Adherence to treatment for tuberculosis infection in children using a comprehensive care strategy: a prospective cohort study with a historical control group

Iader Rodríguez-Márquez,[a,b,c,l,*] Dione Benjumea-Bedoya,[a,b,d,l] Andrea Victoria Restrepo-Gouzy,[e] Claudia Patricia Beltrán-Arroyave,[f,g,h] Diana Marín,[i] Fernando Nicolás Montes-Zuluaga,[j] Juan Carlos Alzate-Ángel,[a] Lina Marcela Cadavid-Álvarez,[e] Lizeth Andrea Paniagua-Saldarriaga,[k] Teresa Realpe,[b] Yesenia Perea-Torres,[b] Lisandra María Arango-García,[b] Natalia Pérez-Doncel,[b,i] María Patricia Arbeláez-Montoya,[a] and Jaime Robledo[b]

[a]Grupo de Investigación en Epidemiología, Facultad Nacional de Salud Pública, Universidad de Antioquia, Antioquia, Medellín, Colombia
[b]Unidad de Bacteriología y Micobacterias, Corporación para Investigaciones Biológicas (CIB), Antioquia, Medellín, Colombia
[c]Unidad de Investigación Aplicada y Epidemiológica, Fundación Ideas Auna, Antioquia, Medellín, Colombia
[d]Grupo de Investigación en Salud Familiar y Comunitaria, Facultad de Ciencias de la Salud, Corporación Universitaria Remington, Antioquia, Medellín, Colombia
[e]Hospital Pablo Tobón Uribe, Antioquia, Medellín, Colombia
[f]Grupo de Investigación Pediaciencias, Medicine School, Universidad de Antioquia, Antioquia, Medellín, Colombia
[g]Clínica el Rosario, Antioquia, Medellín, Colombia
[h]Clínica del Prado, Antioquia, Medellín, Colombia
[i]Grupo de Investigación en Salud Pública, School of Health Sciences, Universidad Pontificia Bolivariana, Antioquia, Medellín, Colombia
[j]Tuberculosis Program, Secretariat of Health of Medellín, Antioquia, Medellín, Colombia
[k]Tuberculosis Program, Sectional Health Secretariat of Antioquia, Antioquia, Medellín, Colombia

The Lancet Regional Health - Americas 2025;46: 101094
Published Online xxx
https://doi.org/10.1016/j.lana.2025.101094

Summary

Background Low adherence to treatment for tuberculosis infection (TBI) in children threatens tuberculosis (TB) control goals. This research focuses on children with close contact to TB and TBI. This study evaluated adherence to treatment of TBI using a comprehensive care strategy (CCS) for close-contact children with pulmonary TB compared with standard of care (SOC).

Methods A prospective cohort study with a historical control group was conducted on children under five, who were close contacts of patients with bacteriologically confirmed pulmonary TB in three Colombian cities (study registration number: NCT04331262). The CCS comprised clinical evaluations, rifampicin for four months, multidisciplinary care, and logistical support, while the SOC followed program regulations with isoniazid for nine months. The primary outcome was the proportion of children completing 100% treatment during follow-up, and the secondary outcome was treatment-related adverse events (AEs).

Findings 213 children in the SOC group and 86 children in the CCS group were analyzed. The treatment adherence in the SOC group was 40·8% (95% CI 34%; 48%), while in the CCS group it was 76·7% (95% CI 66%; 85%). Children exposed to CCS had 87% higher probability of adherence to TBI treatment compared to SOC (RR 1·87; 95% CI 1·52; 2·31). The incidence of AEs was lower in the CCS group (n = 3) than in those receiving SOC (n = 24).

Interpretation The CCS increases adherence to treatment for TBI in children safely compared to SOC. Future cost-effectiveness studies will help implement this strategy in programmatic settings.

Funding Colombian Ministry of Science, Technology and Innovation.

Keywords: Latent tuberculosis; Comprehensive health care; Treatment adherence and compliance; Medication adherence; Child; Preschool

*Corresponding author. Grupo de Investigación en Epidemiología, Facultad Nacional de Salud Pública, Universidad de Antioquia, Antioquia, Medellín, Colombia.
E-mail address: iader.rodriguez@udea.edu.co (I. Rodríguez-Márquez).
[l]Contributed equally and should be considered as co-first authors.

Research in context

Evidence before this study

Evidence has demonstrated that short-course treatment regimens for TBI improve adherence. However, the impact of complex interventions, which include short-course treatment regimens, and specific interventions to further enhance adherence, remains unclear. A PubMed search was conducted for studies evaluating adherence to TBI treatment through complex interventions in children, without date or language restrictions, using the following strategy ((“Latent Tuberculoses” OR “Latent Tuberculosis” OR (“Latent Tuberculosis” OR (“latent” AND “tuberculosis”) OR “Latent Tuberculosis” OR (“tuberculoses” AND “latent”)) OR “tuberculosis latent” OR “Latent Tuberculosis Infection” OR “infection latent tuberculosis” OR “infections latent tuberculosis” OR “Latent Tuberculosis Infections” OR “tuberculosis infection latent” OR (“Latent Tuberculosis” OR (“latent” AND “tuberculosis”) OR “Latent Tuberculosis” OR (“tuberculosis” AND “infections” AND “latent")) OR “LTBI”) AND (“dropout patient” OR “dropouts patient” OR “Patient Dropout” OR “Therapeutic Adherence and Compliance” OR “Treatment Adherence” OR “adherence treatment” OR “Therapeutic Adherence” OR “adherence therapeutic” OR “adherence medication” OR “Drug Adherence” OR “adherence drug” OR “Medication Nonadherence” OR “nonadherence medication” OR “Medication Noncompliance” OR “noncompliance medication” OR “medication non adherence” OR “medication non adherence” OR “non adherence medication” OR “Medication Persistence” OR “persistence medication” OR “Medication Compliance” OR “compliance medication” OR “medication non compliance” OR “medication non compliance” OR “non compliance medication” OR “Drug Compliance” OR “compliance drug” OR “Patient Dropouts” OR “Treatment Adherence and Compliance” OR “Medication Adherence”)) AND (allchild [Filter]). The search was last updated on September 22, 2024, yielding 66 results. Few studies have been identified that evaluate adherence to TBI treatment in children through complex interventions. The majority of these studies were conducted in high-income countries, focused on adults, and assessed only specific interventions such as changes in service providers, integration of services, utilization of non-professional health workers to support treatment administration, and incentives. The findings regarding treatment adherence are inconsistent and vary depending on the methodology, interventions, and context.

