RePORTBrazil
Regional Prospective Observational Research for Tuberculosis

658

Sex Differences in Latent Tuberculosis Infection among Close Contacts in Brazil

Paul Y. Wada[1], Peter F. Rebeiro[1,2], Allyson G. Costa[3], Rebeca C. Araújo[3], Mariana Araújo-Pereira[4], Beatriz Barreto-Duarte[4], Alexandra B. Souza[3,5], Michael S. Rocha[6], Megan M. Turner[7], Valeria C. Rolla[8], Afrânio L. Kritski[9], Marcelo Cordeiro-Santos[3,5,10], Bruno B. Andrade[4,7,8,11,12,13,14], Timothy R. Sterling[1,7], Regional Prospective Observational Research in Tuberculosis (RePORT) Brazil Consortium

[1]Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, USA. [2]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA. [3]Fundação Medicina Tropical Dr. Heitor Vieira Dourado, Manaus, AM, Brazil. [4]Laboratório de Inflamação e Biomarcadores, Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, BA, Brazil. [5]Programa de Pós-Graduação em Medicina Tropical, Universidade do Estado do Amazonas (UEA), Manaus, AM, Brazil. [6]Multinational Organization Network Sponsoring Translational and Epidemiological Research (MONSTER) Initiative, Instituto Brasileiro para Investigação da Tuberculose, Fundação José Silveira, Salvador, BA, Brazil. [7]Vanderbilt Tuberculosis Center, Vanderbilt University School of Medicine, Nashville, TN, USA. [8]Laboratório de Pesquisa Clínica em Micobacteriose, Instituto Nacional de Infectologia Evandro Chagas, Fiocruz, Rio de Janeiro, RJ, Brazil. [9]Faculdade de Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil. [10]Universidade Nilton Lins, Manaus, AM, Brazil. [11]Curso de Medicine, Universidade Salvador (UNIFACS), Laureate Universities, Salvador, BA, Brazil. [12]Curso de Medicine, Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, BA, Brazil. [13]Faculdade de Tecnologia e Ciências (FTC), Salvador, BA, Brazil. [14]Faculdade de Medicina, Universidade Federal da Bahia, Salvador, BA, Brazil.

BACKGROUND

- Female individuals are less likely to contract and die from active tuberculosis (TB) than males
- Fewer data exist on potential sex differences in latent TB infection (LTBI) among close contacts
- Based on preliminary data, we hypothesized that female close contacts were more likely than males to have LTBI

METHODS

Enrollment:

- Five sites in three regions of Brazil
- August 27, 2015 to June 27, 2019
- Active TB pulmonary cases and associated close contacts

Close Contacts:

- At least four hours with an index case each week
- Follow up every six months for two years

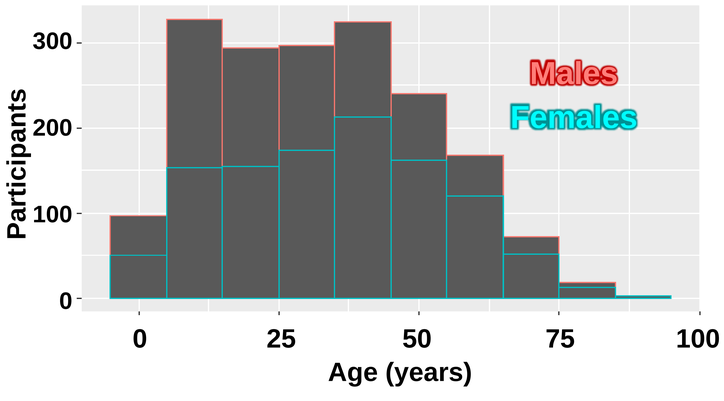
LTBI:

- Positive interferon-gamma release assay (IGRA; QuantiFERON 3rd or 4th generation) at baseline or six months from enrollment

Analysis:

- Multiple imputation with univariate, bivariate, and multivariable regression
- Inverse probability weighting with multivariable regression
- Sensitivity analysis accounting for possible false positive IGRA results

Figure 1: Number of Close Contacts by Age and Sex



Female close contacts were at a small increased risk for IGRA positivity, although not statistically significant after adjustment.

RESULTS

- 1,838 contacts, of whom 1,093 (59.5%) were female
- 504 (46.1%) females and 295 (39.6%) males had a positive IGRA result; 433 (39.6%) and 246 (33.0%) at baseline, and 71 (6.5%) and 49 (6.6%) at six months, respectively
- Unadjusted OR for IGRA positivity in females vs. males was 1.31; unchanged with sensitivity analysis
- Bivariate female-specific ORs ranged from 1.19-1.31
- Multivariable adjusted female-specific OR was 1.10, while weighted female-specific OR was 1.09

Figure 2: Female-Specific Odds Ratios for IGRA Positivity

Adjustment	Female-Specific OR (95% CI)
Unadjusted	1.31 (1.08-1.58)
Bivariate*	
Age	1.19 (0.98-1.45)
Race	1.31 (1.08-1.58)
Region	1.23 (1.01-1.49)
Income	1.24 (1.02-1.50)
Index Case Sex	1.31 (1.08-1.58)
Index Case Cavitary Disease	1.28 (1.06-1.56)
Index Case Smear Positivity	1.28 (1.05-1.55)
Multivariable†	1.09 (0.88-1.34)
Inverse Probability Weighting‡	**1.09 (0.89-1.33)**

