ECONOMIC EVALUATION OF THE INITIATIVE "CONTROL OF TUBERCULOSIS IN LARGE METROPOLITAN CITIES" IN LIMA - PERU

by

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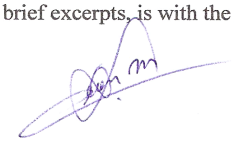

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ABSTRACT

Economic evaluation of the initiative "Control of tuberculosis in large metropolitan cities" in Peru:

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Tuberculosis (TB) is still a major public health concern worldwide and, according to the World Health Organization (WHO), in 2013 there were an estimated 9 million new cases of TB. On the other hand, it is widely recognized that the burden of TB is often greater in urban than rural settings, both in developing and industrialized countries. This fact is certainly true in Latin America and the Caribbean (LAC) and in Peru too.

Lima - the capital of Peru - has twenty-five percent of the country's urban poor, and reports 60% of the tuberculosis cases for the entire country, as well as 85% of drug-resistant tuberculosis cases.

In response to this scenario, PAHO has designed the "Control of Tuberculosis in large metropolitan cities in LAC" initiative, with the goal of reducing the impact of the TB epidemic through a comprehensive intervention that cover all the main barriers of the TB control in large cities. Peru has implemented this focalized intervention to reduce one

of the main problems of TB control in Lima, which is treatment default affecting both the successful treatment and the transmission of TB in the community.

The focalized intervention is based on daily monitoring of the patient treatment, 100% compliance with a baseline comprehensive assessment, and home visits and counseling if the patients missed one day of treatment.

This study had three objectives. First, to determine the incremental effectiveness of the focalized intervention compared to the existing program; to determine the cost-effectiveness and cost-utility of the focalized intervention compared to the existing program; and to determine the cost-benefits of the focalized intervention compared to the existing program. We used a provider perspective.

For the first objective we conducted an Ex-post analysis during the first 5 months of implementation to estimate the effectiveness of the interventions and an Ex-ante analysis for the following twenty years using a compartmental epidemiological model to estimate the impact of the focalized intervention on the incidence of tuberculosis for the twenty-year horizon time.

For the second objective, we did a cost-effectiveness analysis determine the incremental cost-effectiveness ratio (ICER) of the focalized intervention to avert new TB cases. Further, for the cost-utility analysis, we have calculated the disability adjusted life years (DALYs) to determine the cost of per DALY averted.

For the third objective, we did a cost-benefit analysis where we calculated the benefits in terms of the cost of illness, and we compared this cost for both the focalized intervention and the status quo, to determine the net return of investment.

Our findings demonstrated that the focalized intervention reduced the treatment default from 10.42% to 1.46% and treatment interruption from 18.79% to 5.82%. Furthermore, this strategy was cost-effective and cost-utilitarian over a twenty years period for both non-resistant and resistant TB, with an estimated cost per case averted of 16.00 USD for non-resistant, and an estimated cost per DALY averted of 2,680.00 USD for resistant TB; and with an estimated cost per case averted of 13.25 USD and an estimated cost per DALY averted of 2,252.80 USD for resistant TB. This strategy would potentially produce a saving of 10,228,902.00 USD over the twenty years of intervention.

We strongly recommend that Peruvian Ministry of Health continue funding and expand this strategy, because could be one of the tools that will help Peru, and maybe other countries with similar problems of treatment default, to reach the goal of the initiative End TB supported by the World Health Organization.

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GLOSSARY

Cured – "A pulmonary TB patient with bacteriologically-confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion" (152).

Completed treatment – "A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable" (152).

Died – "A TB patient who died from any cause during treatment" (152).

Failed – "A TB patient whose sputum smear or culture is positive at month five or later during treatment" (152).

Treatment default – "A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more" (152).

Not evaluated – "a TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit" (152).

Successfully treated – this parameter was used in the model but not the parameter cured - is defined as "a patient who was cured or who completed treatment" (152).

Cohort – "A group of patients in whom TB has been diagnosed, and who were registered for treatment during a specified time period (e.g. the cohort of new cases registered in the calendar year 2012). This group forms the denominator for calculating

treatment outcomes. The sum of the patients included in the above treatment outcome categories should equal the number of cases registered" (152).

Treatment interruption – "a TB patient that missed at least three treatment doses during the first phase of the treatment or that missed at least five treatment doses during the whole treatment "(91).

CHAPTER 1: Introduction

OVERVIEW OF TUBERCULOSIS: CURRENT SITUATION

Tuberculosis (TB) is still a major public health concern worldwide and, according to the World Health Organization (WHO), there were an estimated 9 million new cases of TB in 2013, 13% of which were co-infected with human immunodeficiency virus HIV(152). Furthermore 1.5 million people died from TB in 2013 including 1.1 million deaths among HIV-negative individuals and 360,000 among people who were HIV-positive. For the same year, the WHO estimated 480,000 (range: 350,000–610,000) cases of multidrug-resistant tuberculosis (MDR-TB) emerged globally with approximately 210,000 (range: 130,000–290,000) deaths from MDR-TB(152). Among all incident TB cases globally, an estimated 3.5% (95% CI: 2.2–4.7%) of new cases and 20.5% (95%CI: 13.6–27.5%) of previously treated cases have MDR-TB(152). Extensively drug-resistant tuberculosis (XDR-TB) has been reported by 100 countries and the average proportion of MDR-TB cases with XDR-TB is 9.0% (95% CI: 6.5–11.5%)(152).

Despite the rapid decline of tuberculosis incidence rates in recent years, the increase of drug-resistant TB cases has become a major global public health concern. This is especially true for developing countries where it represents a threat to the public health system as an emerging epidemic with different characteristics compared to drug-sensitive tuberculosis(119; 152). These include(1; 4; 20; 38):

- A lower recovery rate (60-70%) because the success of the treatment depends upon the pattern of antimicrobial resistance and the availability of effective drugs;

- A longer duration of infectiousness because patients require a long period of treatment to recover;
- A higher rate of treatment default, because the long and multidrug therapy by itself is associated with a high risk of intolerance and serious toxic effect;
- A higher case fatality rate than sensitive-drug tuberculosis; and
- A high rose of diagnosis of MDR-TB and XDR-TB is expensive and requires diagnostic tools that demand more infrastructure and skills. Not all countries have the necessary laboratory capabilities to test for drug-resistant TB.

These issues make the task of controlling drug-resistant tuberculosis a challenge for public health systems.

The WHO defines drug-resistant tuberculosis as a case of TB (usually pulmonary) excreting bacilli resistant to one or more antituberculosis drugs. If the patients did not have prior treatment with anti-TB drugs, the bacterial resistance is called primary resistance, while in previously treated patients the bacterial resistance is acquired resistance(33; 35).

Among all types of drug-resistant tuberculosis, MDR-TB and XDR-TB are two of the most severe forms of bacterial resistance. MDR-TB is defined as tuberculosis resistant to at least isoniazid (INH) and rifampin (RMP); and XDR-TB is defined as MDR-TB plus resistance to a fluoroquinolone and at least one second-line injectable agent: amikacin, kanamycin and/or capreomycin(7; 24).

It is widely recognized that the burden of TB is often greater in urban than rural settings, both in developing and industrialized countries(5). This fact is certainly true in Latin America and the Caribbean (LAC); for example, almost 50% of all Venezuelan

cases of TB and MDR-TB are concentrated in the city of Caracas(110). Furthermore, the city of San Cruz in Bolivia is home to 58% of total TB cases of the entire country(110).

In LAC, these high-burden areas of TB and MDR-TB cases are mainly urban slums of large cities, including some capitals cities(110). UN-HABITAT defines a slum household as "a group of individuals living under the same roof in an urban area who lack one or more of the following: a) durable housing of a permanent nature that protects against extreme climate conditions; b) sufficient living space which means not more than three people sharing the same room; c) easy access to safe water in sufficient amounts at an affordable price; d) access to adequate sanitation in the form of a private or public toilet shared by a reasonable number of people; and e) security of tenure that prevents forced evictions"(137).

Urban slums are a breeding ground for tuberculosis because they concentrate a large, impoverished population in a small area where living conditions are crowded, education levels are low, unemployment is high, and there are high rates of crime and violence(112).

Peru is located in the South America Andean region and had an estimated 30 million inhabitants in 2011. According to the World Bank, Peru is classified as an upper middle-income country, as over the past five years, Peru has made great strides in development. Achievements include high GDP growth rates, low inflation, macroeconomic stability, reduction of external debt and poverty, and significant advances in social and development indicators, among others(130).

Peru is a diverse country not only for its geography with three distinct geographic regions: coastal, highland, and jungle, but also for its population which is comprised of

45% indigenous peoples, 47% mestizo and 18% mixture of European, Black, Japanese, Chinese and others. There are two official languages: Spanish and Quechua, among other non-official dialects.

Peru is divided into 24 administrative regions (departments) and one constitutional province (Callao). Each region has its own elected regional government, but political control remains centralized in the capital of Lima.

According to the Pan-American Health Organization (PAHO), Peru has the second highest burden of tuberculosis among countries in the Americas and the Caribbean. In 2013, Peru reported roughly 31,052 cases of active tuberculosis, which represent 13% of the total burden for the LAC region. In the same year, Peru reported 1,462 cases of MDR-TB, and through 2013 there were an estimated 100 XDR-TB cases(111).

Lima is the largest city and the capital of Peru with a population approaching 9 million. Lima is the most populous metropolitan area of Peru and the fifth largest city in the Americas. It has a population density of 3,008.8 inhabitants per square kilometer. The province of Lima is made up of forty-three districts, and the city proper (urban area) of Lima is formed by thirty of these districts. The remaining thirteen districts consist of mostly rural and sparsely populated desert and mountainous areas(73). Since 1960s, Lima's population growth has been concentrated in slums and shantytowns. The shantytowns and slums housed 10 percent of the population of Lima in 1955, 25 percent in 1970, and house an estimated 35 percent of the population today(137).

The district of San Juan de Lurigancho has more than 1 million inhabitants and is the most populated district in the country. 24 percent of its population lives in poverty,

and only 48 percent of its economically active population has a job. By comparison, El Agustino has roughly 200,000 inhabitants, 20 percent of its population is poor, and only 50 percent of the economically active population has a job(73).

Lima - the capital of Peru - has twenty-five percent of the country's urban poor, and reports 60% of the tuberculosis cases for the entire country, as well as 85% of drug-resistant tuberculosis cases(85). However, in recent years, MDR-TB and XDR-TB has spread to other regions of the country where they were previously unreported(85).

These high TB burden areas coincide with urban slums as a result of internal migration from Andean rural areas to urban areas of capitals of departments (department is equivalent to state). This migration initially stemmed from terrorist violence, and today is driven by the desire for increased opportunities and improving quality of life. The phenomenon has generated overcrowded living conditions lacking access to clean water or electricity, and where poor nutritional status, unemployment, and access to basic health services are daily challenges(98). In the following sections, we are going to discuss about urban TB epidemiology, rapid urbanization and sprawling slums, and the main drivers of TB epidemic in urban areas.

URBAN TB EPIDEMIOLOGY

In developing countries, data on TB cases in urban or rural areas are scarce, and official notification data rarely reflect the true incidence due to the poor performance of national TB programs. This problem is often worse in rural areas where health access and health infrastructure are both limited. However, some secondary data reviewed for

selected cities and countries indicate that the notification rate for new TB smear-positive cases is consistently, and often considerably, higher in urban areas(5).

Yet, solutions exist for overcoming the problem of poorly performing TB control programs in developing countries which may bias epidemiologic data. Surveys measuring the annual risk of TB infection are one example of a tool which provide better estimates of TB incidence rates than official notification rates(27; 48; 116). Reliable data on the annual risk of TB infection disaggregated by rural and urban settings indicate that higher notification rates in cities are due to higher incidence rather than better notification. For example, a 2002-2003 national survey performed in 26 districts in four defined zones of India found that the proportion of TB infected children was significantly higher in urban than in rural areas in all zones(28). Various studies in India and in other countries like Cambodia, Vietnam, Philippines, have demonstrated similar findings(5; 15; 76; 106; 135).

However, it is not just general TB incidence rates which are higher in cities; the evidence indicates that MDR-TB prevalence is also higher in cities than in rural areas. For example, one study in India highlights a drastically different percentage of MDR-TB isolates in the city of Mumbai (51%), compared to those in a rural area (2%) in Sakawar(2).

Notification data for LAC regions suggests that TB incidence rates are similarly high in capital cities or other large cities including Bogota, Lima, Caracas, Sao Paulo, and Rio de Janeiro(111). In Peru, 80% of the TB burden is concentrated in 9 of the 24 departments in coastal capital cities and two jungle-located capitals. 54% of the total annual TB incidence is reported from the national capital of Lima; a further 82% and

89% of MDR-TB and XDR-TB cases respectively are from Lima. In the province of Lima, 80% of TB cases are concentrated in 15 districts out of a total of 49, and the districts of San Juan de Lurigancho and El Agustino alone are home to roughly 60% of all cases in Lima province(87).

RAPID URBANIZATION AND SPRAWLING SLUMS

According to the World Urbanization Prospects Report, in 2014 more people lived in urban areas worldwide than in rural areas, with 54 percent of the world's population residing in urban areas. Furthermore, 30 percent of the world's population was urban in 1950, and by 2050, 66 percent of the world's population is projected to be urban(138). Today, the most urbanized regions include North America (82 percent living in urban areas in 2014), LAC (80 percent), and Europe (73 percent) (138).

In LAC, the number of cities has increased six-fold over fifty years. Half of the urban population now lives in cities of less than 500,000 inhabitants and 14% in megacities (more than 222 million in the first and 65 million in the second) (112). The internal migration of rural populations to cities in search of higher incomes, improved services and better livelihood opportunities or to avoid social and political conflicts, violations of human rights, and natural disasters are the main drivers of urbanization in LAC(112).

Rapid urbanization has resulted in the growth and proliferation of slums in cities. Slums are a physical and spatial manifestation of urban poverty and intra-city inequality(137). In 2001, 924 million people or 31.6 percent of the world's urban population lived in slums. The majority of slums were located in developing countries,

which accounted for 43 percent of the urban population; in contrast, 6 percent of the population lived in slums in more developed countries. In LAC, 31.9 percent of the total population lives in slums(137). These marginalized populations live in overcrowded conditions without access to clean water or electricity, and often lacking of basic health services. Slums dwellers also suffer from high rates of crime and violence (112).

The majority of slum dwellers in developing country cities earn their living through informal sector activities located either within or outside slum areas, and many informal sector entrepreneurs house their operations within the slums while servicing clientele in other areas of the city(137). The combination of these social determinants generates a breeding ground for TB(69).

DRIVING FORCES BEHIND URBAN TB EPIDEMICS

The high burden of TB in urban settings can be explained by the confluence of demographic, socioeconomic, and environmental factors(46; 69; 114; 115). Well-known risk factors for TB include overcrowding, low socioeconomic conditions, high prevalence of HIV and diabetes, high prevalence of homelessness and violence, and large immigrant populations transitioning from rural to urban areas(10; 66; 115; 124; 136).

As previously established, densely populated areas generate overcrowded conditions. Therefore, with over 40% of urban populations in developing countries living in urban slums, a high burden of TB should be expected(114). For example, a study carried out in Kampala, Uganda, found that the rate of TB in one peri-urban community was exceptionally high - nearly five times higher than the country's estimated incidence (68). Another study, in the Mirpur slum of Dhaka City, a megacity and the capital of Bangladesh, revealed a prevalence of TB more than two times higher than the national

prevalence, and nearly four times higher than the prevalence in all of Bangladesh's urban settings(9).

Yet, overcrowding is not the only risk factor for TB. Frequently, dwellers of these slums live in extreme poverty which may lead to the poor living conditions associated with overcrowding, lack of access to health services, malnutrition, etc.(137). Many studies carried out in various different settings have demonstrated that the relationship between poverty and TB is significant even when adjusting for important confounders like ethnicity, malnutrition, and high HIV prevalence(14; 43; 75; 107; 125).

Molecular epidemiology studies using DNA fingerprinting techniques have confirmed active TB transmission primarily takes place in socioeconomically deprived groups(30; 67; 122). However, a high TB incidence in crowded urban settings also increases the risk of contracting TB among the non-impoverish groups as well. For instance residents of the slums can work in all areas of the city, visit communal recreational places, and use public services (137). Slum dwellers using public transportation may also come into contact with a large number of persons from all social backgrounds, thereby increasing the risk of TB transmission(71).

Internal migration from rural to urban settings is another key factor for TB in developing countries. Because cities offer better education and job opportunities than rural areas, they tend to attract large portions of young and working populations to densely-populated urban slums(112).

Slums also have high rates of MDR-TB and XDR-TB(9) due to the lack of access to health services, weak local TB control programs, inadequate resources for treatment, weak referral management, and high rates of default(114). The high concentration of TB

cases may lead to an increase in the risk of contact with persons with MDR-TB or XDR-TB generating high levels of primary resistant TB. For example, in 2008, a slum called Cerro San Cosme, located in Lima, reported a TB incidence rate of 1,347.2 per 100,000 population(59). In the following section, we are going to talk about major barriers to TB control in large cities.

MAJOR BARRIERS TO TB CONTROL IN LARGE CITIES

TB control in urban slums is challenging as there are many factors related to the health system, socioeconomics, and culture which impede a successful control and localizes efforts to eliminate TB(114). Health system factors impacting TB include inadequate infrastructure, limited healthcare personnel and logistic resources, as well as inadequate or abbreviated programmatic timetables. Broadly speaking, slums generally have a health post or a health center with limited laboratory capability for diagnosis of drug-resistant tuberculosis. These health facilities are staffed by general practitioners who may not be training in the treatment of drug-resistant TB(112). Patients with drug-resistant TB must therefore be referred to health facilities outside of the slum which are better equipped to handle drug-resistant TB but may increase out of pocket expenditures, thereby reducing likelihood they will seek to adhere to necessary treatment(90).

Other problems include overcrowding in health facilities due to high demand for care, lack of comprehensive infection control measures, inadequate infrastructure to avoid mixing of TB patients with non-TB patients, and/or limited health care worker staffing/capacity(84). Community health workers are critical for reaching communities through health promotion and identifying new TB patients. Healthcare workers only

perform recuperative activities and wait until patients decide to come to the health facilities when patients are seriously ill(85).

Socioeconomic factors also play a role in limiting access to health services. Although diagnosis and treatment of TB is intended to be free, patients pay for the first medical consultation (an amount less than 3 USD), an amount which is prohibitive for low-income individuals. Waiting time also plays an important role. Patients may lose from several hours up to a full day of work just waiting to be seen at health facilities(36; 37). This drives patients to look for a quick fix, including seeking care at "Boticas", which are informal drug stores staffed by untrained and/or uncertified personnel. This behavior delays the diagnosis and treatment of TB patients and increases the period of transmissibility.

Additionally, cultural factors and addiction may play a role in timely diagnosis and treatment. There are cultural factors which impede proper care-seeking behaviors, including familiarity and comfort with informal health care sector. Community healers and shamans are often the first point of contact for patients in search for treatment. Further, alcoholism, drug addiction or criminal activities may deter patients from seeking appropriate care, cooperating with health personnel, and adhering to drug regimens(36; 37).

Another problem is the high treatment default rates among in MDR-TB and XDR-TB patient populations. Causes of treatment default include: clinic hours which coincide with work schedules forcing patients to choose between work and treatment; inadequate timetables which disrupt working hours; substance abuse and mental illness that impede the understanding of benefits of the treatment; individual interpretations of recovery

whereby patients feel better before the end of the therapy course and prematurely discontinue treatment, as well as, perceptions around TB and recognition of TB as a disease(36; 37; 100). These barriers are important factors in controlling TB in the slums of large cities. It is therefore necessary to design new interventions with these factors in mind to more effectively target areas with high burden of TB. The next section will address some urban control experiences.

URBAN TB CONTROL EXPERIENCES

Urban TB control strategies include examples which take a structured approach toward addressing main control barriers in urban slums. For example, a 2002 strategy rolled out in Mumbai was designed to address the lack of commitment showed by public and private providers to follow the National TB Control Program (NTCP) policy on diagnosis, treatment, monitoring, and reporting of TB(141). NTCP put in place a number of stepwise strategies to reinforce coordination of services and partnership building(114). This strategy achieved important goals, such as improving rates - of vitals indicators, TB control measures - and individuals receiving standardized treatment in either the public and private sectors(3).

Another illustrative and multi-pronged strategy was implemented by the New York City Department of Health and Mental Hygiene (DOHMH) in the early 1990s. This intervention was prompted by an increase in the notification rates in certain parts of the city such as Harlem where reporting rates exceeded 200/100,000(103). Prior to implementing the strategy, challenges included cure rates below 50%, a high treatment default rate and a public/private sector divide with the majority of TB cases were managed outside DOHMH facilities, mainly in the private sector (56; 60). The DOHMH

intervention consisted of a package of strategies, e.g.: "operational changes included a range of activities to improve case management and TB prevention in all relevant healthcare facilities in the city; legislation to impose diagnostic tests and detention for patients who refused diagnosis or treatment was enforced; and prevention of transmission in the community through downsizing large shelters and working toward non-congregated housing for the homeless"(103; 114). Over time, these strategies reduced the numbers of new TB cases as well as drug-resistant TB patients(103).

In Peru, the strategy "TB Zero plan: an integral approach to control Tuberculosis"(59) was implemented in the shanty area of Cerro San Cosme in the district of la Victoria, in March 2009. This area has a high risk for TB transmission with the highest TB incidence rates for all of Peru, and where conditions such as informal employment, psychosocial disturbances, poverty, high migration rates, and overcrowding had previously hampered the success of many intervention measures(59). This novel multi-pronged approach included the following components: advocacy, clinical management of individuals / families / communities affected by tuberculosis, management of the main nutritional and psychosocial factors of TB and TB-HIV co-infection and other comorbidities (diabetes, etc.), infection control measures, health promotion and communication, and overall plan management(59). The main results of TB Zero after three years of intervention were: 130% increase in the number of persons with respiratory symptoms identified, a reduction in the percentage of therapy withdrawals by 83% of the base line, a 20% reduction in the incidence of pulmonary TB, humanization of family/community healthcare, and the participation of local authorities in the design and execution of public health policies(59).

These previous experiences have demonstrated that this kind of approach – one which is focused on specific strategies, which take into account the epidemiological context and the realities of the health system situation, address health determinants of health, and encourage political and community participation- is viable. The lessons learned are important for informing the design of TB control programs in large metropolitan slums. Further, solid evidence from scientific and health economic evaluations are crucial to gain the support of health authorities for slum-based initiatives. In the following section, we are going to describe, a new strategy, being leading by PAHO, to control tuberculosis in urban settings within LAC.

"TUBERCULOSIS CONTROL IN LARGE METROPOLITAN CITIES IN LAC" INITIATIVE

Despite of the major progresses in reducing tuberculosis cases and deaths in the past two decades(152), much work remains to be done in the area of drug-resistant TB and among those populations most afflicted. In light of this issue, PAHO has designed a new initiative to control tuberculosis called "Control of Tuberculosis in Large Metropolitan Cities in LAC", henceforth abbreviated as the "intervention" to abbreviate. This initiative was born out of the workshop entitled "Regional Meeting on Control of Tuberculosis in Large Cities: Challenges and Approaches" held in Argentina in September 2011(110). After intense discussion, and the sharing of lessons learned from local experiences with TB control in urban slums of countries like countries like Peru, Colombia, and Brazil, the following agreements were reached(110):

1. TB is mainly an urban problem and it has to be faced with an interagency and multi-sectoral approach, including all stakeholders at different levels of the government and the private sector(110).
2. There is a need for operational research and health economics studies of current strategies to control tuberculosis in large cities(110).
3. It is important to address social determinants and community participation, in the fight against TB(110).

The resulting initiative is comprised of the following components (109):

- "Strengthen political commitment at national and local levels, and coordinate with the different health authorities (109)".
- "Conduct epidemiological mapping of the distribution of TB in cities and identify populations at risk (109)".
- "Survey and map the health system and existing healthcare providers (109)".
- "Adapt the health care system to the needs of populations at risk (109)".
- "Take an inter-programmatic approach to TB control to guarantee comprehensive patient care (109)".
- "Take an intersectoral approach to TB control and include TB in social protection programs (109)".
- "Promote civil society engagement in TB prevention and control activities (109)" and
- "Establish an ongoing system of monitoring and evaluation".

Finally, one of the key points of this initiative is that it must be included within the national plan of TB control to ensure adequate funding and the accomplishment of the objectives. However, in addition to the general recommendations of this initiative, participating countries must identify the best strategies to control TB according to their local context.

Peru, Colombia, and Brazil have joined this initiative and gradually implementing it beginning in 2012. In the case of Peru, this initiative is called "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 - 2017". It is taking place in the 106 health facilities in Lima and Callao, which are areas with the highest burden of non-resistant TB, MDR-TB and XDR-TB tuberculosis.

The Minister of Health of Peru, following the recommendations of this initiative has designed the "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 – 2017" to control TB in urban slums of Lima and Callao.

EMERGENCY PLAN FOR THE PREVENTION AND CONTROL OF TUBERCULOSIS IN LIMA AND CALLAO, 2015 – 2017(50)

This plan aims to prudently use the scarce resources available to control tuberculosis and to target the urban areas of large cities with a high burden of tuberculosis. The purpose of this plan is to reduce and control TB in all its forms in metropolitan Lima and the constitutional province of Callao through the rapid implementation of different public health interventions to rapidly close the gaps in the current health services and to address social determinants linked to tuberculosis in the context of territorial management. Local governments (districts level) of Lima, regional, provincial and district governments of Callao, and other sectors of the government will

all actively participate and coordinate in concert with the "Prevention and Control of Tuberculosis in Peru" Act 30287.

This plan has three main strategic objectives:

Objective 1. "To improve the comprehensive and timely delivery of health services to people with sensitive and resistant TB, under the Legislative Decree No. 1166 - Establishment and Operation of Integrated Health Care Networks"(50).

Objective 2. "To strengthen the bacteriological and radiological diagnosis of TB and the rapid detection of drug resistant TB in Lima and Callao" (50).

