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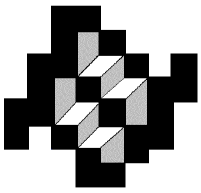

Costo-efectividad de dos estrategias para mejorar la adherencia al tratamiento anti-tuberculosis en Cali, Colombia

Propuesta de artículos para optar al título de Doctora en Salud Pública

Sandra Lorena Girón Vargas

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sandragiron@fundacionfes.org

Comité de Tesis:

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Mtro. Julio César Mateus - Asesor

Dr. Ernesto Jaramillo - Asesor

Mtro Miguel Elizondo – Asesor

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Tabla de contenido

Página

Introducción

La tuberculosis pulmonar es un problema de salud pública de interés mundial (1-3). A pesar que existen tratamientos con efectividad comprobada, los porcentajes de adherencia son bajos y las consecuencias que acarrea en términos de morbilidad, mortalidad, resistencia antimicrobiana y costos económicos son excesivamente altos, los cuales superan los US$100,000 (4-11).

La tuberculosis (TB) continúa siendo uno de los principales problemas de salud pública mundial (3). Asegurar el diagnóstico y tratamiento completo de todos los casos es la prioridad más importante para el control de esta enfermedad(12). La Organización Mundial de la Salud y las Metas del Milenio de la Organización de las Naciones Unidas se han propuesto curar exitosamente 90% de los casos diagnosticados, disminuir a la mitad la prevalencia y la mortalidad para el año 2015 y reducir la incidencia anual a menos de un caso por millón de habitantes (1).

El Tratamiento Acortado Estrictamente Supervisado (DOTS), uno de los componentes fundamentales de la estrategia Alto a la Tuberculosis, es considerado el más efectivo para el tratamiento de la TB. Sin embargo, la baja adherencia continúa afectando la efectividad del tratamiento (13). En 2011 a nivel global se estimó que hubo aproximadamente 2.6 millones de casos nuevos de tuberculosis pulmonar, la forma más frecuente e infecciosa de esta enfermedad, de los cuales 80% se curaron y 4% abandonó el tratamiento (1-3).

En Colombia la estrategia DOTS se adoptó desde 1997 y Cali fue una de las primeras ciudades donde se inició la implementación de esta estrategia. Sin embargo, en esta ciudad aún se registran altos niveles de no adherencia al tratamiento, los cuales según registros de vigilancia se han estimado en

7.6% (Secretaría Municipal de Salud de Cali. Informe de la Secretaría de Salud Municipal de Cali. Mortalidad tuberculosis. Santiago de Cali a Diciembre de 2012. Cali: Secretaría Municipal de Salud de Cali; 2012.); mientras que estudios prospectivos han estimado una proporción de pacientes sin tratamiento completo de 65.6% (**14**).

La no-adherencia al tratamiento no sólo incrementa la morbilidad y mortalidad de los pacientes, también disminuye la tasa de curación, eleva la transmisión poblacional, aumenta el número de enfermos crónicos, posibilita la aparición de tuberculosis multi-resistente a drogas (MDR-TB) y aumenta los costos del tratamiento a niveles considerados catastróficos(4-11).

No obstante y a pesar que la estrategia DOTS requiere la supervisión de la toma de los medicamentos, no necesariamente por parte de personal de salud, ni dentro de las instituciones de salud(**15**) y que se han identificado otras alternativas de entrega del tratamiento (8, 16-21), en Colombia aún la única forma vigente de entrega del tratamiento anti-TB es intra-mural.

De esta manera, la actual forma de entrega implica que los pacientes vayan diariamente a la unidad de salud en la primera fase y tres veces a la semana en la segunda fase e impone costos a los servicios de salud, en términos del tiempo del personal que hace la supervisión y a pacientes y familias, en términos de gastos de desplazamiento, alimentación y tiempo dedicado.

Por lo anterior, se ha enfatizado la necesidad de fortalecer la estrategia DOTS con el diseño de intervenciones que, según el contexto, contribuyan a mejorar la adherencia(12). En Colombia son escasos los estudios que estiman los costos y resultados de la actual forma de entrega del DOTS y que identifiquen alternativas para mejorar la adherencia y curación de los pacientes con TB.

Esta investigación tiene como objetivo estimar la razón costo-efectividad incremental comparando la actual forma de entrega del DOTS con una alternativa de entrega extra-mural del tratamiento anti-TB en el área urbana de Cali.

En este documento se presentan dos propuestas de artículos que reportan los métodos y los resultados de un estudio que comparó dos estrategias de entrega del tratamiento anti-tuberculosis en aras de establecer si existe una alternativa que mejore la adherencia a costos razonables, tanto para los servicios de salud como para los pacientes. En particular, se comparó una estrategia de entrega del tratamiento anti-TB en las instituciones de salud, con otra estrategia de entrega del mismo tratamiento en un lugar elegido por el paciente. En esta comparación solo varió el lugar de entrega de los medicamentos, dado que entre las principales razones aducidas por los pacientes para abandonar el tratamiento están los costos de transporte y el tener que ir repetidas veces a la unidad de salud (14).

El primer artículo se centra en los métodos desarrollados los cuales están basados en un ensayo clínico controlado, aleatorizado, en el cual se obtuvieron datos para realizar estimaciones de la adherencia y curación en cada estrategia, como también datos para estimar los costos directos e indirectos, institucionales y familiares de cada rama del estudio. En este estudio se realizó el análisis de costo-efectividad desde la perspectiva institucional y familiar para identificar la estrategia más costo-efectiva, considerando como medida de efectividad la adherencia al tratamiento.

En el segundo artículo presentan los resultados de la investigación donde se observan las diferencias de efectividad, de costos institucionales, familiares y de costo-efectividad de las intervenciones en comparación.

Se espera con este proyecto aportar evidencia de nuevas alternativas para mejorar la adherencia y la curación de una enfermedad con amplias consecuencias para los individuos, los servicios de salud, la economía nacional y la sociedad en general. En particular, se espera contribuir con una alternativa de entrega del tratamiento para apoyar la implementación de los planes y programas de control de la tuberculosis a nivel de Cali y otras ciudad des Colombianas, así como aportar evidencia para otras ciudades Latinoamericanas.

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Artículo 1

Double blind, randomized control trial to measure the cost-effectiveness of two delivery alternatives of directly observed treatment for tuberculosis in Cali, Colombia: Study protocol

Girón Sandra L. Researcher. Fundación FES. Professor. School of Public Health. Universidad del Valle. Avenida 5N #22AN-15. Cali, Valle del Cauca, Colombia

E-mail: sandragiron@fundacionfes.org

Sosa-Rubí Sandra G. Researcher. National Institute of Public Health (INSP), Cuernavaca, Mexico, Centre for Health System Research. Avenida Universidad 655, col. Santa María Ahuacatitlán. 62100 Cuernavaca, Morelos, México.

E-mail: srubi@insp.mx

Elizondo-Cano M.

National Institute of Public Health (INSP), Cuernavaca, Mexico, Centre for Health System Research. Avenida Universidad 655, col. Santa María Ahuacatitlán. 62100 Cuernavaca, Morelos, México.

E-mail: miguel_elizondo_cano@hotmail.com

Mateus Julio C.

Health Area Director. Fundación FES. Professor. School of Public Health. Universidad del Valle. Avenida 5N #22AN-15. Cali, Valle del Cauca, Colombia

E-mail: jcmateus@fundacionfes.org

*Corresponding Author: Sandra Lorena Girón-Vargas. Avenida 8 Norte No. 22AN-15

Cali, Colombia. Phone number: 2-6534141. Email: sandragiron@fundacionfes.org - sandralgiron@gmail.com

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Double blind, randomized control trial to measure the cost-effectiveness of two delivery alternatives of directly observed treatment for tuberculosis in Cali, Colombia: Study protocol

Abstract

Introduction: Although other cost-effective ways of delivering anti-tuberculosis treatment have already been found, few studies have established the costs and results of the current standard of care in Latin-American countries. The objective of this study is to measure the cost-effectiveness of two forms for anti-tuberculosis treatment delivery, one facility-based and one domicile-based, to improve treatment adherence.

Methods: A randomized controlled clinical trial with double masking has been designed to carry out a cost-effectiveness analysis. Through block randomization, 132 patients has been assigned to one of two alternatives of treatment delivery: i) Facility-based delivery alternative: treatment delivery in the health care institution, ii) Domicile-based delivery alternative: treatment delivery in a place chosen by the patient. Currently, measurements of adherence, cure and institutional and family costs are taken.

Discussion: The design and evaluation of new forms of anti-tuberculosis treatment delivery contributes to identifying alternatives that reduce the impact of TB on institutions, individuals and families.

Ethics and dissemination: All the patients receive treatment free of charge, and according to national protocols for TB management. Two papers are planed: one to report the results and other to discuss public health policy implications.

Trial registration: NCT01945905. Date: 09/16/2013.

Introduction

Tuberculosis (TB) is still one of the main problems in world public health(**1**).The targets of the Millennium Development Goals project, supported by the Stop TB Partnership, aim at reducing prevalence and deaths due to TB in 2015 by 50% with respect to 1990 levels and by 2050 to eliminate TB as a public health problem(**2**).

