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Sex and age differences in *Mycobacterium tuberculosis* infection in Brazil

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Abstract

Globally, the prevalence of tuberculosis (TB) disease is higher in males. This study examined the effect of sex and age on *Mycobacterium tuberculosis* (Mtb) infection. Demographic and exposure data were collected on household contacts of sputum smear-positive pulmonary TB patients in Brazil. Contacts with tuberculin skin test induration ⩾10 mm at baseline or 12 weeks were considered Mtb infected. The study enrolled 917 household contacts from 160 households; 508 (55.4%) were female, median age was 21.0 years (range 0.30–87.0) and 609 (66.4%) had Mtb infection. The proportion infected increased with age from 63.3% in girls <5 years to 75.4% in women ⩾40 years and from 44.9% in boys <5 years to 73.6% in men ⩾40 years. Multivariable modelling showed the odds of infection increased between age 5 and 14 years among female contacts (OR 1.5 per 5-year age increase; 95% CI 1.1–2.2; $P = 0.02$) and between ages 0–4 and 15–39 years among male contacts (OR 2.7, 95% CI 0.83–8.9 and 1.1, 95% CI 0.99–1.3 per 5-year age increase; $P = 0.10$, 0.07, respectively). The study suggests that the age at which Mtb infection increases most is different in females compared with males. Studies are needed to explore whether these findings are due to differences in host susceptibility, exposure outside the household or other factors.

Introduction

There were 10.4 million cases of tuberculosis (TB) globally in 2015 and 1.8 million people died from the disease [1]. A state of clinically absent disease with a persistent immune response to stimulation by *Mycobacterium tuberculosis* (Mtb) antigens is defined as latent TB infection [2], hereby referred to as 'Mtb infection' [3]. It is estimated that 5–10% of those with Mtb infection will progress to clinically active disease over their lifetime [2].

Controlling TB requires understanding which epidemiological and medical factors place individuals at higher risk of TB and which are protective. It is surprising that little is known about the potential impact of one's sex given the fact that the male:female ratio of TB cases is 1.7:1 worldwide and as high as 3.1:1 in certain settings such as Vietnam; the excess in male cases becomes most pronounced in early adulthood [1, 4, 5]. Postulated reasons include greater exposure of males to infectious TB cases outside of the home, higher prevalence of risk factors for progression to disease in males (e.g. smoking, alcohol use) and under-detection of females due to differences in the volume or quality of expectorated sputum or access to care, although the latter likely varies greatly by setting [6–10].

Data from community-based surveys suggest that some of the sex differences observed in active TB may reflect differences in Mtb infection prevalence between males and females [4, 6, 11]. Surveys conducted between 1948 and 1951 in 15 countries concluded that the prevalence of infection was equal in males and females at younger ages, but that around puberty, male prevalence began to exceed that of females [12]. Similar patterns have been found more recently in India, Korea and several African countries [4, 13–16]. As with the active TB sex differences, this increased likelihood of infection in males has been attributed to greater exposure in the community after adolescence, but this hypothesis is difficult to confirm [6].

In the present study, we assess how the prevalence of Mtb infection varies with sex and age. We sought to determine whether there are biological sex differences that could affect the risk of Mtb infection. By using data from a study of pulmonary TB cases and their household contacts in Brazil, we overcame one major limitation of community-based studies in that comparable household exposure to infectious cases was known.

