Clinical Infectious Diseases

MAJOR ARTICLE

Excess Risk of Tuberculosis Infection Among Extra-household Contacts of Tuberculosis Cases in an African City

Robert Kakaire,[1,2,a] Noah Kiwanuka,[3] Sarah Zalwango,[4] Juliet N. Sekandi,[1,2] Trang Ho Thu Quach,[1,2,5] Maria Eugenia Castellanos,[1,2] Frederick Quinn,[6] and Christopher C. Whalen[1,2]

[1]Global Health Institute, College of Public Health, University of Georgia, Athens, Georgia, USA, [2]Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, Georgia, USA, [3]Department of Epidemiology and Biostatistics, School of Public Health, College of Health Sciences, Makerere University, Kampala, Uganda, [4]Kampala Capital City Authority, Kampala, Uganda, [5]Faculty of Pharmacy, Ho Chi Minh City University of Technology, Ho Chi Minh City, Vietnam, and [6]Department of Infectious Diseases, College of Veterinary Medicine, University of Georgia, Athens, Georgia, USA

Background. Although households of tuberculosis (TB) cases represent a setting for intense transmission of *Mycobacterium tuberculosis*, household exposure accounts for <20% of transmission within a community. The aim of this study was to estimate excess risk of *M. tuberculosis* infection among household and extra-household contacts of index cases.

Methods. We performed a cross-sectional study in Kampala, Uganda, to delineate social networks of TB cases and matched controls without TB. We estimated the age-stratified prevalence difference of TB infection between case and control networks, partitioned as household and extra-household contacts.

Results. We enrolled 123 index cases, 124 index controls, and 2415 first-degree network contacts. The prevalence of infection was highest among household contacts of cases (61.5%), lowest among household contacts of controls (25.2%), and intermediary among extra-household TB contacts (44.9%) and extra-household control contacts (41.2%). The age-adjusted prevalence difference between extra-household contacts of cases and their controls was 5.4%. The prevalence of infection was similar among the majority of extra-household case contacts and corresponding controls (47%).

Conclusions. Most first-degree social network members of TB cases do not have adequate contact with the index case to experience additional risk for infection, but appear instead to acquire infection through unrecognized exposures with infectious cases in the community.

Keywords. tuberculosis; latent tuberculosis infection; household contact investigation; transmission; tuberculin skin test.

The global burden of tuberculosis (TB) peaked in 2000 and has since declined by 1.5% per year. Although encouraging, there are unambiguous signs that global control of TB is not yet achieved, especially in sub-Saharan Africa. Tuberculosis is the ninth leading cause of death worldwide and the leading cause of death from an infectious disease, as >1.3 million people die per year [1].

The cornerstone of TB control today depends on the detection and treatment of infectious cases. The household of an infectious index case an ideal setting for active case finding [2, 3] because it is an environment of intense transmission of *Mycobacterium tuberculosis* [4]. The effectiveness of household investigation on TB control, however, is unclear [5–7]. One reason for its limited effectiveness is that <20% of TB infection in a community is attributable to household exposures [8–12], meaning that most new infections occur through exposures outside of the household. What remains unknown are the patterns of adequate contact between infectious cases and their contacts in the community. Anecdotal reports of well-documented outbreaks show that TB is transmitted in community settings, such as homeless shelters, bars, prisons, and hospitals [13–16], but these studies do not quantify the rate of transmission nor do they delineate the full scope of interactions between index cases and their extra-household contacts.

The current study was designed to estimate community transmission of *M. tuberculosis* by evaluating both household and extra-household contacts of infectious index cases of TB. Our hypothesis was that infectious TB cases place some of their first-degree social network members at high risk for infection during the weeks and months before diagnosis whether they live in the household or not. To address this hypothesis, we used self-reported social networks of TB cases to create a formal framework for estimating both household and extra-household transmission.

METHODS

Between June 2013 and January 2017, we conducted a cross-sectional study of index TB cases and their first-degree contacts

---

Received 4 June 2020; editorial decision 2 October 2020; published online 16 October 2020.

[a]R. K. and N. K. contributed equally to this work.

Correspondence: C. C. Whalen, Global Health Institute, College of Public Health, 100 Foster Drive, Athens, GA 30602 (ccwhalen@uga.edu).