A patient-centered approach to early case detection and full adherence until treatment completion is one of the pillars of the new TB strategy approved by the World Health Assembly in 2014(**3**). Poor adherence to treatment continues to affect treatment effectiveness(**4**). In 2011 there was a global estimate of approximately 2.6 million new smear positive cases of TB, of which 80% were cured, 7% completed the treatment, 4% died, 4% were not evaluated, 2% presented failure to the treatment and 4% were lost to follow up (**1**).

In the region of the Americas in 2011, treatment outcomes show a 77% treatment success, 5% death, 9% not evaluated, 2% treatment failure and 7% were lost to follow up(**1**). In the specific case of loss to follow up, the numbers are even higher within Latin America; they vary from 10% in Brazil, Panama and Colombia, 12% in Venezuela, to even 15% to 16% in Trinidad and Tobago and Guyana(**1**).

The poor adherence to treatment does not only increase patients' morbidity and mortality, but also reduces the cure rate, increases transmission, and facilitates the selection of resistant strains (**5-10**). The treatment cost of a multi-drug resistant TB patient can be up 100 times higher in comparison with the

cost of treating a non-resistant TB, which goes from US$2,381 in low-income countries to US$85,000 –120,000 in high-income countries(**10-12**).

In Colombia the WHO DOTS-based strategy was formally adopted in 1997, although an equivalent strategy was widely used since the late 1970s. Adherence to treatment is a major issue in the implementation of the strategy. In Cali in 2012, according to surveillance records, there was 7.6% of loss to follow up (*Secretaría Municipal de Salud de Cali*. Report of the *Secretaría de Salud Municipal de Cali*. Tuberculosis Mortality. Santiago de Cali up to December 2012. Cali: *Secretaría Municipal de Salud de Cali*; 2012.). In contrast, in a prospective study carried out in Cali, it was observed that 65.6% of new TB cases do not adhere to treatment and that 43% of patients would have preferred to receive treatment at home (**13**).

The DOTS strategy requires the direct observation of treatment (DOT), that is, the supervision of medication intake (not necessarily by health care staff, or inside health care institutions) in order to ensure adherence to treatment (**14**). There are different modalities for treatment delivery including those based on community workers, peers or family members, using on economic incentives or enablers (food baskets, clothes support, transport ticket) and delivering of several doses for self-administration in order to reduce the number of visits(**9, 15-20**). However, the only current way to deliver anti-TB treatment in Colombia, according to the national policy for DOT, is still at health care facility.

This way, the DOT means that the patients go to the health care unit every day during the first phase and three times a week during the second phase, and it imposes costs on the health-care services in

terms of the time of the staff that does the supervision, and to patients and families in terms of traveling, food time and other expenses incurred.

The introduction of domicile-based delivery strategies with community workers has reduced staff costs in 74% (**15**). Likewise, it is estimated that family costs vary from US$727 to US$921, representing between 38% and 80% of the total cost of the disease and around 7.5 times the average daily salary of the patients (**20, 21**). Given the bi-directional relationship between TB and poverty (22, 23), it is very possible that the economic impact caused by the disease explains, for the most part, the low levels of adherence to the anti-TB treatment (7, 23).

Due to this, the need to strengthen the DOTS strategy has been emphasized with the design of interventions that, according to the context, contribute to improve adherence to anti-TB treatment(24). In Colombia there are few studies that estimate the costs and results of the current form of delivery of the treatment, and that identify alternatives to improve adherence and curing of TB patients.

Therefore, the objective of this research is to measure the incremental cost-effectiveness ratio by comparing the current form of delivery of anti-TB treatment with an alternative of domicile-based delivery in the urban area of Cali. It is hoped that the evidence generated by this project contributes to revise the current national policies and strengthen the implementation of the TB Strategic Plan.

Methods

Type of study

Controlled, randomized trial, with double masking in which a study of cost-effectiveness was designed to compare two forms of anti-TB treatment delivery: an institutional one in which the patients go to the

health care institutions to receive the treatment, and another domicile-based delivery one in which health care staff take the treatment to a place chosen by the patients. The study is carried out from a social perspective (institutional and family), with prospective data collection(25). The measurement of the costs is carried out based on the activities and resource identification(25). Effectiveness of the interventions is given by adherence as a primary variable and the cure as a secondary variable. Follow up consists of 6 months as of the beginning of the treatment.

Hypothesis:

The domicile-based delivery and supervision of the anti-TB treatment is more cost-effective than the current form of facility-based delivery and supervision.

Interventions

According to the National TB care guidelines in Colombia, the treatment for patients with a new pulmonary TB diagnosis and whose health state thus allows it, is given ambulatory and free of charge, with the following plan: each dose of the treatment in the first phase (intensive) includes combined fixed oral doses of 150 mg of Rifampicin, 75 mg of Isoniazid, 400 mg of Pyrazinamide and 275 mg of Etambutol. In the second phase (continuation) each combined oral dose of the treatment includes 100 mg Isoniazid and 300 mg Rifampicin with 150 mg of Isoniazid (26).The alternatives in comparison are the following:

1. Alternative of facility-based delivery: Under this alternative, the patients go to the health care unit to receive the treatment under direct observation of a nurse auxiliary from each one of the 21 units. During the 8-week intensive phase, they go 6 days a week. During the 16-week continuation phase, they should go to the institution 3 times a week.

2. Alternative of domicile-based delivery: In this alternative the treatment is delivered to the place chosen by the patients by 3 nurse auxiliaries who supervise the intake of the medication. During the 8-week intensive phase the nurse auxiliaries go to the place chosen by the patients 6 days a week, and during the continuation phase (16 weeks) they go 3 times a week. The assistant nurses go by motorcycles, which are rented with their respective driver, to deliver DOT. This comparison alternative is called domicile-based delivery to give the connotation that the medication is delivered outside of the health care unit, even when the follow-ups, the treatment regime and the procedures are kept at the health care institutions where the patients are diagnosed. During the follow-up the patients can change the place to receive the treatment.

For both alternatives, the follow-up appointments and the lab tests required (smear at two, four and six months) are carried out according to the current health care guidelines and in the labs of the health care institutions where the patient is seen. In every case, for any of the two forms of delivery, the recommended standards of treatment and the recommendations of the medical staff of the institutions where the diagnosis is carried out are followed, and only the place of delivery varies.

In coordination with the health care institutions and the Secretariat of Public Health of Cali, the medications for each patient included in the domicile-based delivery alternative are requested weekly.

Area:

The study is carried out in the urban area of Cali, which is the largest urban center of the Colombian South-West. Cali is considered high-risk for the transmission of pulmonary TB: while the accumulated annual incidence in Cali in 2012 was 41 cases per 100.000, in Colombia it was 25 cases per 100,000 inhabitants.

Study population:

New cases of pulmonary TB diagnosed in 21 health care units where the diagnosis and treatment is carried out. Patients are included according to the following inclusion criteria: a) Patients over 18 years of age; b) men and women; c) residents of the urban area of Cali; d) new diagnosis of pulmonary TB and e) people in conditions to respond to a survey and receive outpatient treatment.

Patients are excluded according to the following criteria: a) pregnant patients; patients with hemoptysis or with any condition that required special treatment such as liver disease, kidney failure, silico-tuberculosis and HIV/AIDS. These patients are excluded because TB treatment under these conditions requires the consideration of other clinical particularities, so including them in the study would not comply with the patient safety criteria required.

Sample size:

Assuming a difference of 20% in the percentages of patients with complete treatment among the alternatives in comparison, 46% in the facility-based delivery alternative and 66% in the domicile-based delivery alternative, an 80% power, an alpha error of 5% and a ratio of patients assigned to each form of delivery of 1:1, 20% of losses and using the sample size formula for comparison of two proportions with Fleiss continuity correction, a necessary number of 132 patients in each group was estimated.

Randomization and masking:

With previous consent, the patients were randomly assigned to one of the alternatives of treatment delivery. The randomization was carried out through balanced blocks, with which each patient had a probability of 0.50 of being assigned to any intervention. The gathering of the patients was carried out

in the order of TB diagnoses. The form of delivery to which each patient was assigned was written in individual envelopes numbered sequentially. These envelopes were opened in strict order, and only when the patient accepted to enter the study.

To ensure the masking, the field coordinator did the allocation of each patient to a form of treatment delivery and assigned an alphabetical code to each study group. Since the treatment delivery is an intervention that cannot be concealed for the patients, the data collection to measure the variables are carried out by auxiliaries that do not know the group assigned to each patient. The follow-up and delivery of the medication to the domicile-based delivery group is carried out by nurse auxiliaries that do not have any relation with the group that carries out the follow-up of the patients of the facility-based delivery alternative. Researchers in charge of the project are also concealed to the allocation status of each patient.

Follow-up termination and study losses criteria:

Once the patient is assigned to one of the two alternatives, the delivery of the medication and the follow-up is carried out for 6 months. It is considered that a patient has terminated the follow-up when he has met any of the following situations: a) when he has finished the treatment and b) when medical orders indicate the need for treatment that is different from the standard treatment described.