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Materials and methods

Study design

This was a secondary data analysis using previously collected data from a household contact study conducted in Vitória, Brazil between 2008 and 2013. Study methods have been reported previously [17]. Briefly, inclusion criteria for pulmonary TB patients were (1) age ⩾18 years; (2) cough ⩾3 weeks; (3) new TB episode with sputum smear ⩾2+ acid-fast bacilli (AFB) and subsequent Mtb growth in culture; and (4) having ⩾3 household contacts. Index TB patients who were HIV-infected (or refused testing) or had a history of TB treatment were excluded from the primary study of the effect of Mtb strain on disease transmission. The rationale behind this was that HIV infection could alter host-susceptibility to and/or transmission of TB disease [18, 19] and prior treatment could affect the current strain of Mtb and the immune response [20]. In addition, the incidence rate of HIV and TB coinfection was relatively low in Brazil (<10/100 000 population) [21], preventing robust analysis in this coinfected sub-population without a marked increase in study sample size. All household contacts of the index case were enrolled within 2 weeks of index case enrolment if they met ⩾1 of the following culturally-adapted criteria for close contact with the index case for ⩾3 months: (1) sleeping under the same roof or sharing meals ⩾5 days/week; (2) watching television nights/weekends, or; (3) other significant contact (85% visited the household ⩾18 days/month). For the purposes of this analysis, household contacts were excluded if they had a history of TB disease.

Study measurements

Demographic and clinical data were collected to assess infectiousness of index cases and household contact exposure. Index case cough severity was measured using a self-reported visual analogue cough scale (1–10 for increasing severity) [22], which was categorised into three groups (0–3, 4–6 and 7–10). Functional status was recorded using the Karnofsky performance scale (0–100; ⩽70 represents a significant restriction of daily activities) [23]. Up to three sputum specimens were collected for AFB smear microscopy and culture at enrolment. Chest X-rays (CXR) were performed and scored based on a validated score (percentage of lung infected plus 40 points for cavitation) [24].

Clinical information was collected on household contacts and all TB suspects were referred for further evaluation to the Municipal TB clinic. Exposure of the household contact to the index case was assessed by sleeping proximity, contact hours, whether the contact was the caregiver, a number of meals shared and relationship (categorised as spousal, parental/child or other). Bacille Calmette-Guérin (BCG) vaccination status was based on visualisation of a scar; uncertain scar status was considered vaccinated. A tuberculin skin test (TST; Tubersol®, Sanofi Pasteur) was performed at baseline; those with TST <10 mm had a repeat TST after 8–12 weeks to identify TST converters. To ensure consistency in test performance, staff were trained in TST placement and reading and completed inter- and intra-reader evaluations ($\kappa > 90\%$) [17]. For this analysis, Mtb infection was defined as TST ⩾10 mm at baseline or follow-up.

Statistical methods, ethics

We assessed univariate associations between index case and contact characteristics and Mtb infection status (our outcome of interest) by considering these one at a time in a model with contact age, sex and their interaction (our covariates of principal interest). Attributes with $P < 0.10$ in univariate analyses and/or biologically plausible attributes were included in the multivariable logistic regression models predicting the same outcome of interest. Both univariate and multivariable analyses were performed by logistic regression models fit using generalised estimating equations with a compound symmetry structure to account for household clustering. Using a penalised spline transformation and a piecewise-linear model of contact age, we established age categories of 0–4, 5–14, 15–39 and ⩾40 to determine the relationship between age and odds of Mtb infection in contacts within each age group. The oldest age category was chosen as such because once individuals were 40 years old, the risk of TST infection did not change with age. We report odds ratios for a 1- and 5-year age increase. We report the adjusted probability of Mtb infection by age and sex by transforming the odds to the probability scale and calculate corresponding Wald-type confidence intervals. Analyses were conducted in SAS 9.3 (SAS Institute, Cary NC) and R version 3.2.2 (r-project.org).

The study was approved by the Comitê de Ética em Pesquisa do Centro de Ciências da Saúde – Universidade Federal do Espírito Santo, the Comissão Nacional de Ética em Pesquisa (CONEP) and the Institutional Review Boards of Boston University Medical Campus and New Jersey Medical School–Rutgers University (formerly University of Medicine and Dentistry of New Jersey). Written informed consent and assent were obtained in accordance with age-specific ethical guidelines from participating institutions.

Results

Index case and contact characteristics

Details of study non-participation have been reported previously [17]. Among the 160 participating index cases, the median age was 35.7 years (range: 18.0–81.8 years) and 107 (66.9%) of them were male (Table 1). The median duration of symptoms prior to enrolment was 13.0 weeks (range: 2.0–52.2 weeks). The median CXR score was 73.3 (range: 0.0–140.0); sputum AFB grade was 3+ in 128 (80.0%) of cases.