Clinical Infectious Diseases® 2021;73(9):e3438–45

DOI: 10.1093/cid/ciaa1556

within egocentric social networks in Lubaga Division, Kampala, Uganda. We enrolled index TB cases 15 years or older through Lubaga Hospital and the Kitebi and Kawaala clinics of the Kampala Capital City Authority. All TB cases were registered in and treated by the Uganda National Tuberculosis Control Program. A case of infectious TB was defined as a patient with symptoms consistent with pulmonary TB who had at least 1 positive sputum smear for acid-fast bacilli. Index controls were selected from residents of Lubaga Division who did not have TB as determined by symptom screening and were frequency-matched to the index cases based on age, sex, and parish.

To identify first-degree contacts from the networks of TB cases and index controls, we performed structured interviews of index participants to list individuals with whom the participant had a personal relationship. To limit recall bias, we used standard prompts and recent time-frames [17]. Contacts were classified as household contacts if they resided in the household of an index participant for the previous 3 months and had eaten meals in the household at least weekly; otherwise, contacts were classified as extra-household.

Index participants and first-degree contacts in the study were evaluated for active TB, latent TB infection (LTBI), and human immunodeficiency virus (HIV) infection using routine interviews and diagnostic testing. All TB cases were confirmed by growth of *M. tuberculosis* in culture. The tuberculin skin test was performed using the Mantoux method (Tubersol, Sanofi Pasteur). LTBI was defined as an induration of ≥10 mm among HIV-seronegative contacts and 5 mm among children and HIV-seropositive contacts [18]. Tuberculous infection was defined as infection with *M. tuberculosis*, either as active TB or as LTBI. Contacts who did not meet definitions for TB infection were classified as uninfected.

The main objective of this analysis was to determine the excess risk of TB by comparing the prevalence of TB infection among the first-degree contacts of the index cases and controls in both household and extra-household settings. The sample size was chosen to detect a 12.5% difference between household contacts of index cases and their controls and a 6.5% difference between extra-household contacts of index cases and controls, using a 5% error and 80% power. After determining the characteristics of index TB cases and frequency-matched controls, we stratified the analysis by household or extra-household status within the index groups of case or control to compare the distributions of the prevalence of infection among contacts. Because of imbalances in age, we stratified further by age category (<15 years and ≥15 years) to evaluate for confounding and effect modification. To estimate the excess risk of TB infection [19] among the household and extra-household contacts of index cases, we calculated the age-adjusted prevalence difference between contacts of index cases and controls. We also identified a subset of close extra-household contacts to determine whether social proximity was associated with infection. We categorized close contact using kin relationship to the index and the index's perception of social closeness. We performed a hierarchical, generalized linear model [20] to account for nested exposure within the social networks of index cases and potential residual confounding. We estimated the prevalence difference according to contact setting, controlling sex, and HIV serostatus, and stratified by age category. Data were analyzed using SAS version 9.3 and R version 3.5.1 software packages.

The study was approved by the University of Georgia Institutional Review Board, the Higher Degrees Research and Ethics Committee at Makerere University School of Public Health, and the Uganda National Council for Science and Technology.

RESULTS

We enrolled 247 index participants: 123 TB cases and 124 frequency-matched controls (Figure 1). Index participants were similar as regards to matched characteristics, education, and religious affiliation (Table 1), though differed by marital status. The mean age was 30.6 years (standard deviation [SD], 10.1 years) for index cases and 32.0 years (SD, 9.5 years) for controls. HIV prevalence was higher among TB cases than among index controls. The majority of cases had a smear grade of 3+; by design, index controls were smear negative. Index participants reported 2415 first-degree contacts, of whom 2050 (85%) were traced and agreed to participate in the study (Figure 1). Of the 2050 contacts, 1006 (49%) were contacts of TB cases and 1044 (51%) were contacts of index controls. Of the 1006 TB case contacts, 382 (38%) were household contacts and 624 (62%) were extra-household contacts; of the 1044 control contacts, 214 (21%) were household contacts and 830 (79%) extra-household contacts. Child contacts of index cases outnumbered those of index controls (267 and 172, respectively); they were similar in all characteristics except for religious affiliation (Table 2). Adult contacts of index cases were more often HIV seropositive, female, and lived in the household of the index case (Table 2).