At the same time, study losses are considered as patients that meet the following conditions: a) they declare that they do not wish to continue participating in the study, in which case they are transferred to the Tuberculosis Program to continue treatment, but not as part of the study; b) when the patient cannot be located in the chosen place after thirty days for treatment delivery in the case of the domicile-based

delivery alternative, and when the patient has not returned to the health care unit to receive treatment after thirty days in spite of calls and searches, in the case of the facility-based delivery alternative; c) when the patient moves outside of Cali and d) when the patient dies. To detect a possible selection bias, it is verified if the lost patients are receiving treatment at another health care unit through city surveillance records. In case of deaths, the reason is sought in order to identify if there is a difference in the therapeutic response among the interventions.

Effectiveness Variables:

Adherence defined as the agreement between patient behavior and the recommended medical treatment. In this study adherence as a primary variable measures the percentage of patients that finished the treatment at the end of 6 months. The cure variable as a secondary variable represents the percentage of patients whose cure has been confirmed, according to the records of the *Programa Municipal de Control de Tuberculosis de Cali*. According to international standards (27, 28), the Program considers that the patient has been cured when the follow-up smears of the fourth and sixth months of treatment are negative.

Institutional Costs Variables:

Direct costs for both alternatives are measured. In the facility-based delivery alternative, these costs are represented by the time dedicated by the nursing staff for patient attention: medication delivery, supervision of the intake, orientation and filling out the control card. In the domicile-based delivery alternative, the institutional costs correspond to the time dedicated by the nursing staff in visits to the patients for the delivery and supervision of medication intake, the orientation and filling out the control card. Besides, the direct costs of transportation and the market value of the necessary supplies to

transport medication are measured in this alternative. For both alternatives, the time dedicated by the health care staff is valued in terms of their registered salary.

The costs of medical attention, medication and lab test processing are not measured, since they are equal for both alternatives, and therefore are not relevant to determining which of these alternatives is cost-effective.

The indirect institutional costs such as costs of the use of the facilities or of the fraction of time dedicated by the administrative staff for the operation of patient service are not measured either, given that the other medical, administrative, nursing and lab processes are still being developed in the facilities of the health care unit, even when the patient receives the medication at the chosen place.

Family Costs Variables:

In the facility-based delivery alternative, the direct costs of transportation to receive the medication, to attend medical and nursing follow-ups and for bacteriological tests are measured. Besides, the costs of meals and snacks for patients and their companions when they go to the health care unit are measured. In the domicile-based delivery alternative, the direct family costs include transportation and meals and snacks for medical, nursing and bacteriological follow-ups that are carried out in the health care unit. For both alternatives, other consultations, tests and medications that are different to those in the TB program, the purchase of homemade remedies, and the costs of transportation associated to these activities are included as a part of the direct costs.

At the same time, the indirect costs of the facility-based delivery alternative include the cost of the time that patients and their families invest in going to the health care unit to take the medication, get the lab tests and go to the follow-ups. As indirect family costs of the domicile-based delivery alternative, the costs of the time invested by patients and their families, if necessary, to get the visit of the medication delivery and the supervision of its intake at the chosen place selected. For both alternatives, the value of the time invested by the patients and their families are valued with the current minimum legal wage in Colombia.

Co-variables:

To compare the baseline characteristics at the moment of the randomization, the following variables are measured: patient gender, age, marital status, education, occupation, health service regime and time taken to the health facility.

Data collection procedures:

Field instruments and equipment: Instruments were designed to request consent, to measure the costs and to measure the effectiveness of the alternatives. In coordination with the health care units, the nurse auxiliaries recruited the patients and conducted their first interview after having received the diagnosis and the first medication intake at the health care unit. Then, the randomization was carried out.

Three nurse auxiliaries has been selected and trained to collect the data from patients assigned to the facility-based delivery alternative. At the same time, the 3 nursing auxiliaries that deliver the medication in the domicile-based delivery alternative conduct the patients' interviews. A supervisor assigned to each group does quality control of the procedures and data.

Obtaining data: Each patient's card is checked weekly to obtain the data of the doses taken and thus measure the number of patients with complete treatment. The data of the cured patients are being obtained from the records of the Tuberculosis Program of Cali, once the patient finishes treatment and until 4 months after the last dose.

In order to measure the institutional costs of the time invested by the health care staff, 8 weeks after the training, during one week considered typical, the time invested in the attention of the patients was measured to obtain the average time invested in this activity. The data of the salaries are obtained from the records of the *Secretaría de Salud Pública Municipal de Cali*.

The data of transportation generated in the domicile-based delivery alternative is obtained as they occur, keeping in mind the negotiated monthly rate for the rent of motorcycles and the number of transportations generated. The data to estimate family costs is obtained through a patients' survey each week, whether in the health institution or at the chosen place.

The data collection is carried out in portable electronic devices (*Personal Digital Assistant*), which, when connected to a server, send the information and allow monitoring the data collection.

Analysis Plan:

The effectiveness analysis will be guided by the reporting standards of clinical trials(29). A flow chart of patient collection and follow-up will be built. To evaluate the randomization, the distribution of the socio-demographic co-variables of the patients assigned to each form of delivery of the treatment in relation to the socio-demographic co-variables will be compared. Subsequently, the proportion of

adherent patients and cured patients will be estimated, with their respective confidence intervals of 95%. The statistical significance of the difference in the effectiveness among the alternatives will be evaluated with the Chi-Squared test. Intention to treatment analysis will be carried out.

With regards to the costs, exploratory analysis of total, direct and indirect family and institutional costs generated in each alternative will be carried out, in Colombian Pesos and in U.S. dollars of 2013. To estimate the mean costs and their confidence intervals of each alternative, non-parametrical bootstrap techniques will be used. The estimation will be carried out with the generation of 1.000 samples. These techniques are recommended to analyze biased distributions, such as the ones that costs usually present. Means will be compared through Student's t-test. Stata software will be used to perform effectiveness and cost analysis.

The estimation of cost-effectiveness ratios of each alternative will be carried out through the quotient of the total costs and the number of adhered patients. The ratio of incremental cost-effectiveness among the interventions(25) will also be estimated to establish if the marginal cost of obtaining an additional point of percentage of adherence is justified with regards to the costs of not improving adherence. Sensitivity analysis of the cost-effectiveness ratios of each alternative and the ratio of incremental cost-effectiveness will be carried out to identify if it changes with adherence and cost variations. The sensitivity analyses carried out will be presented in graphic form. Cost-effectiveness analysis will be done with TreeAge software.

Given that the costs and the results are produced in a six-month time span, discount rates will not be applied, since the costs are in a period of time in which significant changes in the purchasing power are

not expected, and in regards to the results, there will be no discounts because the adherence effectiveness measurement used is produced during the follow up and the projection of its future benefits or damages are not being estimated.

Discussion

Colombia is the fifth country with the greatest burden of new TB cases, and the eighth for MDR-TB in Latin America. Likewise, Cali, which is the third city in the country, surpasses the national incidence by 60% and presents 7.6% of loss to follow up of TB patients, and even 11% and 19% in some of its administrative areas. Nevertheless, the form of delivery DOT has been the same one since the adoption of the WHO DOTS-based strategy in 1997, which although it is ambulatory and considered free of charge, represents costs to patients and their families due to the continuous attendance to the health care service during six months.

In spite of this situation, it has not been evaluated in Colombia and in Cali if the form in which the DOT is being delivered is the most cost-effective way to ensure adherence, increase cure rates and reduce the financial impact of TB in the services, the patients and their families. This article details the methods of a study oriented to evaluate the cost-effectiveness of an alternative of anti-tuberculosis treatment delivery to a place chosen by the patient, in comparison with the current treatment delivery in the facilities of the health care units.

Establishing if the DOT delivery in a place selected by the patient contributes to improve the levels of adherence would allow identifying a more efficient alternative of delivery and reducing the financial impact of TB in the families. Although delivering DOT at a place chosen by the patient could increase

adherence and cure, as well as reduce family and individual costs, this alternative may increase the costs of the health care staff that would deliver and supervise the treatment, as well as the associated costs of transportation. Nevertheless, this increase of institutional costs could be justifiable if adherence and cures increased, keeping in mind the costs of not achieving these treatment results: greater morbidity, mortality, productivity losses, greater population transmission and greater resistance, among others.

As strengths of this study, it is possible to consider carrying out the study maintaining the same conditions in which the TB program usually operates for the facility-based treatment delivery, and the implementation of the domicile-based delivery alternative in the conditions in which it would work in case it were adopted by the program. The design of this alternative and its operation was agreed upon with the Coordination of the Tuberculosis Program of Cali in order to evaluate an alternative whose implementation is feasible. Therefore, an economic evaluation in this context allows a more precise approximation of the measurement of costs and effectiveness than the one that would be obtained with other types of studies.

Since it is a randomized trial, it is possible to expect the balance and control of most of the possible confusion factors, observed and not observed, that can affect adherence to anti-TB treatment among the alternatives in comparison.

This study seek to ensure external validity of the findings through the use of inclusion and exclusion criteria that integrate most TB patients diagnosed for the first time in Cali. Thus, only those who require hospitalization because they are detected in later phases of the disease, and those who have health conditions that require a different treatment plan, are being excluded.

