Overweight, Obesity, and Older Age Favor Latent Tuberculosis Infection among Household Contacts in Low Tuberculosis-Incidence Settings within Panama

Idalina Cubilla-Batista,^{1,2†} Nadia Ruiz,^{1,2,3†} Dilcia Sambrano,¹ Juan Castillo,⁴ Markela O. de Quinzada,³ Begoña Gasteluiturri,² and Amador Goodridge^{1*}

¹Tuberculosis Biomarker Research Unit, Centro de Biología Molecular y Celular de Enfermedades, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT-AIP), Ciudad del Saber, Panama; ²Laboratorio Clínico, Hospital Rafael Estevez, Caja de Seguro Social, Aguadulce, Panama; ³Maestría de Ciencias Biomédicas, Facultad de Medicina de la Universidad de Panamá, Panama City, Panama; ⁴Facultad de Informática, Electrónica y Comunicación, Extensión Universitaria de Aguadulce, Universidad de Panamá, Coclé, Panama

Abstract. Latent tuberculosis infection (LTBI) remains the main source of new active tuberculosis (TB) cases worldwide. Household close contacts (HCCs) are at high risk of acquiring LTBI and subsequent development of TB. In this study, we aim to identify risk factors associated with LTBI in HCCs of TB patients living in a low TB-incidence setting. Our results revealed that HCCs who are aged more than 50 years (OR = 4.05) and overweight (OR = 15.3) are at higher risk of acquiring LTBI. None of these LTBI household contacts progressed to active TB. These findings suggest that HCCs who are young adults and children with normal and low body mass index are less likely to acquire LTBI after exposure to TB patients, even in low TB-incidence settings.

Tuberculosis (TB) is considered a global health problem because of its high prevalence and morbidity and mortality rates. According to the WHO, in 2017, 10.4 million people became ill with TB and 1.8 million died from this disease.¹ More than 95% of TB deaths occur in low- and middle-income countries, and TB remains the main cause of death in people infected with HIV.² Unfortunately, one quarter of the world's population suffers from latent tuberculosis infection (LTBI). The vast majority of these LTBI cases are unaware of their infection status, and 10% progress to active disease if not treated.³ Consequently, understanding risk factors for LTBI and disease progression remains key to ending the worldwide epidemic.

Interferon gamma release assays (IGRAs) and tuberculin skin tests (TSTs) have been proposed to identify individuals with LTBI in high-income countries with low TB incidence.⁴ Both tests are based on the adaptive immune response to *Mycobacterium tuberculosis* derivatives. A worldwide effort is underway to identify novel biomarker tests for LTBI diagnosis and disease progression.⁵ Despite their usefulness for LTBI monitoring and diagnosis, IGRA and TST outcomes are affected by the high TB burden across the world.^{6,7} In fact, the WHO has established differential guidelines for the management of LTBI in low TB-incidence settings.⁸ Consequently, identification of LTBI risk factors is essential for TB control even in low TB-burden regions. Our study aimed to determine the risk factors for acquiring LTBI among household close contacts (HCCs) of TB patients in a low TB-incidence setting within Panama. Our findings suggest older adults with a high body mass index (BMI) are more likely to acquire LTBI after exposure to positive sputum smear TB patients.

This pilot study was conducted in Coclé Province, which is located in the central region of Panama (Figure 1) and 150 km from Panama City. From January to December 2015, pulmonary TB patients were identified by acid-fast bacilli sputum

smear. These TB patients were treated with anti-TB drugs for 6 months according to the national guidelines. Household close contacts living in the same house with smear-positive TB patients were invited to participate in our study. Those who provided informed written consent received a survey interview using a standardized questionnaire instrument. These HCCs donated blood samples and were encouraged to report any illness within a 2-year period. Only HIV-negative HCCs were included in our study. The study protocol was approved by the Institutional Review Board of Caja de Seguro Social Committee.

Five milliliters of blood was collected from each HCC participant. We analyzed blood samples with the QuantiFERON-TB Gold In-Tube test (Cellestis Limited, Carnegie, Victoria, Australia) according to the manufacturer's instructions.⁹ All variables were described in percentages, and comparison between the IGRA-positive and IGRA-negative groups was completed using the Fischer exact test because of the small sample size. We used odds ratios and 95% CI to test all the potential associations between the risk factors and IGRA status. All statistical tests were carried out using STATA v12.1 (StataCorp LLC, College Station, TX) and Microsoft Excel software (Microsoft Corporation, Redmond, WA).

A total of 61 HCCs were recruited to participate in our study during 2015. All participants approved and signed the consent/assent form. All participants were intimate HCCs (they lived with the patients during their treatment for a daily period of at least 6 hours). The province of Coclé had an average TB incidence of 13.5/100,000 during the collection year (2015) and the two follow-up years (2016–2017) (Figure 1). Therefore, we can assert that TB transmission to HCCs occurred at home and not at schools, in the community, or in the workplace. A total of four HCCs were excluded from the study: one died naturally, two participants declined to complete the survey, and one participant had respiratory symptoms not related to TB.

