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ORIGINAL ARTICLE

Risk of infection and disease progression in children exposed to tuberculosis at home, Colombia

Riesgo de infección y progresión de la enfermedad en niños expuestos a tuberculosis en el hogar, Colombia

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Abstract

Aim:

To assess the risk of tuberculosis (infection and disease) in children less than 15 years' old who are household contacts of pulmonary tubercul03osis patients in three Colombian cities (Medellín, Cali, and Popayán).

Methods:

A cohort of 1,040 children household contacts of 380 adults with smear-positive pulmonary tuberculosis was followed up for 24 months. Study period 2005-2009.

Results:

Tuberculin skin test was positive (≥10 mm) in 43.7% (95% CI: 39.2-48.2). Tuberculin skin test positivity was associated with age 10-14 years (Prevalence Ratio -PR= 1.43, 95% CI: 1.1-1.9), having a BCG vaccine scar (PR= 1.52, 95% CI: 1.1-2.1), underweight, closer proximity to the index case and exposure time >3 months. The annual risk of infection (tuberculin skin test induration increase of 6 mm or more per year) was 17% (95% CI: 11.8-22.2) and was associated with a bacillary load of the adult index case (Relative Risk -RR= 2.12, 95% CI: 1.0-4.3). The incidence rate of active tuberculosis was 12.4 cases per 1,000 persons-year. Children <5 years without BCG vaccine scar had a greater risk of developing active disease (Hazard Ratio -HR= 6.00, 95% CI: 1.3-28.3) than those with scar (HR= 1.33, 95% CI: 0.5-3.4). The risk of developing active tuberculosis augmented along with the increase from initial tuberculin skin test (tuberculin skin test 5-9 mm HR= 8.55, 95% CI: 2.5-29.2; tuberculin skin test ≥10 mm HR= 8.16, 95% CI: 2.0-32.9).

Conclusions:

There is a need for prompt interruption of adult-to-children tuberculosis transmission within households. Conducting proper contact investigation and offering chemoprophylaxis to infected children could reduce tuberculosis transmission.

Valle.

Conflict of Interest:
None of the authors have conflicts of interest relevant to this article to disclose.

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RESUMEN

Objetivo:
Evaluar el riesgo de tuberculosis (infección y enfermedad) en niños menores de 15 años de edad convivientes de pacientes con tuberculosis pulmonar en tres ciudades colombianas (Medellín, Cali y Popayán).

Métodos:
Se siguió durante 24 meses una cohorte de 1,040 niños convivientes de 380 adultos con tuberculosis pulmonar bacilífera. Periodo de estudio 2005-2009.

Resultados:
La prueba de tuberculina fue positiva (≥10 mm) en el 43.7% (IC 95%: 39.2-48.2), y estuvo asociada con la edad de 10-14 años (Razón de Prevalencia-RP= 1.43, IC 95%: 1.1-1.9), tener cicatriz de la vacuna BCG (RP= 1.52, IC 95%: 1.1-2.1). El riesgo anual de infección (aumento de la induración en la prueba de tuberculina de 6 mm o más al año) fue 17% (IC 95%: 11.8-22.2), y estuvo asociado con mayor carga bacilar en el adulto con tuberculosis pulmonar (Riesgo Relativo-RR= 2.12, IC 95%: 1.0-4.3). La tasa de incidencia de tuberculosis activa fue de 12.4 casos por 1,000 años-persona de seguimiento. Los niños menores de 5 años sin cicatriz de vacuna BCG tuvieron un mayor riesgo de desarrollar tuberculosis activa (Razón de Peligro -HR= 6.00, IC 95%: 1.3-28.3), que quienes tenían cicatriz (HR= 1.33, IC 95%: 0.5-3.4). El riesgo de desarrollar tuberculosis activa aumentó conforme el aumento de la prueba de tuberculina inicial (prueba de tuberculina 5-9 mm HR= 8.55, IC 95%: 2.5-29.2; prueba de tuberculina ≥10 mm HR= 8.16, IC 95%: 2.0-32.9).

Conclusión:
Es necesario interrumpir rápidamente la transmisión de tuberculosis de adultos a niños en los hogares. Realizar investigaciones de contacto apropiadas y ofrecer quimioprofilaxis a los niños infectados podría reducir la transmisión de la tuberculosis.

Remark

1)Why was this study conducted?
Contact investigation is a key strategy in tuberculosis control programs. Children who are contacts of pulmonary tuberculosis cases have a higher risk of developing active tuberculosis. However, childhood tuberculosis is still a major public health issue, and there was not much population data from exposed children to tuberculosis in Colombia.

2) What were the most relevant results of the study?
Household tuberculosis exposed children have high annual risks of infection and disease development. BCG vaccination protection is reasserted for moderate prevalence conditions, especially for the youngest. Tuberculosis transmission chain is not being cut in time and this limits control efficacy.