Added value of this study

This study provides evidence of benefit in adherence to treatment for TBI in children through a multicomponent comprehensive care strategy (multidisciplinary assessment, education, four months rifampicin, transportation incentives, and food assistance packages).

Implications of all the available evidence

The existing body of evidence, together with the data generated locally from this research, should serve as a catalyst to modify the current guideline of the National TB Control Program in Colombia regarding the treatment of TBI in HIV negative children from a six-month isoniazid regimen to a shorter treatment. Future research should focus on conducting cost-effectiveness studies of the comprehensive care strategy prior to scaling up in a programmatic setting.

Introduction

Tuberculosis (TB) in childhood is identified as a public health problem, particularly in low- and middle-income countries.[1] The World Health Organization (WHO) estimated 1·3 million TB cases and 166,000 deaths in children under the age of 15 years during 2023.[2] In the natural history of the disease, from the clinical perspective, two stages are recognized: TB infection (TBI) and active TB. TBI is a state of persistent immune response to *Mycobacterium tuberculosis* antigen stimulation without evidence of clinically active TB.[3]

It is estimated that one quarter of the world’s population has TBI,[4] and of these, 5%–10% develop active TB in their lifetime.[1] In particular, half of the children living in close contact with bacteriologically confirmed pulmonary TB patients are at risk of developing TBI, and of these, 8·5% progress to disease, the majority in the first three to nine months after infection. Despite the recognised risk, not all children who require treatment for TBI initiate or complete it in the context of the contact study in epidemiological field visits.[1,5]

The goal of treatment for TBI is to prevent progression to active TB. Traditionally, TBI treatment has relied on daily isoniazid for 6–12 months.[6] However, recent WHO guidelines recommend short treatment regimens as an alternative approach, which may lead to higher treatment completion rates.[5] Studies indicate that short regimens for TBI in children are as safe and effective as isoniazid monotherapy.[7,8] Despite this, the recommendation since 2020 for the treatment of TBI in Colombia is daily isoniazid for six months in children without human immunodeficiency virus (HIV) infection.[9]

Improving adherence to TBI treatment in the paediatric population remains challenging despite the effectiveness of shorter regimens.[10] Adherence is influenced by structural factors related to community, healthcare system, household, and individual levels, necessitating comprehensive interventions.[11] In addition to the implementation of shorter treatment cycles, approaches to improve adherence have focused on the development of specific programs or strategies.[10] The latter includes treatment delivery strategies, home visits

by nurses, incentives, integration of health services, child-directed rewards, educational interventions, among others.[10,12,13]

In Colombia, contact investigation for TB includes the identification of priority groups, including children under 5 years of age, for the search of TBI. If the child has no symptoms of TB, has a positive tuberculin skin test (TST), and a chest X-ray that does not suggest TB, preventive treatment is recommended.[9] Despite the efforts of TB control programs in contact tracing, adherence to treatment for TBI in children remains suboptimal, with greater impact during the COVID-19 pandemic. It is estimated that in 2019, 72% of children under five who were household contacts of confirmed TB patients received TBI treatment. This indicator dropped to 40% in 2020 and then rose slightly to 48% by 2023.[2]

Therefore, it is necessary to propose an intervention strategy for the comprehensive care of children who are contacts of patients with pulmonary TB. Such a strategy would enable the rapid identification of children with active TB and ensure timely treatment for TBI.[5] This study aimed to evaluate the effect of a comprehensive care strategy (CCS) on adherence to TBI treatment in children under five who are household contacts of pulmonary TB patients, compared to the standard of care (SOC) in Colombia.

Methods

Study design

A prospective cohort study with a historical control group was performed (Fig. 1S, Supplementary material). More information on the design is reported in the study protocol published in a peer-reviewed journal.[14] This study is registered with ClinicalTrials.gov, number NCT04331262.

This study is part of a research program for the care of children contacts of patients with pulmonary TB funded by the Colombian Ministry of Science, Technology and Innovation (Minciencias). The intervention group was evaluated in this study, while the historical control group came from a previous prospective cohort that evaluated the effectiveness of isoniazid treatment for TBI, in the cities from Medellín, Bello, and Itagüí (Colombia). These cities in the sub-region of the Aburra Valley are characterized by a high incidence of TB.[15]

Study population and participants

Both groups shared identical population and selection criteria. The population consisted of children under five years of age who were household contacts of patients with bacteriologically confirmed pulmonary TB residing in Medellín, Bello, and Itagüí (Colombia), notified to the surveillance system during 2015–2016 (control group) and 2021–2022 (intervention group), to whom TBI treatment was prescribed.

Asymptomatic children, without clinical signs of active TB at initial evaluation, with normal chest X-ray, and TST ≥5 mm or a positive interferon gamma release assay (IGRA) were included. In addition, children with recent exposure to pulmonary TB (<8 weeks), negative TST or IGRA, and no evidence of active TB (immune window period) who had started preventive treatment were included. The assessment of test conversion was performed two months after the last exposure.