The analysis of HCC characteristics indicated an average family size of eight members, but 67% lived with more than five people per house. All the HCCs lived in rural or semi-urban areas in multifamily housing units, meaning household members shared common areas, such as kitchens, laundry rooms, and bathrooms with the members of other households. Table 1 shows the sociodemographic characteristics. Majority

* Address correspondence to Amador Goodridge, Tuberculosis Biomarker Research Unit, Centro de Biología Molecular y Celular de Enfermedades, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT-AIP), Edificio 219, City of Knowledge, Ciudad del Saber 0843-01103, Panama. E-mail: agoodridge@indicasat.org.pa

† These authors contributed equally to this work.

FIGURE 1. Tuberculosis (TB) incidence changes in Panama during the 2015–2017 period: Country map shows the TB incidence per 100,000 inhabitants per year. Lighter colors indicate lower incidences and darker colors indicate high-incidence settings within Panama. The study site was Coclé Province. Source: Ministry of Health of the Republic of Panama. This figure appears in color at www.ajtmh.org.

of the patients (34 [56%]) were male. Of the contacts interviewed, 32 (52%) had completed elementary school only; 27 (46%) identified as students and 17 (28%) identified as housewives. All 61 participants (100%) were Panamanians. Majority of the dwellings described by the participants were made of cement blocks (53 [85%]), with most only having one

room. The degree of kinship between the patients and contacts was mostly 1st or 2nd degree of consanguinity (62%).

The IGRA test, QuantiFERON-TB-Gold, identified 11.5% (7/61) of HCCs with LTBI, as shown in Table 1. By gender, the positive LTBI cases represented 10.8% of the female participants and 12.5% of the male participants. All participants

TABLE 1
Description of the study population and univariate analysis of risk factors for latent tuberculosis infection

Characteristic	Total		QGTB+		QGTB-		OR	P-value*
	n	%	N	%	n	%		
Total	61	100	7	11.5	54	88.5	—	—
Age (years)								
≤ 9	17	27.9	0	0	17	100	Reference	—
10–19	19	31.1	0	0	19	100	NA	0.26
20–29	4	6.6	0	0	4	100	NA	0.1
30–39	8	13.1	2	25	6	75	8.3 (0.45–348.5)	0.08
40–49	6	9.8	1	16.7	5	83.3	5.2 (0.09–277.4)	0.19
≥ 50	7	11.5	4	57.1	3	42.9	29.5 (1.65–2,351)	0.01
Gender								
Male	24	39.3	3	12.5	21	87.5	1.18 (0.15–7.7)	> 0.99
Female	37	60.7	4	10.8	33	89.2	Reference	—
Education								
Elementary school or less	32	52.5	5	15.6	27	84.4	Reference	—
Middle school	19	31.1	2	10.5	17	89.5	0.64 (0.06–4.48)	0.95
High school or more	10	16.4	0	0	10	100	0.65 (0.01–7.30)	> 0.99
BMI†								
Underweight	8	13.1	0	0	8	100	2.7 (0.05–150.5)	0.27
Normal	22	36.1	0	0	22	100	Reference	—
Overweight	19	31.1	6	31.6	13	68.4	14.9 (1.23–972.3)	0.014
Obese	12	19.7	1	8.3	11	91.7	3.2 (0.03–327.4)	0.53
Living in overcrowded conditions								
Yes	52	85.2	4	7.7	48.0	92.3	0.17 (0.02–1.47)	0.07
No	9	14.8	3	33.3	6.0	66.7	Reference	—
BCG scar								
Yes	57	93.4	4	7.0	53	93.0	0.03 (0.001–0.33)	0.004
No	4	6.6	3	75.0	1	25.0	Reference	—
Caregiver								
Yes	17	27.9	3	17.6	14	82.4	2.14 (0.28–14.27)	0.39
No	44	72.1	4	9.1	40	90.9	Reference	—
Time of exposure								
≥ 12 hours/day	42	68.9	5	11.9	37	88.1	1.15 (0.17–13.1)	> 0.99
< 12 hours/day	19	31.1	2	10.5	17	89.5	Reference	—
Smear status of source case								
Positive	19	32.2	2	10.5	17	89.5	0.82 (0.07–5.71)	> 0.99
Negative	40	67.8	5	12.5	35	87.5	Reference	—

BCG = Bacillus Calmette-Guerin; BMI = body mass index; NA = not applicable; QGTB = quantiferon gold. Underweight: < 18.5 kg; normal: ≥ 18.5 kg and < 23 kg; overweight: ≥ 23 kg and < 27.5 kg; obese: ≥ 27.5 kg. Bold values resulted statistically significant at $P < 0.005$.

* Fisher exact test P -value (two-tailed).