Among 934 household contacts, 17 (2.0%) had a history of TB disease and were excluded. For the remaining 917 household contacts, they tended to be of the opposite gender of the index case ($P = 0.03$), their median age was 21.0 years (range: 0.30–87.0 years), 508 (55.4%) of them were female and 688 (75.0%) were BCG-vaccinated (Tables 2 and 3). The largest proportion of contacts (404; 44.1%) slept in a different room from the index case but in the same house. Contacts commonly spent ⩽6 h (281; 30.6%) or 7–12 h (277; 30.2%) per day with the index case; most (62.4%) shared at least one meal with the index case. Index cases were parents or children of 319 (34.8%) contacts, brothers or sisters of 142 (16.0%), spouses of 94 (10.3%), other relatives of 247 (27.0%) and unrelated to 115 (13.0%). Male household contacts were younger than female household contacts (median 19.0 *vs.* 23.0 years; $P < 0.01$), less likely to provide care to the IC (15.2% *vs.* 36.0%; $P < 0.01$) and more likely to have a detectable BCG scar (76.8% *vs.* 73.6%; $P = 0.03$).

Mtb infection by household contact age and sex

Overall, 609 (66.4%) household contacts had Mtb infection (Table 3). In a univariate analysis to identify potential predictors

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Table 1. Characteristics of index pulmonary tuberculosis case-patients in Vitória, Brazil ($N = 160$)

Characteristics	Number of cases (%)
Age, median (range) in years	35.7 (18, 81.8)
Male sex, *n* (%)	107 (66.9)
Duration of illness, weeks, median (range)	13 (2, 52.2)
Visual analogue cough scale, *n* (%)	
0–3	22 (13.8)
4–6	43 (26.9)
7–10	90 (56.3)
Missing	5 (3.1)
Karnofsky score, *n* (%)[a]	
⩽70	6 (3.8)
⩾80	154 (96.3)
Sputum AFB grade, *n* (%)	
1+	N/A
2+	32 (20)
3+	128 (80)
Cavities on CXR, *n* (%)	
Absent	37 (23.1)
Present	120 (75)
Missing	3 (1.9)
CXR score, median (range)	73.3 (0, 140)
Occupation, *n* (%)	
At home	62 (38.8)
Office worker	19 (11.9)
Construction	19 (11.9)
Other	60 (37.5)
Number of HHCs, median (range)	5 (3, 18)

AFB, acid-fast bacilli; N/A, not applicable; CXR, chest X-ray; HHCs, household contacts.
[a]Karnofsky score = functional ability performance scale.

of Mtb infection, age and sex emerged as significant predictor variables (*P*-values of <0.01 and 0.05, respectively, Supplemental Table S1). The unadjusted distribution of Mtb infection with age showed that the proportion of Mtb-infected household contacts increased with age from 63.3% in girls age <5 years and 44.9% in boys <5 years to relatively equal proportions in ages >5 years (Fig. 1). By age ⩾40, the proportion of TST-positives was 73.6% in males and 75.4% in females (Fig. 1). The differences in Mtb infection between sexes were not significant within any age category in the unadjusted analysis.

Covariates in the multivariable models were biologically plausible and/or significant on univariate analysis ($P < 0.10$ in Supplementary Table S1) and included measures of index case disease severity (visual analogue cough scale category, AFB grade, CXR score), contact susceptibility (BCG status) and exposure to index case (sleeping proximity, hours of contact, relation). The final multivariable models included 827 contacts (Table 4); because of missing data, 90 were excluded (34 missing TST results, 35 missing BCG and 36 missing relevant exposures as seen in Table 3). The odds of Mtb infection increased with age until 40 years in both sexes but was not significantly different between females and males in any age group (Table 4). Among females, the odds increased most between 5 and 14 years of age (OR 1.5 per 5-year increase; 95% CI 1.1–2.2; $P = 0.02$). In contrast, males had the greatest increase of Mtb infection between 0 and 4 years of age (OR 2.7 per 5-year increase; 95% CI 0.83, 8.9; $P = 0.10$) but the only borderline statistically significant increase in infection occurred between 15 and 39 years of age (OR 1.1 per 5-year increase; 95% CI 0.99–1.3; $P = 0.07$). Within each sex, the rate of change of Mtb infection was not significantly different between age categories. By age 14, females had a somewhat higher adjusted probability of infection compared with males (0.60, 95% CI 0.58–0.62 in females *vs.* 0.53, 95% CI 0.51–0.55 in males). Among older contacts, ages 15–39 years, the probability of infection was similar between sexes (range: 0.62–0.74 for females; range: 0.54–0.75 for males).