Among the limitations it is precise to mention that, since it is a study that requires follow-up, it is not possible to rule out an overestimation of adherence and reported costs. Nevertheless, just as it has been found in other studies in the Colombian population, the DOT by itself fails to ensure the levels of adherence needed (**13**), and although it is not possible to rule out a possible error in the costs report, it is necessary to keep in mind that it is feasible for its occurrence to be lower given the effect that small expenses have on low income populations, and if said error were produced in the report, it would not be differential between the interventions(30, 31).

This project will support one of the main components of the national TB Strategy oriented to promote operational research in local contexts, which is oriented to evaluate new interventions on delivery of TB treatment, and thus to improve the performance of the TB program (32). Therefore, this project will bring evidence based on the real context that would support the Strategic Plan *Colombia Libre de Tuberculosis* 2011-2015, due to this study will contribute to the identification of an alternative that improve the program efficiency and that reduces economic impact of TB on institutions, patients, and families in Cali and other Colombian cities.

Ethical aspects

This study was revised and approved by the Ethics Committee of the Fundación FES, and is carried out according to the principles of the Helsinki Statement and Resolution 8430 of 1993 of the Department of Health of Colombia. Additionally, the Ethics Committee of the National Institute of Health of Mexico declared the study exempt of revision to be the first author's doctoral thesis. Written consent is requested from all patients, and they do not receive any financial compensation for participating in the study.

List of abbreviations

TB: Tuberculosis.

Authors' contributions

SLG and JCM designed the study, obtained the financing and are in charge of conducting the study. SGSR and MEC have contributed to the design and implement methods and procedures for the measurement of costs and cost-effectiveness estimation. All the authors contributed in the conception, writing, critical reading and approval of the whole article.

Author's Information

SLG: Economist. MSc in Epidemiology. Researcher in the Area of Health of the Fundación FES. Assistant Professor in the School of Public Health, Universidad del Valle. This protocol has been accepted by the National Institute of Public Health of Mexico to be the thesis of the Doctorate in Public Health. It is expected to obtain qualification in the first semester of 2015.

JCM: Medical Doctor. MSc in Epidemiology. Director of the Health Area of the Fundación FES. Associated Professor in the School of Public Health, Universidad del Valle.

SGSR: Economist, MSc in Health Economics. Doctorate in Economics (With specialization in Health Economics). Researcher of the Center for Health Systems Research in the National Institute of Public Health of Mexico.

MEC: Economist, MSc in Economics. Masters in Health Sciences (with specialization in Health Economics). Researcher in the Center for Health Systems Research in the National Institute of Public Health of Mexico.

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Dissemination plan

We expect that the results of this study and the paper on public health policy implications be published in the same peer review journal of the protocol publication. Presentations of study findings will be done to the Doctoral Board of the National Institute of Public Health of Mexico and to the technical team of the Secretariat of Health from Cali and to those from the Ministry of Health of Colombia. In additions, presentations will be done in relevant local and international research conferences. Additionally, to ensure coverage of our findings we will send a short summary to the main media from Colombia.

Conflict of interests

The authors declare that there is no conflict of interests in the development of this project.

Data sharing statement

Additional information of all aspects of the protocol is available on request from the corresponding author.

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Artículo 2

Double blind, randomized control trial to measure the cost-effectiveness of two service delivery models of tuberculosis treatment in Cali, Colombia.

Girón Sandra L. Researcher. Fundación FES. Assistant Professor. School of Public Health. Universidad del Valle. Avenida 5N #22AN-15. Cali, Valle del Cauca, Colombia

E-mail: sandragiron@fundacionfes.org

Mateus Julio C.

Health Area Director. Fundación FES. Associate Professor. School of Public Health. Universidad del Valle. Avenida 5N #22AN-15. Cali, Valle del Cauca, Colombia

E-mail: jcmateus@fundacionfes.org

Elizondo-Cano M.

National Institute of Public Health (INSP), Cuernavaca, Mexico, Centre for Health System Research. Avenida Universidad 655, col. Santa María Ahuacatitlán. 62100 Cuernavaca, Morelos, México.

E-mail: miguel.elizondo@insp.mx

Sosa-Rubí Sandra G. Researcher. National Institute of Public Health (INSP), Cuernavaca, Mexico, Centre for Health System Research. Avenida Universidad 655, col. Santa María Ahuacatitlán. 62100 Cuernavaca, Morelos, México.

E-mail: srubi@insp.mx

*Corresponding Author: Sandra Lorena Girón-Vargas. Avenida 8 Norte No. 22AN-15

Cali, Colombia. Telephone number: 2-6534141. Email: sandragiron@fundacionfes.org - sandralgiron@gmail.com

Double blind, randomized control trial to measure the cost-effectiveness of two service delivery models of tuberculosis treatment in Cali, Colombia.

Abstract

Objectives: to measure the cost-effectiveness of two forms of delivery of anti-tuberculosis treatment: one facility-based and one home-based, to improve adherence to the treatment.

Design: A randomized controlled clinical trial with double masking was designed to carry out a cost-effectiveness analysis.

Setting: The study was carried out in the urban area of Cali, which is the largest urban center of the Colombian South-West. Patients were recruited in 21 health care units of primary and secondary level of care.

Participants: After written informed consent, 264 new outpatient cases of diagnosed pulmonary TB were recruited. Half were randomized to the facility-based delivery of treatment and the rest to the alternative of home-based delivery. The inclusion criteria were: a) Patients over 18 years of age; b) men and women; c) residents of the urban area of Cali; d) new diagnosis of pulmonary TB and e) people in conditions to respond to a survey and receive outpatient treatment. The exclusion criteria were: a) pregnant women; patients with hemoptysis or with any condition that required special treatment such as liver disease, kidney failure, silico-tuberculosis and HIV/AIDS.

Interventions: in the facility-based delivery alternative, patients received the treatment at health care units. In the home-based delivery alternative, nurse auxiliaries went to the place chosen by the patients to give and supervise the treatment. All the patients received treatment according to Colombian TB care guidelines.

Outcome measures: Adherence and cure were the primary and secondary outcome variables, respectively.

Results: The cost-effectiveness ratio of home-based delivery was U$5.83, and in the cases of facility-based delivery it was U$5.88 per adherent patient. The incremental cost-effectiveness between the alternatives was U$6.29.

Conclusions: Deliver the TB treatment at the place chosen by the patient is a cost-effective option to improve adherence and reduce the financial impact of TB on the institutions, the patients and their families. *Trial registration*: NCT01945905.

Keywords: medication adherence, randomized controlled trial, cost-effectiveness, tuberculosis, Colombia.

Background

Tuberculosis (TB) is one of the main public health problems worldwide(**1**). Although direct observation of treatment for each patient is the strategy approved by the World Health Assembly (**2**), poor adherence continues to affect treatment effectiveness(**3**). Poor adherence has different type of negative consequences in terms of morbidity, mortality, transmission, resistance to treatment, higher costs of treatment, and socio-economic impact on patients and their families (**5-10**)(**10-12**).

In 2011 the treatment success rate of 85% were not reached: 80% were cured, while 4% were lost to follow up (**1**). In Cali, the third largest city of Colombia, in 2012 there was 7.6% of loss to follow up (*Secretariat of Public Health of Cali. Report of the Secretariat of Public Health of Cali. Tuberculosis Mortality. Santiago de Cali up to December 2012. Cali: Secretariat of Public Health of Cali; 2012.*). However, a prospective cohort study have reported that 65.6% of new TB cases do not adhere to treatment and that 43% of patients would prefer to receive treatment at home (**4**).

Although different alternatives have been found cost-effective to increase adherence to TB treatment, including the supervision by community workers, peers or family members, the financial incentives or enablers (food baskets, clothes support, transport fare) and even the delivering of several doses for self-administration, in Colombia, there are not alternatives that have been evaluated, the only current way to deliver anti-TB treatment, according to the national policy for DOT, is still at the health care facilities. With this form of treatment delivery, patients and families have to deal with direct and indirect costs of travelling, food and time to receive the treatment during six months. These costs represent between

38% and 80% of the total cost of the disease and around 7.5 times the average daily salary of the patients (**13, 14**).

This paper reports the results of a randomized trial directed to evaluate the cost-effectiveness of two service delivery modes in the urban area of Cali: one was facility-based delivery of anti-TB treatment and the other was home-based delivery of anti-TB treatment. We expect the results of this study will to contribute to strengthen the implementation of the TB Strategic Plan.

Methods

The detailed protocol of this study has been previously published; therefore, this paper presents a short description of the methods performed.

Type of study

Controlled, randomized trial with double masking to establish the cost-effectiveness of two forms of anti-TB treatment delivery: a facility-based alternative in which patients go to the health care units to receive treatment, and a home-based delivery alternative in which health care staff takes the treatment to a place chosen by the patients. The study was carried out from a social perspective (institutional and family), with prospective data collection(**15**). The measurement of the costs was carried out based on the activities and resource identification(**15**). Effectiveness of the interventions was given by adherence as a primary variable and cure as a secondary variable. Follow up consisted of 6 months as of the beginning of the treatment.