Participants with a history of liver disease, severe asthma, contraindication to rifampicin, contraindication to perform induced sputum, children with symptoms, or signs of active TB whose disease have not been ruled out, and those with plans to travel outside the study coverage area, were excluded.

Comprehensive care strategy

Between July 2021 and May 2022, patients in the intervention group were enrolled to receive a 12-month CCS (last follow-up in June 2023). This strategy included eight clinical evaluations (15 days after starting the strategy, every month for 5 months, and at the 8th and 12th month of recruitment) by a nursing assistant, general practitioner or paediatrician; assessments by a multidisciplinary team (social worker, nutritionist, and psychologist); provision of oral rifampicin suspension (10–20 mg/kg/day), self-administered for four months; transportation incentives; food assistance; and ongoing TB education. This strategy was provided at a scientific research center of reference in the immunological and microbiological diagnosis of TB in the country: *Corporación para Investigaciones Biológicas* (CIB).

The transportation incentive was an economic stipend of approximately US$5 per round trip on public transportation to attend each project activity. The food assistance included a basic monthly family food basket for four months, based on the recommendations of Antioquia's Ten-Year Food and Nutritional Security Plan.[16] The basic basket was designed by a nutritionist and reviewed by two experts (Table 1S, Supplementary material). To support education, leaflets on the TST process, brochures on TBI and TB, and material with nutritional recommendations were designed. These were provided by the nursing assistant and the nutritionist. In all evaluations, healthcare professionals provided information to improve adherence to treatment.

In addition, the children underwent TST and/or IGRA (QuantiFERON®-TB Gold Plus) at the initial evaluation. However, due to technical difficulties, it was not possible to perform both tests on all children. To rule out active TB, two blinded, independent radiologists interpreted the chest X-rays of each child using a standardised reading report.[17] Two induced sputum and two gastric aspirate samples were obtained for smear analysis, culture in solid and liquid medium, and Xpert® MTB/RIF Ultra in children with findings suggestive of active TB.

Standard of care

The control group corresponded to a prospective cohort of children under five years of age who lived with patients with pulmonary TB, recruited between January 2015 and May 2016, and followed for 24 months (last follow-up in December 2018). Participants received the standard care protocol according to national TB program regulations, with a schedule of oral isoniazid at 7–15 mg/kg/day for nine months (according to the guidelines of the TB control program of the time), provided by a health care institution designated by the health system. Clinical follow-up was conducted at three, six, 12 and 24 months, and telephone follow-up at one, five, nine and 18 months.[15]

Additionally, the study covered diagnostic procedures. TST and/or IGRA (QuantiFERON® -TB Gold) tests were performed, but it was not possible to perform both tests in all children due to technical difficulties. The standardized chest X-ray reading report to rule out active TB was performed by two blinded, independent radiologists.[17,18] If active TB was suspected, induced sputum and gastric aspirates were collected for smear microscopy, Xpert® MTB/RIF and culture. A financial incentive of approximately US$5 per round trip by public transportation was offered to attend diagnostic tests, but not for follow-up visits. Participants received a brochure on TBI and TB.

Outcomes

The primary endpoint was adherence to treatment for TBI, defined as the proportion of children who completed 100% treatment for TBI by the end of the prescription period (four months in the SOC group and nine months in CCS). Children with recent TB exposure (<8 weeks), negative TST or IGRA, and no signs of active TB who started treatment underwent TST two months after. If the TST remained negative (<5 mm), treatment was stopped based on clinical evaluation and they were considered adherent; otherwise, treatment was continued for four months (CCS group) or nine months (SOC group). TBI treatment was provided by the CIB in the intervention group and by the local TB control program in the historical control group. Doses received for TBI treatment were measured by self-report and sometimes by pill counts in the SOC group (month 3, 6, 12, and 24), and by bottle counts consumed in the CCS group (month 1–4).

Adverse events (AEs), as a secondary outcome, were defined as the proportion of children who presented any treatment-related AEs. AEs were assessed at follow-up visits using the Common Terminology Criteria for Adverse Events v4.0 (CTCAE), and then categorized as gastrointestinal, neurological, dermatological allergic, and hepatic. The severity of adverse events was classified as mild (mild symptoms, intervention not indicated, did not require discontinuation of TBI treatment), moderate (local or non-invasive intervention, required discontinuation of treatment), severe (medically significant but not immediately life-threatening, required hospital management), Life-threatening consequences, or death related to AEs.

Variables

The study collected sociodemographic variables (age, sex, ethnicity, municipality of residence, socioeconomic stratum, health insurance, schooling, and migration of the family), and degree of exposure (vaccination, relationship and proximity to the index case). In addition, the results of TST, IGRA, doses of treatment received for TBI, temporary or definitive treatment discontinuations and their causes were assessed.

Sex assigned at birth was obtained from the identification document and ethnicity through self-reporting. Socioeconomic stratum was defined based on a classification of residential characteristics that allows differential charging for public services and was categorized as low (strata 1–2) and medium (strata 3–5) resources. Schooling was defined as school attendance at kindergarten or preschool at initial evaluation. We inquired about the presence of migration of the child's family nucleus, defined as the geographical movement of the family from one state to another or internationally, voluntary or forced.

Bacille Calmette-Guerin (BCG) vaccination status was defined if documented by vaccination card or by visualization of the scar in the scapular area. The degree of relationship to the index case was grouped into first degree (parents and children), second degree (grandparents, grandchildren, and siblings), third degree (aunts, uncles, nieces, nephews, great-nieces, great-nephews, and great-grandparents), and fourth degree or more (cousins or other relatives). Temporary discontinuation was defined as a temporary interruption of treatment for TBI greater than two weeks. Definitive discontinuation was defined as discontinuation of treatment for TBI and restart ≥90 days, or discontinuation without restart.