Discussion

The objective of this study was to determine whether there are potential sex differences in Mtb infection by analyzing results from a household contact study in Brazil. We assessed differences in Mtb infection by sex and age that occurred independent of exposure to the TB case. This study found 66.4% of household contacts had evidence of Mtb infection compared with the community prevalence of 33.0% [2], reflecting greater exposure in a closed setting. The prevalence of infection increased with age, with the unadjusted analysis showing a 12.0% and 29.0% difference between the youngest and the oldest age groups in females and males, respectively. In multivariable models, the increase in infection was significant at a younger age in females (ages 5–14 years) in contrast to males, in whom the increase in infection was borderline significant at an older age (ages 15–39 years). Young female contacts (age 5–14) also had an overall higher probability of infection within that age group that was not seen for males the same age nor for females of other age groups. Sex differences in Mtb prevalence disappeared by age 40.

Household contact studies have shown increased Mtb infection risk with older age [8, 16, 25–27] and among male contacts for some [8, 16]. To our knowledge, however, only one other household contact study directly examined the interaction of age and sex [8]. In a study in The Gambia, the odds of infection increased with age similarly in both sexes up to age 15, after which males were at a greater risk; the model did not examine how the effects varied within age groups after age 15. Our study, by contrast, evaluated the effect of sex in older age groups as well and we found young girls and older men were more likely to be infected. It is possible that our findings were different because we controlled for other factors that may have influenced Mtb infection (including index case sputum grade and contact hours between case and contact, among others). Another possibility is that we observed sex differences at a younger age because social interactions and exposure within households and the community differ between countries.

There are several potential explanations why young girls (age 5–14) are at increased odds of Mtb infection. It is plausible that young girls are more exposed to Mtb in the household than young boys, perhaps because they perform more activities within the home; however, we controlled for the amount of time spent with the index case and whether the household contact was their caregiver. Another explanation could be biological

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Table 2. Index case characteristics for 917 household contacts in Vitória, Brazil, stratified by the gender of the contacts[a]

Characteristics	Total $N = 917$ HHC	Male HHC $N = 409$ HHC (44.6%)	Female HHC $N = 508$ HHC (55.4%)	*P*-value
Age, median (range) in years	35.6 (18–81.8)	35 (18–81.8)	35.7 (18–81.8)	0.84
Male sex of index case, *n* (%)	608	262 (64.1)	346 (68.1)	0.03
Duration of illness, weeks, median (range)	13 (2–52.2)	13 (2–52.2)	13 (2–52.2)	0.80
Visual analogue cough scale, *n* (%)				0.04
0–3	149 (16.3)	63 (15.4)	86 (16.9)	
4–6	228 (24.9)	113 (27.6)	115 (22.6)	
7–10	505 (55.1)	217 (53.1)	288 (56.7)	
Missing	35 (3.8)	16 (3.9)	19 (3.7)	
Karnofsky score, *n* (%)[b]				0.13
⩽70	45 (4.9)	18 (4.4)	27 (5.3)	
⩾80	872 (95.1)	391 (95.6)	481 (94.7)	
Sputum AFB grade, *n* (%)				0.28
1+	NA	NA	NA	
2+	173 (18.9)	73 (17.9)	100 (19.7)	
3+	744 (81.1)	336 (82.2)	408 (80.3)	
Cavities on CXR, *n* (%)				
Absent	228 (24.9)	98 (24)	130 (25.6)	0.83
Present	677 (73.8)	308 (75.3)	369 (72.6)	
Missing	12 (1.3)	3 (0.70)	9 (1.8)	
CXR score, median (range)	73.3 (0–140)	73.3 (0–140)	73.3 (0–140)	0.55
Number of HHCs, median (range)	6 (3–18)	6 (3–18)	6 (3–18)	0.37