Objective 3. "To promote and develop strategic proposals and multi-sectorial coordination mechanisms for the prevention of TB and to address the social determinants of health associated with TB" (50).

This plan targets 93-health facilities within metropolitan Lima and 13-health facilities in Callao with the largest burden of tuberculosis based on an epidemiological mapping.

The health system and existing health-care providers mapping was incorrectly performed limiting its use in the diagnosis of TB.

The main interventions of this plan are listed in the following paragraphs(50):

1. Address human resources gaps in the National Sanitary Strategy of Control and Prevention of Tuberculosis.
2. Active participation of community actors in TB control.
3. Intervene to reduce TB treatment default.
4. Infection control in health services and patients homes.
5. Establishment of surgical centers to perform pulmonary surgery for TB patients.

6. Creating sanatoriums for the institutionalized and extending management of XDR-TB among socially abandoned patient populations.
7. Improving TB diagnostic using digital radiology, fluorescence smears, and cultures in liquid medium.
8. Universalizing rapid drug-susceptibility testing for all TB patients.
9. Managing co-infection TB/HIV.
10. Addressing the social determinants related to TB.
11. Managing based on nominal and real time data from information systems.

This plan is broad and lacks the specific objectives necessary for successful implementation. Furthermore, this plan is similar to "Multi-Sectorial and Strategic Plan for the National Response Against Tuberculosis in Peru, 2010-2019 encompassing similar interventions already covered by the National plan. Due to this redundancy, the newly proposed interventions fail to follow the proposals of the TB control in large metropolitan cities initiative instead focusing on a higher-level national perspective. To address this issue, the National Sanitary Strategy of Control and Prevention of Tuberculosis has designed a focalized intervention to address treatment interruption and treatment default, which are the main problems of the control of TB in Lima. Treatment default causes low rates of treatment success, high mortality rates, and increased TB transmission in the community.

CURRENT AND NEW APPROACH OF TB CONTROL IN LARGE METROPOLITAN CITIES IN LIMA, PERU

Current approach to control TB in Peru

The current strategy of TB control in Peru follows the recommendation of DOTS/DOTS plus and Stop TB strategy and the national TB guidelines(86). This program has a national perspective with an information system based on aggregated operational aggregated reports for non-resistant TB and an individual based system for resistant TB. However in 2014, the national program implemented an individual based system for non-resistant TB as well. It is still being implemented and is expected to be fully operational by the end of 2016. The lack of more detailed information at the local level is a primary barrier to identifying problems with and innovating solutions to the control of tuberculosis. Another barrier is the lack of competent personnel to perform a comprehensive evaluation of TB control and to design creative and innovative interventions based on the conclusions.

Control measures focus mainly on diagnosis confirming by sputum smear and culture, rapid susceptibility testing (MODS, GRIESS, GENOTYPE® MTBDRplus assay), and on receiving appropriate and supervised treatment at a health facility. Furthermore, efforts focus on looking for symptomatic respiratory patients at the health facilities, identifying and medically examining of all TB contacts, and administering isoniazid chemoprophylaxis for latent TB among other things. It is important to note that the universalization of rapid susceptibility testing with MODS and GRIESS was implemented in 2013 and while the GENOTYPE® MTBDRplus assay in 2014(90). Finally, further control measures included two months of initial hospital-based treatment and home based-treatment for XDR-TB both implements in 2014.

All of the aforementioned strategies have been very important to control tuberculosis but do not adequately address treatment default, mainly in non-resistant and MDR treatment.

Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 - 2017(92)

This new strategy called "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 - 2017" follows the recommendations of the "Control of Tuberculosis in large metropolitan cities in LAC" Initiative(109) and the "Multi-sectorial and Strategic Plan for the National Response against Tuberculosis in Peru, 2010-2019"(49). In reality, this strategy is similar to the "Multi-sectorial and Strategic Plan for the National Response against Tuberculosis in Peru, 2010-2019", except for the focalized intervention in twenty health facilities of the 93 prioritized for Metropolitan Lima focused on addressing the high rates of default and treatment interruption in both resistant and non-resistant TB treatment, low rates of census and medical examination of TB contact, low rates of TB cases with comprehensive care, and isoniazid Chemoprophylaxis of Tuberculosis.

One of the problems with the "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 – 2017" is its lack of specific objectives. This plan lays forth general principles but fails to dictate how to address the main determinants of tuberculosis in large cities such as Lima. In order to fill this gap, the national program and the Institute of Health Services Management decided to implement a focalized intervention (which we plan to evalute) to address the main problems of tuberculosis in Metropolitan Lima, which are:

- High rate of treatment default of non-resistant treatment: 8.1%
- High rate of treatment default of resistant treatment: 24%
- Low rates of contact examination of TB patients: 85%
- Low rates of TB cases with comprehensive care: 40%

These main problems are due to a shortage of health personnel at the health facilities which impede the monitoring of the treatment of TB patients, provision of comprehensive care, and the tracing of contacts and their healthcare evaluation. These conclusions were supported by a prior health system evaluation which guided the design of the focalized intervention.

Focalized intervention to address treatment interruption and treatment default, and contact examination of TB patients(51)

This intervention was developed by the National Sanitary Strategy of Control and Prevention of Tuberculosis, and the Institute of Health Services Management and PAHO's technical advisers after rigorous analysis of the main causes of these three problems (treatment interruption, treatment default, and contact examination of TB patients). For this purpose they reviewed the scientific literature and developed a theoretical model based on PRECEED/PROCEED model to understand root cause of these risk factors. To identify and evaluate these causes, they performed various operational research at different levels including: patients, healthcare workers and health facilities.

They concluded that the main causes of treatment interruption and treatment default included(51):

- Lack of treatment follow-up and the missed identification of patients with treatment interruption due to insufficient of human resources.
- Lack of comprehensive package of care for TB patients that includes a medical, nursing, social, psychological, and nutritional assessment during the first week of treatment onset because of insufficient commitment of health care workers, and inadequate schedules for patients and their contacts.
- The administration of TB treatment is not centered on the patient's needs and daily schedule because most of the health facilities open only 6 hours per day. Furthermore, the health facility based-treatment approach (DOTS) is a barrier for some TB patients who cannot reach health facilities because of physical impairment.
- Lack of addressing predisposing, reinforcing and enabling factors, such as a lack of motivation to continue the treatment, insufficient reminders, inconvenient clinics hours, and limited patient-centered care, etc., all attributes to poor health system organization and manpower shortages.

According to the main causes identified in the operational studies, they designed and implemented the following intervention:

Nursing intervention: There was a dedicated nurse in each prioritized health facility tasked with performing the following activities:

1. Daily follow-up of all patients on TB treatment.
2. Home visits and nursing counseling for all patients with treatment interruption.
3. Improved coordination of patient's appointments to fulfill requirement of comprehensive care that include medical assessment (It includes a baseline

clinical evaluation of the TB patients by a general practitioner, treatment scheme and labs test), nursing assessment (it includes assessment of the knowledge and attitudes of patients about TB, counseling and education), psychological assessment (it incudes (it includes emotional evaluation of TB patients, as well identification of alcoholism and drug addiction), social services assessment (it include a social and economical assessment) and laboratory pack (it include a set of lab test – see appendices 2a and 2e for more details).

4. Identification of patients with social risk factors such as alcoholism, drug abuse, justice problems and patients that live alone.

This intervention also has included provisions to improve information systems and monitoring and evaluation activities.

Monthly supervision of the local Sanitary Strategy of Control and Prevention of Tuberculosis

A monthly review of the prioritized health faculties was established to monitor the performance of the TB team, and the dedicated nurse. Contact tracing of patients was orchestrated by dedicated nursed staff who were responsible for scheduling individuals who had contact with TB patients.

This intervention was implemented in 20 health facilities with the largest burden of treatment interruption and treatment default within metropolitan Lima.

This new intervention needs to be assessed in order to prove its effectiveness at controlling this problem and possibly including it among standard control measures to be expanded to other areas with similar treatment default problems. Addressing this significant need for objective evaluation, we will perform a cost-effective, cost-utility and

cost-benefit analysis of this intervention. In the following section we will discuss the role of health economic assessment in public health and decision-making.

WHO'S END TB STRATEGY 2016-2035

The 67th World Health Assembly of 2014 adopted the "End TB Strategy" with a vision of ridding the world of TB and with a goal of ending the global TB epidemic by the year 2035(139).This strategy has three pillars: 1) integrated, patient-centered care and prevention; 2) bold policies and supportive system; and 3) intensified research and innovation. Similarly there are three corresponding high-level indicators 1) reductions in TB deaths; 2) reductions in TB incidence rate; and 3) reductions in the percentage of TB patients and their households experiencing catastrophic costs(140; 153).

The third pillar of the "End TB Strategy" emphasizes "the discovery, development and rapid uptake of new tools, interventions and strategies" (140; 153). The "Tuberculosis control in large metropolitan cities in LAC" initiative directly aligns with this component of the "End TB Strategy as the initiative is a new, innovative and is designed to identify and target the main problems of TB control through a comprehensive assessment (50).

Further, in order to achieve the pillars and goal of the "End TB Strategy," countries must address the issue of treatment default, which has implications for disease transmission as well as mortality rates – two high-level indicators adopted by the Strategy. This is a key area of focus for the "Control of TB in large metropolitan cities" initiative in Peru, which aims to reduce the TB incidence rate through addressing and reducing treatment default (51).

THE ROLE OF HEALTH ECONOMIC ASSESSMENT IN PUBLIC HEALTH

Decision-making in public health is a complex process infrequently used among government officials and health care systems administrators(117). Many factors should be taken into considerations such as population's needs, economic resources, etc. Economic evaluation is an important decision-making tool helping determine the relative efficiency of different public health interventions ultimately leading to the efficient management of scarce health care resources(147).

Despite the advantages of leveraging health economics analysis in the decision-making process, it is scarcely used in developing countries and even in some developed countries. A qualitative study of Australian senior managers found that "there was a high level of awareness of economic evaluation among the group of decision makers interviewed and that some had used it in their decision-making"(117). A systematic review completed in the United Kingdom, found that "local decision-making focused primarily on evidence of clinical benefit and cost implications rather than cost-effectiveness information"(148). Similar results regarding the use of cost-effectiveness in decision-making were supported by another study in Australia(142). If cost-effectiveness analysis is barely used at local, regional, and national levels in most of the developing countries, then cost-benefit analysis is also rarely used(40).

Despite the value of health economic evaluations in public health decision-making, there are some caveats to consider within the welfare economics theory. The Pareto Improvement principle state that "if one person can be made better off without another being made worse off, there is global improvement in welfare. This value judgment is uncontroversial but, in policy terms, practically useless: few policies benefit

some individuals without affecting others"(31). Finally, the threshold at which one considers an intervention cost-effective is subjective and not always well received by decision makers(31).

The last few years have seen a renaissance in health economic techniques. Nowadays we have sophisticated methods based on modeling, such as Markov chain, Monte Carlo or probabilistic simulation, microsimulation modeling, agent-based modeling, and transmission model based on ordinary differential equation, etc.(34; 144), that have allowed more realistic and complex healthcare models to be more rapidly simulated. The advantage modeling techniques facilitate an improved decision-making process allowing a more comprehensive breadth of scenarios to consider(52; 146; 147).

HEALTH ECONOMIC STUDIES IN TUBERCULOSIS CONTROL

In the field of tuberculosis, the majority of the health economic evaluations have focused on new diagnostic tools for resistant TB such as MODS, genetic test, etc.,(41; 42; 145); treatment resistant TB(127; 134), TB vaccine(29) and latent TB chemoprophylaxis(39; 81). All of these health economic studies have supported the introduction and implementation of rapid susceptibility tests (molecular and non-molecular) in all TB control programs around the world. Furthermore, other health economic studies have supported the use of home-based treatment, community based approaches to reduce treatment default, and active case finding to reduce the burden of disease in TB hot zones(12; 21; 79; 93; 94; 155).

Directly Observed Therapy Short Course (DOTS) strategy was first implemented in 1995 by WHO in an effort to address non-adherence of TB patients and high mortality

rates(149). This intervention was originally implemented in a spite if dearth of health economic evidence. Recent studies have shown that DOTS to be cost-effective, for example one study sponsored by WHO showed that the DOTS program cost was 6-8 USD (2000 international dollars) per DALY averted in new cases of smear-positive tuberculosis at coverage levels of 50-95%(8). The same study showed that DOTS-Plus treatment for multidrug resistant cases cost 123 USD (2000 international dollars) per DALY averted(8). A 2007 study showed that the incremental cost effectiveness ratio (ICER) for DOTS was $300 per case averted, and the ICER for DOTS was $86 per DALY saved(95). Notably, Peru has implemented DOTS from the beginning of the National TB Program in 1990, and DOTS-plus was implemented in 2005.

There is a wealth of economic literature to suggest that rapid susceptibility testing against second-line drugs for tuberculosis is cost-effective. For example, Dowdy et al. demonstrated that rapid susceptibility testing against second-line drugs for tuberculosis cost 633 USD per DALY averted in low-income setting and 675 USD per DALY averted in middle-income setting(42). In 2012, The Peruvian National Program universalized rapid susceptibility testing against second-line drugs for tuberculosis because of this public health evidence, mentioned above.

Furthermore, one study found that the combination of sputum smear and chest x-ray was more cost-effective than sputum smear alone and chest x-ray alone, because it had a high probability of correct pulmonary TB diagnosis and could be accomplished in two visits.(65). In Peru, sputum smear and culture is used as a routinely diagnostic, followed by rapid susceptibility testing against second-line drugs for tuberculosis in a sputum smear positive patient.

Other strategies have also been evaluated from the health economic point of view. For example: tuberculosis active case finding program have been shown to be highly cost-effective in reducing mortality from 14% to 2% at a cost of 330 USD per DALY averted(154). However, the Peruvian National TB Program has not yet to able to implement tuberculosis active case finding strategy in TB hot spots TB areas.

Additionally, the cost-effectiveness of home-based care versus hospital care strategies for chronically ill tuberculosis patients have also been evaluated. One study found home-based care was more cost-effective with a cost of 1726 USD per patient complying with home-based treatment versus a cost of 2970 USD for treatment receiving during hospitalization(94). Since 2012, XDR-TB patients, in Peru are hospitalized and treated for two-months, following by delivery care in the home until the injectable regimen is complete. Alternative treatment strategies which have been evaluated include community-based DOT which has been shown to be cost-effective and to increase treatment completion rates at a cost of 200 USD per patient(53). Community-based DOTS has not been undertaken by the Peruvian National Program as a health intervention strategy

Economic evaluation plays an important role in determining cost-effective public health and TB control-specific strategies. To our knowledge, our study is the first economic evaluation of this new strategy to control TB in large cities, and could serve as a model for other countries in LAC and other WHO regions.

CHAPTER 2: Methods

CHARACTERISTICS OF THE POPULATION AND AREA OF STUDY

This study took place in the districts of San Juan de Lurigancho and El Agustino in Lima, Peru, where the new strategy was implemented in 22 health facilities of the San Juan de Lurigancho health network and 4 health facilities of the El Agustino micro network.

The district of San Juan de Lurigancho reported 2,090 TB cases, 122 MDR-TB, 5 XDR-TB during 2012. El Agustino reported 460 TB cases, 54 MDR-TB and 11 XDR-TB during the same year. San Juan de Lurigancho and El Agustino both have TB incidence rates above the national average of 93 per 100,000 population with incidences of 203 per 100,000 population and 242 per 100,000 respectively(85).

Furthermore, San Juan de Lurigancho has a treatment default in non-resistant TB of 9.8% and 31% in resistant TB. Meanwhile, El Agustino has a treatment default in non-resistant TB of 10.1% and 22.4% in resistant TB.

In Table 1, San Juan de Lurigancho and El Agustino epidemiologic and operational indicators are compared against Lima and Peru.

Table 1. Characteristics of the study population

Features	Peru	Lima	San Juan de Lurigancho	El Agustino
Population	30 million	9 million	2 million	200,000
Poverty	23.9%	12.8%	24%	20%
TB incidence rate per 100,000 population	93	154.6	203	242
New TB cases	27,504	16,255	2,090	460
MDR-TB cases	2,453	1,791	122	54
Treatment default rate in non-resistant TB	6.7%	8.1%	9.8%	10.1%
Treatment default rate in resistant TB	17%	19%	31%	22.4%

EFFECTIVENESS OF THE FOCALIZED INTERVENTION

General Objective

The main objective of this study was to determine the impact of the focalized intervention compared to the status quo to decrease the TB incidence rates over a twenty years period. To meet this general aim we accomplished the following specific objectives:

1. To determine the effectiveness of the focalized intervention effectiveness to reduce the treatment default rate during the first five months of this intervention in an Ex-post analysis.

2. To determine the impact of the focalized intervention to reduce the TB incidence rate over a twenty-years period in an Ex-ante analysis.
3. To determine if the focalized strategy is cost-effectiveness over a twenty-years period in an Ex-ante analysis.
4. To determine if the focalized strategy is cost-utilitarian over a twenty-years period in an Ex-ante analysis.
5. To determine if the focalized strategy is cost-benefit over a twenty-years period in an Ex-ante analysis.

General study design

We conducted an Ex-post analysis during the first 5 months of implementation of the focalized intervention to estimate the effectiveness of this intervention upon the reduction of the treatment default rate, and an Ex-ante analysis using a compartmental epidemiological model to estimate the impact of the focalized intervention upon the reduction of the incidence of tuberculosis for the following twenty-year. Now we are going to describe both Ex-post and Ex-ante analysis.

Ex-post analysis

This analysis was centered on determining the effectiveness of this focalized intervention for treatment interruption and treatment default during the five months of implementation compared with the status quo. It also sought to determine the total cost and the cost of illness of both the baseline case and the focalized intervention. To accomplish this goal, we used intervention data to compare the rates of treatment interruption and treatment default of the status quo with the ongoing focalized

intervention scenario. Furthermore, we have estimated the cost of the focalized intervention using the financial reporting forms.

To estimate the cost of illness of resistant TB in San Juan de Lurigancho and El Agustino, we have used the Electronic Medical Record dataset of the Sanitary Strategy of Control and Prevention of Tuberculosis, and for non-resistant TB we have used the individual dataset from the San Juan de Lurigancho health network. We could not get data from The El Agustino health network. We describe each dataset in the following paragraphs.

Data sources

Global baseline

We collected epidemiological data and operational outcomes for the focalized intervention and status quo scenario by reviewing the operational report and TB cohort report of local health facilities located in the target and non-target areas from 2012 to 2014. These data are aggregated by health facility.

These sources included the following data:

- *Demographic data*: estimated population and population age groups in the two target areas.
- *Administrative data*: outpatients and inpatients, number of respiratory symptomatic subjects identified and examined with sputum smear and culture, number of patients with GENOTYPE® MTBDRplus test, and default treatment rate and treatment success rate for each type of TB.

- *Epidemiological data*: new TB cases (MDR-TB, XDR-TB and non-resistant TB), number of deaths, number of pulmonary tuberculosis cases both smear positive and smear negative, number of TB patients both culture positive and culture negative, number of extrapulmonary TB cases, mortality rate, case fatality rate.

These sources were used to calibrate the compartmental transmission dynamic model. We will describe in detail this model in the Ex-ante analysis section.

Individual secondary data for resistant and non-resistant TB

We use the de-identified dataset from the Electronic Medical Record for resistant TB that has data encompassing age, sex, type of resistance, onset of treatment, date of discharge and treatment outcome. Furthermore, this dataset has information on the baseline laboratory and health assessment, and also data on the treatment, follow-up laboratory test, and health assessment.

For non-resistant TB, we have used the individual de-identified nominal dataset from the San Juan de Lurigancho health network. This dataset contains the following: age, sex, type of resistant, onset of treatment, date of discharge, and treatment outcome. Moreover, this dataset has information on baseline laboratory testing and health assessments, and also data on treatment and any follow-up laboratory test and health assessment.

These sources were used to describe the study population and to estimate the quantities of items used in the cost of illness calculations.

Focalized Intervention

We used the focalized intervention dataset that gather data from the following sources:

- Medical records
- Follow-up treatment records of patients taking first line TB drugs
- Follow-up treatment records of patients taking second line TB drugs
- Treatment control cards of patients taking first line TB drugs
- Treatment control cards of patients taking second line TB drugs

These sources included the following individual data:

- Demographics data: Age, sex, social factors
- Diagnosis, treatment and follow up data: Date of onset of treatment, type of TB, date of diagnosis, sputum TB smear, TB treatment, weekly adherence to treatment, reason to absence to treatment, default treatment.

Cost data sources

The cost analysis (cost of the program and cost of illness) included the use of the following sources of data:

- *Focalized intervention cost dataset* that include the following cost: nurse salary, monitoring costs, Monday's coordination meetings costs with nurses, transportation costs, and supervision costs of health facilities.
- *Ministry of Health price lists* that include the following costs: TB consultant physician encounters, psychiatrist encounters only if the patient is taking cycloserine or has a mental comorbidity; audiometry and otolaryngology services only if the patients is having injection aminoglycosides drugs such as streptomycin, amikacin, capreomycine. It also includes the diagnostic cost of: sputum smear, culture, rapid tests for the diagnosis of drug-resistant tuberculosis such as MODS, GRIESS, and GENOTYPE® MTBDRplus test, and culture for second-line drug resistant tests.

- *Comprehensive Health Insurance price lists* that include the following costs: general practitioner, nurse, psychologist, and social services staff encounters. It also includes the cost of nutritional and family planning counseling, as well as the cost of chest X-ray, hemogram, fasting blood glucose, electrolyte testing (sodium, potassium and chloride) only if patients is taking aminoglycosides drugs, creatinine blood test, liver blood test, thyroid-stimulating hormone (TSH) blood test only if the patients is taking ethionamide or p-aminosalicylic acid drugs, HIV rapid test or Elisa for HIV, and pregnancy test.

We have provided a full explanation about the cost methodology in the cost-effectiveness section.

Operational definitions

In this section we state the operational definitions for treatment outcomes, according to WHO and the National Sanitary Strategy of Control and Prevention of Tuberculosis (91):

Cured – "A pulmonary TB patient with bacteriologically-confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion" (152).

Completed treatment – "A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable" (152).

Died – "A TB patient who died from any cause during treatment" (152).

Failed – “A TB patient whose sputum smear or culture is positive at month five or later during treatment” (152).

Treatment default – “A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more” (152).

Not evaluated – “a TB patient for whom no treatment outcome is assigned. This includes cases ‘transferred out’ to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit” (152).

Successfully treated – this parameter was used in the model but not the parameter cured - is defined as “a patient who was cured or who completed treatment” (152).

Cohort – “A group of patients in whom TB has been diagnosed, and who were registered for treatment during a specified time period (e.g. the cohort of new cases registered in the calendar year 2012). This group forms the denominator for calculating treatment outcomes. The sum of the patients included in the above treatment outcome categories should equal the number of cases registered” (152).

Treatment interruption – “a TB patient that missed at least three treatment doses during the first phase of the treatment or that missed at least five treatment doses during the whole treatment ”(91).

Data management

Data was entered into an MS Excel database and then transferred to a MySQL dataset to conduct data mining. The relational database structure is depicted in Figure 1. We have created a relational database in MySQL with different tables that correspond to health facility, operational and epidemiological data, cost of the program, and cost of illness data. The HF_ID key links all these tables together. The cost tables were linked by

type of intervention (intervention or status quo) and economic study design (CEA, CUA, CBA).

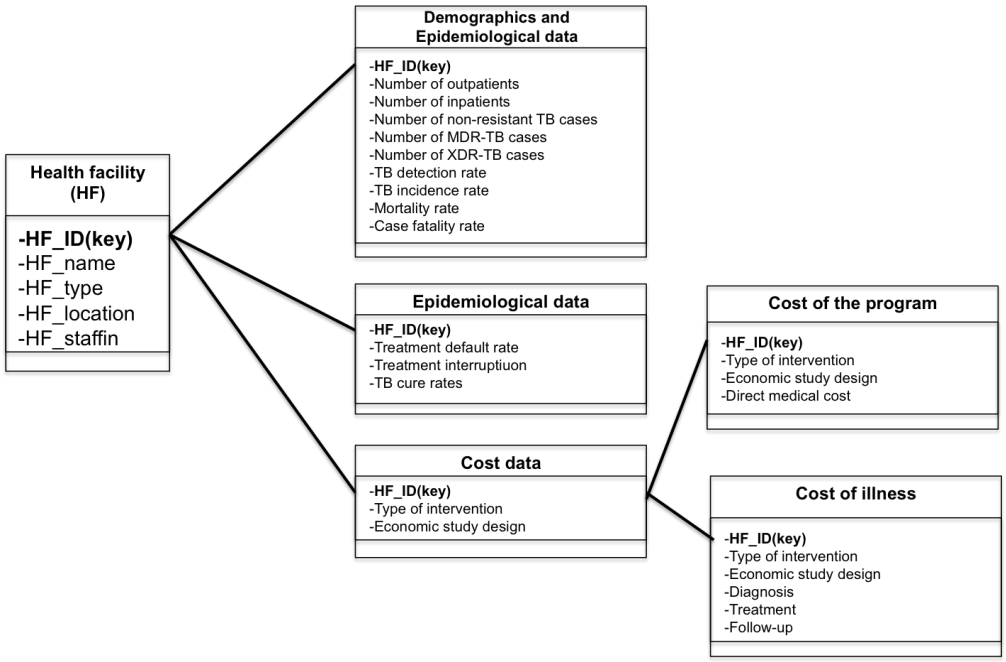


Figure 1. Relational database structure

Effectiveness calculation

The effectiveness of the focalized intervention during the five-month of implementation was calculated as the rate of change of the default treatment and treatment interruption between the status quo and intervention scenarios.

We have used the following formula to calculate the effectiveness of the focalized intervention:

$$\text{Effectiveness} = \frac{(\text{Treatment default rate}_{\text{focalized intervention}} - \text{Treatment default rate}_{\text{Status quo}})}{\text{Treatment default rate}_{\text{Status quo}}}$$

To estimate the effectiveness of the focalized intervention on treatment interruption, replace the treatment interruption rate in the formula for the focalized intervention and status quo.