3) What do these results contribute?
First study in Colombia that assessed risk of tuberculosis (infection and disease) among household contact children. Findings of present study allowed to prolong the follow-up time to household contacts seeking active disease, and promoting isoniazid preventive therapy in guidelines for children age <5 years in Colombia.

Introduction

Tuberculosis in children is considered a public health emergency that affects mainly low-income countries [1]. In these countries, it is estimated to represent 15% of reported tuberculosis cases [2-4]. The pathogenesis and epidemiology of childhood tuberculosis are still poorly understood, possibly because most of the actions in tuberculosis prevention, diagnostic, and therapeutic options are focused mainly on adults [1]. Further, there are surveillance gaps. However, since 2011 WHO estimates tuberculosis incidence for patients <15 years of age, accounting 1.01 million (10%) of the 10 million new tuberculosis cases reported worldwide in 2017, 234,000 of which died [5].

In Colombia, 16,000 new tuberculosis cases were estimated in 2017, 11.3% of which would be children [6]. However, only 12,439 cases were reported, 598 of which were <15 years old, and represented 4.8% of total reported cases [7].

Tracing contacts of patients with microbiologically confirmed tuberculosis is one of the main strategies to control this disease. It aims early identification of infected individuals in order to initiate preventive therapy, especially in those most at risk of developing active disease such as children <5 years old [4,8]. This strategy has proved to be cost-effective for the detection of new cases [9] when combined with the required access to diagnosis and treatment [10].

Children household contacts of adult tuberculosis patients who become infected but do not develop active childhood tuberculosis (primary tuberculosis), represent the main reservoir for tuberculosis transmission once reactivation occurs in adulthood (post-primary tuberculosis) [1]. In a given community, a decrease in the number of children with active tuberculosis is an indicator of transmission decrease because they usually get infected within the nuclear family [11].

Previous studies showed that among children (<15 years of age) in close contact with patients with pulmonary tuberculosis, the proportion of active tuberculosis cases can range from 6.0% to 8.0%, being higher in children <5 years. Also, the proportion of children with tuberculosis infection is estimated at 40.4% (95% CI: 38.7-42.2%) being lower in children <5 years [12].

This study, the first of its kind in Colombia, aimed to assess the risk of tuberculosis infection and disease in children <15 years old household contacts of adult patients with tuberculosis disease through a cohort study in three major Colombian cities.

Materials and Methods

Study design and setting

A cohort study of children household contacts of patients with pulmonary tuberculosis in three Colombian cities (Medellín's metropolitan area, Cali, and Popayán -including five small towns nearby-) was performed between 2005 and 2009. In this study were included the children household contacts of 382 adult index cases with smear-positive pulmonary tuberculosis recruited (275 from Medellín, 77 from Cali and 30 from Popayán).

Between 2005-2009 Medellín reported a tuberculosis incidence of 43.2-50.4 cases per 100,000 [13], in Cali was 46-43 cases per 100,000 [14] and in Popayán 24.5-12.4 [15,16] cases per 100,000. During 2005, characteristics of these cities included population size of 2,219,861 in Medellín, 2,075,380 in Cali, and 258,653 in Popayán; and an Unsatisfied Basic Necessities indicator of 12.42 in Medellín, 11.01 in Cali and 18.07 in Popayán [17]. The sample size was calculated assuming an estimated infection prevalence of 50%, an active tuberculosis incidence rate of 5%, confidence of 95%, power of 80% and over sampling of 25% to compensate for loss to follow-up. This resulted in a sample size of 2,816 household contacts of all ages.

Participants

A children household contact was defined as an individual who had spent time every week with an index case in the same household, for at least one month before the confirmation of the tuberculosis case. An index case was defined as the first tuberculosis case identified in each household, diagnosed with active pulmonary, smear-positive tuberculosis. (Adapted from CDC)[18].

Recruitment conditions for index cases and children household contacts were the same for all cities, as previously published about Medellin [19]. Briefly, once an adult case was notified to the local tuberculosis control program, the patient and children household contacts were invited to participate in the study, followed by the signature of informed consent.

Follow-up

After index cases were identified and they approved a first (baseline) visit, the research team went to the household to explain the study and obtain written informed consent from parents or responsible adult guardians, to collect socio-demographic and exposure information, and to perform the tuberculin skin test. Follow-up occurred throughout visits every six months and telephone calls every three months. The total follow-up time was at least 24 months. Also, local epidemiological surveillance databases were checked for active tuberculosis cases reported.

Mycobacterium tuberculosis was confirmed by culture in liquid (BD Bactec MGIT960) and/or solid media (Lowenstein-Jensen) from sputum (in adults) and gastric aspirate (in children) for all index and incident cases. Tuberculin skin test was done by intradermal injection of 2 IU of RT23 tuberculin (Staten Serum Institute, Copenhagen, Denmark) in the inner surface of the forearm. Tuberculin skin test reading was done 48 to 72 hours after injection and was considered to be positive when measured induration was ≥10 mm, according to the Colombian National tuberculosis Program. Following the recommendations of the American Thoracic Society [20], an analysis of tuberculin skin test positivity using a cutoff of 5 mm of induration was also included. The annual risk of infection was determined through the tuberculin skin test conversion of a children household contact with a negative tuberculin skin test at baseline. The conversion was defined as an increase of at least 6 mm of induration a year after the initial test [21].