HHCs, household contacts; AFB, acid-fast bacilli; NA, not applicable; CXR, chest X-ray.
[a]Data for each index case are reported as many times as the number of household contacts they have (e.g. data are reported three times for the same index case if they have three household contacts).
[b]Karnofsky score = functional ability performance scale.

differences in susceptibility to Mtb infection. Studies in mice have shown that sex hormones may alter susceptibility to mycobacterial infections [28, 29]. In experimental conditions, estrogen is protective against Mtb infection, increasing the Th1 immune response, cytokine production (i.e. TNFα, IFNγ) and macrophage activity that facilitate control of Mtb [30–32]. Since girls 5–14 years are mostly pre-pubertal (average age of menarche in Brazil is 11.7 years) [33] and the suggested protective effect of estrogen has not yet become dominant, they could be more susceptible to infection.

Our finding of increasing odds of Mtb infection in older males has been seen in contact studies [8, 16]. It has been suggested that older males have increased exposure through greater social contact, particularly to other adult males in the community [34]. An increased prevalence of risk factors among males like smoking [9] and alcoholism [35], which increase susceptibility to Mtb infection, could also explain the higher rate of infection in older males. Biological differences between sexes in immune responses to Mtb infection may play a role as well [36].

The increased odds of infection for males age 15–39 years is notable given the higher prevalence of TB disease in adult males compared with adult females [1]. The increased prevalence of TB disease in adult males may reflect the fact that those recently infected are more likely to develop the active disease; hence more Mtb infection in adult males suggests greater TB disease prevalence. Although our study was not designed to assess progression to disease, it is also possible that due to biological reasons or comorbidities (e.g. alcohol use), males may be more likely to progress from infection to TB disease [6–10]. Gender differences in rates of progression to disease have been reported previously [4].

Our study had a few limitations. Although we attempted to measure interaction between the household contact and index case as quantitatively as possible (e.g. number of hours spent together, number of meals shared, bed sharing, etc), one cannot easily measure all interactions between individuals; hence, it is possible that the observed differences in infection reflected unmeasured differences in household exposure. Future studies could evaluate more objective measures of exposure to Mtb (such as aerosol production) [37] as well as sociological measurements of family interactions to better define transmission dynamics. Similarly, we were unable to assess exposure to all potentially infectious individuals outside the household, so it is plausible (and likely) that some of the risk observed in older males reflected community exposure. Even so, the observed sex differences in the younger ages still underscore that biologic differences may play a role in the timing of Mtb infection. Index cases with HIV infection and household contacts with a prior history of TB disease were excluded from the analysis and therefore extrapolation of our results to these populations may be inappropriate. Furthermore, we used a visible scar as evidence of BCG vaccination, but scar formation can be variable [38, 39]. We defined infection as TST ⩾10 mm to standardise interpretation of results irrespective of

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Table 3. Characteristics of household contacts of pulmonary tuberculosis case-patients in Vitória, Brazil ($N = 917$)