Sample size

To estimate the sample size for the CCS group, it was noted that 250–300 children are annually evaluated as home contacts of pulmonary TB patients in Medellín and the Metropolitan Area, with 73·5% developing TBI.[15] A treatment adherence ratio of 59% in the SOC group (considering the lower limit of the confidence interval for 80% adherence) and a 21% expected difference in adherence between groups were considered,[15] with 95% confidence and 80% power. Assuming a 10% follow-up loss, the sample size was estimated at 85 children using incidental sampling and a test of differences in proportions between two independent samples in Epidat 4.2.

Statistical analysis

The sociodemographic, exposure, immune response, and treatment delivery characteristics of the participants were described in each group by univariate analysis. In addition, differences in these characteristics between the SOC group and CCS were compared using the Mann–Whitney U test, Fisher's Exact test, and Pearson's Chi-square test, considering a significance level of $p < 0{\cdot}05$. A similar analysis was performed for the immune response stratified by age, and on the characteristics of the index cases.

The proportion of TST, and TST and/or IGRA positivity was estimated with their respective 95% confidence intervals (95% CI). AEs and their severity in each group were described. The proportion of adherence to treatment for TBI in each group and its difference with 95% CI were also reported.

Missing values for the variables ranged from 12% to 0·3%. These missing values were imputed using multiple imputation by chained equations, assuming random missing data. This process generated 10 data sets and 20 iterations, which were used in the multivariate analysis by applying Rubin's rules. To evaluate the effect of the CCS on adherence to treatment for TBI, we used a generalized estimating equations model with Poisson distribution, log link function, exchangeable correlation structure and robust standard errors. This mixed model was used considering the correlation of children between the strata of the index case. Confounding variables were identified (insurance, age, schooling, ethnicity, migration, municipality, sex, TST ≥5 mm and/or IGRA positive at baseline) using a directed acyclic graph (Fig. 2S, Supplementary material). Crude and adjusted relative risks (RR) with 95% CI were reported.

Post hoc sensitivity analyses assessed the robustness of the primary outcome, considering adherence scenarios of ≥90% and ≥80% of the planned dose,[8,19] and in participants with positive baseline TST and/or IGRA. Statistical analyses were performed with R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and the following packages were implemented: mice, miceadds, gee, geepack.

Ethics approval

The study was approved by the Research Ethics Committee of *Corporación para Investigaciones Biológicas*

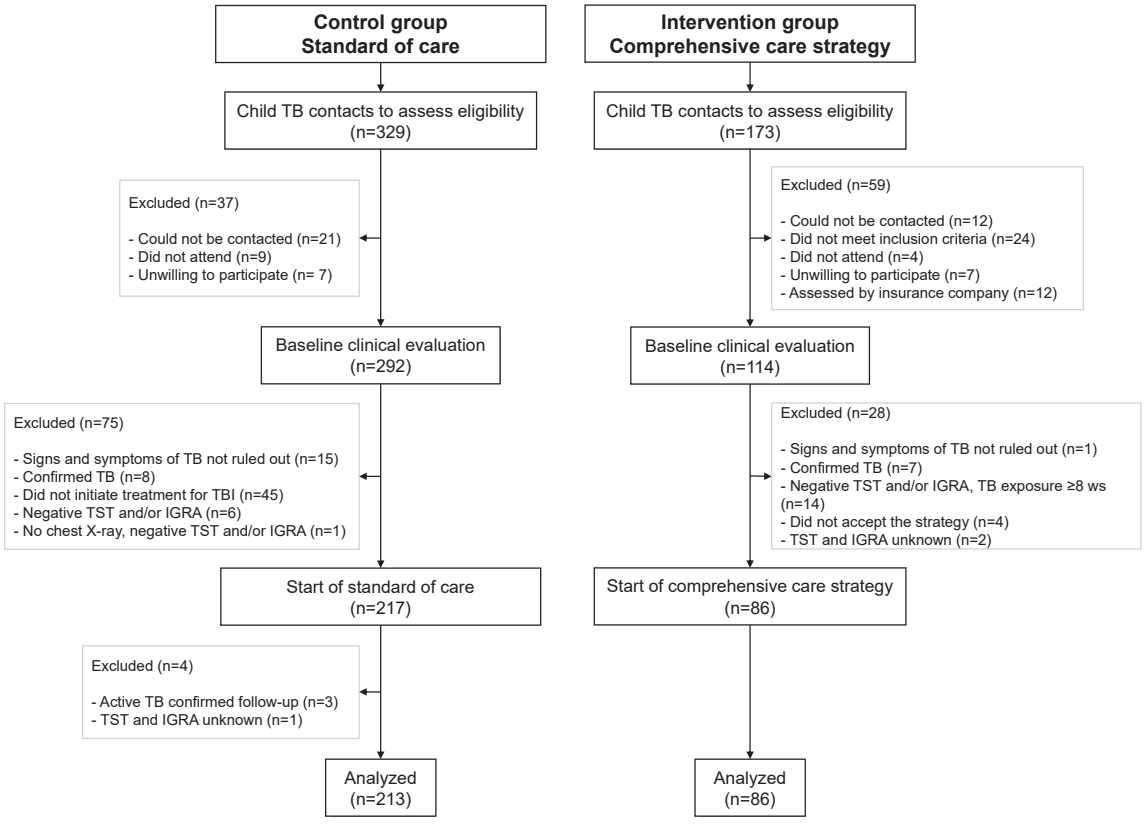

Fig. 1: Flow diagram of the study participants. TB, tuberculosis; TBI, tuberculosis infection; TST, tuberculin skin test; IGRA, interferon gamma release assay; wk, week.