For detecting infection, the tuberculin skin test was available to perform in 458 (44%) of the household contacts <15 years old from whom were willing to attended from Cali and Popayán, and an incidental sample from Medellín. From protocol design, participants from Medellín were assessed with an in-house interferon-gamma release assay, data related to the immune response to *M. tuberculosis,* and incident tuberculosis in household contacts (adults and children) was published previously for the Medellín cohort [19].

Nutritional status was evaluated according to Z score for weight and height as follows: between -1 and 1, normal; less than -1, underweight; and score >1, overweight [22]. Socioeconomic strata were recorded according to classifications used by local public services provider and categorized as low socioeconomic strata yes or not. Proximity to the index case was classified as follows: children household contact slept in other households, children household contact slept in the same household, children's household contact slept in the same room. Crowding was considered when three or more persons shared the same bedroom [19]. Having other relatives with tuberculosis was defined as an additional contact with a tuberculosis case besides the index case.

Incident active tuberculosis cases were diagnosed following the Stop tuberculosis Partnership Childhood tuberculosis subgroup's guidelines [23], considering contact history, clinical, immunological, microbiological, and radiographic criteria. Evaluation of children in Cali was performed through a diagnostic algorithm [24]. This tool was not applied for Medellín and Popayán´s cohorts.

Statistical analysis

Social, demographic and clinical characteristics, as well as the degree of proximity to the index case, were compared using the distribution of absolute and relative frequencies. Also, the chi-square test was calculated to establish significance (p <0.05).

The tuberculin skin test positivity and its association with children's characteristics were analyzed using a prevalence ratio. Adjusted prevalence ratio was estimated using binomial regression. The annual risk of infection and its association with the index case's characteristics were calculated using relative risk (RR) adjusted in a binomial regression. Incidence estimated for active tuberculosis was calculated for each city and four age groups (<1-year-old, 1-4 years old, 5-9 and 10-14), as well as for other household associate characteristics by using the hazard ratio (HR). Hazard ratio was adjusted by a Cox regression. Age groups were selected based on described children's tuberculosis risk and immune responses[25]. Finally, two multivariate models were built using BCG vaccination status (evidenced by the presence of a vaccine's scar), given that an additive interaction was found when using a stratified Mantel-Haenzel method. The Kaplan-Meir method was used to estimate time to the disease for each age group. Every association measure and multivariate model was adjusted by cluster, given that outcomes (positive tuberculin skin test and active tuberculosis) could be influenced by natural clusters such as family and city, 95% confidence interval (95% CI) was estimated. p values <0.05 were considered significant. Analyses were done using Stata 12.0, SPSS 22.0, and Epidat 3.1.

Ethical aspects

This study, including the informed consent used, was approved by the Ethical Committee of Facultad de Medicina, Universidad de Antioquia, and it applied for each city. The study was also supported by the National Tuberculosis Program and the regional public health authorities. At the time of data collection, national health policies only included the recommendation of isoniazid preventive therapy for children <5 years old with tuberculin skin test >10 mm without BCG vaccination. Most children involved in the study did not receive isoniazid preventive therapy because the majority were vaccinated. Active tuberculosis cases received tuberculosis treatment according to National Tuberculosis Program.

Results

Of the total household contacts, 1,040 were children <15 years' old, included in this analysis. 742 (71.3%) from Medellín, 216 (20.8%) from Cali and, 82 (7.9%) from Popayán. Children represented 35% of household contacts in the overall cohort study. The demographic and epidemiological characteristics of the 1,040 children included in this study are shown in Table 1. Most children belonged to low socioeconomic strata (79.2%), had a BCG vaccination scar (80.6%), and were household contacts of an index case with a high bacillary load. From the whole cohort, 1.8% of Medellín, 4.8% from Cali, and 1.7% from Popayán were voluntarily withdrawn; and 1.0% from Medellín, 5.0% from Cali and 1.3% from Popayán were lost of follow-up.

From the 458 tuberculin skin test performed, 205 were performed in Cali, 81 in Popayán, and 172 in Medellín. The tuberculin skin test at baseline was positive (≥10 mm) in 43.7% (95% CI: 39.2-48.2) of tested children. Regardless of cutoff, factors associated with having a positive tuberculin skin test were age 10-14 years and the presence of a BCG scar (p <0.05). Underweight, being a household contact for more than 3 months, and closer proximity to the index case were associated with a higher prevalence of a positive tuberculin skin test (≥10 mm). The same factors showed a similar trend, although not significant when a cutoff point of 5 mm was applied (Table 2). An association trend was found between both tuberculin skin test cutoff points and proximity to the index case (chi-square test for trend p <0.01).

Tabla 1. Characteristics of children (<15 years old) household contacts of adult patients with pulmonary tuberculosis (TB) by city, in three Colombian cities, 2005-2009.