† For ages 2–20 years, we used CDC growth charts for boys and girls.

were classified into six age groups. In the LTBI risk factor analysis, we found that HCCs aged more than 50 years had a significant OR of 29.5 (95% CI = 2.24–1,163). In this study, all positive LTBI HCCs were aged more than 30 years. The proportion of positive LTBI HCCs was higher among the group of participants with less than elementary school education than in the groups with at least middle or high school education. Although the association between education level and LTBI was not significant among all HCCs, the trend showed that higher levels of education could be a potential protective factor against LTBI. Body mass index was calculated and used as a proxy for adult nutritional status. For children, the BMI-for-age percentile tables for boys and girls developed by the CDC were used to classify the HCCs as underweight, normal, overweight, or obese.¹⁰ When using normal weight as a reference, we found that overweight significantly increased the risk for LTBI among HCCs (OR = 14.93, 95% CI = 1.57–483.3). Meanwhile, the presence of a Bacillus Calmette-Guerin vaccine scar proved to be a protective factor against LTBI among HCCs (OR = 0.029, 95% CI = 0.001–0.33).

Nearly 69% of participants reported being exposed to the source case for more than 12 hours per day and reported living in overcrowded conditions; however, these were not identified

as significant risk factors. Similarly, the acid-fast smear status of the index TB patient was not related to the LTBI status among HCCs included in our study. Other health history information gathered from the 61 HCCs showed that all (100%) were nonsmokers, and three patients (4.9%) had coexisting diseases. When analyzed using a multivariable approach, age and overweight increased the risk of LTBI in HCCs (Table 2).

The aforementioned results revealed an LTBI prevalence of 11.5% among HCCs in Cocle Province, Panama. This region holds the lowest TB incidence rate, and thus the HCCs were likely exposed to TB only at home. Our study also found that obese, overweight, and older HCCs have a higher risk of establishing LTBI. Recent systematic reviews have found that the opposite malnutrition status—low BMI—did not increase the yield of LTBI cases among household contacts.¹¹ Others have indicated that malnutrition, in the form of excess intake of

TABLE 2
Exact logistic regression on risk factors for latent tuberculosis infection

Variables	OR	Suff	P-value	95% CI
Age (every 10 years)	4.05	37	0.0008	1.49–26.92
BMI (overweight)	15.29	6	0.04	1.09–1,065.75

BMI = body mass index; normal and underweight used as reference.

nutrients, could be a potential risk factor for LTBI.¹² From a public health standpoint, obesity and overweight are risk factors for various other chronic diseases, including diabetes. Thus, malnutrition should not only be considered for individuals with a low BMI (underweight).¹³ Paradoxically, although obese adult HCCs are potentially more likely to harbor *M. tuberculosis* infection, they are less likely to progress to active TB.^{14,15} By contrast, bodyweight control in obese adults could lead to the development of TB. Future studies should evaluate whether malnutrition (either as an excess or deficiency of nutrients and energy) is related to LTBI. It is also necessary to clarify whether obesity induces an exaggerated immune response to a mycobacterial challenge and, thus, the clearance of *M. tuberculosis* or a pro-inflammatory response, which may result in establishing LTBI and stopping disease progression.¹⁴

Because of the sample size of our study, we were not able to adjust LTBI incidence for concomitant chronic diseases. The small number of participants precludes dividing them based on other risk factors. Our future plans include exploring the relationship between BMI and LTBI with the presence of other clinical conditions, such as diabetes, kidney diseases, immunological disorders, HIV, and autoimmune diseases, in both low and high TB-incidence settings. None of the participants in our study developed secondary TB after 2 years of follow-up. Thus, we could not estimate the OR of developing secondary TB after baseline LTBI. Further studies are necessary to investigate the role of overcrowding, exposure time, age, and/or BMI in developing secondary TB among overweight HCCs, especially in a low TB-incidence setting.

In summary, our findings support the notion that young HCCs with normal BMI are less likely to acquire LTBI after exposure to a positive sputum smear TB patient. A plausible explanation is that the immune response in lower BMI and/or older age individuals is impaired, and thus IGRA tests are negatively affected.^{11,16,17} Thus, LTBI screening among such an HCC group would result in minimal LTBI cases. Nevertheless, further studies using a much larger sample size are warranted to confirm the role of obesity and age in acquiring LTBI, possibly using a logistic regression with backward analysis adjusting for other variables. For now, we recommend providing close follow-up with HCCs who are aged more than 50 years and overweight in low TB-incidence settings.

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Authors' addresses: Idalina Cubilla-Batista, Nadia Ruiz, and Begoña Gasteluiturri, Laboratorio Clínico, Hospital Rafael Estevez, Aguadulce, Panama, E-mails: idacubilla@yahoo.com, lisy82@hotmail.com, and begogastelu@hotmail.com. Dilcia Sambrano and Amador Goodridge,

Tuberculosis Biomarker Research Unit, Centro de Biología Molecular y Celular de Enfermedades, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT-AIP), Ciudad del Saber, Panama, E-mails: ludy25305@gmail.com and agoodridge@indicat.org.pa. Juan Castillo, Facultad de Informática, Universidad de Panamá, Panama City, Panama, E-mail: juanneloy07@gmail.com. Markela O. de Quinzada, Facultad de Medicina, Universidad de Panamá, Panama City, Panama, E-mail: markelaq@hotmail.com.

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