We have also calculated the incremental effectiveness of the treatment interruption and treatment default by subtracting the treatment interruption rate of the focalized intervention from the treatment interruption rate of baseline; and by subtracting the treatment default rate of the focalized intervention from the treatment default rate of baseline.

Cost analysis

The cost analysis has included the estimation of program costs, and cost of illness. The program cost is the same for the three economic designs (CEA, CUA, CUA). The cost of illness represents the monetized benefit for the CBA.

We have used the "resource use" approach to determine the cost. The "resource use" items can be then combined with unit of cost to produce a 'cost' item for use within our economic evaluation(83). The cost of the program and the cost of illness have been determined using Macro-costing methodology. Macro-costing methodology uses readily available cost data such as hospital price lists or program cost lists, to determine costs, e.g. of health care episodes. In our case, TB episode is the unit of health care episode. This approach is good for calculating long-run average costs(83; 118).

Cost of the program

The cost analysis of the program was based on the identification of health sector resources used for both the intervention and status quo scenarios. The resources used are depicted in Table 2.

Table 2. Type of resources use for inclusion in this health economic analysis

Status quo	Focalized intervention
Cost of illness	Cost of illness
	Salary of dedicated nurses that perform the follow up of the treatment
	Monitoring of the focalized intervention by the team of the Institute of Health Services Management and the National Sanitary Strategy of Control and Prevention of Tuberculosis
	Supervision of prioritized health faculties to monitoring the performance of TB team, and the dedicated nurses by the team of the Institute of Health Services Management and the National Sanitary Strategy of Control and Prevention of Tuberculosis
	Monday's coordination meetings with dedicated nurses

Cost of illness

The cost of illness includes:

- The resources used for diagnosis: sputum smear and culture, X rays, rapid tests for the diagnosis of drug-resistant tuberculosis, proportions method in 7H10 agar in plates for first and second line-resistant drug.
- Baseline health examination: general practitioner, expert physician in resistant TB management, psychiatric (only if the patient in taking cycloserine or has a mental comorbidity), nurse, psychologist, and social services staff encounters; and nutritional and family planning counseling.

- Baseline Laboratory test: cost of chest X-ray, hemogram, fasting blood glucose, electrolyte testing (sodium, potassium and chloride) only if patients is taking aminoglycosides drugs, creatinine blood test, liver blood test, thyroid-stimulating hormone (TSH) blood test only if the patients is taking ethionamide or p-aminosalicylic acid drugs, HIV rapid test or Elisa for HIV, pregnancy test (women of childbearing age), and audiometry assessment (if the patients is having injection aminoglycosides drugs).
- TB treatment: non-resistant TB, MDR-TB or XDR-TB
- Follow-up: sputum smear and culture, chest X-ray; laboratory test: hemogram, fasting blood glucose, electrolyte testing (sodium, potassium and chloride) only if patients is taking aminoglycosides drugs, creatinine blood test, liver blood test. Lobectomy or pneumonectomy for resistant pulmonary TB. Medical and social follow up: general practitioner, expert physician in resistant TB management (could be a pulmonologist or not), nurse, psychologist, and social services staff encounters; and nutritional and family planning counseling.

It is important to note that in the estimation of cost of illness for the status quo, we used only direct medical costs and we not used used indirect costs, and for the focalized intervention we used direct medical costs, administration program cost (direct non-medical costs), and we not used used indirect costs.

Unit cost adjusted by inflation

The unit cost was estimated in dollars and adjusted by inflation according to Consumer Price Index (CPI) inflation methodology(44) for the year 2011 using the following formula:

$R_{(2011)} = (N/CPI)*CPI_{(2011)}$

Where:

R: real value (constant dollar)

N = nominal value (current dollar)

CPI = consumer price index

Table 3. Consumer price index* by year(99)

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
CPI	87.13	88.87	90.45	95.69	98.49	100.00	103.37	107.15	110.17	113.72

*The value for Consumer price index (2010 = 100) in Peru

"The Consumer price index reflects changes in the cost to the average consumer of acquiring a basket of goods and services that may be fixed or changed at specified intervals, such as annually"(99).

Discount rates

Discounting makes it possible to compare benefits and costs that occur at different times by adjusting their values according to time preferences corresponding to the chosen perspective(62). We have used a discount rates of 3%.

Converting costs into USD

To convert "Nuevos soles" (Peruvian currency) to USD we have used the purchasing power parity (PPP) conversion factor, Gross Domestic Product (GDP) (Local Currency Unit (LCU) per international $) that is "the number of units of a country's currency required to buy the same amounts of goods and services in the domestic market as U.S. dollar would buy in the United States"(131). This conversion factor is for GDP.

For most economies PPP figures are extrapolated from the 2011 International Comparison Program (ICP) benchmark estimates or imputed using a statistical model based on the 2011 ICP.

We have used the following formula:

Dollar = Item Cost (Nuevos soles) * Purchasing power parity conversion factor

Table 4. Purchasing power parity conversion factor by year(99)

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
PPP	1.33	1.40	1.40	1.40	1.41	1.48	1.52	1.53	1.53	1.55

Ex-ante analysis

The objective of the Ex-ante analysis was to estimate the incremental effectiveness of the TB incidence rate of the focalized intervention for the following twenty-years in the San Juan de Lurigancho health network. We have used a compartmental dynamic epidemiological model based on the natural history of tuberculosis to estimate the TB incidence rate.

Description of the compartmental dynamic epidemiological model

We built a deterministic model to study the transmission dynamics for non-resistant TB and MDR-TB at the health network level; this model assumes homogeneous mixing within the entire population of interest. Figure 3 depicts the compartment model based on the model analyzed in Blower and Small et al(18), Blower and Gerberding(17), and Horn and Simonett(70).

The model is composed of 8 compartments, 5 for the disease itself (S, L_S, L_R, T_S, T_R,), and 3 for the interventions (C_S -this compartment is not in the figure 2, E_S, E_R). The notations used in this section are explained in the following table.

S	Number of individuals susceptible
L_S	Number of individuals latently infected with drug-susceptible tuberculosis
L_R	Number of individuals latently infected with drug-resistant tuberculosis
C_S	Proportion of non-resistant cases with TB chemoprophylaxis
T_S	Number of cases of drug-sensitive tuberculosis
T_R	Number of cases of drug-resistant tuberculosis
E_S	Number of cases of effectively treated drug-sensitive cases
E_R	Number of cases of effectively treated drug-resistant cases
Π	Birth and immigration rate
β_S	Transmission coefficient for drug-sensitive *M. tuberculosis*
β_R	$= \alpha\beta_S$
α	Relative transmissibility
$1/\mu$	Average life expectancy
p	Proportion of new infections that develop disease within 1 year
ν	Progression rate to disease (for latently infected individuals)
μ_T	Mortality rate due to tuberculosis
r	Probability of drug resistance emerging during treatment
δ	Relative treatment efficacy
Φ	Per capita effective treatment rate

In this model a susceptible person could be infected by a resistant or non-resistant TB infectious case and then move from the susceptible box to the resistant latently infected or the non-resistant latently infected box if the infectious tuberculosis case has resistant or non-resistant tuberculosis respectively according to λ_S*(1-p) or λ_R*(1-p). Note that $\lambda_S=\beta_S T_S$ and $\lambda_R=\beta_R T_R$.

From there, the resistant latently infected or non-resistant latently infected persons could move to the resistant active TB box or to the non-resistant active TB box with a rate ν. Some susceptible cases move to resistant or non- resistant active TB at a rate of λ_S*p or λ_R*p.

Persons with resistant or non-resistant active TB could get treatment at a rate of Φ. Some non-resistant individuals could develop resistant TB over the course of an inadequate treatment at a rate r. Finally, a person in treatment could be cured at a rate δ.

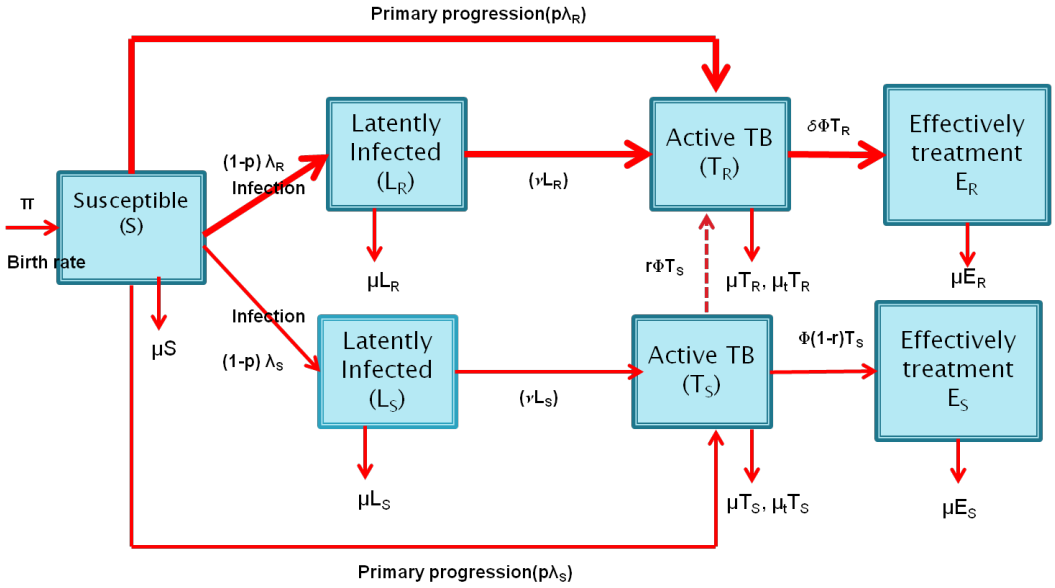


Figure 2. Compartmental epidemiological model modified from(17; 18; 70)

The model is specified by the following eight ordinary differential equations (ODE) (17; 18; 70):

1. $\frac{dS}{dt} = \pi - S(\lambda_s + \lambda_R) - \mu S,$
2. $\frac{dL_S}{dt} = (1-p)\lambda_s S - (\nu + \mu + \sigma)L_S,$
3. $\frac{dC_S}{dt} = \sigma L_S - \mu C_S,$
4. $\frac{dL_R}{dt} = (1-p)\lambda_R S - (\nu + \mu)L_R,$
5. $\frac{dT_S}{dt} = p\lambda_s S - \nu L_S - (\mu + \mu_t + \phi)T_S,$
6. $\frac{dE_S}{dt} = \phi(1-r)T_S - \mu E_S,$

7. $\frac{dT_R}{dt} = p\lambda_R\, S + \nu L_R + \phi r T_S - (\mu + \mu_t + \delta\phi)T_R,$

8. $\frac{dE_R}{dt} = \delta\phi T_R - \mu E_R,$

We calibrated the model by letting it run freely from 1967 to 1990, until it reach the incidence rate of 200 per 100,000 population, which is the year where TB program begun. After that, we run the status quo scenario (TB program before the focalized intervention) until the model reach the 2014 TB incidence rates (110 per 100,000 population) in San Juan de Lurigancho, and then we run the focalized intervention scenario to estimate the TB incidence rates and the MDR-TB proportion in both scenarios, over a twenty years period.

The ordinary differential equations system was solved numerically with Matlab® using the ode45 which is a versatile ODE solver(129).

We used nonlinear curve-fitting least square to estimate βS, for this task we used Matlab lsqcurvefit function that fit the model to the data.

COST-EFFECTIVENESS AND COST UTILITY ANALYSIS.

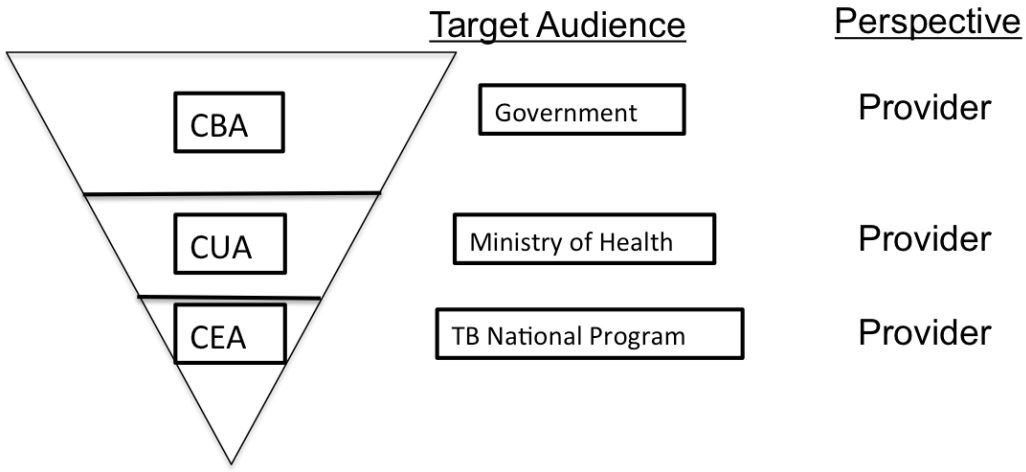
General Objective

The main objective of this study was to determine the cost-effectiveness of the focalized intervention using as outcomes: TB cases averted (classic cost-effectiveness analysis) and DALYs (cost-utility analysis). This analysis used the results of the compartmental epidemiological model in a twenty-year long run.

Study design

We have performed a health economic analysis to assess the cost-effectiveness of the focalized intervention in the San Juan de Lurigancho health network.

This health economic analysis has two different target audiences and perspectives according to each specific economic design (see Figure 3). The audience for the cost-effectiveness analysis (CEA) is the National Sanitary Strategy of Control and Prevention of Tuberculosis as it has a provider perspective. The cost-utility analysis (CUA) targets the Peruvian Ministry of Health approaching the issue from a provider perspective too.



CBA: Cost-benefit analysis, CUA: cost-utility analysis, CEA: cost-effectiveness analysis.

Figure 3. Target audience and perspective of the health economic analysis

The results obtained in the ex-post analysis (default treatment rate and the cost of the program and cost of illness) have fed a decision tree model and a compartmental epidemiological model to perform the ex-ante analysis.

The time frame of the economic analysis, which is the same for the three economic designs (CEA, CUA, CBA), is three-years. The analytic horizon is twenty-years.

The theoretical framework behind the study design is explained graphically in Figure 4. This economic analysis has two specific economic designs: CEA, CUA. In both analyses we have compared status quo scenarios in San Juan de Lurigancho (Alternative 1) versus the focalized "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 - 2017" in the same two districts (alternative 2).

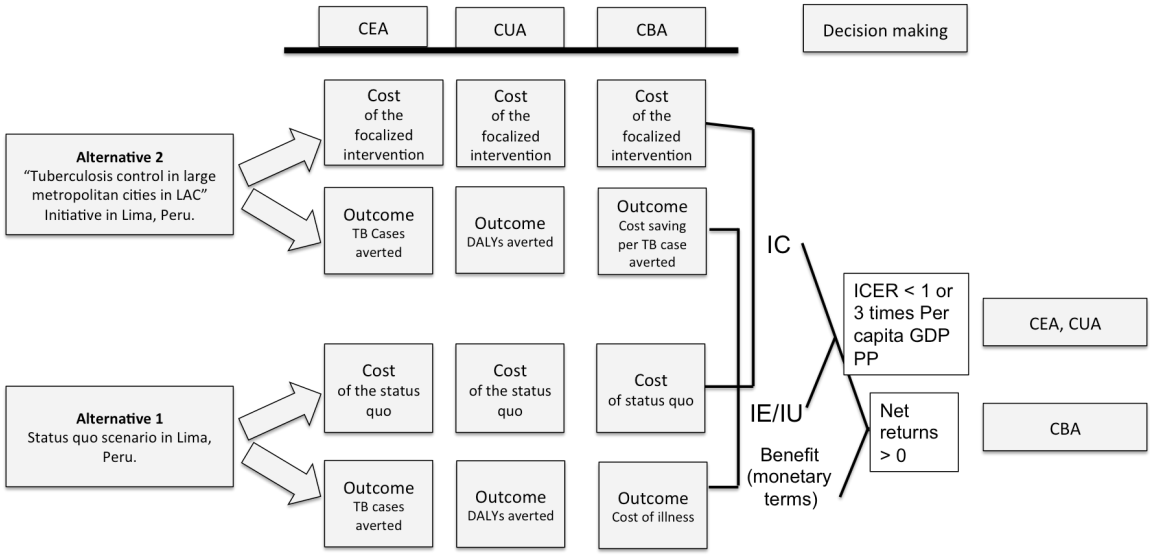


Figure 4. Theoretical framework behind the study design

The outcome will vary with each specific economic design. For the CEA, the outcome was TB cases averted, and for the CUA the outcome was Disability Adjusted Life Years (DALYS) averted (see Table 5).

Table 5. Health outcomes for each specific economic study design

	CEA	CUA
Health outcome	Cost per TB case averted	Cost per DALY averted

For both studies, we have calculated: the incremental cost (IC), the incremental effectiveness (IE), and the incremental utility (IU). With these results, we calculated the incremental cost effectiveness ratio (ICER) for the CEA and CUA, and the net returns for the CBA. Conclusions are based upon a comparison of the ICER with 1 or 3 times Peruvian per capita GDP PPP in 2014 (11,513.95 USD) for CEA and CUA.

Outcome measurement

The health outcomes of the CEA and CUA have been shown in Table 3. The following is an explanation of how to calculate the different health outcomes for CEA and CUA.

CEA health outcomes calculation

The cases averted will be calculate using the following formula:

$$IE = E_{\text{Focalized intervention}} - E_{\text{Estatus quo}}$$

IE is incremental effectiveness and E is effectiveness in the focalized intervention or status quo.

CUA health outcomes calculation

The health outcome of the CUA is Disability Adjusted Life Years (DALYs). DALYs are healthy life years lost, calculated by adding the adjusted number of years lived with disability (YLDs) and the number of years of life lost due to premature mortality (YLLs):

YLD = Number of new TB cases x duration till remission x disability weight

YLL = Number of TB deaths x life expectancy at the age of death

$$DALY = YLD + YLL$$

The DALY has the following formula:

$$-\left[\frac{DCe^{-\beta a}}{(\beta+r)^2}\left[e^{-(\beta+r)(L)}\left(1+(\beta+r)(L+a)\right)-\left(1+(\beta+r)a\right)\right]\right]$$

Where, D is disability weight, r is discount rate, C is age weighting correction constant, β is the parameter from the age-weighting function, a is age of onset, L is duration of disability or time lost due to premature mortality. More information on the parameters is shown below.

Disability weight (D): "is a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death)" (101). We will be using the disability weight of the Global Burden of Disease 2004 update of WHO(151).

Discount rate (r): "discounts the years of healthy life lived in the future, at a rate of (usually) 3%. The incorporation of a time discount rate reflects similar practices in economic assessments, and would prevent policy makers from saving resources for a possible future eradication program, instead of investing in currently available, but less effective, intervention measures" (the so-called "disease eradication and research paradox"(101).

The standard time discounting formula is as follows:

Weight = e(-0.03 * (age – a)),

Where "a" is the age at onset or death.

Age weighting (C): "The initial Global Burden of Disease study, and many ensuing studies, applied non-uniform age weights, implying that the value of life depends on age. A higher weight is given to the healthy life years lived between the age of 9 and 54, as this period of life is considered to be socially more important than the younger and older life spans"(101).

The standard age weighting formula is as follows:

Weight = 0.1658 * age * e(-0.04 * age)

DALYs were calculated using the programming language R®, for this purpose, we wrote a code to find a solution to the DALYs formula(113).

Cost effectiveness ratio

We will calculate the Incremental cost-effectiveness ratio (ICER) which compares the differences between the costs and health outcomes of the status quo and the new strategy, it is generally described as the additional cost per additional health outcome(44; 62; 63; 97).

The ICER we will be calculated according the following formula:

$$\text{ICER} = \frac{(\text{Total cost}_{\text{Focalized intervention}} - \text{Total cost}_{\text{Status quo}})}{(\text{Total outcomes}_{\text{Status quo}} - \text{Total outcomes}_{\text{Focalized interventions}})}$$

Decision-making

The cost-effectiveness of the intervention against the status quo scenario based on the economic feasibility of the incremental cost-effectiveness ratio (ICER) will be assessed in relation to 1 or 3 times the per capita GDP PPP of Peru in 2014(131), following the recommendations of the Commission on Macroeconomics and Health of the WHO (108; 120; 150).

Sensitivity analysis

We performed a one-way, multivariate, and threshold sensitivity analysis to assess how the variation of selected parameters including time horizon, discount rate, and intervention effectiveness affect the results of the ICER.

COST-BENEFIT ANALYSIS

General Objective

The main objective of this study was to determine the cost-benefit of the focalized intervention. To meet this general objective we accomplished the following specific objectives:

1. To determine the benefit of this intervention (expressed in monetary terms) compared with the existing one.
2. To determine the cost saving per TB case averted of this intervention compared to the existing one.

Study design

We have performed a health economic analysis to assess the cost-benefit of the focalized "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 – 2017" in the districts of San Juan de Lurigancho and El Agustino located in the province of Lima, Peru.

The target audience for cost-benefit analysis (CBA) includes government officials making allocative decisions from a provider (see Figure 6).

In this analysis, we have compared status quo scenarios in the two districts Lima, Peru (Alternative 1) versus the "Emergency Plan for the Prevention and Control of Tuberculosis in Lima and Callao, 2015 – 2017" in the same two districts (alternative 2).

We have calculated the cost of the program and the benefits (cost of illness) for the status quo and intervention scenarios (see Figure 8, Table 3). The cost of the program was based on macro and micro-costing methodologies and the accrued benefits in economics terms.

We have calculated the incremental cost (IC) and the benefits in monetary terms. The intervention was determined to pass cost-benefit analysis if the net return is greater than 0.

Cost analysis

Program cost and the cost of illness (benefit in monetary terms) were taken from the Ex-post analysis.

Outcome measurement

The health outcome of this study was the cost saving per TB case averted. The following is an explanation of how to calculate the different health outcomes for CBA.

Estimating benefits under investigation

We have used cost-of-illness method to generate health valuation. The benefits of this initiative will be expressed as the cost-of-illness savings from outcomes averted.

Net returns of investment

The summary measures of the analysis were estimated as the differences between the benefits and the cost(22; 83; 118).

Net returns = Savings from the outcomes averted in population – cost of the intervention

$$\textbf{Saving from outcomes averted} = \sum_{Outcomes} \begin{bmatrix} Number\ with\ outcome\ pre-\ intervention * strategy\ performance \\ * Intervention\ effectiveness * \$\,Value\ of\ the\ outcome\ prevented \end{bmatrix}$$

Decision-making

The net returns are considered important if the savings are greater than zero.

Sensitivity analysis

Sensitivity analysis

We performed a one-way, multivariate, and threshold sensitivity analysis to assess how the variation of selected parameters including time horizon, discount rate, and intervention effectiveness affect the results of the cost saving.

CHAPTER 3: Results

EFFECTIVENESS OF THE FOCALIZED INTERVENTION (EX-POST ANALYSIS)

The treatment default for the status quo was 10.42%(95% CI: 8.28% – 12.57%) and for focalized intervention was 1.46% (95% CI: 0.56% – 2.35%) (see Table 6). The effectiveness of the focalized intervention to reduce treatment default was 86.08% (95% CI: 81.30% – 93.23%) and the incremental effectiveness was -8.97% (95% CI: -10.22% – -7.72%)(see Table 6).

The treatment interruption for the status quo was 18.79% (95% CI: 16.04% – 21.54%) and the treatment interruption for the focalized intervention was 5.82% (95% CI: 4.07% – 7.57%). The effectiveness of the focalized intervention to reduce treatment irregularity was 69.03% (95% CI: 64.83% – 74.62%) and the incremental effectiveness was -12.97% (95% CI: -11.97% – -13.96%) (see Table 6).

Table 6. Summary results of the focalized intervention. 2015

Comprehensive health care	Baseline		Focalized intervention		Risk difference	Impact
	n	%	n	%	%	%
Medical assessment	398/777	51.22	629/687	91.56	↑40.34	↑78.76%
Nursing assessment	554/777	71.30	665/687	96.80	↑25.50	↑35.76%
Psychological assessment	445/777	57.27	371/687	54.01	↓3.26	↓5.69
Social services assessment	443/777	56.87	580/687	84.43	↑27.56	↑48.46
Laboratory pack	485/777	62.42	564/687	82.10	↑19.68	↑31.52
Treatment default	**81/777**	**10.42**	**10/687**	**1.485**	**↓8.97**	**↓86.08**
Treatment interruption	**146/777**	**18.79**	**40/687**	**5.82**	**↓12.97**	**↓69.03**

Source: National Sanitary Strategy of Prevention and Control of Tuberculosis

See section “Focalized intervention to address treatment interruption and treatment default, and contact examination of TB patients” at the introduction for terms definitions of medical care, nursing assessment, psychological assessment, social services assessment and laboratory pack.

EFFECTIVENESS OF THE FOCALIZED INTERVENTION (EX-ANTE ANALYSIS)

In the following table we show the parameters used to run the model for the status quo scenario. We also have included the sources of the parameters. Some of them were obtained from scientific literature, and some were obtained from the model (see Table 7).

For the focalized intervention scenario, we have changed the following treatment parameters: per capita effective treatment rate (Φ) from 0.48 to 0.70; relative treatment efficacy (δ) from 0.6 to 0.7. As a result, the focalized intervention will have a reduced treatment default of at least in 8 points for non-resistant TB and 20 points for resistant TB. We also reduce the probability of drug resistance emerging during treatment (r) because of standardized treatment, from 0.10 to 0.06.