Characteristic	Medellín	Cali	Popayán	Total
	n= 742 (%)	n= 216 (%)	n= 82 (%)	n= 1040 (%)
Age in years				
< 1	30 (4.0)	9 (4.2)	7 (8.5)	46 (4.4)
1-4	207 (27.9)	59 (27.3)	31 (37.8)	297 (28.6)
5-9	241 (32.5)	72 (33.3)	28 (34.1)	341 (32.8)
10-14	264 (35.6)	76 (35.2)	16 (19.5)	356 (34.2)
Sex				
Female	365 (49.2)	97 (44.9)	39 (47.6)	501 (48.2)
Low socioeconomic stratum				
Yes	551 (74.3)	184 (85.2)	80 (97.6)	815 (78.4)
No information	8	3	0	11
Nutritional condition				
Normal	427 (57.5)	119 (55.1)	46 (56.1)	592 (56.9)
Underweight	178 (24.0)	57 (26.4)	17 (20.7)	252 (24.2)
Overeight	129 (17.4)	37 (17.1)	19 (23.2)	185 (17.8)
No information	8	3	0	11
BCG scar				
Yes	626 (84.4)	138 (63.9)	69 (84.1)	833 (80.1)
No information	6	1	0	7
History of another relative with TB*				
Yes	256 (34.5)	85 (39.4)	37 (45.1)	378 (36.3)
Proximity to the index case				
HHC slept in other household	171 (23.0)	36 (16.7)	15 (18.3)	222 (21.3)
HHC slept in same household	340 (45.8)	111 (51.4)	38 (46.3)	489 (47.0)
HHC slept in same room	231 (31.1)	69 (31.9)	29 (35.4)	329 (31.6)
Persons per room				
< 3	493 (66.8)	137 (64.3)	49 (59.8)	679 (65.7)
≥ 3	245 (33.2)	76 (35.7)	33 (40.2)	354 (34.3)
Sputum smear load				
+	287 (38.7)	54 (25.1)	18 (22.0)	359 (34.6)
++	192 (25.9)	78 (36.3)	33 (40.2)	303 (29.2)
+++	263 (35.4)	83 (38.6)	31 (37.8)	377 (36.3)
Exposure time				
≤ 3 months	487 (65.8)	166 (76.9)	49 (59.8)	702 (67.6)
> 3 months	253 (34.2)	50 (23.1)	33 (40.2)	336 (32.4)

HHC: household contact

* History of another relative with TB: had had any other relative with tuberculosis besides the identified index case in the cohort.

For those children with a baseline tuberculin skin test <5 mm (173 children), the *M. tuberculosis* annual risk of infection was 12.1% (95% CI: 7.2-17.1), whereas in the group of children with initial tuberculin skin test <10 mm (206 children) annual risk of infection was 17% (95% CI: 11.8-22.2). A significant correlation was found between M. tuberculosis annual risk of infection and a higher bacillary load of the index case for those with an initial tuberculin skin test <5 mm (RR= 2.61, 95% CI: 1.2-5.9, p= 0.020 adjusted by age, low socioeconomic stratum, history of another relative with tuberculosis and exposure time) as well as for those with an initial tuberculin skin test <10 mm (RR= 2.12, 95% CI: 1.0-4.3, p= 0.037 adjusted by age and nutritional condition) (Table 3).

Nineteen children developed active tuberculosis during follow-up (7.2%, 95% CI: 3.9-10.5), among those with an initial tuberculin skin test ≥5 mm (18/243) or an increase of 6 mm of induration per year (1/21). Active tuberculosis incidence was higher in children without BCG scar (8/55, 14.5%, 95% CI: 7.3-26.4) than in those with a BCG scar (11/207, 5.3% 95% CI: 2.9-9.4) (p= 0.033). Among children without documented tuberculosis infection (initial tuberculin skin test <5 mm and less than 6 mm induration increase per year), incidence of active tuberculosis was 0.7% (1/152, 95% CI: 0.02-3.6). Figure 1 shows the number of children who developed active tuberculosis according to the result of the initial tuberculin skin test and the increase of tuberculin skin test induration per year.

Table 2. Associated characteristics to positive tuberculin skin test prevalence in children (<15 years old) household contacts of adult patients with pulmonary tuberculosis (TB), in three Colombian cities, 2005-2009.