Of the 1006 TB case contacts, 515 had TB infection for a prevalence of 51.2% (95% confidence interval [CI], 48.1%–54.3%) and 19 (1.9%) had TB disease (1 with HIV on antiretroviral therapy). Of the 1044 control contacts, 396 had TB infection for a prevalence of 37.9% (95% CI, 35.0%–40.9%) and 4 (0.4%) had TB disease without HIV coinfection. The prevalence of TB infection was highest among household contacts of TB cases (61.5%; Table 3), lowest among household contacts of controls (25.2%), and intermediary among extra-household contacts of TB cases (44.9%) and extra-household contacts of controls (41.2%).

When we stratified by age category among household contacts of TB cases, the risk of infection was 50.6% for children aged <5 years, 62.6% for children aged 5–14 years, and 65.3% for contacts 15 years or older (Table 4; Figure 2). The adjusted overall prevalence difference between household contacts of index cases and index controls was 36.8% (95% CI, 26.8%–46.9%), but was lower among older contacts (31.7%; Table 4) compared with younger ones (47.2%). The prevalence of TB

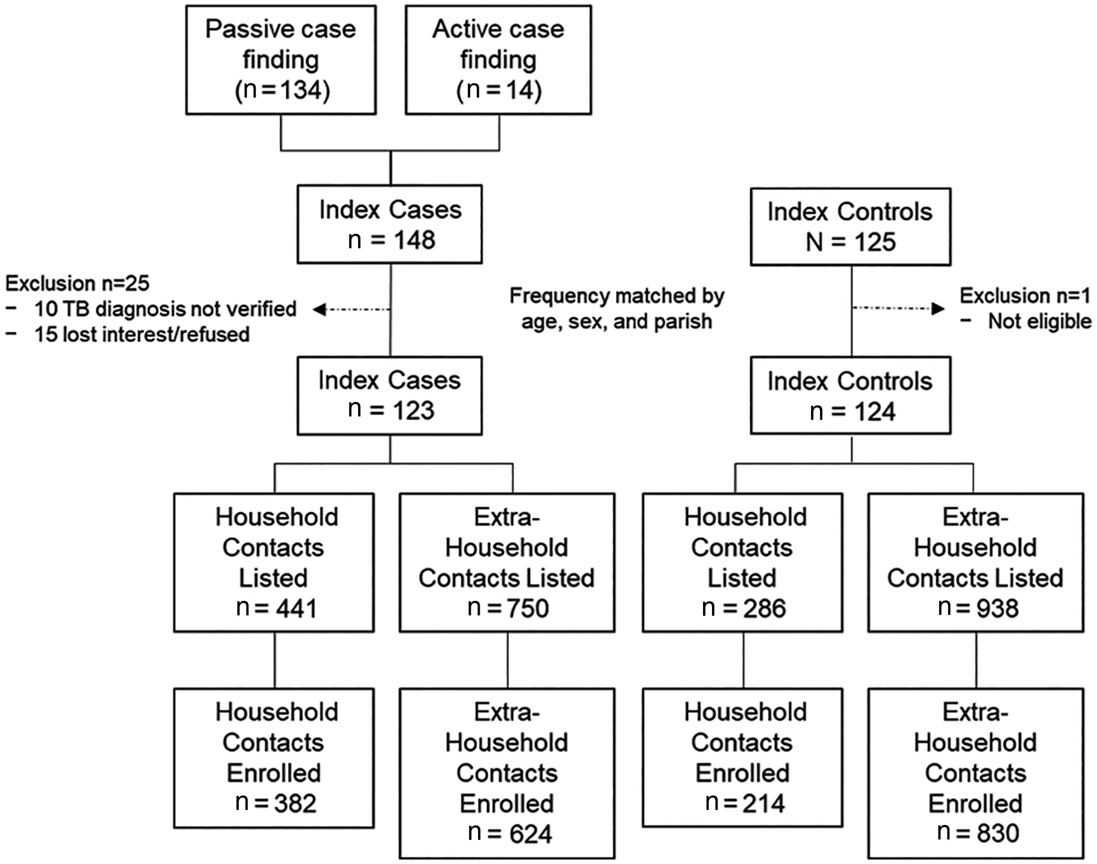

Figure 1. Enrollment of index participants and social network members. Abbreviation: TB, tuberculosis.

infection among extra-household contacts of index cases was 5 times greater among older contacts compared with children (50.5% vs 10.3%; *P* = .000). The adjusted prevalence difference between extra-household contacts of index cases and controls was 5.4% (95% CI, .6%–10.1%). Despite the difference in prevalence by age, the prevalence difference was similar for younger (6.8%; Table 4) and older (7.6%) contacts.