Table 7. Parameters, parameters values and sources of the compartmental dynamic epidemiological model

Parameters	Definitions	Value of the parameter	Sources
		Status quo	
Π	Birth rate/rate of arrival of new susceptible	28000	Vitals statistic of Peru
β_S	Transmission coefficient for drug-sensitive M. tuberculosis	0.00009	Model
β_R	$\alpha\beta_S$	0.000045	
α	Relative transmissibility	0.5	(Dye et al., 1998)
$1/\mu$	Average life expectancy	1/70	Vitals statistic of Peru
p	Proportion of new infections that develop disease within 1 year	0.01	(Dye et al., 1998)
ν	Progression rate to disease (for latently infected individuals)	0.00156	(Dye and Espinal, 2001;Williams et al., 2005)
$\boldsymbol{\sigma}$	Per capita rate of effective chemoprophylaxis	0.01	MoH of Peru
μ_T	Mortality rate due to tuberculosis	0.03	MoH of Peru
Φ	Per capita effective treatment rate	0.48	(Dye et al., 1998)
r	Probability of drug resistance emerging during treatment	0.10	(Dye et al., 1998) and MoH of Peru
δ	Relative treatment efficacy	0.6	MoH of Peru

The Figures 5, 6 and 7 show the results of the compartmental, dynamic and epidemiological model. Figure 6 depicts the TB epidemic curve in San Juan de Lurigancho, from the foundation of this district in 1967 with about 60,000 inhabitants through present day. This figure shows, the evolution of the TB epidemic before and after the National TB program was implemented in 1986. Furthermore, this figure depicts projected impact of the focalized intervention from its inception in 2015 through to 2035. This strategy has an important effect on the number of resistant and non-resistant TB cases. For model fitting see appendix 3a, and for sensitivity analysis of the parameters Φ y δ upon the incidence rate of TB, see appendix 3b.

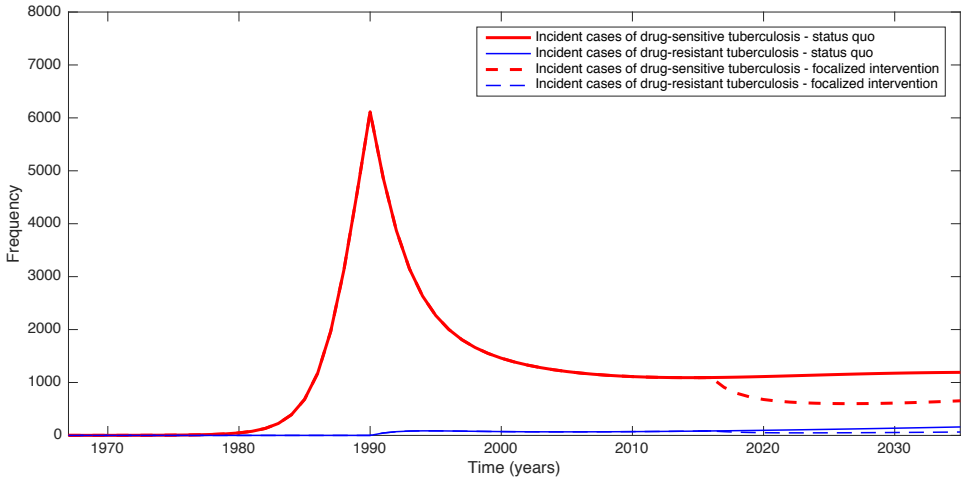


Figure 5. Impact of the focalized intervention upon resistant and non-resistant TB epidemic.

Figure 6 depicts the impact of the focalized intervention upon the non-resistant TB. Non-resistant TB incidence rates dropped from 110.24 incident cases per 100,000 populations at the intervention outset, to 53.49 incident cases per 100,000 populations over the twenty-years focalized intervention.

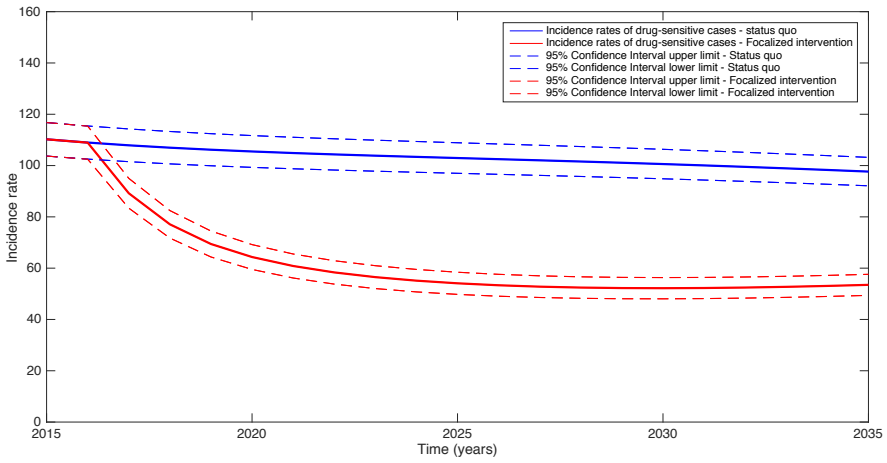


Figure 6. Impact of the focalized intervention upon non-resistant TB incidence rate.

Additionally, the impact of the focalized intervention upon the prevalence of MDR-TB (Proportion of MDR-TB incident from the total TB incident cases) was to slow

down of the MDR-TB epidemic. The focalized intervention slowed down the MDR-TB epidemic from 13.42% to 9.80% at the end of 2035 (see Figure 7).

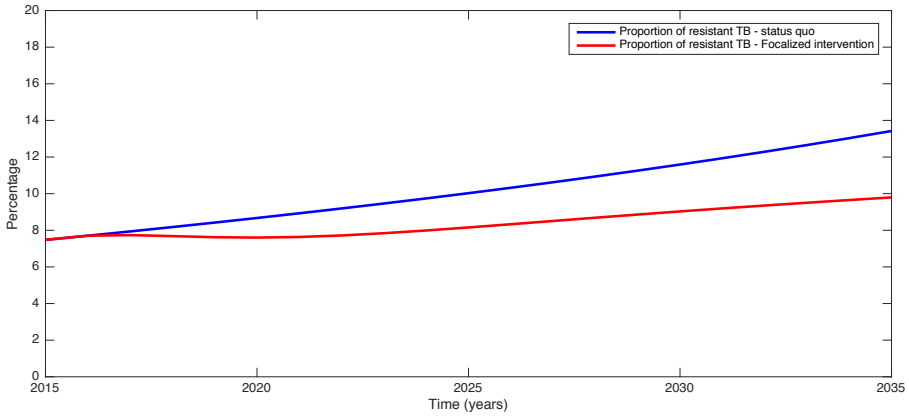


Figure 7. Impact of the focalized intervention upon the proportion of resistant TB of all TB cases.

COST ANALYSIS

The cost analysis for resistant TB was based on 2,174 TB cases from San Juan de Lurigancho and El Agustino health networks. Of the total TB cases, 1,013 cases belonged to San Juan de Lurigancho health network and 261 cases belonged to El Agustino health network.

The cost analysis for non-resistant TB was based on 1,677 TB cases from San Juan de Lurigancho health network. Unfortunately, we did not have data from El Agustino health network, but this area has similar epidemiological and operational characteristics to San Juan de Lurigancho. Consequently, we suggest than these data from San Juan de Lurtigancho can be used as a proxy for data from El Agustino.

General characteristics of resistant and non-resistant TB patients

Table 8 shows general characteristics of cases with resistant and non-resistant TB included in the cost analysis.

Most patients with resistant TB fell in the age groups of 16-25 (40.9%) and 26-60 (46.5%) years old. Furthermore, 63.65% of resistant TB cases were male, and all cases were distributed in 6 cohorts: 2009, 2010, 2011, 2012, 2013 and 2014. Notably, treatment for resistant TB last an average of 18 to 24 months. In the case of the 2013 and 2014 cohorts, not all patients had finished their treatment at the end of July 2016. This was due to use of data updated through August 2015, and duration of treatment considerations. For example, cases from the cohort 2013 should finish treatment in 2015, and cases from the 2014 cohort should finish treatment in 2016 (see Table 8).

At the end of July 2016, in those with resistant TB, 27.9% of the resistant TB cases were cured, 10.1% had completed treatment, and 25.2% were still in treatment.

Furthermore, 5.25% of resistant TB cases died, 3.25% failed treatment, and 22.8% defaulted from treatment (see Table 8.

Those with non-resistant TB have similar demographics characteristics (age distribution and gender) to patients with resistant TB. 41.1% and 38.7% of non-resistant TB cases were between 16-25 and 26-60 years old, respectively, and 63.7% were male (see Table 8).

With regard to the type of TB, most of the TB cases were Pulmonary TB (80.6%). In the 2014 cohort of non-resistant TB, the outcomes of this cohort were as follows: 81.9% cured, 2.2% died, and 0.2% failed. Additionally, 9.8% were treatment default and 4.1% were not evaluated (see Table 8).

Table 8. General characteristics of resistant and non-resistant TB cases from San Juan de Lurigancho and El Agustino health networks. 2015.

General Characteristics	Resistant TB patients		Non-resistant TB patients	
	n	%	n	%
Age distribution				
0-5 year old	25	2.0	30	1.8
6-15 year old	71	5.6	96	5.7
16-25 year old	521	40.9	689	41.1
26-60 year old	593	46.5	649	38.7
Greater than 60 year old	64	5.0	126	7.5
No age data			87	5.2
Gender				
Male	810	63.6	1069	63.7
Female	464	36.4	608	36.3
Cohort				
2009	204	16.0		
2010	179	14.1		
2011	255	20.0		
2012	250	19.6		
2013	192	15.1		
2014	194	15.2	1,677	100.0
Type of Tuberculosis				
Pulmonary tuberculosis			1,351	80.6
Extrapulmonary tuberculosis			326	19.9
Current status				
Excluded	71	5.6		
Cured	353	27.9	1,373	81.9
Died	66	5.2	37	2.2
Treatment default	289	22.8	164	9.8
Failed	41	3.2	3	0.2
Completed treatment	128	10.1	30	1.8
In treatment	319	25.2		
Non-evaluated			69	4.1

Source: National Sanitary Strategy of Prevention and Control of Tuberculosis

Cost of the program

The Table 9 shows the cost of the focalized intervention per month and per year in Metropolitan Lima. This focalized intervention includes 7 items listed in the table below, including a 4 days training meeting for the dedicated nurses, and their salaries to monitoring and supervision of the intervention by the two levels of health government. The most expensive cost is the salary of the dedicated nurses which is approximately 1,333,800.00 USD per year. This cost alone represents roughly 93.78% of the total cost of this intervention. Note that all costs were converted from Nuevos soles (Peruvian currency) to U.S dollar using purchasing power parity and then adjusted by inflation.

Table 9. Cost of the focalized intervention per month in 26 health facilities with higher burden of treatment default at Metropolitan Lima.

Item	Number	Unit measure	Unit cost ($)	Total cost per month ($)	Total cost per year ($)
-4 days training meeting of dedicated nurses	1	Training meeting	3,000.00		3,000.00
-Salary of dedicated nurses that perform the follow up of the treatment	26	Nurse per month	4,275.00	111,150.00	1,333,800.00
-Monitoring of the focalized intervention by the team of the Institute of Health Services Management and the National Sanitary Strategy of Control and Prevention of Tuberculosis	25	Hours per month	45.00	1,125.00	13,500.00
-Supervision of prioritized health faculties to monitoring the performance of TB team, and the dedicated nurses by the team of the Institute of Health Services Management and the National Sanitary Strategy of Control and Prevention of Tuberculosis	10	Supervision visits per month	150.00	1,500.00	18,000.00
-Transportation to health facilities to perform supervisions	10	Ride per month	105.00	1,050.00	12,600.00
-Monday's coordination meetings with dedicated nurses	4	Meetings per month	487.50	1,950.00	23,400.00
-Household visits transportation fees	200	Household visits per month	7.50	1,500.00	18,000.00
TOTAL				121,275.00	1,422,300.00

The total estimated cost of the focalized intervention for the 5 health facilities in San Juan de Lurigancho health network and for the 3 health facilities in El Agustino micro-network was $437,630.8 USD per year (not in Table 9).

Cost of illness

We estimated the cost of illness for resistant and non-resistant TB for each of the 6 cohorts of resistant TB and for the 2014 cohort for non-resistant TB. We describe these costs in the following paragraphs, considering individual and total costs of illness.

It is important to note that these costs are time dependent as the items delivered during follow-up depend on the time the patients are in treatment (see appendix 2 for non-resistant TB, and appendix 3 for resistant TB, for services delivered to the patient during the time in the National Sanitary Strategy of Control and Prevention of Tuberculosis). There is one exception which is for treatment as the National Sanitary Strategy of Control and Prevention of Tuberculosis prepares a completed treatment package as soon as the patient enrolls in the program (see appendices 4 and 5 for the cost of the treatment for non-resistant and resistant TB, respectively). For the purpose of this economic health assessment, we considered the treatment as a time dependent, in order to quantify the cost loss in treatment if the patient does not finish treatment.

Cost of illness for non-resistant TB

Table 9, shows the individual and total costs of illness for non-resistant TB in San Juan de Lurigancho health network for the 2014 cohort were 1,056.58 USD and 1,505,631.00 USD, respectively. We have divided the cost of illness in three main groups: baseline assessment, TB treatment and follow-up assessment. We also divided the baseline assessment and follow-up assessment by subgroups.

The total cost of illness for the baseline assessment was 465,373.80 USD and the individual cost was 326.58 USD. The baseline assessment cost represented 30.91% of the total cost of illness. The diagnostic test for resistant TB was the most expensive item of the baseline assessment, and represented 61.60% (286,678.10 USD) of the baseline total cost.

TB treatment total and individual costs were 333,398.40 USD and 233.96 USD, respectively. TB treatment cost represented 22.14% of the total cost of illness.

Finally, the follow-up assessment cost represented 46.95% of the cost of illness, or 482,037.60 USD for the follow-up laboratory assessment and 224,821.50 USD for the follow-up health assessment, respectively.

Table 10. Total cost of illness for non-resistant TB in San Juan de Lurigancho health network, 2014 cohort.

Item	Total cost ($)	Individual cost ($)
Baseline assessment	465,373.80	326.58
TB Diagnostic	60,727.37	42.62
TB resistant diagnostic	286,678.10	201.18
Baseline laboratory assessment	72,814.76	51.10
Baseline health assessment	45,153.58	31.69
TB Treatment	333,398.40	233.96
Follow-up assessment	706,859.10	496.04
Follow-up laboratory assessment	482,037.60	338.27
Follow-up health assessment	224,821.50	157.77
TOTAL	1,505,631.00	1,056.58

Cost of illness for resistant TB

Calculations for the cost of illness for resistant TB are more nuanced, in part due to more complicated treatment required compared to non-resistant cases. For example,

various resistant patterns have specified treatments and treatment durations which may varies. Further, patients that are not resistant cases but who have received a treatment with second-line anti-tuberculosis drugs are also included in this cost of illness calculation.

We found the following groups of treatment for resistant and non-resistant cases received second-line antituberculosis drugs: 1) MDR-TB, 2) XDR-TB, 3) Isoniazid monoresistant tuberculosis, 4) Rifampicin monoresistant tuberculosis, 5) Pansensitive tuberculosis, 6) Poly-drug resistant TB and Isoniazid resistance, 7) Poly-drug resistant TB and Rifampicin resistance, 8) Drug resistant non-Isoniazid non-Rifampicin resistance, and 9) those with no resistance pattern data available. Despite efforts to cost all resistant patterns, we focus here on MDR-TB, since other resistant groups tended to be small in numbers and were not considered in the focalized intervention.

MDR-TB accounted for 68% of all TB cases that have received second-line antituberculosis drugs. Other TB cases, noted above, accounted for the following proportion of all TB cases receiving second-line drugs: 0.4% XDR-TB; 5.1% Isoniazid monoresistant tuberculosis; 3.5% Rifampicin monoresistant tuberculosis; 5.9% Pansensitive tuberculosis; 6.6% Poly-drug resistant TB and Isoniazid resistance; 0.2% Poly-drug resistant TB and Rifampicin resistance; 1.0% Drug resistant non-Isoniazid non-Rifampicin resistance; and 9.4% no resistance pattern data available

Table 11 shows the individual mean cost of illness for resistant TB in San Juan Lurigancho and El Agustino Health networks for the 2009 to 2014 cohorts.

The baseline laboratory assessment ranged from a mean of 447.19 (SD: 124.72) USD per TB patients in the 2009 cohort, to 523.13 (SD: 127.83) USD per TB patients in

the 2014 cohort. The baseline laboratory assessment costs included: TB diagnostic, and baseline laboratory and health assessments. Within these categories, there are subcategories which were also costed. For further details, please see appendix 6. We assumed the average cost of the baseline laboratory assessment would increase annually because of universal access to rapid tests for the diagnosis of drug-resistant tuberculosis, resulting in an increase in the total number of resistant cases detected.

The average TB treatment cost varied a lot according to the resistant pattern, for example: MDR-TB cost ranged from 18,201.44 (SD: 26,168.57) USD in 2009 to 9,286.31 (SD: 10,185.22) USD in 2014. This difference in the cost was due to a decrease of the cost of the TB drugs because of several factors: large scale buying through the Green Light Committee (GLC) Initiative, the duration of the patient in TB treatment, and because there were still patients in treatment from 2013 and 2014 cohorts. The standard deviation of these costs for MDR-TB and other treatment groups varied substantially, mainly due to treatment duration. This may have occurred, as there were patients who exceeded standard treatment, mainly in the 2009 to 2011 cohorts. For XDR-TB, the cost does not include hospitalization for the first two months of the treatment, surgery or house-based treatment for six months, would could result in a cost rise times ten.

Follow-up assessment costs ranged from 734.58 (SD: 403.69) USD per person in 2009 to 724.19 (SD: 244.42) USD per person in 2014.

Finally, the total cost of basal and follow-up assessment was 15,671.95 USD per person (SD: 21,904.76) in 2009 and 9,858.43 USD per person (SD: 9,761.57) in 2014. For further details regarding cost of specifics items, please see appendix 6

Table 11. Individual cost of illness (Mean(SD)) for resistant TB in San Juan Lurigancho and El Agustino health networks, 2009 – 2014 cohorts.

Items	2009 Cohort Mean (SD) ($)	2010 Cohort Mean (SD) ($)	2011 Cohort Mean (SD) ($)	2012 Cohort Mean (SD) ($)	2013 Cohort Mean (SD) ($)	2014 Cohort Mean (SD) ($)
Baseline laboratory assessment	447.19 (124.72)	481.76 (109.78)	486.96 (107.55)	561.6 (129.36)	554.2 (127.74)	523.13 (127.83)
TB Treatment						
MDR-TB resistant	18,201.44 (26168.57)	14,650.69 (13,628.5)	10,085.68 (12,944.98)	10,681.54 (13,833.12)	12,640.07 (12,621.79)	9,286.31 (10,185.22)
XDR-TB resistant	0	0	15,174.92 (16,581.17)	25,804.36 (35,669.89)	13,597.35	
Isoniazid monoresistant tuberculosis	8,260.65 (1,111.69)	9,384.00 (7,837.9)	3,104.66 (2,472.43)	2,987.44 (1,775.89)	21,848.23 (27,161.68)	4,455.93 (2,081.82)
Rifampicin monoresistant tuberculosis	9,650.99 (7,183.73)	6,658.66 (6,489.67)	2,658.58 (1,774.15)	3,671.22 (3,488.25)	5,540.2 (3,273.69)	9,125.14 (9,154.860
Pansensitive TB	5,808.83 (4,259.66)	13,683.64 (15344.3)	4,328.95 (5,795.95)	7,212.2 (10,331.54)	7,526.41 (10,599.62)	10,598.51 (16,669.27)
Poly-drug resistant TB and Isoniazid resistance	5325.3 (7,417.54)	10,769.45 (25,564.91)	19,24.34 (1,989.71)	3,619.12 (3,881.17)	1,602.8	5,352.98 (1,467.84)
Poly-drug resistant TB and Rifampicin resistance	0	0	10,684.8 (6,336.49)	0	0	
Drug resistant non Isoniazid non Rifampicin resistance	5,948.84 (5,185.33)	11,384.85 (20,209.90)	3,921.94 (5,871.37)	5,256.93 (2561.90)	0	5,880.46
No resistance pattern data available	12,334 (13,516.06)	19,568.98 (1,3745.74)	5,776.27 (4,063.59)	9,597.27 (23061.9)	4,649.67 (3,641.33)	3,943.1 (1,825.47)
Follow-up assessment	734.58 (403.69)	800.69 (332.90)	692.94 (346.67)	704.54 (392.98)	863.04 (428.22)	724.19 (244.42)
TOTAL	15,671.95 (21,904.76)	15,598.12 (14,660.75)	8,891.01 (11,250.39)	10,249.29 (14,239.69)	12,993.82 (12,518.73)	9,858.43 (9,761.57)

On average the national program spent roughly 2,694,885.18 USDs each year in resistant TB management for the two study areas. The management of resistant TB includes: 1) a baseline assessment that cost in average 149,290.72 USDs per year; 2) resistant TB treatment that cost 2,312,229.64 USDs per year; and 3) follow-up assessment that cost 233,364.82 USDs per year. For more detailed information on the total cost of each item, please see Table 12.

In term of baseline assessment items, the National Sanitary Strategy of Control and Prevention of Tuberculosis spent an average of 86,758.18 USD in TB diagnostics, 23,676.94 USD in resistant TB diagnostics, 18,749.74 USD in laboratory assessments, and 20,105.86 USD in health assessments. The baseline assessment cost has increased over time because of greater number of resistant TB cases detected. Drug resistant diagnosis has tripled and quadrupled in 2013 and 2014 compare to previous years, largely due to increased number of patients with rapid diagnostic tests for resistant TB. Simultaneously, baseline laboratory and health assessment costs have also increased, due to increased patients access facilitated by the Comprehensive Health Insurance support.

MDR-TB treatment is the most expensive treatment of all, with an average cost of 1,806,951.71 USD per year. Other resistant and non-resistant TB groups account for the following total average expenditures annually. The average total annual expenditure on Isoniazid monoresistant TB 55,482.45 USD; on Rifampicin monoresistant TB the averaged cost was 50,152.96 USD; and for Poly-drug resistant TB and Isoniazid resistance the average cost was 58,524.34 USD. Furthermore, for non-resistant TB cases like pansensitive tuberculosis, the average cost was 98,348.66 USD. In patients for whom

resistance pattern data were not available, the average cost was 206,785.53 USD, even more than resistant TB.

During the follow-up period the National Sanitary Strategy of Control and Prevention of Tuberculosis spent 117,129.19 USD in laboratory assessment and 116,235.63 USD in health assessment.

Table 12. Total cost of illness for resistant TB by year in San Juan Lurigancho and El Agustino districts, 2009 – 2014 cohorts

Item	2009 Cohort Total cost ($)	2010 Cohort Total cost ($)	2011 Cohort Total cost ($)	2012 Cohort Total cost ($)	2013 Cohort Total cost ($)	2014 Cohort Total cost ($)
Baseline assessment						
TB Diagnostic	98,646.37	96,368.74	124,211.91	118,049.59	63,882.38	19,390.09
TB resistant diagnosis	11,212.34	10,170.77	14,880.69	42,685.76	31,626.17	31,485.90
Baseline laboratory assessment	18,232.47	17,887.69	21,319.34	20,291.15	17,480.58	17,287.22
Baseline health assessment	19,470.70	19,326.75	22,353.00	21,606.11	19,048.81	18,829.81
Sub total	147,561.88	143,753.95	182,764.94	202,632.61	132,037.94	86,993.02
TB Treatment						
MDR-TB	2,203,116.23	1,878,002.07	1,734,869.78	1,711,767.70	1,954,165.15	1,359,789.31
XDR-TB	0	0	32,224.49	53,361.78	13,562.48	0
Isoniazid monoresistant tuberculosis	16,522.34	77,608.86	59,341.61	83,373.05	65,398.22	30,650.64
Rifampicin monoresistant tuberculosis	77,202.40	27,533.65	8,467.17	30,360.16	49,733.64	107,620.74
Pansensitive TB	110,364.16	183,898.32	64,346.73	111,841.77	67,562.29	52,078.68
Poly-drug resistant TB and Isoniazid resistance	74,556.94	111,339.05	79,708.78	52,375.44	1,598.58	31,567.23
Poly-drug resistant TB and Rifampicin resistance	0	0	22,687.92	0	0	
Drug resistant non Isoniazid non Rifampicin resistance	17,848.09	47,075.95	12,493.12	10,870.71	0	5,779.44
Not resistance pattern data available	456,383.99	323,649.46	73,588.89	267,924.31	64,919.55	54,246.99
Sub total	2,955,994.15	2,649,107.36	2,087,728.48	2,321,874.92	2,216,939.91	1,641,733.01
Follow up assessment						
Follow up laboratory assessment	128,734.40	127,376.14	156,182.49	148,669.54	93,357.46	48,455.10
Follow-up health assessment	113,456.80	115,636.60	125,182.10	120,761.70	111,154.40	111,222.20
Subtotal	242,191.20	243,012.74	281,364.59	269,431.24	204,511.86	159,677.30

The Table 13 and 14 presents the individual and total costs by specific drug resistant patterns, respectively. Table 12 shows the individual costs by specific drug resistant patterns. MDR-TB costs ranged from 19,520.14 (SD: 2,6430.58) USD in 2 to 10,556.18 (SD: 10,271.21) USD in 2014. MDR-TB costs were the greatest compa to other resistant and non-resistant patterns. In the case of isoniazid monoresistant tuberculosis, costs ranged from 9,276.55 (SD: 9,62.21) USD in 2009 to 5,623.23 (S 2,037.48) USD in 2014. This apparent decrease may due to patients from 2014 coho who are still in treatment. Furthermore, costs for non-resistant TB cases, such as pansensitive tuberculosis, and those with no data on resistance were higher than cos resistant TB. While the cost of pansensitive tuberculosis has increased over time, th costs for those missing resistance pattern data have been decreased overtime, likely to increased access to universal rapid tests for the diagnosis of drug-resistant TB.