Hypothesis:

It is hypothesize that the home-based delivery of anti-TB treatment is more cost-effective than the provision of anti-TB treatment at the health facility in a period of 6 months of treatment.

Interventions

Two alternatives were compared:

1. Facility-based delivery alternative: As currently in Colombia, patients went to the health care unit to receive the treatment under direct observation of a nurse auxiliary from each one of the 21 units. During the 8-week intensive phase, they went 6 days a week. During the 16-week continuation phase, they went to the institution 3 times a week.

2. Home-based delivery alternative: In this alternative the treatment was delivered at the place chosen by the patients by 3 nurse auxiliaries who supervised the intake of the medication and its potential adverse effects. During the 8-week intensive phase the nurse auxiliaries went to the place chosen by the patients 6 days a week, and during the continuation phase (16 weeks) they went 3 times a week. The nurse auxiliaries went in rented motorcycles, with their respective drivers, to deliver the DOT. The selected place could be the patient's home, the job place or other that did not represent unsafe situations for the staff.

All patients received the treatment according to the National TB care guidelines from Colombia: the treatment for new pulmonary TB cases is given ambulatory and free of charge to patients whose health state thus allows it, with the following plan: each dose of the treatment in the first phase (intensive)

includes combined fixed oral doses of 150 mg of Rifampicin, 75 mg of Isoniazid, 400 mg of Pyrazinamide and 275 mg of Etambutol. In the second phase (continuation) each combined oral dose of the treatment includes 100 mg Isoniazid and 300 mg Rifampicin with 150 mg of Isoniazid (**16**).

For both alternatives, the follow-up appointments and the lab tests required (smear at two, four and six months) were carried out according to the current health care guidelines and in the labs of the health care institutions where the treatment is registered.

In coordination with the health care institutions and the Secretariat of Public Health of Cali, the field coordinator requested the medication for each patient included in the home-based delivery alternative weekly.

Area:

The study was carried out in the urban area of Cali, which is considered a city with a high-risk for the transmission of pulmonary TB: while the accumulated annual incidence in Cali in 2012 was 41 cases per 100.000, in Colombia it was 25 cases per 100,000 inhabitants.

Study population:

New cases of pulmonary TB diagnosed in 21 health care units were included according to the following inclusion criteria: a) Patients over 18 years of age; b) men and women; c) residents of the urban area of Cali; d) new diagnosis of pulmonary TB and e) people in conditions to respond to a survey and receive outpatient treatment. The exclusion criteria were the following: a) pregnant women;

patients with hemoptysis or with any condition that required special treatment such as liver disease, kidney failure, silico-tuberculosis, and HIV/AIDS.

Sample size:

Taking into consideration a 20% difference in patients with complete treatment among the alternatives in comparison, 46% in the facility-based delivery alternative and 66% in the home-based delivery alternative, a power of 80%, an alpha error of 5%, a ratio of patients assigned to each form of delivery of 1:1, 20% of losses and using the sample size formula for comparison of two proportions with Fleiss continuity correction, a necessary number of 132 patients in each group was estimated.

Randomization and masking:

The randomization of patients to the alternatives was carried out through balanced blocks. Patients were enrolled in the order of TB diagnoses. The allocation was done by using individual envelopes sequentially numbered. These envelopes were opened in strict order, to the extent that patients endorsed their participation in the study.

A field coordinator did the allocation of each patient and assigned an alphabetical code to each study group. Since the treatment delivery is an intervention that cannot be concealed for the patients or the operative team, the follow-up and delivery of the medication to the home-based delivery group was carried out by nurse auxiliaries that did not have any relation with the group that carries out the follow-up of the patients of the facility-based delivery alternative. Researchers in charge of the project were also concealed to the allocation status of each patient, until the end of statistical analysis.

Follow-up termination and study losses criteria:

The follow-up for each patient was done for 6 months or until one of the following situations occurred: a) when the patient finalized the treatment and b) when medical orders indicate the need for a different treatment from the standard treatment described.

A patient was considered lost by the study according to the following conditions: a) declared that he/she did not wish to continue in the study, in which case they were transferred to the Tuberculosis Program to continue treatment in the case of the home-based delivery alternative; b) when the patient cannot be located in the chosen place after thirty days for treatment delivery in the case of the home-based delivery alternative, and when the patient has not returned to the health care unit to receive treatment after thirty days in spite of calls and searches, in the case of the facility-based delivery alternative; c) when the patient moves outside of Cali and d) when the patient dies.

Effectiveness Variables:

Adherence and cure were the primary and secondary variables of study, respectively. Treatment adherence was defined as the percentage of patients that finished the TB treatment at the end of 6 months. The cure variable represents the percentage of patients whose cure was confirmed, according to the records of the *Program for Tuberculosis Control of Cali*. According to international standards (**17, 18**), the Program establishes that the patient is cured when the follow-up smears of the fourth and sixth months of treatment were negative.

Institutional Costs Variables:

Direct costs for both alternatives were measured through the assessment of time spent by nursing staff to deliver the treatment: The cost of the staff was assessed using their annual salary and the time devoted to the provision of the intervention. Additionally, in the home-based delivery alternative, the direct costs of the staff transportation to deliver the treatment and the use of supplies (gloves, plastic boxes to carry the medication, and foam coolers with gel packs) were measured and valued according to the market price.

The costs of medical attention, medication, lab test processing and administrative costs were not measured, since they were equal for both alternatives.

Family Costs Variables:

Direct and indirect costs were measured for both alternatives. In the facility-based delivery alternative, direct costs were represented by the family's costs of transportation to the health facility, and for associated costs of meals and snacks for patients and their companions. In the home-based delivery alternative, the direct family costs included transportation and meals and snacks for medical, nursing and bacteriological follow-ups that were carried out at the health care unit. For both alternatives, other consultations, tests and other medications, the purchase of homemade remedies and the costs of transportation associated were measured as direct costs.

Indirect family costs of both alternatives included the cost of the time spent by patients and their families to get the lab tests and follow-ups, and to receive the medication. This time was economically valued using the minimum legal wage in Colombia.

Co-variables: patient gender, age, marital status, education, occupation, health service regime, and time taken to arrive to the health facility were measured to verify the balance of baseline characteristics between control and treatment groups after the randomization of the patients.

Data collection:

Six nurse auxiliaries were selected and trained: three to collect the data from patients assigned to the facility-based delivery alternative, and three to deliver the medication and collect data in the home-based delivery alternative. A supervisor assigned for each group did quality control.

To measure the adherence variable, each patient's card was checked weekly to obtain the data of the doses taken. The data of the cured patients was obtained from the records of the Tuberculosis Program of Cali.

To measure the institutional costs of the time invested by the health care staff, the field coordinator observed and measured the time devoted by them in the attention of patients. This measure was done in the 21 health care units where patients were recruited, 8 weeks after the training and during a week considered typical. Then the average time invested was obtained and valued. The data of the salaries was obtained from the records of the Secretariat of Public Health of Cali.

Institutional costs of transportation for the home-based delivery alternative was estimated by dividing the monthly rate for the rent of motorcycles and the number of visits carried out during the same period.

The data of family costs was obtained through a patients' survey applied each week during the treatment provision either in the health institution or at the selected place (patient's home or job place). Data was collected in portable electronic devices (*Personal Digital Assistant*).

Analysis Plan:

For analyzing the effectiveness of each alternative, using adherence as main result, intention to treatment analysis was carried out. We divided the analysis in three sections. The first section described the process of randomization analyzing the balance of socio-demographic and co-variables of the patients between the two alternatives. The second evaluated the statistical differences of effectiveness between the two alternatives for the two main result variables, percentage of adherent patients and percentage of cured patients, using the Chi-Square at 95% of confidence.

The third section estimated the costs and cost-effectiveness of the interventions. Costs were estimated in Colombian Pesos and in U.S. dollars, year 2013. Non-parametrical bootstrap techniques with 1000 samples were used to estimate the mean family costs and their confidence intervals of each alternative. Mean institutional costs were estimated by dividing the costs by the number of patients covered.

Cost-effectiveness ratios of each alternative were obtained through the quotient of the total costs (institutional and family costs) and the percentage of adhered patients. The ratio of incremental cost-effectiveness among the interventions (home *vs* facility) was estimated by the quotient of the differences of mean costs and the differences of adherence. Sensitivity analysis was done to identify changes in cost-effectiveness ratios and in the incremental cost-effectiveness ratio, according to minimum and maximum observed values of costs and adherence. The sensitivity analysis included the

following variables: adherence, institutional direct cost (staff, transportation, and supplies), family direct costs (transportation, meals and snacks, consultations, medicines, home remedies), and family indirect costs (cost of the time spent by patients and cost of the time spent by their families).

Discount rates were not being applied, since the costs were generated in a period where significant changes in the purchasing power were not recorded. Discounts to adherence variable were not applied because its future benefits or damages were not estimated.

Effectiveness and cost analysis were done with Stata software, while cost-effectiveness analysis was carried out with TreeAge software.

Results

Recruitment of participants and randomization: Between December 2012 and March 2013, 132 patients were randomized to each alternative. The follow-up finished in September 2013. Data on outcome results, specifically for cure variable, was collected until August 2014. No statistically significant differences were observed per gender, ***age,*** marital status, level of education, occupation**,** health care affiliation, and time taken to arrive to the health facility among the patients assigned to each one of the alternatives (see Table 1).