Characteristics	Standard of care	Comprehensive care strategy	p-value
	n = 213 (%)	n = 86 (%)	
Age (months)			0·41[a]
Median (IQR)	33 (17–45)	33 (16–49)	
Range	0–61	1–59	
Age grouped			0·73[b]
<12 months	35 (16·4)	12 (14·0)	
≥12 months	178 (83·6)	74 (86·0)	
Sex			0·37[b]
Male	125 (58·7)	45 (52·3)	
Female	88 (41·3)	41 (47·7)	
Ethnicity			0·34[b]
Other	180 (95·2)	83 (96·5)	
Indigenous	5 (2·7)	0 (0·0)	
Afrodescendant	4 (2·1)	3 (3·5)	
Unknown	24	0	
Municipality of residence			0·036[b]
Medellín	198 (93·0)	80 (93·0)	
Bello	9 (4·2)	0 (0·0)	
Itagüí	6 (2·8)	6 (7·0)	
Socioeconomic stratum			0·86[b]
Low	180 (84·5)	72 (83·7)	
Medium	33 (15·5)	14 (16·3)	
Health insurance			0·06[c]
Contributive	99 (46·9)	36 (41·9)	
Subsidized	95 (45·0)	35 (40·7)	
Another	17 (8·1)	15 (17·4)	
Unknown	2	0	
Schooling			0·003[b]
No	91 (42·7)	53 (61·6)	
Yes	122 (57·3)	33 (38·4)	
Family migration			0·44[b]
No	148 (79·1)	64 (74·4)	
Yes	39 (20·9)	22 (25·6)	
Unknown	26	0	
Evidence of BCG vaccination			0·72[b]
No	6 (2·8)	3 (3·5)	
Yes	207 (97·2)	83 (96·5)	
Relationship index case			0·26[b]
First grade	67 (31·5)	31 (36·1)	
Second grade	60 (28·2)	19 (22·1)	
Third grade	68 (31·8)	23 (26·7)	
Fourth grade or higher	11 (5·2)	6 (7·0)	
None	7 (3·3)	7 (8·1)	
Proximity to index case			0·44[c]
Sleeps in the same bed	44 (20·7)	21 (24·4)	
Sleeps in the same room	26 (12·2)	6 (7·0)	
Lives in the same house	89 (41·8)	33 (38·4)	
Does not live in the same house	54 (25·3)	26 (30·2)	

IQR, interquartile range; BCG, bacillus Calmette and Guérin. [a]Mann–Whitney U test. [b]Fisher's Exact Test. [c]Pearson's chi-square test.

Table 1: **Sociodemographic and exposure characteristics of child contacts of persons with tuberculosis in the standard of care group and comprehensive care strategy.**

(June 10, 2019) and the *Universidad Pontificia Bolivariana* (Registration No. 24 of November 30, 2020). Written assent and informed consent were obtained from all participants.

Role of the funding source

This study was financially supported by the Colombian Ministry of Science, Technology and Innovation (Minciencias), grant numbers 902-2019 and 088-2021. The funding entity was not involved in the drafting of the manuscript or in the decision to submit it for publication. The authors did not receive payments from the pharmaceutical industry or other entities for writing the manuscript. The corresponding author did not prevent the other authors from accessing the study data and they accept responsibility for submitting them for publication.

Results

In total, 329 children were reported to evaluate eligibility criteria in the control group during January 2015 to May 2016. Of these, 292 children underwent initial clinical evaluation, and 217 started the SOC. However, four participants were excluded, for a total of 213 children included in the analysis. On the other hand, 173 children were referred for eligibility assessment in the intervention group during July 2021 to May 2022. Baseline clinical evaluation of this group was performed on 114 participants, of which 28 were excluded, and the CCS was received by 86 participants (Fig. 1).

Twenty percent (61/299) of the participants' records had some missing data. The variables with the most missing data were IGRA results (36/299), family migration (26/299), ethnicity (24/299), type and severity of AEs (7/299), health insurance regimen (2/299), and temporary discontinuation of treatment (2/299). There was no missing data on the primary outcome. Ethnicity, family migration, and health insurance regime were the imputed variables included in the final model. Evaluation details for the multiple imputation model are available in Supplementary material, section three.

The median age was 33 months for both groups and the proportion of male participants was 58·7% (125/213) in the SOC group and 52·3% (45/86) in the CCS group. Most children in both groups resided in Medellín and came from a low socioeconomic stratum. Significant differences between the groups were observed in the municipality of residence (p-value = 0·036) and schooling (p-value = 0·003) (Table 1). Children in the SOC group lived with 168 index cases, of whom 46 (27%) lived in overcrowded conditions. In contrast, the children who received the CCS lived with 67 index cases, 25 of whom (38%) lived in overcrowded conditions (Table 2S, Supplementary material).

Regarding the immune response, no significant differences were identified between groups, independent of the age group (Tables 3S and 4S, Supplementary material). The proportion of TST positivity ≥5 mm was 75·8% (n = 160; 95% CI 69·4%; 81·3%) for the SOC group, and 66·3% (n = 57; 95% CI 55·2%; 75·9%) for the CCS group. When combining TST and/or IGRA test

results the proportion of positivity increased to 78·4% (n = 167; 95% CI 72·1%; 83·6%) in the SOC group and 68·6% (n = 59; 95% CI 57·6%; 77·9%) in the CCS group.

Table 2 describes the doses received and causes of treatment discontinuation for TBI in both groups. Temporary discontinuation of treatment in the SOC group, which received isoniazid, was higher than in the CCS group, who received rifampicin (21·2% Vs 2·3%, p-value<0·0001). The same occurred with definitive discontinuation of treatment (40·4% Vs. 20·3%, p-value = 0·005).