Table 13. Individual cost of illness (Mean (SD)) by type of resistant pattern in San Juan Lurigancho and El Agustino districts 2009 – 2014

Item	2009 Cohort Mean (SD) ($)	2010 Cohort Mean (SD) ($)	2011 Cohort Mean (SD) ($)	2012 Cohort Mean (SD) ($)	2013 Cohort Mean (SD) ($)	2014 Cohort Mean (SD) ($)
MDR-TB	19,520.14 (2,6430.58)	15,980.79 (13,809.99)	11,353.92 (13,069.81)	12,040.95 (13,986.42)	14,119.95 (12,803.29)	10,556.18 (10,271.21)
XDR-TB	0	0	16,221.74 (17,560.27)	26,716.06 (36,362.62)	15,647.05	7,145.45
Isoniazid monoresistant tuberculosis	9,276.55 (9,62.21)	10,442.22 (8,130.74)	4,102.65 (2,633.77)	4,000.08 (1,981.14)	23,264.62 (27,552.79)	5,623.23 (2,037.48)
Rifampicin monoresistant tuberculosis	10,917.6 (7,273.7)	7,775.5 (6,589.13)	3,602.84 (2,252.95)	4,556.87 (3,981.77)	6,751.46 (3,659.77)	10,486.18 (9,141.51)
Pansensitive TB	6,683.09 (4,538.64)	15,020.25 (15,914.91)	5,289.49 (5,962.62)	8,361.59 (1,0874.07)	8,464.16 (10,932.89)	11,502.07 (16,950.88)
Poly-drug resistant TB and Isoniazid resistance	6,450.28 (7,656.12)	11,944.9 (25,788.09)	2,967.91 (2,197.41)	4,740.84 (4,001.19)	2,834.41	6,613.08 (1,438.7)
Poly-drug resistant TB and Rifampicin resistance	0	0	11,988.85 (6,444.46)	0	0	0
Drug resistant non Isoniazid non Rifampicin resistance	7,204.06 (4,996.36)	12,487.03 (20,369.90)	5,082.73 (5,921.98)	6,375.39 (2,526.53)	0	0
Not resistance pattern data available	13,237.5 (13,744.72)	20,692.33 (13,833.3)	6,800.3 (4,277.35)	10,872.02 (23,276.84)	5,784.41 (4,122.32)	5,002.95 (2,078.09)

Table 14 shows the total cost of illness for specific resistant TB pattern, so w see that MDR-TB cost is the most expensive, at an average 2,003,739.72 USD per y ranging from 2,362,509.39 USD in 2009 to 1,545,824.87 USD in 2014. It is thought th this cost has decreased overtime due to improved clinical practices. The cost for the monoresistant to either isoniazid or rifampin was an average 17,547.12 USD and 67,216.62 USD, respectively. The cost for isoniazid monoresistant cases increased through 2012 and then decreased in the last two years of study. The cost for rifampi monoresistant was variable.

Patients with no resistance evidence but who received second-line TB drugs treatment fell into two categories: pansensitive and those with no resistance pattern available. The average costs per year for theses groups respectively was 111,608.08 and 228,646.26 USD.

Table 14. Total cost of illness by type of resistant pattern in San Juan Lurigancho and El Agustino districts 2009 – 2014

Item	2009 Cohort Total cost ($)	2010 Cohort Total cost ($)	2011 Cohort Total cost ($)	2012 Cohort Total cost ($)	2013 Cohort Total cost ($)	2014 Cohort Total cost ($)
MDR-TB	2,362,509.39	2,048,609.42	1,953,016.46	1,929,557.96	2,182,920.19	1,545,824.87
XDR-TB	0	0	34,446.89	55,229.50	15,606.34	0
Isoniazid monoresistant tuberculosis	18,553.19	86,357.12	78,412.05	111,678.57	69,620.36	38,678.43
Rifampicin monoresistant tuberculosis	87,334.38	32,153.17	11,474.20	37,684.04	60,602.92	123,653.41
Pansensitive TB	126,987.83	201,855.25	78,629.05	129,667.79	75,986.83	56,521.72
Poly-drug resistant TB and Isoniazid resistance	90,302.85	123,483.71	122,910.87	68,622.53	2,826.69	38,996.72
Poly-drug resistant TB and Rifampicin resistance	0	0	25,456.51	0	0	0
Drug resistant non Isoniazid non Rifampicin resistance	21,611.73	51,635.57	16,189.79	13,182.56	0	7,021.63
Not resistance pattern data available	489,777.40	342,328.76	86,641.31	303,509.89	80,779.47	68,840.75
TOTAL	3,197,076.77	2,886,423.00	2,407,177.13	2,649,132.84	2,488,342.81	1,879,537.53

COST-EFFECTIVENESS ANALYSIS.

Cost-effectiveness analysis for non-resistant TB

Table 15 shows the results of the cost-effectiveness analysis for the focalized intervention in the San Juan de Lurigancho health network for non-resistant TB. The projected cost according to status quo over the twenty years horizon was 18,530,649 USD. By comparison, the total projected cost for the focalized intervention was 18,381,987.21 USD. Both figures are for adjusted costs (Discount rates= 3%). The incremental cost was -148,662 USD and the incremental effectiveness was 9,430 non-resistant TB cases averted. According to these data, the focalized intervention is more effective and less costly.

According to the cost-effectiveness analysis, the focalized intervention is cost-effective because the ICER (16 USD) is less than 1 or 3 times the Peruvian GDP PP 2014 (11,513.95 USD or 34,542.00 (131)) (see Figure 9 and Table 15). The focalized intervention is a dominant intervention, because it costs less and is more effective as status quo, at least with a discount rates less that 5%.

Table 15. Summary results of the cost-effectiveness analysis of the focalized interv vs. status quo for non-resistant TB.

Discount rate	Total cost of Status quo	Total cost of Focalized intervention	Non-resistant TB cases status quo	Non-resistant TB cases Focalized intervention	Non-resistant TB cases averted	IC
Unadjusted	25,379,051.60	24,605,749.00	24,020	14,590	9430	
Adjusted (Discount rate = 3%)	**18,530,649.09**	**18,381,987.21**	**24,020**	**14,590**	**9430**	
Adjusted (Discount rate = 4%)	16,835,763.24	16,831,851.83	24,020	14,590	9430	
Adjusted (Discount rate = 5%)	15,360,308.03	15,477,863.52	24,020	14,590	9430	(dor

Finally, the cost per non-resistant TB case averted was estimated to be 16 USD (see Table 15).

Cost-effectiveness analysis for resistant TB

Table 16 shows the results of the cost-effectiveness analysis for the focalized intervention in the San Juan de Lurigancho health network for non-resistant TB. The total projected cost according to status quo over the twenty years horizon was 20,924,756.47 USD. By comparison, the total projected cost for the focalized intervention was 17,590,605.70 USD. Both figures are for adjusted costs (Discount rates= 3%). The incremental cost was -3,334,151 USD and the incremental effectiveness was 1,244 resistant TB cases averted. According to these data, the focalized intervention is more effective and less costly.

According to the cost-effectiveness analysis, the focalized intervention is a dominant intervention because is less costly and more effective (ICER = -2,680 USD) (see Table 16).

Table 16. Summary results of the cost-effectiveness analysis of the focalized intervention vs. status quo for resistant TB.

Discount rate	Total cost of Status quo	Total cost of Focalized intervention	Resistant TB cases status quo	Resistant TB cases Focalized intervention	Resistant TB cases averted	ICER
Unadjusted	23,783,878.20	29,572,573.20	2,456	1,212	1,244	4,653
Adjusted (Discount rate = 3%)	**20,924,756.47**	**17,590,605.70**	**2,456**	**1,212**	**1,244**	**-2,680** (dominant)
Adjusted (Discount rate = 4%)	18,817,202.68	16,056,876.13	2,456	1,212	1,244	-2,219 (dominant)
Adjusted (Discount rate = 5%)	16,996,245.87	14,720,912.41	2,456	1,212	1,244	-1,829 (dominant)

Finally, the cost per non-resistant TB case averted was estimated to be 2,680 USD (see Table 16).

Figure 8 depicts the cumulative costs of cost of the focalized intervention and status quo over a twenty years period for non-resistant TB. The cumulative cost of the focalized intervention was higher than the status quo until the year 2033, where this cost decline.

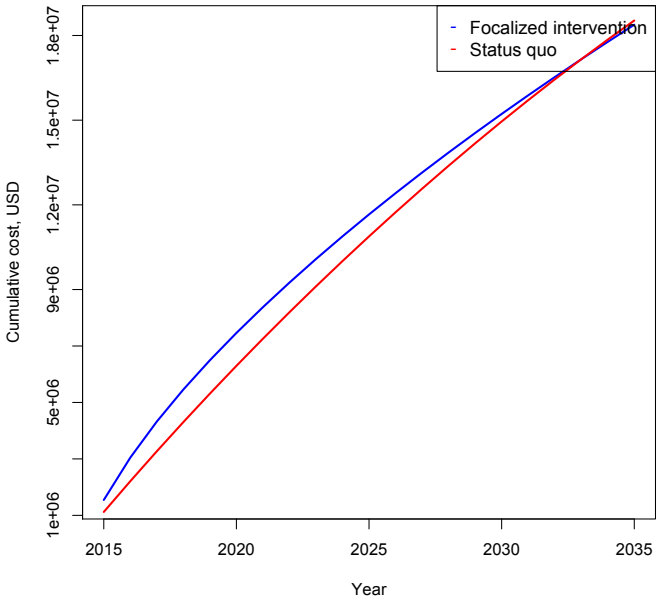


Figure 8. Cumulative cost of the focalized intervention and the status quo for non-resistant TB, over a twenty years period. This cost was adjusted by a 3% discount rate.

Figure 9 depicts the cumulative costs of cost of the focalized intervention and status quo for resistant TB, over a twenty years period. The cumulative cost of the focalized intervention was higher than the status quo until y=the year 2025, where this cost decline.

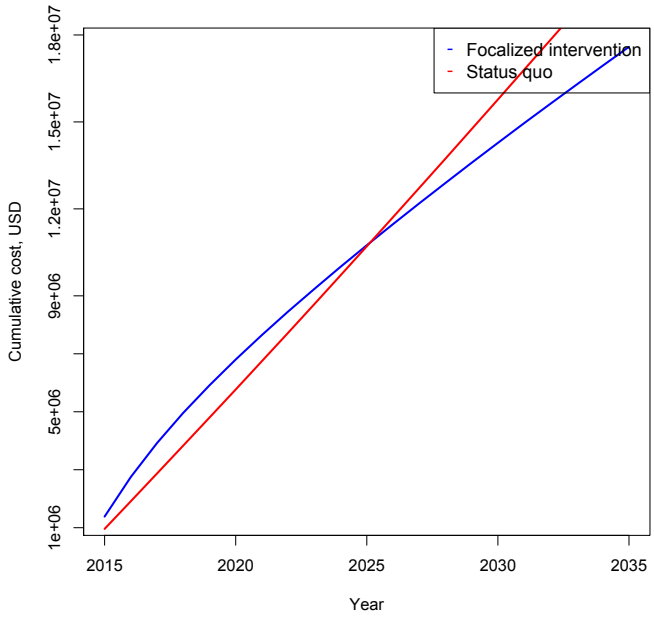


Figure 9. Cumulative cost of the focalized intervention and the status quo for resistant TB, over a twenty years period. This cost was adjusted by a 3% discount rate.

Sensitivity analysis

Figure 10 depicts the sensitivity analysis of the time horizon upon the ICER, holding the discount rate fixed at 3% for A) non-resistant and B) resistant TB. In both non-resistant and resistant TB, the ICER begins with high values and then decline to values less than zero, more rapid decline for non-resistant TB than resistant TB.

Further, the focalized strategy for non-resistant TB becomes highly cost-effective after the second year of intervention at a threshold of 1 times GDP. But the focalized intervention for resistant TB becomes highly cost-effective after the third year at a threshold of 3 time GDP and after the fifth year at a threshold of 1 times GDP (see please Figure 10).

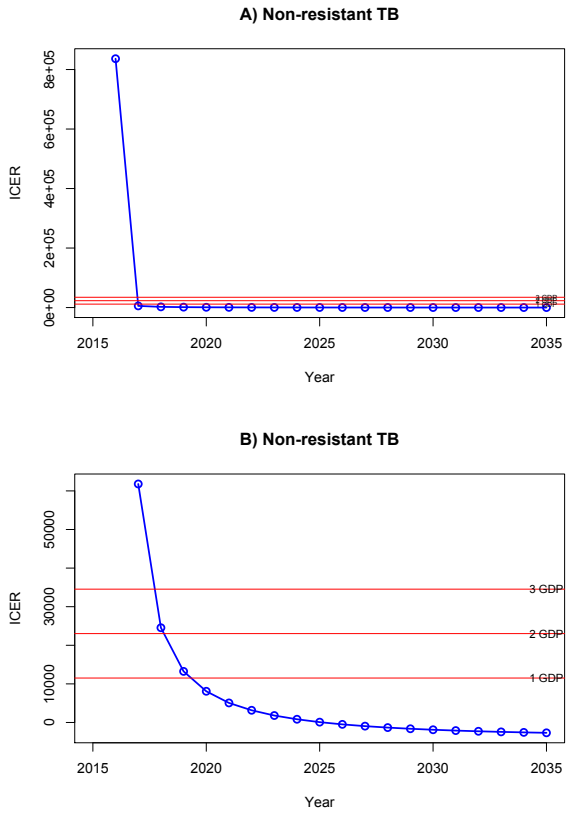


Figure 10. Sensitivity analysis of the time horizon upon the ICER for cost-effectiveness analysis, holding the discount rate fixed at 3%, for A) non-resistant and B) resistant TB.

Figure 11 shows that the change of the time horizon and the discount rate do not have much effect on the ICER over a twenty years period.

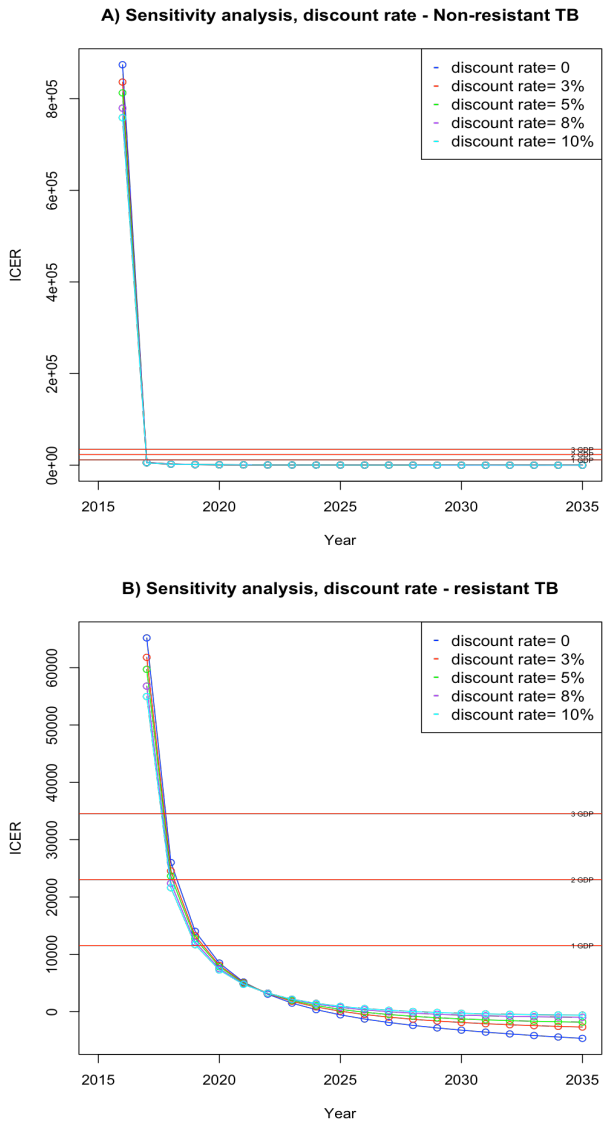


Figure 11. Sensitivity analysis of discount rate and time horizon upon the ICER for A) non-resistant TB and B) resistant at discount rate levels of 0, 3%, 5%, 8% and 10%.

Figure 12 shows that the variation of the time horizon and effectiveness do not have much effect on the ICER over a twenty years period.

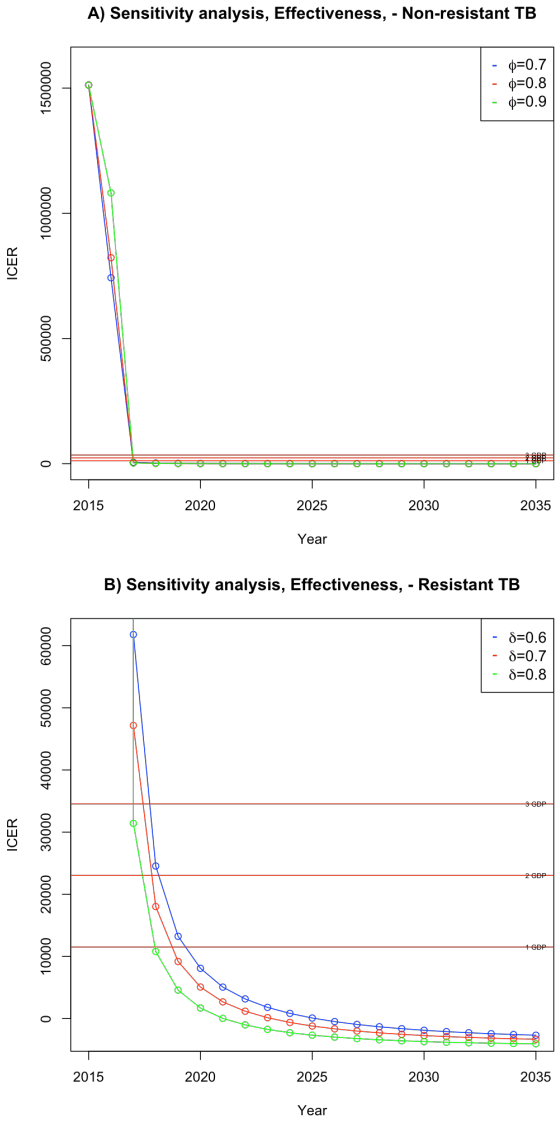


Figure 12. Sensitivity analysis of effectiveness and time horizon upon the ICER for A) non-resistant TB and B) resistant at a fixed discount rate of 3%.

COST-UTILITY ANALYSIS.

Table 17 shows the results of the cost-utility analysis for the focalized intervention in the San Juan de Lurigancho health network for non-resistant TB. The total projected cost according to status quo over the twenty years horizon was 18,530,649.09 USD. By comparison, the total projected cost for the focalized intervention was 18,381,987.21 USD. Both figures are for adjusted costs (Discount rates= 3%). The incremental cost was -148,662 USD and the incremental effectiveness was 11,218.80 DALYs (see the appendix 4a and 4b for more detail). According to these data, the focalized intervention is more effective and less costly, so it is a dominant intervention.

We estimated an ICER of -13.25, which suggest the strategy is dominant, because is less costly and more effective.

Table 17. Summary results of the cost-utility analysis of the focalized intervention vs. status quo for non-resistant TB.

Discount rate	Total cost of Status quo	Total cost of Focalized intervention	DALYs status quo	DALYs Focalized intervention	ICER
Unadjusted	25,379,051.60	24,605,749.00	28,576	17,358	-68.93 (Dominant)
Adjusted (Discount rate = 3%)	**18,530,649.09**	**18,381,987.21**	**28,576**	**17,358**	**-13.25** (Dominant)
Adjusted (Discount rate = 4%)	16,835,763.24	16,831,851.83	28,576	17,358	-0.35 (Dominant)
Adjusted (Discount rate = 5%)	15,360,308.03	15,477,863.52	28,576	17,358	10.48

When we adjusted the cost by different discount rates, the costs of both the status quo and focalized interventions decrease, and the ICER decrease (see Table 17).

Finally, the cost per DALY averted was estimated to be 13.25 USD, and this cost per DALY averted decreased, when we adjusted the cost of the status quo and focalized interventions by different discount rates (see Table 17).

Table 18 shows the results of the cost-utility analysis for the focalized intervention in the San Juan de Lurigancho health network for MDR-TB. The total projected cost according to status quo over the twenty years horizon was 20,924,756.47 USD. By comparison, the total projected cost for the focalized intervention was 23,783,878.20 USD. Both figures are for adjusted costs (Discount rates= 3%). The incremental cost was -3,334,151 USD and the incremental effectiveness was 1,480 DALYs (see the appendix 4c and 4d for more detail). According to these data, the focalized intervention is more effective and less costly, so it is a dominant intervention.

We estimated an ICER of 2,252.80, which suggest the strategy is cost-effective compared to a benchmark of 1 or 3 times Peruvian GDP for 2014 (11,513.95 USD or 34,542.00 USD (131)).

Table 18. Summary results of the cost-utility analysis of the focalized intervention vs. status quo for resistant TB.

Discount rate	Total cost of Status quo	Total cost of Focalized intervention	DALYs status quo	DALYs Focalized intervention	ICER
Unadjusted	29,572,573.20	23,783,878.20	2,922	1,442	3,911.28
Adjusted (Discount rate = 3%)	**20,924,756.47**	**17,590,605.70**	**2,922**	**1,442**	**2,252.80**
Adjusted (Discount rate = 4%)	18,817,202.68	16,056,876.13	2,922	1,442	1,865.09
Adjusted (Discount rate = 5%)	16,996,245.87	14,720,912.41	2,922	1,442	1,537.39

Finally, the cost per DALY averted was estimated to be 2252.80 USD, and this cost per DALY averted decreased, when we adjusted the cost of the status quo and focalized interventions by different discount rates (see Table 18).

Sensitivity analysis

Figure 13 depicts the sensitivity analysis of the time horizon upon the ICER, holding the discount rate fixed at 3%, for A) non-resistant and B) resistant TB. In both non-resistant and resistant TB, the ICER begins with high values and then decline to values less than zero, more rapid decline for non-resistant TB than resistant TB.

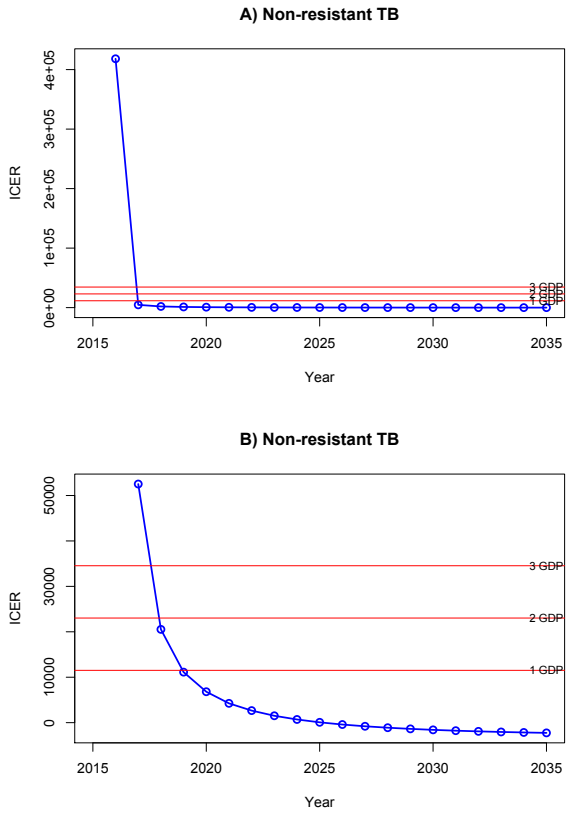


Figure 13. Sensitivity analysis of the time horizon upon ICER for cost-utility analysis, holding discount rate fixed at 3%, for A) non-resistant and B) resistant TB.

Further, the focalized strategy for non-resistant TB becomes highly cost-utilitarian after the second year of intervention at a threshold of 1 times GDP. But the focalized intervention for resistant TB becomes highly cost-utilitarian after the third year at a threshold of 3 time GDP and after the fifth year at a threshold of 1 times GDP (see please Figure 13).

Figure 14 shows that the variation of the time horizon and the discount rate does not have much effect on the ICER over a twenty years period for both non-resistant and resistant TB.

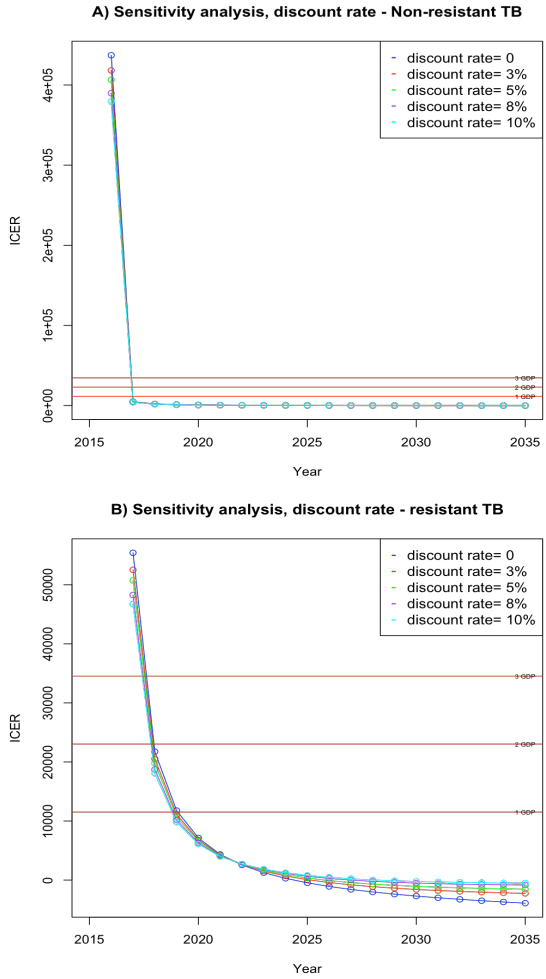


Figure 14. Sensitivity analysis of discount rate and time horizon upon the ICER for A) non-resistant TB and B) resistant at discount rate levels of 0, 3%, 5%, 8% and 10%.

COST-BENEFIT ANALYSIS

The Table 19 shows the results of the cost benefit analysis of the focalized intervention in the San Juan de Lurigancho health network.