Out of the 132 patients randomized to the home-based delivery, only one chose the delivery at the work place and the rest chose their homes. However, during the first month of follow-up, the patient who chose his workplace requested changing the delivery of the treatment to his home.

In both alternatives, 7 randomized patients rejected continuing with the study, which means that 5.3% decided not to continue with the study, even when they continued receiving treatment by the Tuberculosis **Program of** Cali (see Figure 1). There were 2 deaths in the group assigned to the home-based delivery alternative, one due to heart attack and the other one due to meningeal TB. Likewise, there were 4 deaths in the group that was randomized to the delivery facility-based alternatives: one due to gastric cancer, one due to liver disease, one due to tuberculosis and one whose cause of death could not be established. None of the patients died during the follow-up; the data of the treatment ***outcome***s were obtained from the records of the Tuberculosis **Program of** Cali, after finishing follow-up. Given that the analysis presented below is on ***intention to*** treat, the number of patients to analyze in each group is 132.

Effectiveness results*:*

Adherence: A trend towards greater effectiveness was observed in the patients assigned to the home-based treatment delivery alternative. Thus, while 84.09% of the patients assigned to the home-based delivery alternative adhered to the treatment, 75.00% of the patients randomized to the facility-based delivery alternative adhered. This difference was found in the limit of the statistical significance (p=0.067) (see Table 2).

No statistical differences were observed in the intensive phase of the treatment. In the second phase, a trend towards a higher percentage of adherent patients in the home-based delivery alternative was observed (81.82%), compared to the patients randomized to the facility-based delivery alternative (72.73%) (p=0.078) (see Table 2).

Cure: No statistical differences were observed with respect to the cure among the compared alternatives. Among the patients that received the full treatment at home, a cure of 68.18% was reported, while only the 2.27% of patients was not cured in this alternative. Similarly, among the ones who received the treatment at the heath care institution, 61.36% were cured and 3.03% were not (p=0.506). For both forms of treatment delivery, around 30% of patients could not be proven as cured at the moment of closing the gathering of the data, mainly due to administrative reasons and because the patient did not return for further testing.

Costs Estimation*:*

Institutional Costs: In the home-based delivery alternative, treatment delivery costs were observed for US$57727 for the 132 patients in the study. From these costs, 58.2% correspond to the costs of the time spent by the auxiliary nursing staff in the delivery of the treatment, 38.6% to the transportation costs, and the last 3.2% to the costs of the materials necessary to transport in accordance with the recommended biosecurity measures (see Table 3).

On the other hand, the cost of treatment delivery for the 132 patients randomized to the facility-based delivery alternative was US$41330. In this alternative, the measured costs are represented by the cost of the time spent by the nursing staff to deliver the treatment to 132 patients randomized to this alternative. This means that the home-based delivery alternative had higher total costs of US$16397 and a cost per patient of U$437, while the facility-based delivery alternative had a cost per patient of US$313. Therefore, delivering the treatment to the patient's home cost an average of US$124 more per patient (see Table 3).

Family Costs: The measurement of the family costs showed statistically significant differences in the direct, indirect and total costs (see Table 4). In regards to the direct costs, it was observed that the patients who received treatment at the health care unit were responsible for the average transportation costs that were statistically higher in US$58.55, i.e., 13 times higher compared to the patients who received the treatment at home. This difference ranges between US$42.25 and US$74.84 (p=0.000) (Table 4).

Greater expenses in medications and home remedies was found in patients who received treatment at the health care unit; however, the US$6.07 difference in the costs for this component was not significant at 5% (p=0.074) (see Table 4).

Patients who received the treatment at home had an average snack costs that were statistically greater in US$18.83, which varied from US$7.33 and US$30.33. The difference in costs was 38% higher compared to the snacks costs of patients who received treatment at the health care units (p=0.001) (see Table 4).

Therefore, the average direct costs were statistically higher in US$45.41 in patients who received treatment at the health care unit; this difference varies between US$23.87 and US$66.95. This means that the direct costs of the patients who received facility-based treatment were 80% higher, compared to the patients who received home-based treatment (p=0.000) (see Table 4).

In relation to the average indirect costs, significantly higher costs were observed in the patients randomized to the facility-based delivery alternative in terms of the costs of the time spent by the patient, the time spent by family members, and in the total indirect costs. Particularly, opportunity

costs were greater in an average of US$19.49 for the patients of facility-based delivery; this difference was observed between US$16.81 and US$22.18 (p=0.000). Likewise, the average costs of the time of the companion were greater in US$3.12 in patients in the facility-based treatment delivery alternative, which were from US$1.75 to US$4.48 (p=0.000). In total, the indirect costs in patients of said alternative were significantly higher in an average of U$22.61, difference which varied between U$19.25 and U$25.97 (p=0.000) (see Table 4).

In average total family costs were statistically higher (U$68.02) in patients assigned to the facility-based treatment delivery alternative than patients assigned to the home-based treatment delivery alternative. This difference in average costs varied from U$45.14 to U$90.91(p=0.000) (see Table 4). Overall, including family and institutional costs, the cost per adherent patient was U$494.27 in the home-based alternative and U$437.12 in the facility based alternative. Thus the costs of home-based alternative were higher in U$57.15 (see Table 5).

Cost-effectiveness Analysis: The cost effectiveness ratios of the alternatives were almost equal. While the cost effectiveness ratio for the home-based alternative was U$5.88, for the facility-based alternative it was U$5.83. The incremental cost-effectiveness ratio among the alternatives was of U$6.29, i.e., compared to the treatment delivery at the health care unit, obtaining an additional percentage point of adherent patients with the delivery at home means an additional cost of U$6.29 (see Table 5). Figure 2 shows the relation of costs and effectiveness in terms of the percentage of patients that adhere to the treatment. This incremental cost-effectiveness ratio was maintained ***at justifiable limits in each*** phase II of the treatment delivery***:*** U$***3.58 in the first phase and*** U$ ***4.29 in the second one*** (see Table 5).

The sensibility analysis showed that, set against variations in the family cost transportation, as well as in the family costs medication, the home-based treatment delivery can even result in a cost-saving strategy (more effective and less costly) compared to the facility-based delivery alternative. On the other hand, it was observed that the increases in the family costs of the snacks, in the proportion of adherent patients in patients assigned to the facility-based delivery alternative, as well as the reduction in the proportion of adherent patients of the ones assigned to the facility-based delivery alternative, increase the incremental cost-effectiveness of extra-mural delivery in up to U$40.00 (see Figure 3).

In general, treatment delivery to the patient's home showed a better cost-effectiveness and incremental cost-effectiveness relationship to improve adherence, compared to the delivery at the health care unit. Although the delivery at the health care unit showed lower cost per adhered patient, this alternative presented lower adherence in comparison to the delivery at the place chosen by the patient.

Discussion

This study compared two forms of treatment delivery for new TB cases in the urban area of Cali, and managed to establish that the delivery at the patient's home is more cost-effective than the delivery at the heath care institution, as it is usually done in Colombia. Although it was observed that the cost per covered patient was US$124 higher with the delivery at home, a greater percentage of adherent patients was also observed and the cost per adhered patient was only US$57.15. This cost could be considered fair when taking into account the costs of poor adherence, represented by the treatment of cases that have failed, hospitalizations or even the costs of multi-drug resistant, the costs of transmission or the costs of premature deaths.

Additionally, the delivery of the treatment to the patient's home showed significantly lower family costs than the ones observed in families of patients that received treatment at the health care unit. These differences were generated mainly at the expense of the savings in transportation and the shorter time spent by the patient and his companions to receive the treatment. Nevertheless, it comes to our attention that the direct costs of the patients that received treatment at home were greater in the purchase of snacks for the patient. This means that the savings in transportation in this form of delivery are dedicated to the purchase of food to improve the patient's nutrition and reduce the treatment's side effects. From the estimated costs, it is possible to infer that the population affected by TB in Cali takes on a financial burden that could affect adherence and at the same time lead them to expenses considered catastrophic, every time that they are not able to earn at least a Colombian minimum wage regularly. Even more, if they had earned the legal wage of U$313, the costs to support the treatment would represent until 105% in the home-based alternative and 215% in the facility based alternative.

These results show the need to revise the TB treatment delivery strategy in Colombia, which upon being intensive in the patient's visits to the health care unit imposes high institutional costs in terms of time of the staff and also an important financial burden to patients and families of patients with TB. This way, even if the implementation of a home-based delivery may be not considered for all ambulatory patients, it may at least be considered for those who have high-risk factors to abandon the treatment or to support the second phase of the treatment in which the patients tend to abandon the treatment with a higher frequency.

Likewise, other anti-TB treatment delivery strategies have been found cost-effective, in comparison to the delivery concentrated in the health care unit. Thus, the supervision through community workers(**19, 20**), people that live with the patient(**21**) and even the use of videophones(**22**) have been found cost-

effective to improve the adherence to the treatment. Nevertheless, most of these studies have been carried out retrospectively and have been carried out in rural contexts and in other very different to the Colombian context.