In children who received isoniazid (SOC), 24 (11·3%) AEs were identified, of which 19 (79·2%) were gastrointestinal (11 mild, eight moderate), three (12·5%) were allergic-dermatological (two mild, one moderate), and two (8·3%) were neurological (one mild, one severe). On the other hand, in children who received rifampicin (CCS), three (3·5%) AEs were identified, two gastrointestinal (one mild, one moderate) and one mild skin allergy. Gastrointestinal AEs in the isoniazid group included: vomiting (n = 10), abdominal pain (n = 4), loss of appetite (n = 2), diarrhoea (n = 1), constipation (n = 1), and nausea (n = 1); while in the group receiving rifampicin: abdominal pain (n = 1), and vomiting (n = 1). Neurological AEs included one case of mild headache and one case of seizures requiring hospitalization. The aetiology of the latter event and its relationship to treatment could not be conclusively determined (Table 3).

Adherence to treatment for TBI in children who received the SOC (including isoniazid) was 40·8% (n = 86; 95% CI 34%; 48%) while in children who received the CCS (including rifampicin) it was 76·7% (n = 66; 95% CI 66%; 85%). The absolute percentage-point difference was 36% (95% CI 48%; 24%) in favour of the CCS (Table 2; Table 5S, Supplementary material).

The unadjusted model showed that the CCS resulted in higher treatment adherence for TBI in children close contacts of pulmonary TB patients compared to the SOC (RR 1·88; 95% CI 1·53; 2·32). These findings persisted even after adjusting for age, sex, ethnicity, municipality of residence, insurance, schooling, family migration, and TST and/or IGRA test (RR 1·87; 95% CI 1·52; 2·31) (Table 4). Sensitivity analysis confirmed that the adjusted effect was robust in terms of the direction of the effect and the statistical significance (Table 6S, Supplementary material).

Characteristics	Standard of care	Comprehensive care strategy	p-value
	n = 213 (%)	n = 86 (%)	
Total dose received			<0·0001[a]
Median (IQR)	240 (154–275)	120 (87–120)	
Range	2–379	0–128	
Proportion of dose received (%)			0·64[a]
Median (IQR)	89 (57–102)	100 (73–100)	
Range	1–140	0–107	
Adherence to treatment			<0·0001[b]
No	126 (59·2)	20 (23·3)	
Yes	87 (40·8)	66 (76·7)	
Temporary discontinuation			<0·0001[b]
No	167 (78·8)	84 (97·7)	
Yes	45 (21·2)	2 (2·3)	
Unknown	1	0	
Cause of temporary discontinuation			–
Family matters[c]	15	1	
Administrative[d]	13	0	
Caregiver's decision	5	1	
TB control program recommendation[e]	5	0	
Medical condition other than adverse event	4	0	
Adverse event	2	0	
Forced displacement	1	0	
Definitive discontinuation			0·005[b]
No	127 (59·6)	66 (76·7)	
Yes	86 (40·4)	20 (23·3)	
Cause of definitive discontinuation			–
TB control program recommendation[e]	21	0	
Caregiver's decision	19	4	
Family matters[c]	12	0	
Negative TST control	11	15	
Adverse event	9	1	
Administrative[d]	6	0	
Forced displacement	3	0	
Resistance index case	3	0	
Unknown	2	0	

IQR, interquartile range; TST, tuberculin skin test. [a]Mann–Whitney U test. [b]Fisher's Exact Test. [c]Situations or events related to the family that were prioritized and that prevented the continuation of treatment (for example: change of address, vacations, economic commitments, etc.). [d]Bureaucratic processes or formal procedures required by institutions to continue or complete treatment (for example: documentation requirements, authorization processes by insurers or health care providers, etc.). [e]The TB control programme health staff inappropriately recommended discontinuing treatment, but the children should have continued it.

Table 2: **Characteristics of treatment administration for tuberculosis infection in children close contact with patients with pulmonary tuberculosis in the standard of care group (isoniazid) and comprehensive care strategy (rifampicin).**

Discussion

The CCS evaluated in this study was associated with greater adherence to treatment for TBI, compared to the SOC, in child contacts of patients with bacteriologically confirmed pulmonary. In addition, the incidence and severity of AEs were lower in children who received the CCS compared to the SOC group, showing a good safety profile.

Most interventions to enhance adherence to TBI treatment have emphasized shorter regimens, while others have targeted specific programs or strategies.[10] A multicentre randomized clinical trial in children under 18 years with TBI reported treatment completion of 76·4% with the nine-month isoniazid regimen compared to 85·3% with the four-month rifampicin regimen.[8] In Brazil, an observational follow-up study of children and adolescents with TBI treated with isoniazid for nine months showed a treatment adherence rate of 63·5% (95% CI 54·7; 72·3).[20] In our study, adherence to

Characteristics	Standard of care	Comprehensive care strategy
	n = 24 (%)	n = 3 (%)
Type of adverse event		
Allergic dermatological	3 (12·5)	1 (33·3)
Gastrointestinal	19 (79·2)	2 (66·7)
Neurological	2 (8·3)	0 (0·0)
Grade of adverse event		
Mild	14 (58·3)	2 (66·7)
Moderate	9 (37·5)	1 (33·3)
Severe	1 (4·2)	0 (0·0)

Table 3: **Adverse events of treatment for tuberculosis infection in children close contact with patients with pulmonary tuberculosis in the standard of care group (isoniazid) and comprehensive care strategy (rifampicin).**

treatment was lower in both groups, however, comparability with these studies is limited due to differences in study design, components of the interventions and outcome measures.