Characteristic	N	Positive TST (≥5mm)			Positive TST (≥10 mm)		
		n (%)	PR	(95%CI)*	n (%)	PR	(95%CI)*
Age in years n(%)							
<1	19	7 (36.8)	0.81	(0.4 - 1.6)	2 (10.5)	0.37	(0.1 - 1.4)
1-4	137	66 (48.2)	1	(0.8 - 1.3)	55 (40.1)	1.03	(0.8 - 1.3)
5-9	153	74 (48.4)	1		59 (38.6)	1	
10-14	149	96 (64.4)	1.3	(1.1 - 1.6)†	84 (56.4)	1.43	(1.1 - 1.9)‡
Sex n (%)							
Male	244	125 (51.2)	1		105 (43.0)	1	
Female	214	118 (55.1)	1.17	(1.0 - 1.4)	95 (44.4)	1.17	(1.0 - 1.4)
Low socioeconomic stratum							
No	54	24 (44.4)	1		23 (42.6)	1	
Yes	401	217 (54.1)	1.04	(0.7 - 1.7)	175 (43.6)	0.84	(0.5 - 1.4)
Nutritional condition							
Normal	255	139 (54.5)	1		111 (43.5)	1	
Underweight	125	68 (54.4)	1.07	(0.9 - 1.3)	61 (48.8)	1.27	(1.0 - 1.6)†
Overeight	75	35 (46.7)	0.96	(0.7 - 1.3)	28 (37.3)	0.97	(0.7 - 1.4)
BCG scar							
No	109	48 (44.0)	1		35 (32.1)	1	
Yes	346	193 (55.8)	1.34	(1.0 - 1.7)†	163 (47.1)	1.52	(1.1 - 2.1)†
History of another relative with TB**							
No	289	152 (52.6)	1		122 (42.2)	1	
Yes	169	91 (53.8)	1.05	(0.8 - 1.3)	78 (46.2)	1.1	(0.8 - 1.4)
Proximity to the index case							
HHC slept in other household	99	42 (42.4)	1		27 (27.3)	1	
HHC slept in same household	224	119 (53.1)	1.25	(0.9 - 1.7)	100 (44.6)	1.61	(1.1 - 2.4)†
HHC slept in same room	135	82 (60.7)	1.34	(1.0 - 1.8)	73 (54.1)	1.79	(1.1 - 2.8)†
Persons per room							
<3	289	137 (47.4)	1		108 (37.4)	1	
≥3	166	104 (62.6)	1.27	(0.9 - 1.8)	90 (54.2)	1.44	(0.9 - 2.2)
Sputum smear load							
+ or ++	296	161 (54.4)	1		129 (43.6)	1	
+++	161	82 (50.9)	1.07	(0.8 - 1.4)	71 (44.1)	1.23	(0.9 - 1.7)
Exposure time							
≤3 months	303	146 (48.2)	1		115 (38.0)	1	
>3 months	155	97 (62.6)	1.24	(1.0 - 1.6)	85 (54.8)	1.37	(1.0 - 1.8)†

TST: Tuberculin Skin Test. HHC: household contact.

* PR: Prevalence Ratio adjusted by all the other variables in the table and adjusted by family and city intraclass correlation.

** History of another relative with TB: had had any other relative with tuberculosis besides the identified index case in the cohort.

† p <0.05

‡ p <0.01

The general incidence rate for active tuberculosis was 12.4 per 1,000 persons-year. As shown in Figure 2, the rate at which active tuberculosis develops differs according to age (Log-rank=10.10, p= 0.006). In particular, early development of active tuberculosis was found more frequently in children without BCG scar HR= 6.00 (95% CI: 1.3-28.3 adjusted by the history of another relative with tuberculosis, proximity to the index case, and persons per room). Also, a positive association was found between crowding and the early development of active tuberculosis, but it was not significant when the BCG scar was considered. Having an initial tuberculin skin test ≥5 mm had a significant positive association with the earlier development of active tuberculosis (tuberculin skin test 5-9 mm HR= 8.55, 95% CI: 2.5-29.2; tuberculin skin test ≥10 mm HR= 8.16, 95% CI: 2.0-32.9) (Table 4).

Discussion

This study showed a high prevalence of tuberculosis infection in children (age <15 years) household contacts of adult patients with pulmonary tuberculosis, associated with having a BCG scar and age between 10-14 years. Closer proximity and time spent with the index case (exposure) greater than three months had a positive association with tuberculin skin test ≥10 mm. A systematic review and meta-analysis of the evidence on the yield of household contact investigations in countries with similar epidemiological characteristics than Colombia, found

Table 3. Associated characteristics to Annual Risk of Infection in children household contacts of adult patients with pulmonary tuberculosis (TB), in three Colombian cities, 2005-2009.