This is the first randomized study that look for the cost-effectiveness impact of two delivery models of TB treatment in Colombia and in Latin America, and that, hence, make it possible to avoid the bias attributed to the confusion factors generated by those individuals that could prefer to receive the treatment at home and those individuals who prefer to go to the health facility. Additionally, the 5% loss observed during the follow-up can be considered low and was equal among the interventions, which contributes to ruling out a possible bias in the selection. The study was carried out taking into account the institutional and family points of view in order to extensively evaluate the cost-effectiveness of the alternatives.

As limitations, it should be noted that, since it is a prospective study, it is not possible to rule out an improvement in the levels of adherence and higher costs reported, as a consequence of follow-up. Nevertheless, there is no evidence of differential over-reports between the alternatives. The measurement of the cure variable was based on the treatment results of the TB Program of the Department of Health of Cali. On the closing date of the collection of data, we did not have the entire closing of the patients of the cohort of the year 2013, by which approximately 40% of patients were found without treatment result data for the cure variable.

This operative research offers a cost-effective alternative to improve adherence to the anti-TB treatment that allows supporting the Strategic Plan *Colombia Libre de Tuberculosis* 2011-2015

reducing the financial and social burden of TB on institutions, patients and families in Cali and other cities in Colombia.

Ethical aspects

This study was revised and approved by the Ethics Committee of the Fundación FES, and was carried out according to the principles of the Helsinki Statement and Resolution 8430 of 1993 of the Department of Health of Colombia. Additionally, the Ethics Committee of the National Institute of Health of Mexico approved it to be the first author's doctoral thesis. Written consent was requested from all patients, and they did not receive any financial compensation for participating in the study.

List of abbreviations

TB: Tuberculosis.

Authors' contributions

SLG and JCM designed the study, obtained the financing and are in charge of conducting the study. SGSR and MEC have contributed to the adjustment of the methods and procedures for the estimation of costs. All the authors contributed in the conception, writing, critical reading and approval of the whole article.

Author's Information

SLG: Economist. MSc in Epidemiology. Researcher in the Area of Health of the Fundación FES. Assistant Professor in the School of Public Health, Universidad del Valle. This protocol has been accepted by the National Institute of Public Health of Mexico to be the thesis of the Doctorate in Public Health. It is expected to obtain qualification in the first semester of 2015.

JCM: Medical Doctor. MSc in Epidemiology. Director of the Health Area of the Fundación FES. Associate Professor in the School of Public Health, Universidad del Valle.

MEC: Economist, MSc in Economics. Masters in Health Sciences (with specialization in Health Economics). Researcher in the Center for Health Systems Research in the National Institute of Public Health of Mexico.

SGSR: Economist, MSc in Health Economics. Doctorate in Economics (With specialization in Health Economics). Researcher of the Center for Health Systems Research in the National Institute of Public Health of Mexico.

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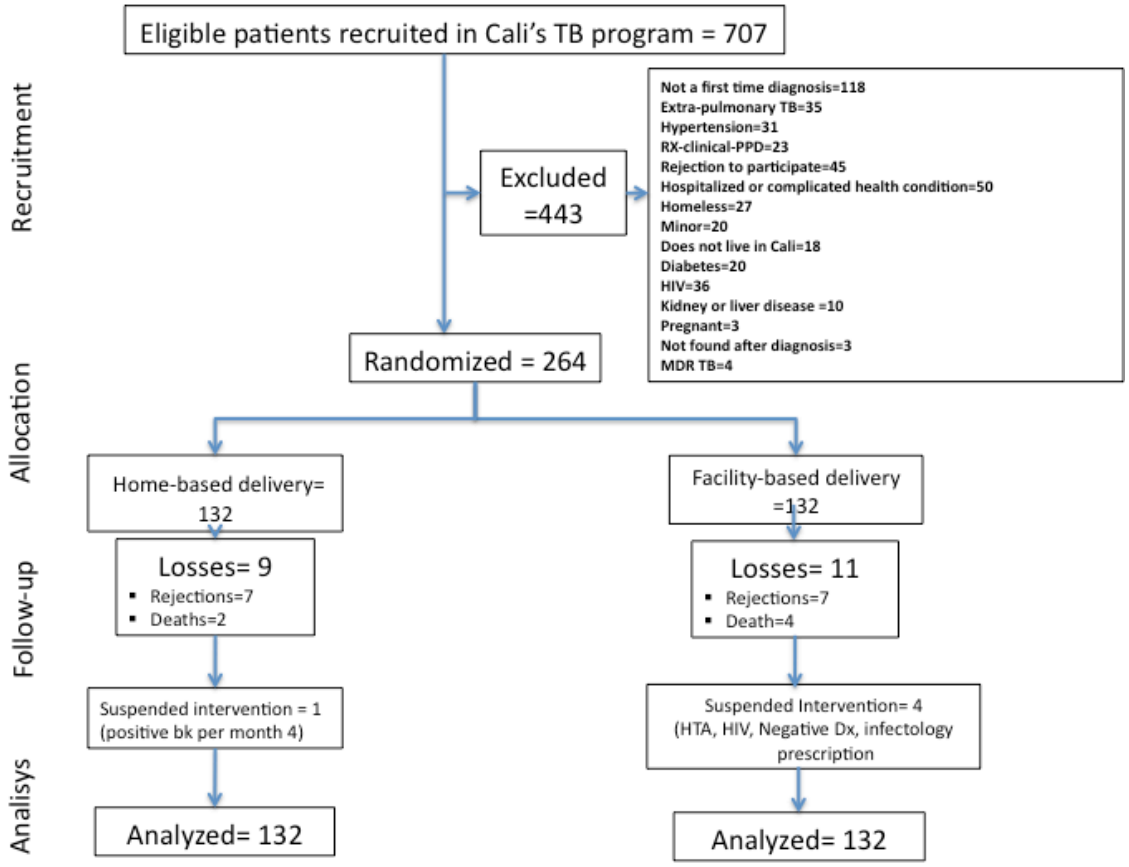
Conflict of interests

The authors declare that they do not have conflict of interests in the development of this project.

Figure 1. Flow chart of the patients' progress during the study.



Source: Figured elaborated based on data collected.

Table 1. Distribution of the participants' socio-demographic basal characteristics by alternative.

Characteristic	Home delivery	%	Facility-delivery	%	p
Gender					
Male	75	56.82	68	51.52	0.387
Female	57	43.18	64	48.48	
Age (median)	42.5	Range(18-88)	41	Range(18-86)	0.337
Marital status					
Single	56	42.42	62	46.97	0.356
Married	31	23.48	34	25.76	
Common law marriage	28	21.21	17	12.88	
Separated/Divorced	17	12.88	19	14.39	
Level of Education					
None	5	3.79	3	2.27	0.565
Primary	48	36.36	50	37.88	
High school	72	54.55	67	50.76	
College	7	5.30	12	9.09	
Occupation					
Home	57	43.18	44	33.33	0.163
Work	47	35.61	67	50.76	
Studies	3	2.27	3	2.27	
Looking for a job	8	6.06	7	5.30	
Another activity	17	12.88	11	8.33	
Health care affiliation					
Contributive	42	31.82	38	28.79	0.425
Subsidized	75	56.82	84	63.64	
Not affiliated	15	11.36	10	7.58	
Minutes to health facility	61	Range(2-240)	61	Range(4-122)	0.793
Total	**132**	**50.00**	**132**	**50.00**	

Source: Table elaborated based on data collected.

Table 2. Adherence and cure according to the alternative.

	Alternative of home-based delivery			Alternative of facility-based delivery			
Adherence	**n**	**%**	**Confidence Interval 95%**	**n**	**%**	**Confidence Interval 95%**	**p**
First Phase							
Yes	121	91.67	86.89; 96.44	114	86.36	80.43; 92.30	0.168
No	11	8.33	3.56; 13.11	18	13.64	7.70; 19.57	
Second Phase							
Yes	108	81.82	75.15; 88.48	96	72.73	65.03; 80.42	0.078
No	24	18.18	11.52; 24.85	36	27.27	19.58; 34.97	
Total							
Yes *	111	84.09	77.77; 90.41	99	75.00	67.52; 82.48	0.067
No	21	15.91	9,59; 22.23	33	25.00	17,52; 32.48	

Source: Table elaborated based on data collected.

Table 3. Description of institutional costs per alternative in US dollars of 2013 by alternative.

	Alternative of home-based delivery		Alternative of facility-based delivery	
Item	**Value**	**Average per patient**	**Value**	**Average per patient**
Staff	33596	255	41330	313
Transportation to deliver and supervise treatment	22272	169		
Materials to deliver and supervise treatment	1859	14		
Total	57727	437	41330	313

US$1 = COP$1880.91

Source: Table elaborated based on data collected.