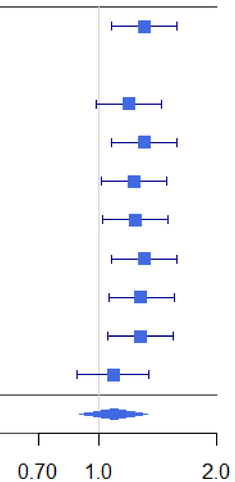


Figure 2:

*For bivariate adjusted OR, IGRA positivity was adjusted for sex and the following factor.

†For multivariable adjusted OR, IGRA positivity was adjusted for sex, age, region, income, index case sex, index case cavitary disease, and index case smear positivity.

‡Inverse probability weighting with multivariable regression adjusted for sex, age, region, index case sex, index case cavitary disease, and index case smear positivity.

Table: Factors Associated with IGRA Positivity

Characteristic	IGRA Negative or Indeterminate N (%) or Median (IQR)	IGRA Positive N (%) or Median (IQR)	Unadjusted OR (95% CI)
Sex			
Male	450 (60.4)	295 (39.6)	Referent
Female	589 (53.9)	504 (46.1)	1.31 (1.08-1.58)
Age	29.5 (14.7-43.6)	36.0 (18.5-49.9)	1.02 (1.01-1.02)
Race			
White	227 (63.6)	130 (36.4)	Referent
Black	173 (46.5)	199 (53.5)	2.01 (1.49-2.70)
Pardo/Mixed	629 (57.8)	460 (42.2)	1.28 (1.00-1.64)
Region			
Rio de Janeiro	301 (44.8)	371 (55.2)	Referent
Manaus	590 (68.6)	270 (31.4)	0.37 (0.30-0.46)
Salvador	145 (48.2)	156 (51.8)	0.87 (0.66-1.15)
Income			
> Minimum	405 (60)	269 (40)	Referent
<= Minimum	375 (52)	353 (48)	1.38 (1.13-1.69)
Index Case, Sex			
Female	393 (55.9)	310 (44.1)	1.04 (0.86-1.26)
Index Case, Cavitary			
Yes	442 (46.4)	511 (53.6)	2.32 (1.89-2.86)
Index Case, Smear			
1-9	124 (71.7)	90 (28.3)	Referent
1+	322 (59.2)	222 (40.8)	1.63 (1.13-2.33)
2+	163 (45.9)	192 (54.1)	2.79 (1.91-4.07)
3+	203 (46.9)	230 (53.1)	2.81 (2.06-4.03)

CONCLUSIONS

- Even with loss of statistical significance, the point estimate for LTBI among female close contacts was higher than among males
- Bivariate adjustments, including for age, had limited effect on female-specific effect size
- Potential for selection bias if differences in enrolled vs not enrolled; however, most close contact likely via household exposure
- If association is confirmed in a larger sample size, studies of underlying biology may be warranted

FUNDING

This work was supported by the Departamento de Ciência e Tecnologia (DECIT) – Secretaria de Ciência e Tecnologia (SCTIE) – Ministério da Saúde (MS), Brazil, and the National Institutes of Allergy and Infectious Diseases: U01 AI069923, R01 AI147765, K01 AI131895.

REFERENCES

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
2. Rhines AS. The role of sex differences in the prevalence and transmission of tuberculosis. Tuberculosis (Edinb). 2013 Jan;93(1):104-7. PMID: 23219235
3. Nhamoyebonde S, Leslie A. Biological differences between the sexes and susceptibility to tuberculosis. J Infect Dis. 2014 Jul 15;209 Suppl 3:S100-6. PMID: 24966189.
4. Horton KC, Hoey AL, Béraud G, Corbett EL, White RG. Systematic Review and Meta-Analysis of Sex Differences in Social Contact Patterns and Implications for Tuberculosis Transmission and Control. Emerg Infect Dis. 2020;26(5):910-919. PMID: 32310063
5. Ting WY, Huang SF, Lee MC, et al. Gender disparities in latent tuberculosis infection in high-risk individuals: a cross-sectional study. PLoS One. 2014;9(11):e110104. PMID: 25369472
6. Reichler MR, Khan A, Yuan Y, Chen B, McAuley J, Mangura B, Sterling TR; Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team. Duration of Exposure Among Close Contacts of Patients With Infectious Tuberculosis and Risk of Latent Tuberculosis Infection. Clin Infect Dis. 2020 Oct 23;71(7):1627-1634. PMID: 32044987
7. Fiske CT, Yan FX, Hirsch-Moverman Y, Sterling TR, Reichler MR; Tuberculosis Epidemiologic Studies Consortium Task Order 2 Team. Risk factors for treatment default in close contacts with latent tuberculous infection. Int J Tuberc Lung Dis. 2014 Apr;18(4):421-7. PMID: 24670696