Characteristic	ARI (baseline TST <5 mm)*				ARI (baseline TST <10 mm)			
	N=173	n (%)	RR	(95%CI)**	N=206	n (%)	RR	(95%CI)**
Age in years								
<5	68	5 (7.4)	1		80	9(11.3)	1	
5-14	105	16 (15.2)	2.07	(0.8-5.3)	126	26(20.6)	1.83	(0.9-3.6)
Sex								
Male	97	10 (10.3)	1		111	20(18.0)	1	
Female	76	11 (14.5)	1.4	(0.7-3.0)	95	15(15.8)	0.88	(0.5-1.5)
Low socioeconomic stratum								
No	25	5 (20.0)	1		26	5(19.2)	1	
Yes	147	15 (10.2)	0.51	(0.2-1.4)	179	29(16.2)	0.84	(0.3-2.3)
Nutritional condition								
Normal	89	11 (12.4)	1		111	22(19.8)	1	
Underweight	51	7 (13.7)	1.11	(0.5-2.5)	55	8(14.5)	0.73	(0.4-1.5)
Overweight	31	2 (6.5)	0.52	(0.1-1.9)	37	4(10.8)	0.55	(0.2-1.4)
BCG scar								
No	54	7 (13.0)	1		62	11(17.7)	1	
Yes	118	14 (11.9)	0.92	(0.4-2.1)	143	24(16.8)	0.95	(0.5-1.9)
History of another relative with TB†								
No	114	17 (14.9)	1		136	25(18.4)	1	
Yes	59	4 (6.8)	0.46	(0.2-1.4)	70	10(14.3)	0.78	(0.3-1.8)
Proximity to the index case								
HHC slept in other household	47	6 (12.8)	1		59	11(18.6)	1	
HHC slept in same household	126	15 (11.9)	0.93	(0.4-2.5)	147	24(16.3)	0.88	(0.4-1.8)
Persons per room								
<3	115	15 (13.0)	1		136	26(19.1)	1	
≥3	57	6 (10.5)	0.81	(0.3-2.4)	69	9(13.0)	0.68	(0.3-1.6)
Sputum smear load								
+ or ++	109	9 (8.3)	1		132	17(12.9)	1	
+++	63	12 (19.0)	2.31	(0.9-5.7)	73	18(24.7)	1.91	(0.9-3.9)
Exposure time								
≤3 months	131	17 (13.0)	1		155	24(15.5)	1	
>3 months	42	4 (9.5)	0.73	(0.2-2.6)	51	11(21.6)	1.39	(0.6-3.0)

TST: Tuberculin skin Test. ARI: Annual Risk of Infection (increase ≥6 mm). HHC: household contact.
* Does not include 33 children with a baseline TST ≥10 mm
** RR: Risk Ratio adjusted by family and city intraclass correlation.
† History of another relative with TB: had had any other relative with tuberculosis besides the identified index case in the cohort.
‡ $p<0.05$

a prevalence of tuberculosis infection of 51.4% (95% CI 50.6-52.2), in children ranging from 18.5% to 69.2%, and being greater in children 5-14 years of age than in children <5 years [12], similar to our findings. In Brazilian children exposed to tuberculosis (evaluated by tuberculin skin test and interferon-gamma release assay, significant factors associated with infection were being a contact of an adult with active disease (0-60 days OR= 6.9; >60 days OR= 27.0) and sleeping in the same room with the index case (OR= 5.2) [26], as it was found in the present study.

Additionally, the incidence rate of infection after one year of follow-up was high, suggesting that a significant risk for developing active tuberculosis persists after one year. tuberculosis annual risk of infection gives information about the degree of transmission in a given community, used to focus vaccination programs, and ultimate control of the disease. Usually, it is calculated from the observed infection prevalence in scholar age children, given that even in places where a high transmission occurs, measurement of infection by using tuberculin skin test sequentially will require significant sample sizes, and the results may be influenced by booster effects [27-29].

Performing annual tuberculin skin test, our study showed that annual risk of infection in children household contacts of adults with pulmonary Tuberculosis is higher than the one reported in general population in Russia with a moderate disease incidence (annual risk of infection in 1991: 0.2%, in 2000: 1.6%) [30]. In contrast, in two countries with high tuberculosis

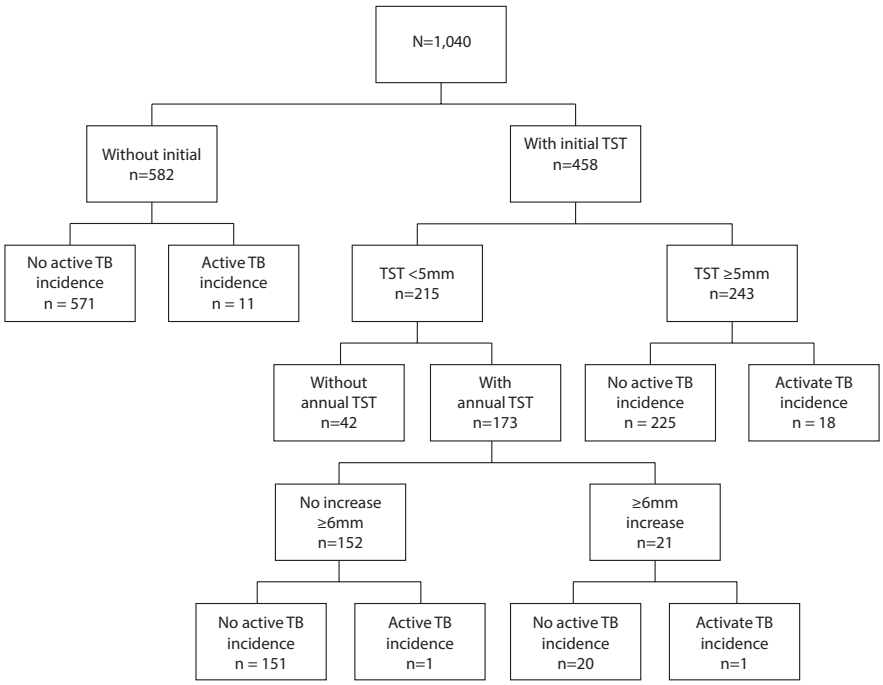

Figure 1. Flow chart of active tuberculosis cases by initial tuberculin skin test result (cutoff point 5 mm) and one year later (infection incidence: increase of 6 mm or more compare to initial tuberculin skin test). TST: Tuberculin Skin Test. TB: tuberculosis.