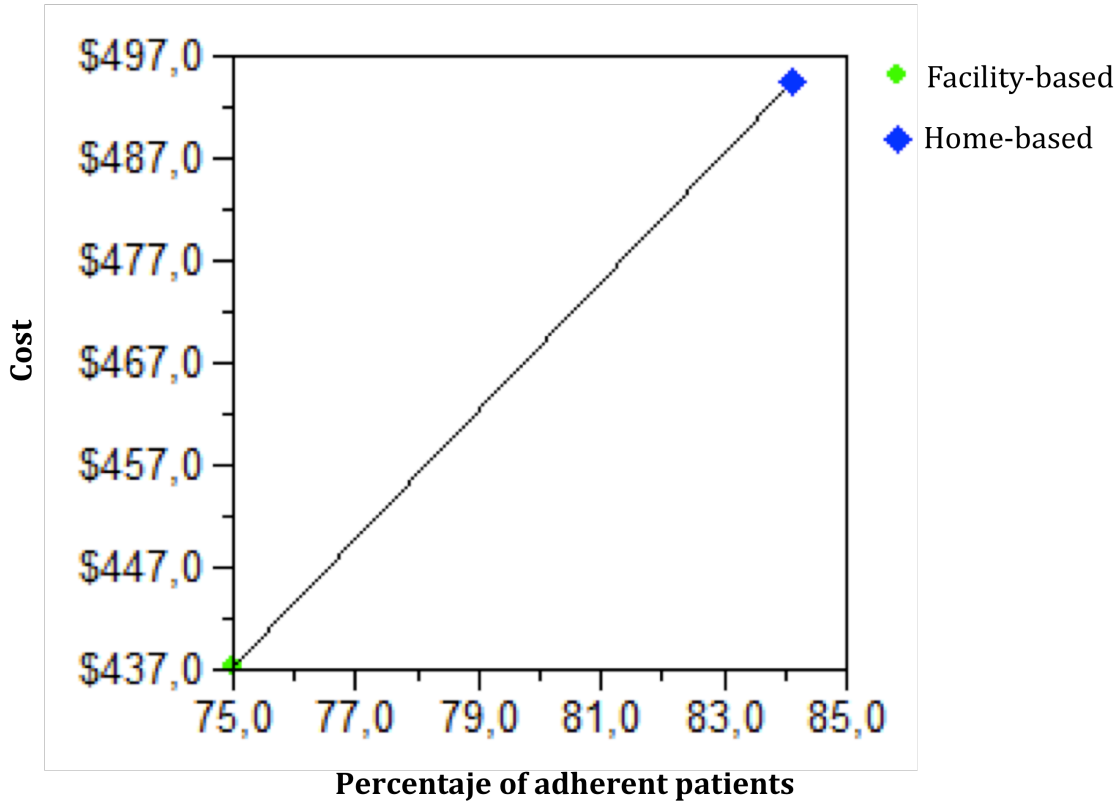
Table 4. Family costs according to the intervention in US dollars of 2013 by alternative.

Item	Alternative of home-based delivery		Alternative of facility-based delivery		Average difference	IC 95%	p
	Minimum value; maximum value	Average	Minimum value; maximum value	Average			
Direct costs							
Consults	0; 33.60	0.51	0; 13.29	0.13	0.38	-0.94; 0.19	0.189
Transportation	**0; 41.47**	**4.87**	**0; 571.53**	**63.40**	**58.55**	**42.25; 74.84**	**0.000**
Medication	0; 43.65	1.67	0; 364.72	7.74	6.07	-0.59; 12.73	0.074
Snacks	**0; 318.99**	**49.07**	**0; 290.29**	**30.24**	**-18.83**	**`-30.33; -7.33**	**0.001**
Total direct costs	**0; 330.16**	**56.11**	**0; 632.14**	**101.52**	**45.41**	**23.87; 66.95**	**0.000**
Indirect costs							
Patient time	**0; 5.06**	**0.14**	**0; 71.79**	**19.63**	**19.49**	**16.81; 22.18**	**0.000**
Family member's time	**0; 1.18**	**0.01**	**0; 63.74**	**3.13**	**3.12**	**1.75; 4.48**	**0.000**
Total indirect costs	**0; 5.06**	**0.15**	**0; 114.34**	**22.76**	**22.61**	**19.25; 25.97**	**0.000**
Total costs							
Total family costs	**0; 330.16**	**56.26**	**0; 674.90**	**124.28**	**68.02**	**45.14; 90.91**	**0.000**

US$1 = COP$1880.91

Source: Table elaborated based on data collected.

Figure 2. Cost-effectiveness of the home-based delivery alternative compared to the facility-based delivery alternative. US dollars of 2013.



US$1 = COP$1880.91

Source: Figure elaborated based on data collected.

Table 5. Analysis of cost-effectiveness of the home-based delivery alternative compared to the facility-based delivery alternative. US dollars of 2013.

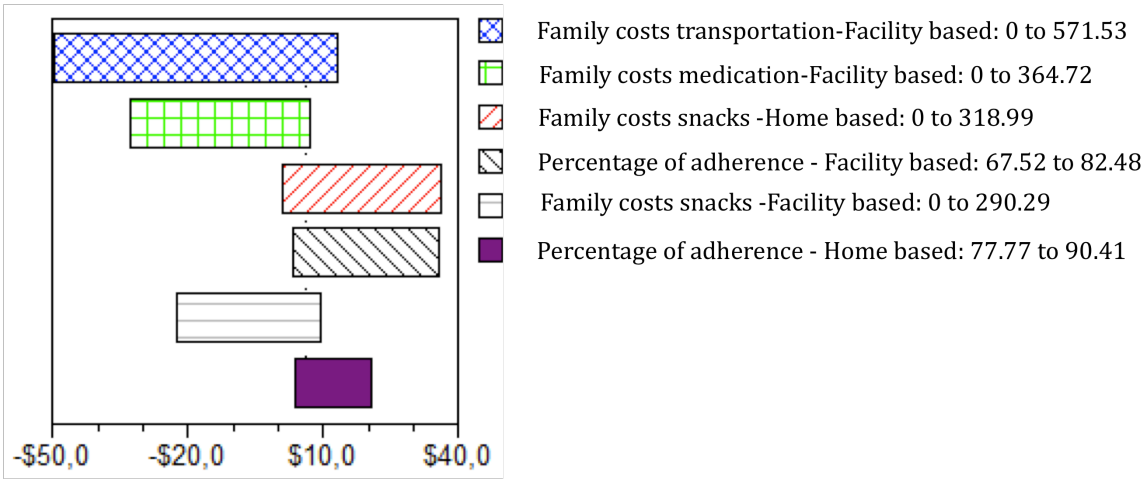
Alternative	Cost per adhered patient	Incremental cost	Effectiveness	Incremental effectiveness	Cost/Effectiveness (C/E)	Incremental C/E
First phase						
Facility-based delivery	$ 145.69		86.36		$1.69	
Home-based delivery	$ 164.74	$ 19.05	91.67	5.31	$1.80	$3.58
Second phase						
Facility-based delivery	$ 291.38		72.73		$4.01	
Home-based delivery	$ 329.48	$ 38.10	81.82	9.09	$4.03	$4.19
Total						
Facility-based delivery	$ 437.12		75.00		$ 5.83	
Home-based delivery	$ 494.27	$ 57.15	84.09	9.09	$ 5.88	$ 6.29

US$1 = COP$1880.91

Source: Table elaborated based on data collected.

Figure 3. Tornado diagram of incremental cost-effectiveness of the home-based delivery alternative, compared to the facility-based delivery alternative.

US dollars of 2013.



US$1 = COP$1880.91

Source: Figure elaborated based on data collected.

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Conclusiones y recomendaciones

Esta investigación logró identificar una estrategia que logra mejorar la adherencia al tratamiento anti-tuberculosis y disminuye el impacto económico de esta enfermedad sobre las familias. En particular, comparado con la entrega del tratamiento en las unidades de salud, la entrega en el domicilio del paciente genera menores costos familiares, costo institucionales por paciente adherido similares y una costo-efectividad incremental estimada de solo US$6,29 para aumentar en un punto porcentual la adherencia. Asumir los costos de esta intervención es justificable si se compara con los costos económicos y sociales de las complicaciones asociadas a la no adhrencia al tratamiento, las cuales pueden variar entre US$2 000 y US$120 000.

Esta investigación hizo evidente el impacto económico familiar que asumen los pacientes con tuberculosis y sus familias para poder adherirse al esquema de tratamiento y a la forma de entrega del mismo. Es decir, asumen costos que pueden llegar a límites considerados catastróficos, los cuales no solo afectan el poder adherirse al tratamiento, sino también llevar a un empobrecimiento de las familias afectadas con esta enfermedad.

De esta manera una intervención como la diseñada, implementada y evaluada en este estudio puede ser implementada como parte de los programas de control de tuberculosis en Cali, en otras ciudades Colombianas y Latinoamericanas. Además considerando que la adherencia es el resultado de factores individuales, sociales, económicos, culturales y administrativos, se recomienda un abordaje intersectorial que aborde el control de esta enfermedad y apoye la adherencia al tratamiento. En particular, programas de transferencias condicionadas que además de llevar el tratamiento a la casa del paciente, introduzcan beneficios nutricionales para el núcleo familiar y un programa de generación de

ingresos podrían contribuir a elevar de manera importante la adherencia al tratamiento y a disminuir los impactos de la tuberculosis en los pacientes y sus familias, los servicios y el sistema de salud y la economía del país.