Over the twenty-year horizon, the focalized intervention averted 9,430 and 1,244 cases of non-resistant and resistant TB, respectively. In addition, this intervention is estimated to save 6,894,751.23 USD and 10,080,240.11 USD as a result of averted non - resistant and resistant TB cases. Both figures are for adjusted costs (Discount rates= 3%). The total benefit of this intervention was 16,974,991.34 USD. According to the net returns of investment, the cost-benefit of this intervention is 10,228,902.00 USD saved. This net return of investment was estimated to decrease when we adjusted the cost by different discount rates (see Table 19).

Table 19. Resume of the cost-benefits analysis of the focalized intervention vs. status quo in the twenty years of intervention.

Discount rate	Total cases of non-resistant TB averted	Total cases of MDR-TB averted	Benefits			Total cost of the focalized intervention	Net returns of investment (Program cost – Benefits)
			Total cost saving of cases of non-resistant TB averted	Total cost saving of cases of resistant TB averted	Total benefits		
Unadjusted	9,430	1,244	9,963,549.40	14,978,941.80	24,942,491.20	9,190,246.80	-15,752,244.40
Adjusted (Discount rate = 3%)	**9,430**	**1,244**	**6,894,751.23**	**10,080,240.11**	**16,974,991.34**	**6,746,089.34**	**-10,228,902.00**
Adjusted (Discount rate = 4%)	9,430	1,244	6,143,503.90	8,899,919.03	15,043,422.94	6,139,592.49	-8,903,830.45
Adjusted (Discount rate = 5%)	9,430	1,244	5,493,375.83	7,886,264.78	13,379,640.61	5,610,931.32	-7,768,709.29

Sensitivity analysis

Figure 15 depicts the sensitivity analysis of the time horizon upon the net returns, holding the discount rate fixed at 3% for A) non-resistant and B) resistant TB. In both non-resistant and resistant TB, the net returns begins with negative values and then positive values. In both non-resistant and resistant TB, at the beginning of the focalized intervention, there is not money saving. For non-resistant TB, the focalized intervention begins to save money after the year 2028, and for resistant TB, the focalized intervention begins to save money after the year 2025.

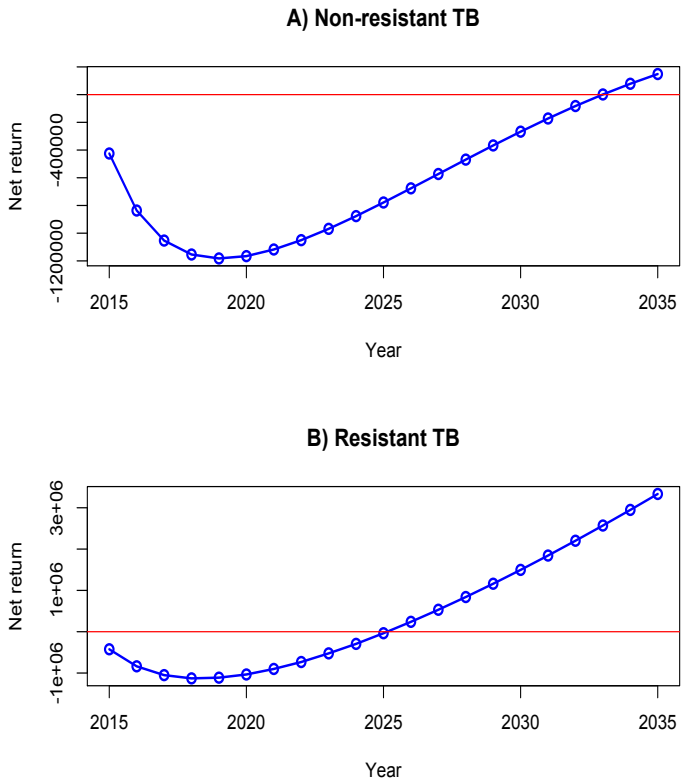


Figure 15. Sensitivity analysis of the time horizon upon the net return for cost-benefit analysis, holding discount rate fixed at 3%, for A) non-resistant and B) resistant TB.

Figure 16 shows the sensitivity analysis of discount rate and time horizon upon the net return for non-resistant TB and resistant TB for different discount rates, where we the changes on the discount rates levels affect the net returns in both non-resistant and resistant.

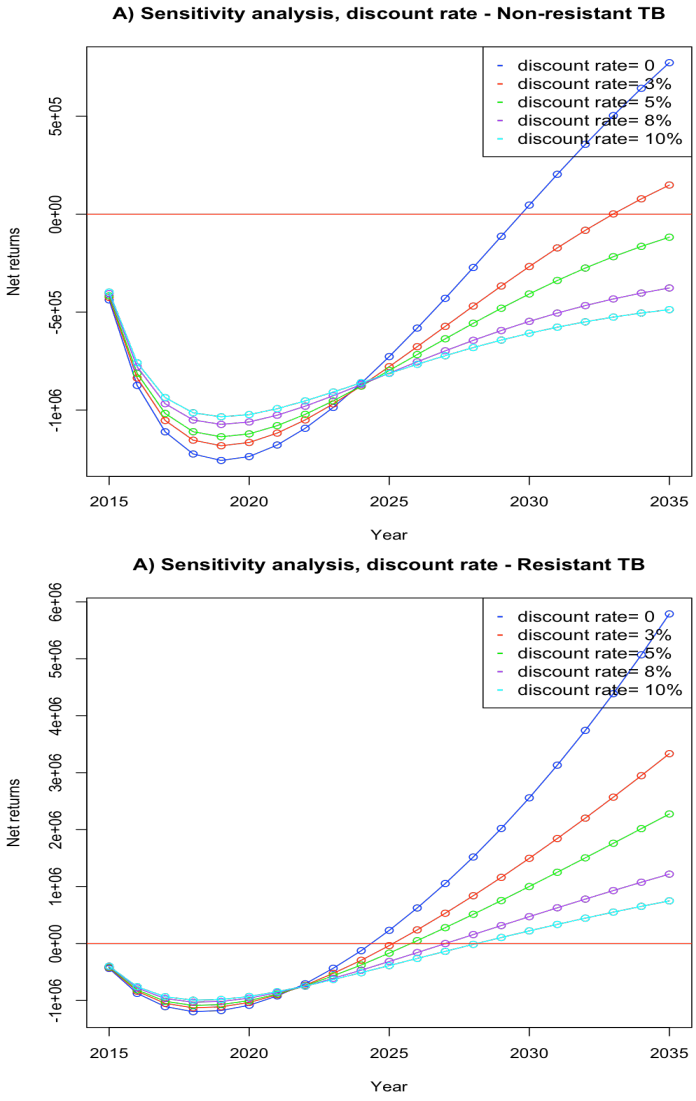


Figure 16. Sensitivity analysis of discount rate and time horizon upon the net return for A) non-resistant TB and B) resistant at discount rate levels of 0, 3%, 5%, 8% and 10%.

Figure 17, shows the sensitivity analysis of effectiveness and time horizon upon the net return for non-resistant TB and resistant TB for different fixed discount rates at 3%, where we the changes on the levels of effectiveness affect the net returns in both non-resistant and resistant.

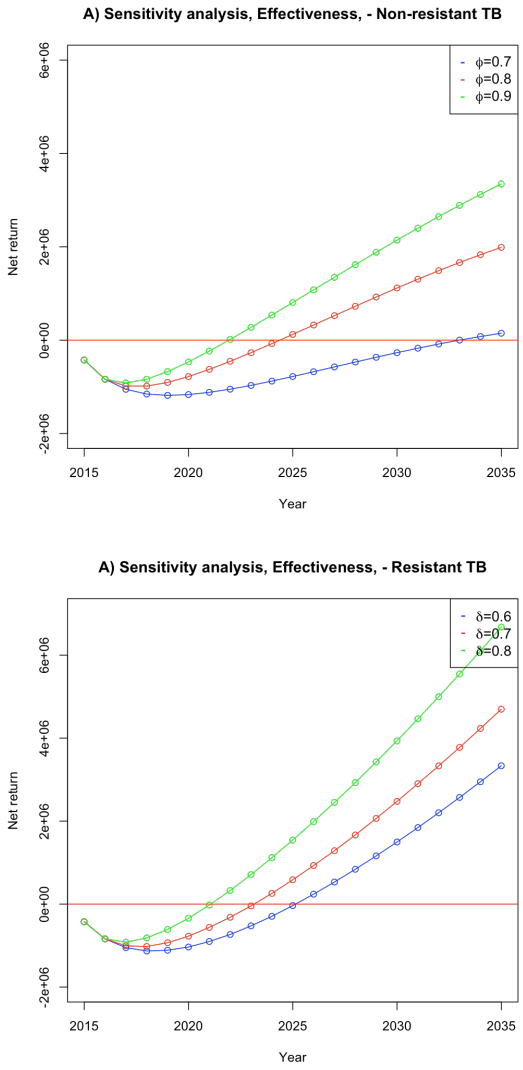


Figure 17. Sensitivity analysis of effectiveness and time horizon upon the net return for A) non-resistant TB and B) resistant at discount rate fixed at 3.

CHAPTER 4: Discussion

OVERVIEW OF MAJOR FINDINGS

Tuberculosis eradication is a formidable goal and will require a shift in the current way of thinking, implementation of interventions in high TB burden areas, and assessment of current control measures. New and innovative strategies, paired with appropriate diagnostic, are needed to deal with the main problems of tuberculosis control (i.e. high rates of treatment default, low rates of treatment success) to mode toward elimination or eradication of tuberculosis in the coming years. In the line, with these needs this research assessed one of the strategies related with the "Control of Tuberculosis in Large Metropolitan Cities" Initiative supported by PAHO in Peru. Finding suggest that for 2014 the National Sanitary Strategy of Control and Prevention of Tuberculosis spent 1,505,631.00 USD in the San Juan de Lurigancho health network for non-resistant TB care, including baseline assessment (TB diagnostics, resistant TB diagnostics, laboratory and health assessment), treatment and follow-up assessment expenses (laboratory and health assessments). In addition, the National Sanitary Strategy of Control and Prevention of Tuberculosis spends an average 1,056.58 USD per non-resistant TB patient.

With respect to resistant TB, the total expenses were an average 2,694,885.18 USDs per year. The cost for MDR-TB only was in average 2,003,739.72 USD per year for both the San Juan de Lurigancho health network and El Agustino micro network combined. In addition, the National Sanitary Strategy of Control and Prevention of Tuberculosis spend an annual average of 14,119.95 USD per MDR-TB patient.

In terms of effectiveness of the focalized intervention to reduce treatment default and treatment interruption, we found that the effectiveness to reduce treatment default was 86.04% (95% CI: 81.30% – 93.23%); the incremental effectiveness was -8.97% (95% CI: -10.22% – -7.72%); the effectiveness to reduce treatment irregularity was 69.01% (95% CI: 64.83% – 74.62%); and the incremental effectiveness was -12.97% (95% CI: -13.96% – -11.97%).

The cost-effectiveness study showed that the focalized intervention is cost-effective for non-resistant TB and resistant TB over a twenty years period, and the cost per TB case averted was 1,965.07 USD (discount rate= 3%) for non-resistant TB, and the cost per TB case averted was 16,821.00 USD (discount rate= 3%) for resistant TB. Further, this was cost-utilitarian over a twenty years period according to the results of the cost-utility study, where the cost per DALY averted was 1,6521.87 USD (discount rate= 3%) for non-resistant TB and 14,138.35 USD (discount rate= 3%) for resistant TB. It is important to note that during the first 5 or 8 years of the focalized intervention this one was not cost-effective or cost utilitarian.

The cost-benefit analysis showed that this intervention is cost-beneficial as it produced a total savings of 10,228,902.00 USD over the course of the twenty years of intervention. But the saving was effective after the 2,028 for non-resistant TB, and after the year 2025 for resistant TB.

LIMITATIONS

Cost analysis

The present study has some limitations which we attempted to deal with as follows, based on the available data. First, despite our best efforts, cost data for all services delivered to TB patients during treatment were not made available to us for this analysis. These missing cost data include: adverse reaction to TB treatment and complications related to TB itself such as hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, malignancy, and chronic pulmonary aspergillosis(6; 55; 72). However, serious complications requiring hospitalization are less common under current practice and guidelines(90) and it will not affect to much our results. Further, we did not include in our analysis the comorbidity treatment cost of HIV/AIDS, diabetes mellitus, renal failure, COPD as these cost data were not available. Again these comorbidities tend to occur infrequently, with the exception of diabetes mellitus(85; 121). While we suggest these costs may not be expected to be large given infrequency of co-morbidities and serious complications, it is likely that our study underestimates the cost of illness associated with these conditions due to data exclusion.

The cost of illness used in this study on focus on the cost of treatment that has some limitations to estimate the cost of illness, because it does not include the counterfactual that the incremental approach(63; 83) does. This new alternative of estimating cost of illness rely on estimating the annual incremental medical care cost for individuals with the condition, in our case TB, compared with those without the condition.

Second, we did not have data from the El Agustino micro network to estimate the cost of illness for non-resistant TB, which meant we could not estimate the total cost of illness for this area. Instead, we address this by using individual cost of illness data from San Juan de Lurigancho as a reference value for El Agustino, because the individual cost of illness is similar. In both areas, the local Sanitary Strategy of Control and Prevention of Tuberculosis provides the same services at the same cost.

A third limitation of our cost analysis is that we did not use the insurance claims data. Instead, we use insurance tariff to estimate the cost of each TB services received by patients. We had access to a detailed database with all services provided to the TB patients, which provides confidence that our estimations are close to the real figures for insurance claims data.

Effectiveness of the focalized intervention

We had limited data for the focalized intervention. At the time of the study was conducted, the focalized intervention had only been running for 5 months. This limits our assessment, and only allowed us to make inferences for non-resistant TB. We could not make inferences for resistant TB, as treatment duration for resistant TB requires between 18 to 24 months, because probably the impact of the focalized intervention would be less than we expected, for non resistant TB, to reduce TB treatment default.

Because this intervention was implemented in a small number of health facilities, probably the extrapolation of its results could be limited only to health facilities with the same characteristics. But the focalized intervention is a good beginning that should be taking into account for policy makers.

Health economic analysis

There are some caveats that we need to point out, one of them is that all three economic studies (cost-effectiveness, cost-utility and cost-benefit studies) depend on an epidemiological compartmental model, and as we know, all models rely on their structure and on their assumptions. In this regard, our model follows the natural history of non-resistant and resistant TB, so the structure of the model guarantees a good representation of reality.

In addition, we have chosen carefully our model assumptions, all our assumption are based on scientific literature, TB program data and only one parameter (β_S = transmission coefficient for drug-sensitive M. tuberculosis) was calculated using the model, through non-linear curve fitting (least squares), were we fit the model to the data.

Another caveat is that this model runs under the assumption that nothing will change over a twenty years period, which is not a real situation, because in reality things changes with the time. But because we cannot know what happens in the years to come, this assumption is fine for our model.

EFFECTIVENESS OF THE FOCALIZED INTERVENTION

The main problem of the control of tuberculosis in Peru is the low rates of treatment success for both non-resistant and resistant TB, mainly due high rates of treatment default. The rates of treatment default in San Juan de Lurigancho for non-resistant TB and resistant TB were 9.85% and 31.00%, respectively; and for El Agustino were 10.1% and 34%, respectively. In this scenario, the National Sanitary Strategy of Control and Prevention of Tuberculosis and the Institute of Health Services Management designed and implemented the focalized strategy after a comprehensive analysis of the main causes of treatment default. Their main goal was to reduce TB treatment default in 93 health facilities of Metropolitan Lima including our two study areas.

Intervention impact can be measured through a comprehensive assessment of the main causes of the problem(61), which in this study was TB treatment default. TB treatment default is a multifactorial problem(26; 47; 54) that has been linked to the treatment itself (long duration of the treatment, injectable, many drugs) (25), to lifestyle factors (64; 128) (illegal drug abuse, alcoholism, etc.), and to environmental factors (poverty, health system response)(36; 37), etc.

We reviewed the scientific literature to identify scientific approaches addressing this problem, and found a range of intervention such as economic incentives(13; 19; 126), directly-observed therapy (DOTS)(57; 58; 74; 132), education and counseling(11; 80; 96), mobile phone text messaging(104; 105), community participation and self administration of treatment(123; 133; 143), and even detention of non-adherent TB patients(32; 77). We did not identify interventions similar to the focalized intervention implemented in Peru, which has a certified nurse who does counseling and education,

manages patient and their contact appointments, tracks daily the TB treatment and performs household visits for patients who miss treatment appointments.

However, when the effectiveness of the focalized intervention to reduce follow-up is compared with the interventions mentioned above, we find that the focalized intervention is equal to or more effective than others intervention. For example: patients in a five-dollar grocery coupon intervention reduced their risk of treatment default by 83% (19) while focalized intervention reduced this risk in 86%, it is important to notice that we cannot compare this two strategies because we don't have a standard indicator like the ICER.

In a study performed in a Brazilian favela(123), DOTS reduced the percent of the population treatment default from 17.8% to 5.5%, while the Peruvian focalized intervention reduced the treatment default from 10.42% to 1.46% in our study areas. Notably, all patients in the focalized group received treatment via DOTS. Further, another intervention focused on counseling and education saw a 47% treatment default in their intervention group compared to 54% in the control group (78).

A Kenyan intervention utilizing SMS reminders increased rates of clinic attendance in 1.56 times on scheduled days compared to standard care(105). Finally, examples of the detention for non-adherent patients are limited as detention of individuals for public health good raises human right considerations(32; 77).

The compartmental, dynamic and epidemiological model showed a reduction of non-resistant TB incidence rates from 110.24 incident cases per 100,000 populations at the intervention outset, to 53.49 incident cases per 100,000 populations over the twenty-

years focalized intervention. The model also showed a slow down of the MDR-TB epidemic over the twenty-years focalized intervention.

COST ANALYSIS

In 2005, the Peruvian government spent 11,671,000 of "Nuevos soles"(82; 88) in health care, which when converted to USD using a PPP conversion factor is 15,522,430 USD; this amount of money represented 5.4% of the Peruvian GDP in 2005. In 2013, Peruvian health expenditure was 5.3% of the Peruvian GDP, similar to 2005. This is less than the Latin American average (between 9 and 10%)(151). In this scenario, the Peruvian government has spent around 94 million USD in 1999 and 80 million USD in 2010 in tuberculosis control activities (89). These data came for the second economic study in Peru to estimate the cost of tuberculosis. In the following subsections, we discuss the cost of illness and the cost of the focalized intervention.

Cost of illness

The economic study "Socioeconomic impact of the tuberculosis in Peru: 2010"(89) estimated that the individual cost of non-resistant TB was in average 632 USD between 2005 -2010, which is less than our estimation of 1,056.58 USD. Furthermore, the same study estimated that the individual cost of MDR-TB was an average 13,769.00 USD which is similar to our estimate of 14,119.95 USD. We cannot compare the total cost of illness for both studies, because our study carried out in only two health networks and the other study was at a national and department level.

Notably, there are key difference in the values used to calculate of the cost of illness in the study "Socioeconomic impact of the tuberculosis in Peru: 2010"and our study. Were our study has used the PPP conversion factor, and the other study may have used exchange rates. We cannot be certain as information on cost methodology for converting "Nuevos soles" to USD was not available. Additionally, other items included

in cost of illness estimation, were cost such as the loss of productivity cost during the treatment, cost of food basket, TST cost, and out of pocket expenses. We did not include these in our study.

Finally, in the Global Tuberculosis Report 2014(152), the WHO estimated the individual cost for drug-susceptible TB in 2013 was in the range of 100 – 500 USD in most high burden TB countries. Further, they estimated the individual cost for MDR-TB ranged from an average of 9,235 USD in low-income countries to 48,553 USD in upper middle-income countries.

Cost of the program

The cost of the focalized intervention to reduce the rate of treatment default in 26 prioritized health facilities of Metropolitan Lima was estimated to be 1,422,300.00 USD per year. The total estimated cost of the focalized intervention to reduce the rate of treatment default for the 5 health facilities in San Juan de Lurigancho health network and for the 3 health facilities in El Agustino micro-network was $437,630.8 USD per year.

While this cost may seem high for some health authorities in Peru (from our experience negotiating with health authorities in Lima to get funding for this intervention), the benefits of this strategy must be taken into account the Ministry of Health where the effectiveness of the focalized intervention is very high 86.04% (95% CI: 93.23% – 81.30%) to reduce treatment default and thus to avert non-resistant and resistant TB (9,430 and 1,244 respectively) over a twenty years period.

HEALTH ECONOMICS ASSESSMENT

Health economics assessment is key decision-making tools(16; 23), particularly in the light of scarce public resources and competing priorities faced by governments of low and middle-income countries.

In our scenario tuberculosis is one of the leading causes of death and morbidity in Peru, and mainly affects poor population living in large metropolitan cities in Peru (110). The incidence rate has been in slow decline over the past ten years, probably because current control measures have reached their limit(85). We need new strategies to address the main challenges of TB control, which should be based on a comprehensive diagnostic tool which is supported by scientific evidence and strong health economic analysis.

As far as we know, the focalized strategy described here is unique in that it is based on a comprehensive diagnostic and addresses the main problems of TB control in Peru, or the lack of close monitoring of the patient treatment which have led to high rates of treatment default(51). This lack of close monitoring of patient treatment may occur in part due to health care worker capacity issues and competing demands on time by other activities such as vaccination, vector control, etc.

Furthermore, the focalized strategy follows the guidelines of the "Control of Tuberculosis in Large Metropolitan Cities on LAC" Initiative supported by PAHO, which encourages countries to develop new strategies to control tuberculosis in a comprehensive way (109).

In this scenario, health economic assessment of the focalized strategy was crucial in order to generate scientific evidence about the impact of this intervention. These data may be used for decision-making purposes at various government levels. This economic

analysis covers three main target audiences: government, Ministry of health and the National Sanitary Strategy of Control and Prevention of Tuberculosis. In this regards, our results will help in the decision-making process at these three levels of government.

The three types of health economic analysis showed that this strategy was cost-effective, cost-utilitarian and cost-beneficial over a twenty years period. The latter finding suggests the government (Ministry of Finance) will save money (10,228,902.00 USD over the twenty years of intervention) by supporting and implementing this strategy, which can then be used to address other health problems like iron anemia in children, vector borne diseases, or to extent this strategy to others departments with high burden of TB disease, like Ica, La Libertad, Madre de Dios, Ucayali, etc.

Additionally, as this strategy is cost-utilitarian, the Ministry of Health could avert DALYs at a reasonable cost. Active tuberculosis may produce moderate to severe disability when patients do not complete the full treatment which contributes to greater DALYs. Consequently, by reducing treatment default in active cases, this strategy is expected to avert associated DALYs. It is important to clarify that the threshold to decide if a strategy is cost utilitarian depends on the target audience(s), the thresholds recommended by the WHO (45), and is based on the GDP PPP (1 o 3 times GDP PPP). In this regard, this focalized strategy is highly cost-effective (ICER = 16 USD per TB case averted) for non-resistant TB and resistant TB (ICER = 2,680 per TB case averted). Agreement over what threshold best captures willingness to pay is in flux .For example the threshold for the U.S. is 50,000 USD but some researchers considered this threshold low(102).

It is important to note that the focalized intervention becomes cost-effective or cost-utilitarian after the second year, and after the year 2,032 the focalized intervention becomes dominant. Similar situation occur with resistant TB, the focalized intervention becomes cost-effective or cost-utilitarian after the third year of and then became dominant after the first ten years. This issue is important because the National TB program must wait some time to see the results of the focalized intervention.

The other important issue is that the focalized intervention will save money only after 17 years of implementation for non-resistant TB. However, for resistant TB, the focalized intervention will save money after 10 years of implementation. The time horizon is a very important point to consider, in order to not misunderstanding the results of this focalized intervention.

The main cost driving total cost is that of the dedicated nurses. However, this cost could be reduced if the Institute of Health Services Management or the National Sanitary Strategy of Control and Prevention of Tuberculosis were to hire these personnel permanently. The current contracting scheme has resulted in a higher nursing salary than the industry standard within the Ministry of Health.

This new way of thinking – to target high TB burden areas in large metropolitan cities based on a comprehensive approach –is an opportunity for LAC countries to consider adopting similar intervention approaches and move toward achievement the goals of End TB by 2035(153). Interventions to target high burden areas are critical given the current situation seen across LAC countries, where by and large, progress toward reducing incidence of tuberculosis has been decelerating(152).

Peru is one of the three LAC countries which have been implemented the PAHO-strategy of "Control of Tuberculosis in Large Metropolitan Cities on LAC" Initiative. Peru now has the opportunity to share key findings on the impact of this strategy, so that countries whit similar contextual challenges like high default rates stemming from lack of monitoring can consider adopting similar approaches.

The focalized intervention is well-aligned with the primary goal of the "End TB Strategy," as it is not only designed to reduce the rates of treatment default and treatment interruption, but also indirectly to reduce TB cases in the community, thus reducing community TB transmission. As a consequence, the focalized strategy will contribute to reaching the global goal to reduce TB incidence below 10 cases per 100,000 population by 2035.

In this research, we assess one component of the focalized strategy, the close monitoring of the patient treatment. However, there are other strategies being implemented (social marketing, community surveillance, etc.), which need evaluation in order to inform novel TB elimination strategies and interventions for roll out across the LAC region.

The Peruvian Ministry of Health, through the National Sanitary Strategy to Prevent and Control Tuberculosis, has implemented most of the cost-effective strategies available for TB control, (i.e. DOTS, DOTS-plus, sputum smear and culture, rapid susceptibility testing against second-line drugs for tuberculosis, and home-based treatment and hospitalization-based treatment for XDR-TB). However, there remain other cost-effective options for implementation, such as active case finding, sputum smear,

culture and chest x-ray diagnoses combined, Xpert MTB/RIF assays in hot spot areas, as well as community-based treatment for patients in default. Comparisons of the focalized intervention against these other options suggest mixed results for cost-effectiveness. For example, tuberculosis active case finding has a cost of 330 USD per DALY averted (154), which is higher than the ICER (13.25 USD) for the focalized intervention for non-resistant cases, but less than the focalized intervention ICER (2.,252.00 USD) for resistant TB cases. Further, the sputum smear and chest x-ray diagnosis combination has an ICER of 56.69 USD, which is higher than the ICER for non-resistant TB but lower than the ICER for resistant TB in the focalized intervention. The ICER for community-based DOTS is 1726 USD for home-based care, which is substantially higher than the ICER for non-resistant TB in the focalized intervention, but less than the ICER for resistant TB cases treated in the focalized intervention. A similar situation occurs for Xpert MTB/RIF assays used in TB hot spots.