incidence as Zambia and South Africa, the reported annual risk of infection in children between 6-11 years old was 2.0% and 4.2%, respectively (tuberculin skin test cutoff 10 mm) in 2009 [31]. Another study in South Africa in 2016 described an annual risk of infection in children <15 years old of 3.1% [32]. These studies differ from our study in the way the annual risk of infection was calculated (estimated from data obtained with prevalence surveys) and in the cutoff point for considering a positive tuberculin skin test; even though, our data support that the infection risk for tuberculosis remains greater in children household contacts of patients with active tuberculosis (annual risk of infection 12.1%), compared to general population even one year after being identified as a tuberculosis contact.

In the same way, a higher incidence of active tuberculosis was demonstrated during the two years of follow-up with an earlier presentation in children <5 years old without a BCG scar. Results from several studies showed an increased risk for developing active tuberculosis in children <5 years old, having HIV, or sharing the bed or the household with an adult with active tuberculosis, proximity to the index case, crowding and being a passive smoker as well as severe undernourished and not having a previous BCG vaccination [33-36], similar to present study findings regarding age less than 5 years and BCG vaccination. The risk of developing active tuberculosis decreases with age, and the protective effect of BCG vaccination for infection, active tuberculosis, and severe disease have been reported [25,33,37] (using interferon-gamma as an infection marker) [38].

Our findings support the protective effect described for the BCG vaccine in children <5 years old in conditions of a moderate prevalence of tuberculosis [38]. However, these effects vary in different geographical regions, which could be related to the genetic dependent immune response that affects even tuberculin skin test results [39].

Although tuberculin skin test is widely used to determine infection by *M. tuberculosis*, the test has several pitfalls, which makes it acceptable but not perfect. Its specificity is poor in BCG vaccinated populations, it has cross-reactivity with non-tuberculous mycobacteria and

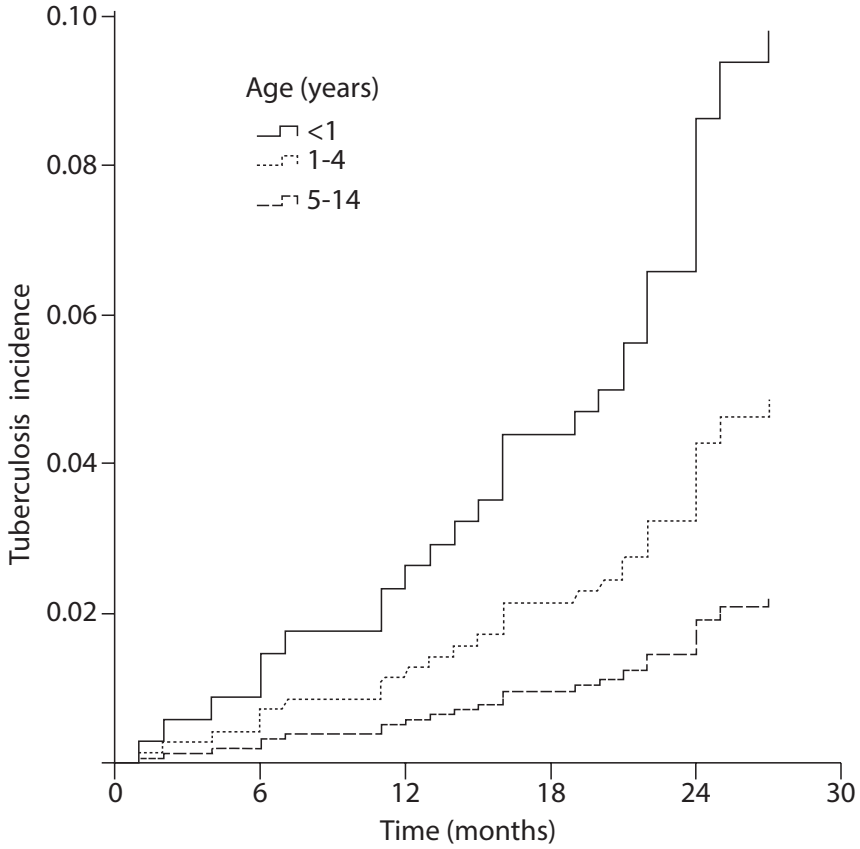

Figure 2. Risk to develop active tuberculosis by age group in children household contacts of adult patients with pulmonary tuberculosis (TB), in three Colombian cities, 2005-2009. Log-rank= 10.10, *p*= 0.006. Age groups 5-9 and 10-14 years were grouped in one because they had a similar trend.

its sensitivity decrease in immunocompromised patients [25,40,41]. These tuberculin skin test characteristics may have a confusing effect, especially in the association found between the presence of BCG vaccination scar and the prevalence of tuberculosis infection.