Evidence supporting specific strategies to enhance adherence to TBI treatment in children is scarce. Strategies such as service provider switching, integration of TB services with community care, or the use of lay health workers to support therapy delivery have been inconclusive. On the other hand, integration of TB and HIV services, monthly treatment follow-up by home nurses, or conditional cash transfers could favor adherence to treatment. Structured behavioral interventions based on rewards, such as the gift of a toy for completing treatment, showed greater chances of adherence to preventive therapy.[10,21–24]

The results of this study should be interpreted considering the total effect of the intervention on adherence to treatment. It was not the purpose of this study to estimate the partial effects of the strategy components; however, the shortened treatment schedule, transport incentive, and food assistance may have had more influence on treatment adherence in the intervention group. Still, considering a programmatic approach and the complexity of TBI care, as well as the determinants of treatment adherence, the challenges faced by this population through multilevel interventions were addressed.[11,25] Consequently, estimating the total effect for these types of strategies is useful for public health.

Models	RR	95% CI	p-value
Not adjusted			
Comprehensive care strategy Vs Standard of care	1·88	1·53; 2·32	<0·0001
Adjusted[a]			
Comprehensive care strategy Vs Standard of care	1·87	1·52; 2·31	<0·0001

RR: relative risk; CI: confidence interval. [a]Model adjusted for age, sex, ethnicity, municipality of residence, insurance, schooling, family migration and TST and/or IGRA test.

Table 4: **Effect of the comprehensive care strategy on adherence to treatment for tuberculosis infection.**

Regarding the safety of the therapeutic regimens evaluated, a randomized clinical trial involving children under 18 years indicated that the safety profiles of isoniazid and rifampicin were similar.[8] In contrast, Cruz et al.[26] found in an observational study that non-serious AEs occurred more frequently with isoniazid than rifampicin. This discrepancy could be due to the longer duration of the isoniazid regimen, which allows for more visits to evaluate AEs.

Among the limitations of the study are those underlying the design. Being a non-randomized study, it is not possible to assume balanced groups, which differ only in strategy. The groups were not concurrent, therefore, the repercussions generated by the COVID-19 pandemic and the changes in the technological development of the IGRA could introduce time trend biases. The way of measuring treatment doses received for TBI in the two groups was different and could also introduce information biases.

Despite this, a prospective cohort study with a historical control group are crucial for assessing the causal effects of health interventions in real-world settings, ensuring robust external validity, and facilitating the transition from evidence to implementation.[27] The design ensured all children received the CCS, which includes diagnostic tests, transportation incentives, and food assistance, to uphold the bioethical principle of justice.[28] Most studies on TBI treatment adherence are retrospective and single-centered.[10] To reduce bias, the SOC group was a prospective cohort with similar selection criteria, variables, and data collection methods to the CCS group.[14,15] Confounding was controlled through multivariate analysis, and showed a consistent sensitivity analysis.

The strengths of the study include the use of multiple imputation techniques and the reporting of pooled parameters in the final models. On the other hand, the results show an apparent comparability of the groups in terms of the observed characteristics. Another aspect of value in this study was the evaluation of a Comprehensive care strategy that involved several interventions such as the provision of rifampicin for four months, interdisciplinary assessment by healthcare professionals, active follow-up, food and transportation incentives, and patient-centred education. Finally, it should be noted that the study was carried out in three cities in the Aburra Valley sub-region of Colombia, which could support the generalization of the findings.

In Colombia, it would be of significant value to describe and implement a multi-component strategy for the diagnosis, treatment, and follow-up of children with TBI. However, the primary challenge lies in translating the strategy from a research context with guaranteed financial resources to the context of the TB control program. Several elements that could potentially

overcome these challenges include: involving various stakeholders (the Ministry of Health, health secretariats, insurers, and health providers), aligning conditional transfers and food packages provided by social assistance programs with the strategy, and updating guidelines on the use of short treatment regimens for TBI.

This study adds to the limited evidence available on the benefits of a CCS that includes multiple components in the context of low- and middle-income countries.[29,30] Cost-effectiveness studies of the CCS prior to scaling up in a programmatic setting are recommended as next steps. In conclusion, the CCS is superior to SOC in increasing the proportion of adherence to treatment for TBI in children who are close contacts of patients with confirmed pulmonary TB.

Contributors

IRM contributed to data analysis, writing, and critical revision of the manuscript. DBB contributed to the design, fundraising, conduct of the study, data interpretation, and critical review of the manuscript. AVRG, CPBA, and LMCA contributed to proposal development, expert clinical assessment, and thematic advice. DM contributed to the design, training, data analysis, meetings with health authorities, critical review of the manuscript. FNMZ and LAPS contributed to the design, management with health authorities, socialization of the project, support in the recruitment of participating children, and socialization of results. JCAA and TR contributed to the design, conduct of the study, and critical review of the manuscript. YPT, LMAG, and NPD contributed to the conduct of the study, and critical revision of the manuscript, MPAM and JR contributed to the design, fundraising, and critical revision of the manuscript. IRM, DBB, and DM accessed and verified the data in this study. All authors read and approved the final manuscript.

Data sharing statement

The study protocol is available at ClinicalTrials.gov (NCT04331262). Anonymized participant databases, a data dictionary, and statistical analysis plan will be available upon reasonable request to the corresponding author following publication.

AI disclaimer

Artificial intelligence assistance was used to improve the style and language of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgements

This study was financially supported by the Colombian Ministry of Science, Technology and Innovation (Minciencias), grant numbers 902-2019 and 088-2021. The funding entity was not involved in the drafting of the manuscript or in the decision to submit it for publication.

Protocol version: Publication date: August 28, 2023, protocol amendment number: 04, changes made to recruitment status, study status, location, and design.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2025.101094.