Characteristics	Total $N = 917$	Male $N = 409$ (44.6%)	Female $N = 508$ (55.4%)	*P*-value
Age, median (range) in years	21 (0.30, 87)	19 (0.30–79)	23 (0.30–87)	<0.01
BMI, kg/m^2, median (range)	21.3 (4.1, 48.4)	20.2 (4.7, 40.9)	21.8 (4.1, 48.4)	<0.01
TST Result, *n* (%)[a]				0.09
Positive	609 (66.4)	255 (62.4)	354 (69.7)	
Negative	274 (29.9)	131 (32)	143 (28.2)	
Missing	34 (3.7)	23 (5.6)	11 (2.2)	
BCG scar *n* (%)				0.03
Absent/uncertain	194 (21.2)	72 (17.6)	122 (24)	
Present	688 (75)	314 (76.8)	374 (73.6)	
Missing	35 (3.8)	23 (5.6)	12 (2.4)	
Sleeping proximity to IC, *n* (%)				0.43
Same room, same bed	140 (15.3)	54 (13.2)	86 (16.9)	
Same room, different bed	69 (7.5)	36 (8.8)	33 (6.5)	
Different room, same house	404 (44.1)	189 (46.2)	215 (42.3)	
Other	269 (29.3)	107 (26.1)	162 (31.9)	
Missing	35 (3.8)	23 (5.6)	12 (2.4)	
Hours contact per day with IC, *n* (%)				0.17
⩽6 h	281 (30.6)	122 (29.8)	159 (31.3)	
7–12 h	277 (30.2)	122 (29.8)	155 (30.5)	
13–18 h	221 (24.1)	107 (26.2)	114 (22.4)	
>18 h	102 (11.1)	34 (8.3)	68 (13.4)	
Missing	36 (3.9)	24 (5.9)	12 (2.4)	
Meals per day with IC, *n* (%)				0.20
None	310 (33.8)	143 (35)	167 (32.9)	
1	204 (22.3)	82 (20.1)	122 (24)	
2	168 (18.3)	78 (19.6)	94 (18.8)	
3	200 (21.8)	86 (21)	114 (22.4)	
Missing	35 (3.8)	23 (5.6)	12 (2.4)	
Provided care for IC, *n* (%)				<0.01
Yes	245 (26.7)	62 (15.2)	183 (36)	
No	637 (69.5)	324 (79.2)	313 (61.6)	
Missing	35 (3.8)	23 (5.6)	12 (2.4)	
IC relation to HHC, *n* (%)				0.18
Child/parent	319 (34.8)	145 (34.4)	180 (35.1)	
Spouse	94 (10.3)	30 (7.3)	64 (12.6)	
Other	504 (55)	237 (58)	267 (52.6)	
Occupation, *n* (%)				<0.01
At home	202 (22)	60 (14.7)	142 (28)	
Office worker	42 (15.5)	21 (5.1)	21 (4.1)	
Other	673 (73.4)	328 (80.2)	345 (67.9)	
Education, *n* (%)				0.39
None/Less than primary	575 (62.7)	259 (63.3)	316 (62.2)	
Primary	151 (16.5)	67 (16.4)	84 (16.5)	

(*Continued*)

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Table 3. (*Continued.*)

Characteristics	Total $N = 917$	Male $N = 409$ (44.6%)	Female $N = 508$ (55.4%)	*P*-value
Secondary	141 (15.4)	54 (13.2)	87 (17.1)	
Post-secondary	14 (1.5)	6 (1.5)	8 (1.6)	
Missing	36 (3.9)	23 (5.6)	13 (2.5)	

BMI, body mass index; TST, tuberculin skin test; BCG, Bacillus Calmette-Guérin vaccine; IC, index case; HHC, household contact.
[a]TST positive if induration ⩾10 mm.

