
<tr>
<td>Describe the scientific evidence related to a public health issue, concern, or, intervention</td>
</tr>
<tr>
<td>Retrieve scientific evidence from a variety of text and electronic sources</td>
</tr>
<tr>
<td>Discuss the limitations of research findings (e.g., limitations of data sources, importance of observations and interrelationships)</td>
</tr>
<tr>
<td>Describe the laws, regulations, policies and procedures for the ethical conduct of research (e.g., patient confidentiality, human subject processes)</td>
</tr>
<tr>
<td>Partner with other public health professionals in building the scientific base of public health</td>
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<tr>
<th><strong>Domain #7: Financial Planning and Management</strong></th>
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</thead>
<tbody>
<tr>
<td>Describe the local, state, and federal public health and health care systems</td>
</tr>
<tr>
<td>Describe the organizational structures, functions, and authorities of local, state, and federal public health agencies</td>
</tr>
<tr>
<td>Adhere to the organization's policies and procedures</td>
</tr>
<tr>
<td>Report program performance</td>
</tr>
<tr>
<td>Translate evaluation report information into program performance improvement action steps</td>
</tr>
<tr>
<td>Apply basic human relations skills to internal collaborations, motivation of colleagues, and resolution of conflicts</td>
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<tr>
<th><strong>Domain #8: Leadership and Systems Thinking</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporate ethical standards of practice as the basis of all interactions with organizations, communities, and individuals</td>
</tr>
<tr>
<td>Describe how public health operates within a larger system</td>
</tr>
<tr>
<td>Use individual, team and organizational learning opportunities for personal and professional development</td>
</tr>
<tr>
<td>Participate in mentoring and peer review or coaching opportunities</td>
</tr>
<tr>
<td>Participate in the measuring, reporting and continuous improvement of organizational performance</td>
</tr>
<tr>
<td>Describe the impact of changes in the public health system, and larger social, political, economic environment on organizational practices</td>
</tr>
</tbody>
</table>