Finally, it is important to note that the implementation of some of these strategies mentioned above (i.e. combination of sputum smear and Chest x-ray diagnosis, Xpert MTB/RIF assay in hot spots, active case finding) may result in an increase in TB caseload at the health facilities due to increased case detection. It is conceivable that increased caseload could lead to an increase in the rate of treatment default because personnel at the health facilities would not be able to monitor TB treatment adequately due to the high caseload. On the other hand, if implemented community-based DOTS could help to reduce treatment default. This suggest that the control of TB should be addressed using a multilevel approach, which takes into account multiple interventions targeting different levels of the health system.

CHAPTER 5: Recommendations

NATIONAL SANITARY STRATEGY OF CONTROL AND PREVENTION OF TUBERCULOSIS

We demonstrate the potential impact of this focalized strategy to reduce not only treatment default and irregular treatment but to reduce TB cases over the long term. Given these findings, there is now an opportunity for the National Sanitary Strategy of Control and Prevention of Tuberculosis and for the Institute of Health Services Management to include the focalized strategy in the "Budget per Results" initiative which is a Peruvian government strategy to distributes funds according to health system performance.

This strategy aligns with the Peruvian government efforts on using its annual budget wisely, and its worries about consider prioritization of funding for TB activities among many public health problems. The "Budget per Results" initiative is an attempt to address public health problems and funding scientifically, but this effort has been overshadowed by a lack of effective, new strategies to control or eradicate major public health problems of the country. This study fills the gaps of the lack of effective, new strategies to control or eradicate TB by 2035, because it gives sounding scientific evidence that the goal of reducing TB incidence rate below 10 new TB cases per 100,000 population is possible if we continue supporting the focalized intervention, obviously with the implementation of more effective and short treatment schemes.

It is important to note that having an exclusive nurse who monitors daily patient treatment is a key intervention feature for reducing treatment default. It is vital that the National Sanitary Strategy of Control and Prevention of Tuberculosis amends the

National Guideline of Control of Tuberculosis to include this exclusive nurse as part of the local TB team. This action will create space to make this a permanent position with an associated permanent salary line item in the associated budget. Simultaneously, it will be important that the fidelity of this position be maintained; that is, this position should not do take on other activities beyond monitoring treatment, so that focus remains on ensuring high treatment completion rates. Our recommendation is that dedicated nurses are needed only in health facilities with a high burden of TB disease and high treatment default.

MINISTRY OF HEALTH

For the first time the Ministry of Health has an important tool ("Control of Tuberculosis in Large Metropolitan Cities on LAC" Initiative) on its hands that would improve the current control of TB in Peru, and will give the opportunity to move forwards towards the elimination of TB of Peru. The Ministry of Health should not miss the opportunity the support this initiative –as it did in the past- and used it as a model for other public health problems.

It is important that the Ministry of Health encourage other sanitary strategies to address major public health problems using a comprehensive approach like "Control of Tuberculosis in Large Metropolitan Cities on LAC" Initiative. Further, The Ministry of Health should encourage or require all control strategies to perform health economic assessments. Results may be used to evaluate and make decisions about prioritization and continuation of strategies. This is the first example of evaluation research to be implemented with support of the Ministry of Health, in spite of numerous current and

past interventions funded by Ministry of Health. “Budget per Results” initiative includes a health economic assessment in its methodology that never has been performed. Moving forward, this mandate creates the necessary space for economic assessment across Ministry of Health -funded public health interventions.

INSTITUTE OF HEALTH SERVICES MANAGEMENT

The Institute of Health Services Management is in charge of the control of tuberculosis in Metropolitan Lima. The focalized strategy for TB control has been implemented with the economic of the National Sanitary Strategy of Control and Prevention of Tuberculosis However, in order to ensure sustainability to this strategy, the Institute of Health Services Management must include the intervention in its annual budget. Expansion of this strategy to other Health Networks with high TB burden and high levels of treatment default would be facilitated by inclusion of a dedicated line in the annual budget of the Institute of Health Services Management.

PAN-AMERICAN HEALTH ORGANIZATION

This is the first time that PAHO has scientific evidence that the “Control of Tuberculosis in Large Metropolitan Cities on LAC” approach really works. In this regards PAHO must promote and expand this new initiative to other countries of the region in order to have better opportunities to reach the goals of “End TB Strategy” and also accelerate the decline of the TB incidence rate in the region that in last ten years it has decelerated.

The PAHO has played an important role in designing this comprehensive strategy. Moving forward, PAHO can play an important role in supporting countries' nascent efforts to adopt and expand such an approach, both from a technical assistance and financial standpoint to the extend feasible. We see a role for PAHO in designing economic assessment guideline for this initiative in other to contexts, based on the pilot experience in Lima - Peru. LAC countries need tools to improve their current control measures and to evaluate the current and potential interventions. PAHO has an important role to play in facilitating country growth in this area of new ones.

OVERALL CONCLUSIONS

Our study has four major findings:

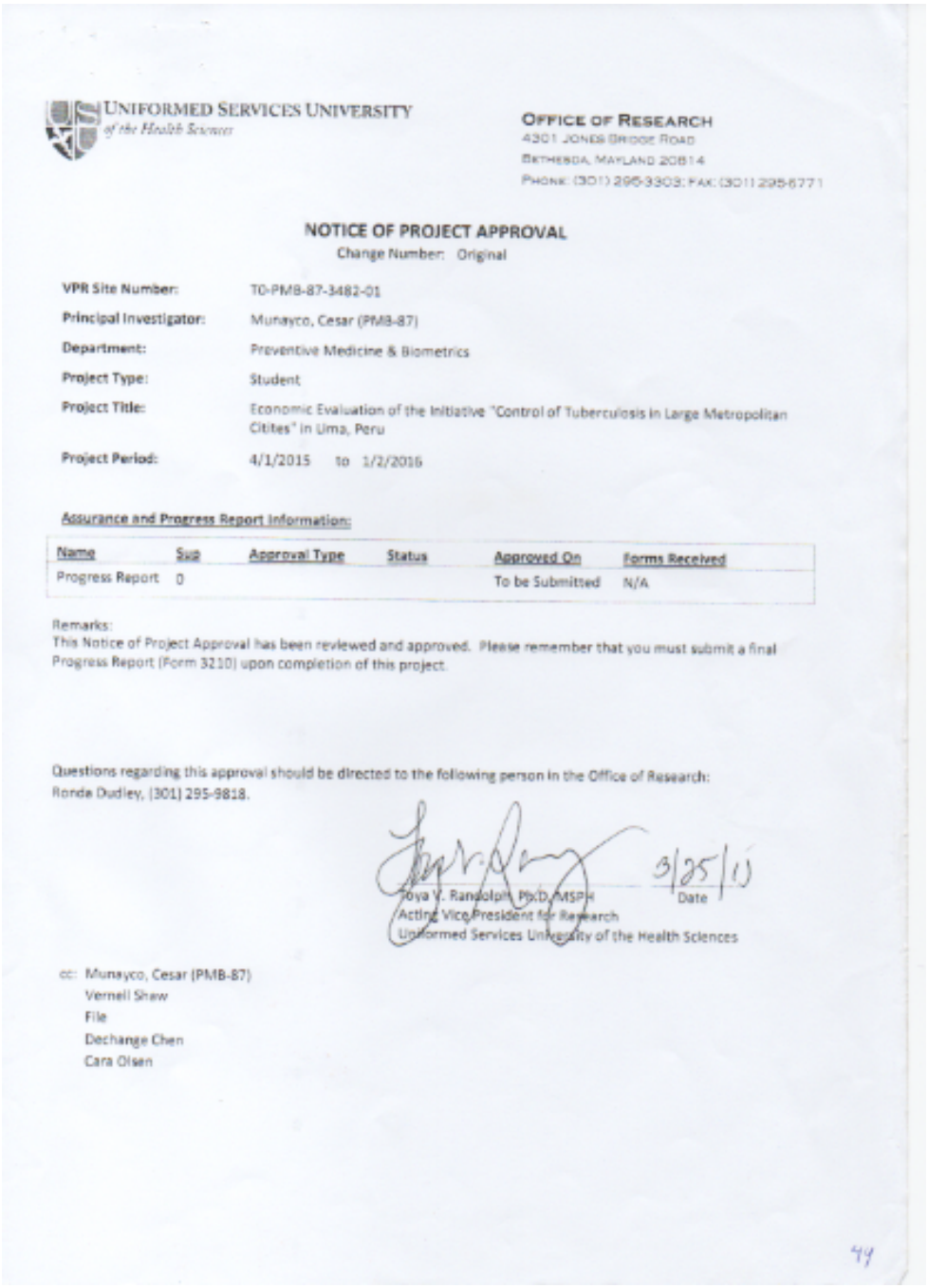
1. This focalized strategy is effective and has the potential to reduce TB treatment default from 10.42% to 1.46% and treatment interruption from 18.79% to 5.82%.
2. In San Juan de Lurigancho and el Agustino, the Ministry of Health spends roughly 2,694,885.18 USDs per year in resistant TB management, and spends 1,505,631.00 in non-resistant TB per year. This large amount of money could be reduced if the focalized strategy is implemented in selected health facilities of these two areas.
3. This strategy has a potential future impact on the control of TB, because reduce the treatment default of resistant and non-resistant TB patients and lead to cure of many TB cases and a reduction of active TB in the community.
4. This strategy is cost-effective, cost-utilitarian and cost-beneficial. We demonstrate this through reduction in the estimated numbers of non-resistant and resistant TB

cases averted, averted DALYs, and estimated money to be saved by the Ministry of Health.

APPENDICES

APPENDIX 1. APPROVAL DOCUMENTS

Appendix 1a. USUHS Office of Research Approval



UNIFORMED SERVICES UNIVERSITY
of the Health Sciences

OFFICE OF RESEARCH
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814
PHONE: (301) 295-3303; FAX: (301) 295-6771

NOTICE OF PROJECT APPROVAL
Change Number: Original

VPR Site Number:	TO-PMB-87-3482-01
Principal Investigator:	Munayco, Cesar (PMB-87)
Department:	Preventive Medicine & Biometrics
Project Type:	Student
Project Title:	Economic Evaluation of the Initiative "Control of Tuberculosis in Large Metropolitan Cities" in Lima, Peru
Project Period:	4/1/2015 to 1/2/2016

Assurance and Progress Report Information:

Name	Sup	Approval Type	Status	Approved On	Forms Received
Progress Report	0			To be Submitted	N/A

Remarks:
This Notice of Project Approval has been reviewed and approved. Please remember that you must submit a final Progress Report (Form 3210) upon completion of this project.

Questions regarding this approval should be directed to the following person in the Office of Research:
Ronda Dudley, (301) 295-9818.

3/25/15
Date

Joya V. Randolph, PhD, MSPH
Acting Vice President for Research
Uniformed Services University of the Health Sciences

cc: Munayco, Cesar (PMB-87)
Vernell Shaw
File
Dechange Chen
Cara Olsen

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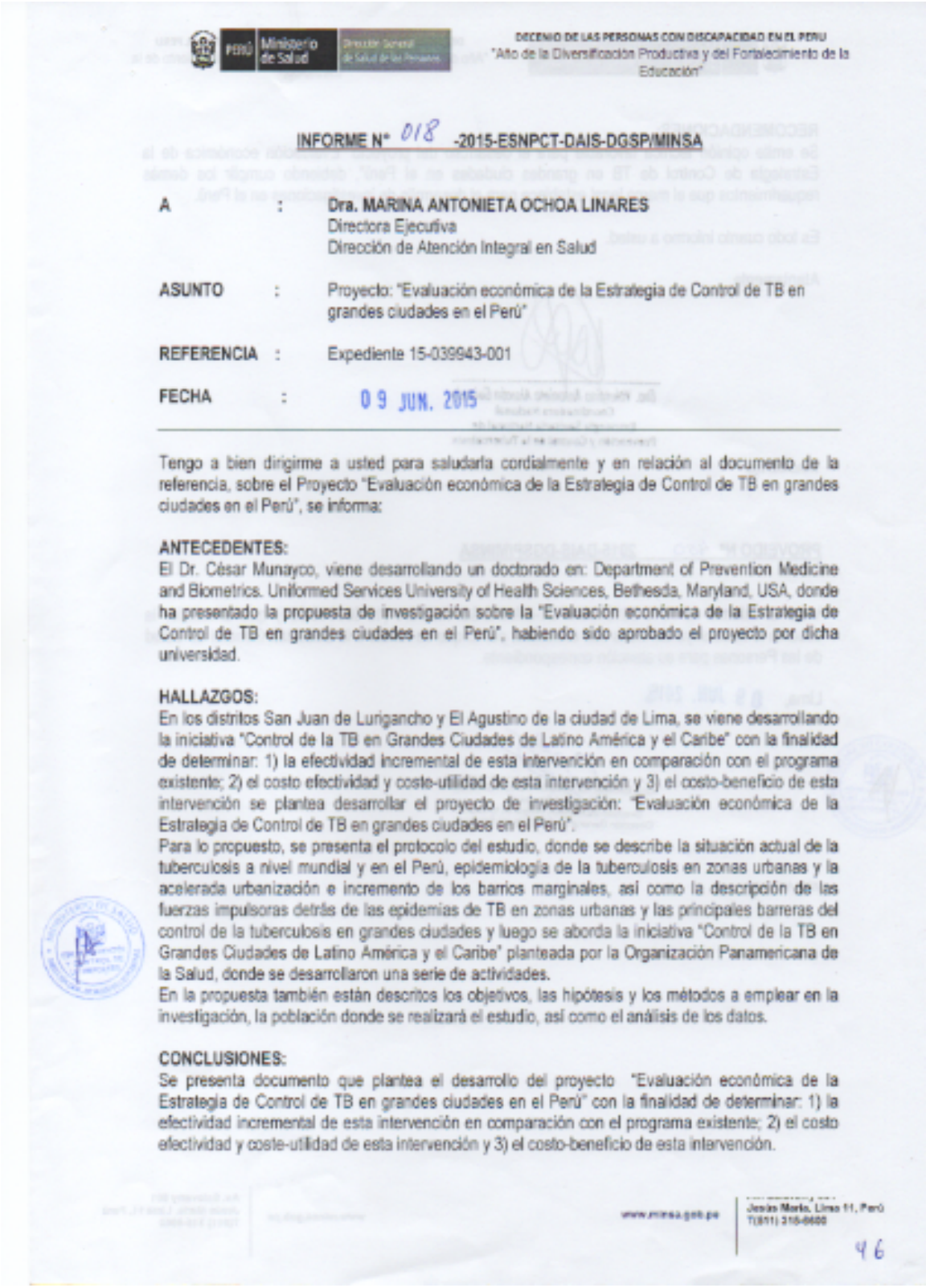
Appendix 1b. Peruvian Ministry of Health – National Sanitary Strategy of Control and Prevention of Tuberculosis Approval



PERÚ | Ministerio de Salud | Dirección General de Salud de las Personas

DECENIO DE LAS PERSONAS CON DISCAPACIDAD EN EL PERÚ
"Año de la Diversificación Productiva y del Fortalecimiento de la Educación"

INFORME N° 018 -2015-ESNPCT-DAIS-DGSP/MINSA

A : Dra. MARINA ANTONIETA OCHOA LINARES
Directora Ejecutiva
Dirección de Atención Integral en Salud

ASUNTO : Proyecto: "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú"

REFERENCIA : Expediente 15-039943-001

FECHA : 09 JUN. 2015

Tengo a bien dirigirme a usted para saludarla cordialmente y en relación al documento de la referencia, sobre el Proyecto "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú", se informa:

ANTECEDENTES:
El Dr. César Munayco, viene desarrollando un doctorado en: Department of Prevention Medicine and Biometrics. Uniformed Services University of Health Sciences, Bethesda, Maryland, USA, donde ha presentado la propuesta de investigación sobre la "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú", habiendo sido aprobado el proyecto por dicha universidad.

HALLAZGOS:
En los distritos San Juan de Lurigancho y El Agustino de la ciudad de Lima, se viene desarrollando la iniciativa "Control de la TB en Grandes Ciudades de Latino América y el Caribe" con la finalidad de determinar: 1) la efectividad incremental de esta intervención en comparación con el programa existente; 2) el costo efectividad y coste-utilidad de esta intervención y 3) el costo-beneficio de esta intervención se plantea desarrollar el proyecto de investigación: "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú".
Para lo propuesto, se presenta el protocolo del estudio, donde se describe la situación actual de la tuberculosis a nivel mundial y en el Perú, epidemiología de la tuberculosis en zonas urbanas y la acelerada urbanización e incremento de los barrios marginales, así como la descripción de las fuerzas impulsoras detrás de las epidemias de TB en zonas urbanas y las principales barreras del control de la tuberculosis en grandes ciudades y luego se aborda la iniciativa "Control de la TB en Grandes Ciudades de Latino América y el Caribe" planteada por la Organización Panamericana de la Salud, donde se desarrollaron una serie de actividades.
En la propuesta también están descritos los objetivos, las hipótesis y los métodos a emplear en la investigación, la población donde se realizará el estudio, así como el análisis de los datos.

CONCLUSIONES:
Se presenta documento que plantea el desarrollo del proyecto "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú" con la finalidad de determinar: 1) la efectividad incremental de esta intervención en comparación con el programa existente; 2) el costo efectividad y coste-utilidad de esta intervención y 3) el costo-beneficio de esta intervención.

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RECOMENDACIONES:

Se emite opinión técnica favorable para el desarrollo del proyecto "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú", debiendo cumplir los demás requerimientos que el marco legal establece para el desarrollo de investigaciones en el Perú.

Es todo cuanto informo a usted.

Atentamente,

Dra. Milagros Antonieta Alcorta Quintado
Coordinadora Nacional
Estrategia Sanitaria Nacional de
Prevención y Control de la Tuberculosis

VAAG/DZR/lg

PROVEIDO Nº 950 2015-DAIS-DGSP/MINSA

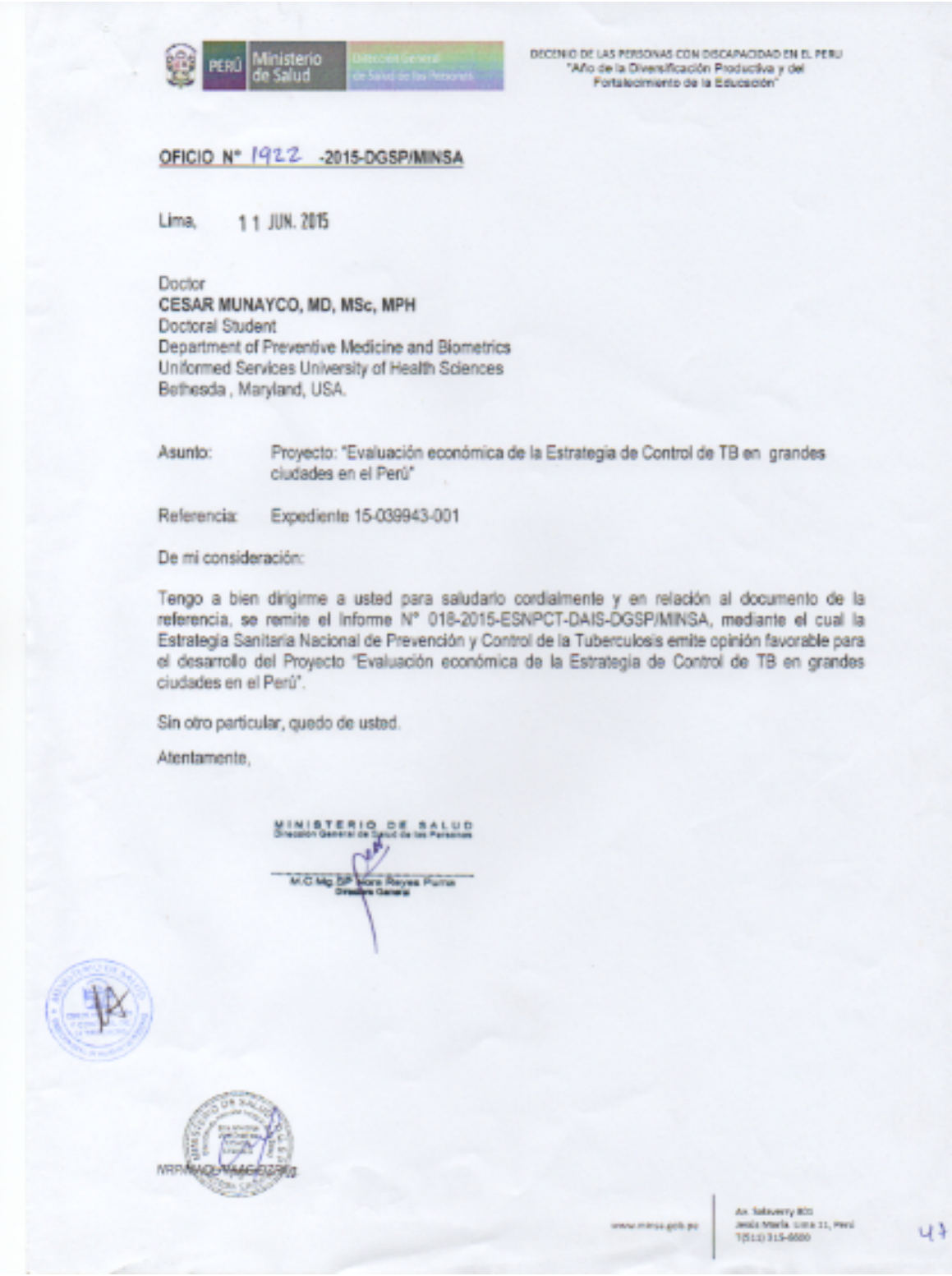
Visto el Informe N° 018-2015-ESNPCT-DAIS-DGSP/MINSA (15-039943-001) que antecede, la suscrita lo hace suyo en todos sus extremos, por lo que se remite a la Dirección General de Salud de las Personas para su atención correspondiente.

Lima, 09 JUN. 2015

Dra. MARINA ANTONIETA OCHOA LINARES
Directora Ejecutiva
Dirección de Atención Integral de la Salud
Dirección General de Salud de las Personas

MAOL/VAAG/lg

Appendix 1c. Peruvian Ministry of Health – General Directorate of People's Health Approval



PERÚ Ministerio de Salud — Dirección General de Salud de las Personas

DECENIO DE LAS PERSONAS CON DISCAPACIDAD EN EL PERU
"Año de la Diversificación Productiva y del Fortalecimiento de la Educación"

OFICIO N° 1922 -2015-DGSP/MINSA

Lima, 11 JUN. 2015

Doctor
CESAR MUNAYCO, MD, MSc, MPH
Doctoral Student
Department of Preventive Medicine and Biometrics
Uniformed Services University of Health Sciences
Bethesda , Maryland, USA.

Asunto: Proyecto: "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú"

Referencia: Expediente 15-039943-001

De mi consideración:

Tengo a bien dirigirme a usted para saludarlo cordialmente y en relación al documento de la referencia, se remite el Informe N° 018-2015-ESNPCT-DAIS-DGSP/MINSA, mediante el cual la Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis emite opinión favorable para el desarrollo del Proyecto "Evaluación económica de la Estrategia de Control de TB en grandes ciudades en el Perú".

Sin otro particular, quedo de usted.