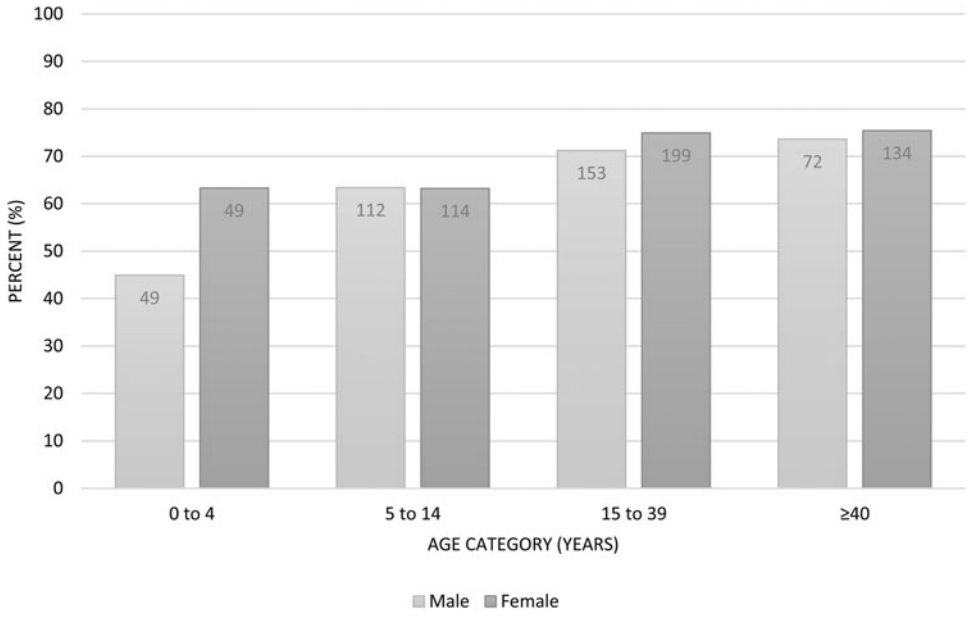

Fig. 1. Distribution of Tuberculin Skin Test positivity (⩾10 mm) of all household contacts by age categories and sex. Numbers within each bar represents the number of study subjects in that category. Differences between males and females within each age group were not significant (*P*-values <0.05).

Table 4. Adjusted 1- and 5-year odds of *Mycobacterium tuberculosis* infection stratified by age and sex of household contact ($N = 827$)[a]

	0–4 years OR (95% CI)[b]	5–14 years OR (95% CI)[b]	15–39 years OR (95% CI)[b]	⩾40 years[c]
Male HHCs[d]	$P = 0.10$*	$P = 0.20$*	$P = 0.07$*	
1-year age increase	1.2 (0.96–1.6)	1.1 (0.97–1.1)	1.0 (0.99–1.1)	N/A
5-year age increase	2.7 (0.83–8.9)	1.3 (0.88–1.9)	1.1 (0.99–1.3)	N/A
Female HHCs[d]	$P = 0.85$*	$P = 0.02$*	$P = 0.49$*	
1-year age increase	1.0 (0.80–1.3)	1.1 (1.0–1.2)	1.0 (0.98–1.0)	N/A
5-year age increase	1.1 (0.34–3.8)	1.5 (1.1–2.2)	1.0 (0.92–1.2)	N/A

HHC, Household contact; N/A, Not applicable.
[a]Variables included in the multivariable model: household contact age categories, sex, interaction term of age category and sex, sleeping proximity to the index case, hours of contact with the index case, relationship to the index case and presence of BCG scar; and index case sputum smear grade, visual analogue cough scale category and chest X-ray score.
[b]Odds ratio and 95% confidence interval of Mtb infection with increasing age. Within each sex, the rate of change of Mtb infection was not significantly different between age categories.
[c]Odds ratio for this age group not reported since the odds are flat for this group and hence there is no change in odds ratio as age increases.
[d]Within each age group, the rate of change of Mtb infection was not significantly different between sexes.
**P*-values for changes in odds ratios within each age category.

BCG vaccination and non-tuberculous mycobacteria (NTM) exposure, which could result in false-positive reactions. It has been shown, however, that false-positive TST reactions due to BCG vaccination at infancy (as in Brazil) and NTM sensitivity are relatively low (~8.5% and ~2.3%, respectively) [40]. Notably, our results were similar when defining infection as TST ⩾5 mm and ⩾10 mm (data not shown). Lastly, it is possible that our *P*-values could have been underestimated since we determined the parameters of a penalised spline used to determine our model from the data we ultimately used in the analysis.

Conclusions

The odds and timing of Mtb infection in close contacts of TB cases varies by their sex. We found the odds of Mtb infection increased significantly with age in young girls (age 5–14) while

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in young adult males (age 15–39), the increase in odds was borderline significant. Studies are needed to determine whether the observed differences are due to sex-based, hormonally mediated changes in biological susceptibility, particularly the development of a protective effect for girls after menarche.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0950268818001450.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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