The present study is the first in our country with these characteristics, which includes the follow-up of a cohort of children exposed to tuberculosis. Currently, the proportion of children with tuberculosis disease reported in Colombia [7] is under the 10% global estimation of new tuberculosis cases. That suggests a weakness in the country activities for identification of children with disease [42]. Although BCG vaccination shows protection against the disease, children <5 years old are yet the most vulnerable population to develop active tuberculosis disease.

Our findings allowed to modify some policies in Colombia, including a prolongation of follow-up time to household contacts seeking active disease, and promoting isoniazid preventive therapy in guidelines for children age <5 years.

Study limitations

Children included in the study were part of a cohort of household contacts of patients with pulmonary tuberculosis. Thus the initial sample size was not calculated exclusively for children. An inverse calculation was done for the cohort of children <5 years' old which consisted in an estimation of the power needed to detect a significant difference (95% confidence value) between the 2% of incidence rate of active tuberculosis in individuals with a BCG scar vaccination (exposed) and the 6% of incidence rate in non-vaccinated individuals.

Table 4. Associated characteristics to active tuberculosis (TB) incidence in children household contacts of adult patients with pulmonary tuberculosis, in three Colombian cities, 2005-2009.

Characteristics	TB incidence n (%)	Total N	HR	(95%CI)* §
Age in years n(%)				
<5	17 (5.0)	343	2.55	(1.3-4.9)‡
5-14	14 (2.0)	697	1	
Sex n (%)				
Male	16 (3.0)	539	1	
Female	15 (3.0)	501	0.99	(0.5-1.9)
Low socioeconomic stratum				
No	4 (1.9)	214	1	
Yes	26 (3.2)	815	1.69	(0.5-6.1)
Nutritional condition				
Normal	18 (3.0)	592	1	
Underweight	6 (2.4)	252	0.8	(0.3-2.0)
Overeight	6 (3.2)	185	1.04	(0.3-3.3)
BCG scar				
No	12 (6.0)	200	1	
Yes	19 (2.3)	833	0.37	(0.2-0.7)‡
History of another relative with TB**				
No	24 (3.6)	662	1	
yes	7 (1.9)	378	0.5	(0.2-1.4)
Proximity to the index case				
HHC slept in other household	3 (1.4)	222	1	
HHC slept in same household	28 (3.4)	818	2.56	(0.9-7.5)
Persons per room				
<3	12 (1.8)	679	1	
≥3	18 (5.1)	354	2.95	(1.2-7.3)†
Sputum smear load				
+ or ++	21 (3.2)	662	1	
+++	10 (2.7)	377	0.84	(0.3-2.1)
Exposure time (months)				
≤3	23 (3.3)	702	1	
>3	8 (2.4)	336	0.75	(0.3-2.0)
Initial tuberculin skin test (mm)				
0-4	2 (0.9)	215	1	
5-9	3 (7.0)	43	8.55	(2.5-29.2)‡
≥10	15 (7.5)	200	8.16	(2.0-32.9)‡

* HR: Hazard Ratio adjusted by family and city intraclass correlation.
** History of another relative with TB: had had any other relative with tuberculosis besides the identified index case in the cohort.
† p<0.05
‡ p<0.01
§Age in years HR stratified by BCG scar and adjusted by the history of another relative with TB, proximity to the index case, and persons per room: without scar HR= 6.00 (95% CI: 1.3-28.3, p: 0.024), with scar HR= 1.33 (95% CI: 0.5-3.4, p: 0.559).

The results showed a power of 81% using sample size software (version 1.1) [43]. A similar result was obtained for comparison of active tuberculosis incidence rate according to the presence or not presence of crowding.

On the other hand, the tuberculin skin test was not available for every child in Medellín; only an incidental sample could access to this test.

Besides, the estimated tuberculosis annual risk of infection is not comparable to traditional methods used. Currently tuberculosis contact tracing with tuberculin skin test is complemented with commercial interferon-gamma release assay, even in children, results from in-house interferon-gamma quantification were reported previously [19].

Conclusions

Tuberculosis infection in children younger than 15 years household contacts of patients with pulmonary tuberculosis is high, as it is the risk of developing active tuberculosis. This finding supports the importance of tracing tuberculosis contacts and the application of measures such

as the isoniazid preventive therapy or other regimens, especially in children <5 years of age, given that a large part of these children become infected in their homes. New studies should be focussed to evaluate the implementation of recommended tuberculosis preventive measures in the context of the household contacts of patients with active tuberculosis, especially children <5 years old.

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