Atentamente,

MINISTERIO DE SALUD
Dirección General de Salud de las Personas

M.C Mg. SP Mora Reyes Purizaca
Directora General

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APPENDIX 2. COST ANALYSIS

Appendix 2a. Unit cost and quantities of items for non-resistant TB

Item	2014 Unit cost ($)	Baseline	Follow up (Time Line in months)					
		Number	1	2	3	4	5	6
TB diagnosis								
Sputum smear	4.60	2	1	1	1	1	1	1
Culture	36.81	1						1
Rapid tests for the diagnosis of drug-resistant tuberculosis		1						
GRIESS	52.33	1						
GENOTYPE® MTBDRplus test	157.23	1						
Laboratory assessment								
Hemogram or complete blood count (CBC)	11.04	1						
Fasting blood glucose	5.61	1						
Creatinine blood test	6.20	1						
Liver blood test	17.87	1		1		1		
HIV rapid test or Elisa for HIV	15.73	1						
Pregnancy test (women of childbearing age)	10.76	1						
Chest X-ray	33.65	1		1				1
Health assessment								
Nursing assessment	9.30	1	1	1	1	1	1	1
General practitioner assessment	13.87	1	1	1				1
Psychological assessment	7.75	1		1				1
Social services assessment	14.09	1		1				1
Nutritional counseling	7.70	1		1				1
Family planning counseling	8.04	1		1				1

APPENDIX 2b. Unit cost and quantities of items for resistant TB

Item	2009 Unit cost ($)	2010 Unit cost ($)	2011 Unit cost ($)	2012 Unit cost ($)	2013 Unit cost ($)	2014 Unit cost ($)	Baseline	Follow up (Time Line in months)				
							Number	3	6	9	12	Between 18 to 24
TB diagnosis												
Sputum smear	4.84	5.00	4.97	4.82	4.69	4.60	2				Monthly	
Culture	38.67	39.97	39.71	38.57	37.51	36.81	1				Monthly	
Rapid tests for the diagnosis of drug-resistant tuberculosis							1					
GRIESS	54.96	56.82	56.45	54.82	53.32	52.33	1					
GENOTYPE® MTBDRplus test	165.15	170.73	169.63	164.72	160.20	157.23	1					
Proportions method in 7H10 agar in plates for first and second line-resistant drug	252.67	261.21	259.52	252.02	245.11	240.56	1					
Laboratory assessment												
Hemogram or complete blood count (CBC)	11.59	11.98	11.91	11.56	11.24	11.04	1	1	1			
Fasting blood glucose	5.89	6.09	6.05	5.88	5.72	5.61	1	1	1			
Creatinine blood test	6.51	6.73	6.69	6.50	6.32	6.20	1	1	1			
Liver blood test	18.77	19.41	19.28	18.72	18.21	17.87	1	1	1		1	
Electrolyte testing (sodium, potassium and chloride) (if the patients is having injection aminoglycosides drugs)	17.66	18.26	18.14	17.62	17.14	16.82	1	1	1			
Thyroid-stimulating hormone (TSH)	29.14	30.13	29.93	29.07	28.27	27.75	1	As recommended by the TB expert physician				
HIV rapid test or Elisa for HIV	16.52	17.08	16.97	16.48	16.03	15.73	1					
Pregnancy test (women of childbearing age)	11.30	11.68	11.61	11.27	10.96	10.76	1					
Chest X-ray	35.34	36.54	36.30	35.25	34.29	33.65	1		1		1	1

Audiometry assessment (if the patients is having injection aminoglycosides drugs)	4.85	5.02	4.98	4.84	4.71	4.62	1		1				
Health assessment													
Nursing assessment	9.77	10.10	10.03	9.74	9.48	9.30	1				Monthly		
General practitioner assessment	14.57	15.06	14.97	14.53	14.13	13.87	1				Monthly		
Expert physician in resistant TB management	17.42	18.01	17.89	17.37	16.90	16.59	1				Quarterly		
Psychological assessment	8.14	8.42	8.36	8.12	7.90	7.75	1		1		1		1
Social services assessment	14.80	15.30	15.20	14.76	14.36	14.09	1				Quarterly		
Nutritional counseling	8.09	8.36	8.31	8.07	7.85	7.70	1		1		1		1
Family planning counseling	8.45	8.74	8.68	8.43	8.20	8.04	1	1	1	1	1		1
Psychiatric assessment (encounter only if the patient in taking cycloserine or has a mental comorbidity)	14.54	15.03	14.93	14.50	14.10	13.84	1				As recommended by the TB expert physician		

APPENDIX 2c. Unit cost, acronym, dosage and presentation of drugs for the treatment of non-resistant TB

Drugs	Acronym	Daily dose	Maximum dose/day	Presentation	Unit cost* ($)
Patients greater than 15 years old					
Isoniazid	INH	5 mg/Kg*	300 mg	500 mg tablet	0.0930
Rifampicin	RIF	10 mg/Kg	600 mg	300 mg capsule	0.4805
Ethambutol	EMB	20 mg/Kg	1600 mg	400 mg tablet	0.1632
Pyrazinamide	PZA	25 mg/kg	2000 mg	500 mg tablet	0.1062
Patients less than 15 years old					
Isoniazid	INH	10 mg/Kg*	300 mg	500 mg tablet	0.0930
Rifampicin	RIF	15 mg/Kg	600 mg	300 mg capsule	0.4805
Ethambutol	EMB	20 mg/Kg	1500 mg	400 mg tablet	0.1632
Pyrazinamide	PZA	35 mg/kg	1200 mg	500 mg tablet	0.1062

Appendix 2d. Unit cost, acronym, daily dose, maximum dose and presentation of drugs for the treatment of resistant TB in Peru

Drugs	Acronym	Daily dose	Maximum dose/day	Presentation	Unit cost* ($)
Isoniazid	INH	15 mg/Kg†	900 mg	500 mg tablet	0.0930
Rifampicin	RIF	10 mg/Kg	600 mg	300 mg capsule	0.4805
Ethambutol	EMB	20 - 25 mg/Kg	1600 mg	400 mg tablet	0.1632
Pyrazinamide	PZA	25 - 30 mg/kg	2000 mg	500 mg tablet	0.1062
Streptomycine	STR	15 mg/Kg	1 gr	1000 mg injection	9.3
Kanamycine	KAN	15 mg/Kg	1 gr	1000 mg injection	0.6355
Ciprofloxacin	CIP	25 mg/Kg	1500 mg	500 mg tablet	0.155
Levofloxacin	LEV	10 - 15 mg/Kg	750 - 1000 mg	250 or 500 mg tablet	3.8409
Moxifloxacin	MOXI	10 mg/Kg	400 mg	400 mg tablet	13.2838
Ethionamide	ETA	15 mg/Kg	1 gr	1000 mg injection	0.5878
Cycloserine	CYS	15 mg/Kg	1 gr	250 mg tablet	1.7859
Para-aminosalicylic acid	PAS	150 mg/Kg	12 gr	4 gr sachet	9.0286
Capreomycin	CAP	15 mg/Kg	1 gr	1000 mg injection	49.6
Amoxicillin clavulanate	AMX/CLV	20 - 40 mg/kg	2000 mg	125 or 500 mg tablet	0.775
Vitamin B6 (pyridoxine)	B6	10-25 mg			0.0347

† High dose for XDR-TB

Appendix 2e. Individual cost and quantities of resistant TB by year of the baseline assessment*

Item	2009 cohort		2010 cohort		2011 cohort		2012 cohort		2013 cohort		2014 cohort	
	Number	Cost	Number	Cost	Number	Cost	Number	Cost	Number	Cost	Number	Cost
	Quantity	Mean (SD)	Quantity	Mean (SD)	Quantity	Mean (SD)	Quantity	Mean (SD)	Quantity	Mean (SD)	Quantity	Mean (SD))
Baseline												
TB diagnosis												
Sputum smear	2	9.67	2	9.65	2	9.21	2	9.65	2	9.38	2	9.21
Culture	1	38.67	1	38.57	1	36.81	1	38.57	1	37.51	1	36.81
Rapid tests for the diagnosis of drug-resistant TB												
GRIESS	1	54.96	1	54.82	1	52.33	1	54.82	1	53.32	1	52.33
GENOTYPE® MTBDRplus test	1	165.15		164.72		157.23		164.72		160.20		157.23
Proportions method for first and second line-resistant drug	1	252.67	1	252.02	1	240.56	1	252.02	1	245.11	1	240.56
Baseline laboratory assessment												
Hemogram or complete blood count (CBC)	1	11.59	1	11.56	1	11.04	1	11.56	1	11.24	1	11.04
Fasting blood glucose	1	5.89	1	5.88	1	5.61	1	5.88	1	5.72	1	5.61
Creatinine blood test	1	6.51	1	6.50	1	6.20	1	6.50	1	6.32	1	6.20
Liver blood test	1	18.77	1	18.72	1	17.87	1	18.72	1	18.21	1	17.87
Electrolyte testing (sodium, potassium and chloride)	1	17.66	1	17.62	1	16.82	1	17.62	1	17.14	1	16.82
Thyroid-stimulating hormone (TSH)	1	29.14	1	29.07	1	27.75	1	29.07	1	28.27	1	27.75
HIV rapid test or Elisa for HIV	1	16.52	1	16.48	1	15.73	1	16.48	1	16.03	1	15.73
Pregnancy test	1	11.30	1	11.27	1	10.76	1	11.27	1	10.96	1	10.76
Chest X-ray	1	35.34	1	35.25	1	33.65	1	35.25	1	34.29	1	33.65
Audiometry assessment	1	4.85	1	4.84	1	4.62	1	4.84	1	4.71	1	4.62
Baseline health assessment												
Nursing assessment	1	9.77	1	9.74	1	9.30	1	9.74	1	9.48	1	9.30
General practitioner assessment	1	14.57	1	14.53	1	13.87	1	14.53	1	14.13	1	13.87
Expert physician in resistant TB management	1	17.42	1	17.37	1	16.59	1	17.37	1	16.90	1	16.59
Psychological assessment	1	8.14	1	8.12	1	7.75	1	8.12	1	7.90	1	7.75
Social services assessment	1	14.80	1	14.76	1	14.09	1	14.76	1	14.36	1	14.09
Nutritional counseling	1	8.09	1	8.07	1	7.70	1	8.07	1	7.85	1	7.70
Family planning counseling	1	8.45	1	8.43	1	8.04	1	8.43	1	8.20	1	8.04
Psychiatric assessment	1	14.54	1	14.50	1	13.84	1	14.50	1	14.10	1	13.84

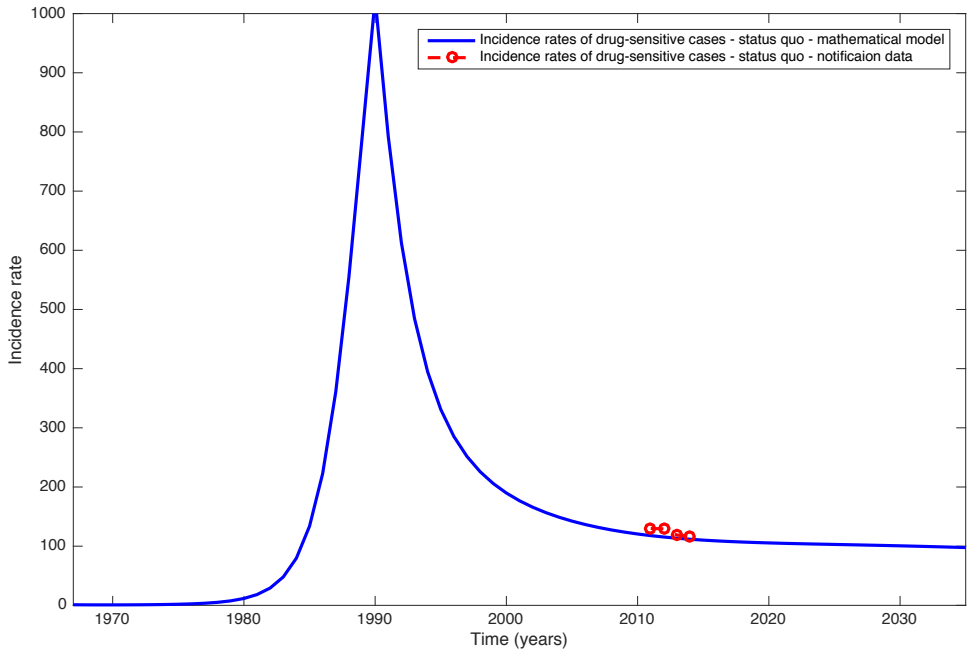
Appendix 2f. Mean (SD) of the individual cost and quantities of resistant TB by year of the treatment and follow-up assessment

Item	2009 cohort		2010 cohort		2011 cohort		2012 cohort		2013 cohort		2014 cohort	
	Number	Cost*	Number	Cost*	Number	Cost*	Number	Cost*	Number	Cost*	Number	Cost*
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Treatment (months in treatment)												
MDR-TB	18.08 (11.27)	11570 (16211.50)	17.95 (8.59)	9,146 (8,359.05)	16.57 (8.83)	6312 (7980.03)	16.05 (8.66)	6561 (8496.82)	21.02 (11.01)	7970 (7749.72)	14.47 (6.43)	5743 (6259.61)
XDR-TB					15.14 (17.49)	9321 (10184.77)	7.95 (9.97)	15850 (21909.78)	34.83†	8352†		
Isoniazid monoresistant tuberculosis	10.02 (1.11)	5074 (682.84)	12.75 (8.64)	5,764 (4814.332)	10.06 (5.74)	2019 (1486.52)	9.32 (7.69)	1835 (1090.82)	19.05 (12.58)	13420 (16683.72)	13.56 (2.25)	3193 (463.20)
Rifampicin monoresistant tuberculosis	23.17 (24.54)	5928 (4412.51)	14.36 (8.65)	5,453 (3,561.39)	9.53 (6.39)	1633 (1089.75)	9.03 (8.75)	2255 (2142.61)	18.33 (8.44)	3828 (1661.27)	17.39 (3.00)	6115 (5599.59)
Pansensitive patient	7.62 (5.36)	3568 (2616.44)	18.72 (19.60)	9,105 (9,484.18)	9.18 (7.57)	2864 (3618.83)	16.09 (17.53)	4430 (6346.01)	10.02 (13.17)	4623 (6510.68)	13.84 (7.77)	8138 (11050.85)
Poly-drug resistant TB and Isoniazid resistance	12.18 (7.39)	3523 (4639.82)	12.13 (6.92)	6,615 (15,702.92)	9.39 (8.71)	1246 (1222.61)	10.04 (10.35)	2394 (2390.29)	9.37†	984.5†	13.75 (0.94)	3288 (901.61)
Poly-drug resistant TB and Rifampicin resistance					18.45 (0.96)	6563 (3892.10)						
Drug resistant non Isoniazid non Rifampicin resistance	10.42 (0.16)	54.81 (507.56)	7.08 (7.15)	9324 (14090.81)	10.1 (5.98)	3614 (4160.07)	6.72 (0.07)	3229 (1573.61)			15†	3612†
Without resistance pattern data	12.58 (8.52)	7787 (8319.14)	17.88 (5.57)	12820 (8085.36)	14.42 (9.97)	3870 (2340.94)	19.77 (13.44)	6367 (14637.44)	16.67 (12.12)	2856 (2236.64)	13.52 (5.88)	2422 (1121.27)
Follow-up												
Laboratory follow-up												
Sputum smear	11.00 (8.71)	53.21 (42.12)	11.86 (8.2)	59.29 (40.53)	10.44 (8.62)	51.83 (42.81)	10.39 (8.59)	50.10 (41.47)	7.56 (6.89)	35.45 (32.31)	2.23 (4.18)	10.25 (19.25)
Culture	11.00 (8.71)	425.51 (336.74)	11.86 (8.2)	474.09 (324.16)	10.44 (8.62)	414.43 (342.31)	10.39 (8.59)	400.62 (331.60)	7.56 (6.89)	283.46 (258.37)	2.23 (4.18)	81.97 (153.96)
Hemogram or complete blood count (CBC)	1.72 (0.63)	19.95 (7.33)	1.816 (0.513)	21.76 (6.16)	1.67 (0.68)	19.84 (8.08)	1.63 (0.72)	18.91 (8.35)	1.65 (0.71)	18.51 (7.98)	1.80 (0.55)	19.91 (6.08)
Fasting blood glucose	1.72 (0.63)	3.50 (5.13)	1.816 (0.513)	3.57 (5.32)	1.67 (0.68)	2.97 (4.87)	1.64 (0.72)	0.96 (2.79)	1.65 (0.71)	0.89 (2.59)	1.80 (0.55)	0.98 (2.91)
Creatinine blood test	1.72 (0.63)	11.20 (4.12)	1.816 (0.513)	12.22 (3.45)	1.67 (0.68)	11.15 (4.53)	1.64 (0.72)	10.63 (4.69)	1.65 (0.71)	10.40 (4.47)	1.80 (0.55)	11.18 (3.41)
Liver blood test	2.54(1.00)	47.66 (18.85)	2.687 (0.836)	52.15 (16.22)	2.45 (1.07)	47.26 (20.72)	2.42 (1.12)	45.23 (21.04)	2.43 (1.11)	44.2 (20.2)	2.68 (0.87)	47.90 (15.55)

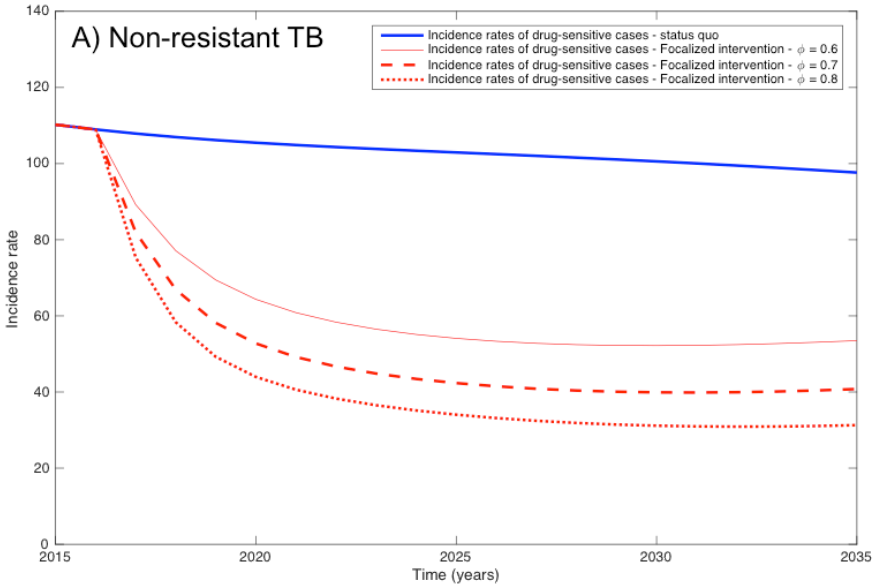
Electrolyte testing (sodium, potassium and chloride)		47.66 (18.85)		52.15 (16.22)	0.04 (0.28)	47.26 (20.72)	0.50 (0.87)	45.23 (21.04)	0.34 (0.76)	44.2 (20.2)	0.16 (0.54)	47.90 (15.55)
Chest X-ray	1.87 (1.18)	66.01 (41.61)	2.19 (1.09)	80.02 (39.84)	1.79 (1.20)	65.20 (43.66)	1.8 (1.22)	63.46 (42.97)	2.15 (1.26)	73.75 (43.16)	2.08 (0.96)	69.9 (32.3)
Follow-up assessment												
Nursing assessment	15.61 (11.08)	152.46 (108.22)	17.21 (8.97)	173.76 (90.60)	14.95 (8.46)	149.95 (84.86)	14.98 (9.71)	145.91 (94.64)	20.1 (10.66)	190.45 (101.04)	14.66 (5.51)	136.34 (51.24)
General practitioner assessment	15.27 (11.26)	211.37 (155.79)	16.73 (9.36)	239.37 (133.90)	14.08 (8.96)	200.11 (127.34)	14.43 (10.00)	199.20 (138.06)	19.39 (11.33)	260.30 (152.06)	14.48 (5.67)	190.83 (74.69)
Expert physician in resistant TB management	4.92 (3.70)	85.65 (64.42)	5.41 (3.01)	97.39 (54.21)	4.49 (2.94)	80.41 (52.61)	4.65 (3.34)	80.76 (57.95)	6.32 (3.69)	106.85 (62.41)	4.59 (1.89)	76.26 (31.42)
Psychological assessment	2.46 (1.16)	19.99 (9.43)	2.62 (1.01)	22.00 (8.47)	2.35 (1.24)	19.67 (10.33)	2.34 (1.25)	19.00 (10.12)	2.34 (1.24)	18.51 (9.82)	2.63 (0.99)	20.37 (7.67)
Social services assessment	5.41 (1.79)	80.09 (26.47)	5.67 (1.38)	86.67 (21.14)	5.29 (1.94)	80.47 (29.45)	5.14 (2.11)	75.81 (31.16)	5.19 (2.06)	74.47 (29.55)	5.57 (1.56)	78.44 (21.93)
Nutritional counseling	13.45 (4.45)	21.89 (7.23)	2.83 (0.69)	23.69 (5.77)	2.65 (0.97)	22.00 (8.04)	2.57 (1.06)	20.72 (8.53)	2.59 (1.03)	20.36 (8.09)	2.78 (0.78)	21.44 (6.00)
Family planning counseling	5.00 (2.15)	10.84 (14.42)	5.30 (1.83)	10.79 (14.81)	4.80 (2.29)	8.09 (13.51)	4.76 (2.36)	9.46 (13.90)	4.77 (2.34)	8.95 (13.49)	5.31 (1.85)	9.26 (13.45)

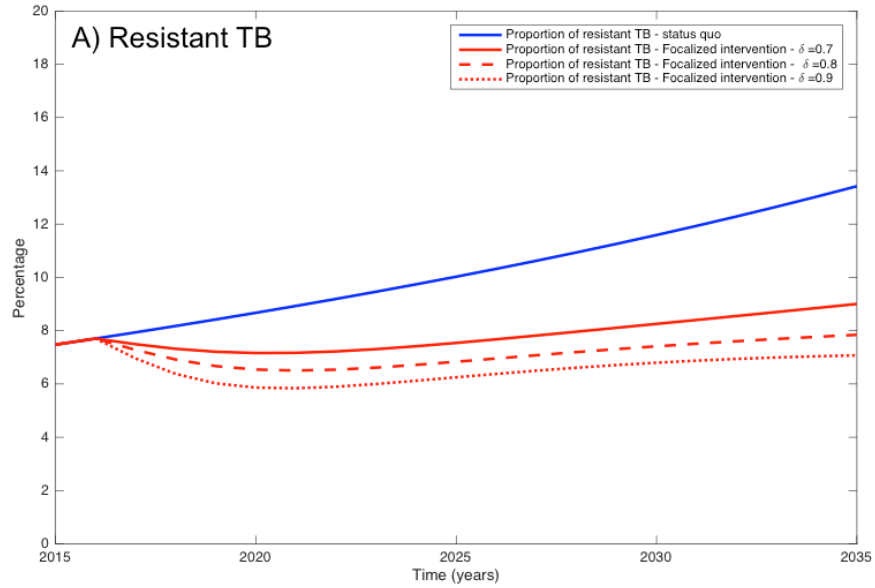
APPENDIX 3. MATHEMATICAL MODEL

Appendix 3a. Model fitting



Appendix 3b. Sensitivity analysis, effectiveness of the focalized intervention





APPENDIX 4. GLOBAL BURDEN OF TB

Appendix 4a. Global burden of non-resistant TB for Status quo scenario

AVP			AVAD			AVISAS		
Male	Female	Total	Male	Female	Total	Male	Female	Total
680	366	1,047	164	88	252	844	455	1,299
682	367	1,049	164	89	253	846	456	1,302
683	368	1,052	165	89	254	848	457	1,305
686	369	1,055	165	89	254	851	458	1,310
689	371	1,060	166	89	256	855	461	1,316
693	373	1,066	167	90	257	860	463	1,323
697	375	1,073	168	91	259	865	466	1,331
701	377	1,078	169	91	260	870	468	1,338
705	380	1,085	170	92	262	875	471	1,347
710	382	1,092	171	92	263	881	474	1,355
714	384	1,098	172	93	265	886	477	1,363
718	387	1,105	173	93	267	892	480	1,372
722	389	1,111	174	94	268	896	483	1,379
726	391	1,117	175	94	269	901	485	1,386
730	393	1,122	176	95	271	906	488	1,393
733	395	1,127	177	95	272	909	490	1,399
735	396	1,131	177	95	273	912	491	1,404
738	397	1,135	178	96	274	916	493	1,409
740	398	1,138	178	96	274	918	494	1,412
741	399	1,141	179	96	275	920	496	1,416
743	400	1143	179	96	276	922	496	1,418
14966	8059	23,024	3,609	1,943	5,552	18,575	10,002	28,576

Appendix 4b. Global burden of non-resistant TB for Focalized intervention scenario

AVP			AVAD			AVISAS		
Male	Female	Total	Male	Female	Total	Male	Female	Total
680	366	1047	164	88	252	844	455	1,299
681	367	1048	164	88	253	845	455	1,300
565	304	869	136	73	210	701	378	1,079
495	266	761	119	64	184	614	331	945
450	243	693	109	58	167	559	301	860
423	228	651	102	55	157	525	283	808
404	218	622	98	53	150	502	270	772
393	211	604	95	51	146	487	262	750
384	207	591	93	50	143	477	257	734
379	204	583	91	49	141	470	253	723
376	202	578	91	49	139	466	251	717
374	202	576	90	49	139	465	250	715
374	202	576	90	49	139	465	250	715
375	202	577	90	49	139	466	251	716
378	203	581	91	49	140	469	252	721
381	205	586	92	49	141	472	254	727
384	207	591	93	50	143	477	257	734
389	210	599	94	51	144	483	260	744
395	213	608	95	51	147	490	264	754
401	216	617	97	52	149	498	268	766
407	219	627	98	53	151	506	272	778
9,090	4,895	13,985	2,192	1,180	3,372	11,282	6,075	17,358

Appendix 4c. Global burden of MDR TB for Status quo scenario

AVP			AVAD			AVISAS		
Male	Female	Total	Male	Female	Total	Male	Female	Total
51	28	79	12	7	19	63	34	98
52	28	81	13	7	19	65	35	100
54	29	83	13	7	20	67	36	104
56	30	86	14	7	21	70	37	107
58	31	89	14	8	21	72	39	111
60	32	92	14	8	22	74	40	114
62	34	96	15	8	23	77	42	119
64	35	99	15	8	24	80	43	123
67	36	103	16	9	25	83	45	127
69	37	106	17	9	26	86	46	132
72	39	110	17	9	27	89	48	137
74	40	114	18	10	28	92	50	142
77	41	118	18	10	28	95	51	146
79	43	122	19	10	29	98	53	151
82	44	127	20	11	31	102	55	157
85	46	130	20	11	31	105	57	162
88	47	135	21	11	33	109	59	168
90	49	139	22	12	34	112	60	173
93	50	144	23	12	35	116	62	178
97	52	149	23	13	36	120	65	184
100	54	153	24	13	37	124	67	190
1530	824	2354	369	199	568	1899	1023	2922

Appendix 4d. Global burden of MDR TB for Status quo scenario

AVP			AVAD			AVISAS		
Male	Female	Total	Male	Female	Total	Male	Female	Total
51	28	79	12	7	19	63	34	98
52	28	81	13	7	19	65	35	100
44	23	67	11	6	16	54	29	83
38	20	58	9	5	14	47	25	73
34	18	53	8	4	13	43	23	65
32	17	50	8	4	12	40	22	62
31	17	48	8	4	12	39	21	59
31	16	47	7	4	11	38	20	58
30	16	46	7	4	11	37	20	57
31	16	47	7	4	11	38	20	58
31	16	47	7	4	11	38	20	58
31	17	48	8	4	12	39	21	59
32	17	49	8	4	12	39	21	61
32	17	50	8	4	12	40	22	62
34	18	52	8	4	12	42	22	64
34	18	53	8	4	13	43	23	65
36	19	55	9	5	13	44	24	68
36	19	56	9	5	13	45	24	69
37	20	58	9	5	14	46	25	71
39	21	59	9	5	14	48	26	74
40	21	61	10	5	15	49	27	76
755	407	1162	182	98	280	937	505	1,442

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