References

1 Harries AD, Kumar AMV, Satyanarayana S, Takarinda KC, Timire C, Dlodlo RA. Treatment for latent tuberculosis infection in low- and middle-income countries: progress and challenges with implementation and scale-up. *Expert Rev Respir Med*. 2020;14:195–208.
2 World Health Organization. *Global tuberculosis report 2024*. Geneva: World Health Organization; 2024.
3 Shah M, Dorman SE. Latent tuberculosis infection. *N Engl J Med*. 2021;385:2271–2280.
4 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a Re-estimation using mathematical modelling. *PLoS Med*. 2016;13:e1002152.
5 World Health Organization, WHO consolidated guidelines on tuberculosis Module 5: management of tuberculosis in children and adolescents. https://www.who.int/publications/i/item/9789240046764; 2022. Accessed October 5, 2024.
6 Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. *N Engl J Med*. 2015;372:2127–2135.
7 Santos JM, Fachi MM, Beraldi-Magalhães F, et al. Systematic review with network meta-analysis on the treatments for latent tuberculosis infection in children and adolescents. *J Infect Chemother*. 2022;28:1645–1653.
8 Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med*. 2018;379:454–463.
9 Ministerio de Salud y Protección Social de Colombia. *Resolución 227 de 2020 por medio de la cual se adoptan los lineamientos técnicos y operativos del programa nacional de prevención y control de la tuberculosis y se dictan otras disposiciones*. Bogotá: El Ministro de Salud Y Proteccion Social (E); 2020:1–175.
10 Campbell JI, Sandora TJ, Haberer JE. A scoping review of paediatric latent tuberculosis infection care cascades: initial steps are lacking. *BMJ Glob Health*. 2021;6:e004836.
11 Leddy AM, Jaganath D, Triasih R, et al. Social determinants of adherence to treatment for tuberculosis infection and disease among children, adolescents, and young adults: a narrative review. *J Pediatric Infect Dis Soc*. 2022;11:S79–S84.
12 M'Imunya JM, Kredo T, Volmink J. Patient education and counselling for promoting adherence to treatment for tuberculosis. *Cochrane Database Syst Rev*. 2012. https://doi.org/10.1002/14651858.CD006591.pub2.
13 Lutge EE, Wiysonge CS, Knight SE, Sinclair D, Volmink J. Incentives and enablers to improve adherence in tuberculosis. *Cochrane Database Syst Rev*. 2015;2015. https://doi.org/10.1002/14651858.CD007952.pub3.
14 Benjumea-Bedoya D, Villegas Arbeláez E, Martínez-Peñaloza D, et al. Implementation of an integrated care strategy for child contacts of tuberculosis patients: a quasi-experimental study protocol. *BMC Pediatr*. 2023;23:28.
15 Benjumea BD. *Efectividad del tratamiento para infección latente por tuberculosis en niños menores de cinco años convivientes de pacientes con tuberculosis pulmonar de Medellín. Bello e Itagüí (Doctoral dissertation, Tesis Doctorado en Salud Pública: Universidad de Antioquia)*. 2018.
16 Carreño Aguirre C, Córdoba Torres LG, Giraldo López PA, et al. Plan Docenal de Seguridad Alimentaria y Nutricional 2020-2031. https://antioquia.gov.co/index.php/pdsan; 2020. Accessed October 5, 2024.
17 Andronikou S, McHugh K, Abdurahman N, et al. Paediatric radiology seen from Africa. Part I: providing diagnostic imaging to a young population. *Pediatr Radiol*. 2011;41:811–825.
18 Lozano-Acosta MM, Rubiano-Arenas MA, Cadavid LM, et al. Reproducibility of a protocol for standardized reading of chest X-rays of children household contact of patients with tuberculosis. *BMC Pediatr*. 2022;22:307.
19 Rangaka MX, Hamada Y, Duong T, et al. Evaluating the effect of short-course rifapentine-based regimens with or without enhanced behaviour-targeted treatment support on adherence and completion of treatment for latent tuberculosis infection among adults in the UK (RID-TB: treat): protocol for an open-label, multicentre, randomised controlled trial. *BMJ Open*. 2022;12:e057717.
20 Silva APB, Hill P, Belo MTCT, Rabelo SG, Menzies D, Trajman A. Non-completion of latent tuberculous infection treatment among children in Rio de Janeiro State, Brazil. *Int J Tuberc Lung Dis*. 2016;20:479–486.
21 Cass AD, Talavera GA, Gresham LS, Moser KS, Joy W. Structured behavioral intervention to increase children's adherence to treatment for latent tuberculosis infection. *Int J Tuberc Lung Dis*. 2005;9:415–420.
22 Adams LV, Talbot EA, Odato K, Blunt H, Steingart KR. Interventions to improve delivery of isoniazid preventive therapy: an overview of systematic reviews. *BMC Infect Dis*. 2014;14:281.

23 Chang AH, Polesky A, Bhatia G. House calls by community health workers and public health nurses to improve adherence to isoniazid monotherapy for latent tuberculosis infection: a retrospective study. *BMC Public Health*. 2013;13:894.

24 Wingfield T, Tovar MA, Huff D, et al. A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. *Bull World Health Organ*. 2017;95:270–280.

25 Adusumelli Y, Tabatneck M, Sherman S, et al. Pediatric tuberculosis infection care facilitators and barriers: a qualitative study. *Pediatrics*. 2024;153. https://doi.org/10.1542/peds.2023-063949.

26 Cruz AT, Starke JR. Safety and completion of a 4-month course of rifampicin for latent tuberculous infection in children. *Int J Tuberc Lung Dis*. 2014;18:1057–1061.

27 Bärnighausen T, Tugwell P, Røttingen JA, et al. Quasi-experimental study designs series—paper 4: uses and value. *J Clin Epidemiol*. 2017;89:21–29.

28 Ghadessi M, Tang R, Zhou J, et al. A roadmap to using historical controls in clinical trials – by drug information association adaptive design scientific working group (DIA-ADSWG). *Orphanet J Rare Dis*. 2020;15:69.

29 Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents. *JAMA Pediatr*. 2015;169:247.

30 Bamrah S, Brostrom R, Dorina F, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. *Int J Tuberc Lung Dis*. 2014;18:912–918.