When stratified by sputum smear grade, the prevalence difference increased among household contacts, from 23.4% (95% CI, 6.2%–40.7%) to 32.5% (95% CI, 17.7%–47.2%) to 38.6 (95% CI, 30.6%–46.6%) for exposure to cases with low, 2+, and 3+ sputum smear grade, respectively. The crude prevalence difference among extra-household contacts did not vary according to smear grade.

Among 597 extra-household contacts of index cases with complete social network information, 521 contacts (87%) were older than 15 years. In this group, a subset of contacts had a prevalence of TB infection comparable to that of household contacts (64.7% [95% CI, 55.3%–74.1%]). This subset comprised 70 close family members and 32 close work associates (Figure 3). This subset accounted for 19.6% of older extra-household contacts. The remaining extra-household contacts (n = 419) of index cases had a prevalence that was similar to the prevalence in adult extra-household contacts of index controls (47.3% vs 45.8%, respectively; *P* = .65). Of 76 child extra-household contacts, 21 were close family members, and only 2 of these family members (9.5%) had TB infection.

DISCUSSION

In this study, we used first-degree contacts in egocentric social networks of infectious index TB cases to create a framework for understanding transmission of *M. tuberculosis* in an African urban setting. When we partitioned the social network members into household and extra-household components, we found, as expected, that the household of index cases was an environment for intense transmission of *M. tuberculosis* [6], but outside of the household, we found that risk of infection attributable to the index case was modest and substantially lower than household exposure. This modest excess risk of infection due to extra-household exposure to infectious index cases may not fully account for the high prevalence of infection observed among adults in the community.

A fundamental challenge in understanding *M. tuberculosis* transmission in the community is to characterize social mixing between cases and contacts, especially over long and variable infectious periods of cases. To add structure to these mixing patterns, we expanded our previous household contact study design [21, 22] by enrolling first-degree members from

Table 1. Comparison of Demographic and Clinical Characteristics of Tuberculosis Index Cases and Matched Index Controls

Characteristics	TB Cases (n = 123, %)	Matched Controls (n = 124, %)	All (N = 247)	*P* Value
Sex, No.				
Male	84 (68)	85 (69)	169 (68)	1.000
Female	39 (32)	39 (31)	78 (32)	
Age category, y				
15–19	5 (4.1)	3 (2.4)	8 (3.2)	.392
20–29	59 (48.0)	49 (39.5)	108 (43.7)	
30–39	37 (30.1)	42 (33.9)	79 (32.0)	
≥40	22 (17.9)	30 (24.2)	52 (21.1)	
Marital status				<.001
Married	57 (46.3)	91 (73.4)	148 (59.9)	
Not married	66 (53.7)	33 (26.6)	99 (40.1)	
Religion				.785
Christian	86 (69.9)	89 (71.8)	175 (70.9)	
Muslim	27 (22.0)	28 (22.6)	55 (22.3)	
Other	10 (8.1)	7 (5.6)	17 (6.9)	
Education				.170
None	7 (5.7)	2 (1.6)	9 (3.6)	
Primary level	41 (33.3)	49 (39.5)	90 (36.4)	
Post primary level	75 (61.0)	73 (58.9)	148 (59.9)	
Income, USD/mo				.089
<80	88 (71.5)	75 (60.5)	163 (66.0)	
≥80	35 (28.5)	49 (39.5)	84 (34.0)	
Egocentric network size, mean (IQR)	8 (7–9)	8 (7–9)	8 (7–9)	.437
Household, median (IQR)	3 (1–5)	1 (0–3)	2 (0–4)	<.001
Extra-household, median (IQR)	5 (3–7)	7 (5–8)	6 (4–8)	<.001
HIV status				.002
Positive	20 (16.3)	6 (4.8)	26 (10.5)	
Negative	98 (79.7)	118 (95.2)	216 (87.4)	
Other	5 (4.1)	0 (0.0)	5 (2.0)	
Microscopy				<.001
0 to 1+	15 (12.1)	124 (100)[a]	139 (56.2)	
2+	20 (16.3)	…	20 (8.1)	
3+	88 (71.5)	…	88 (35.6)	

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; TB, tuberculosis; USD, United States dollars.

[a] Controls were smear negative by definition.

the social networks of index cases, regardless of whether the contact lived in the household or not. In this way, we created a formal framework for estimating the infection risk conferred by the index case not only in the household but also outside the household in the community.

A unique aspect of the study was the sampling strategy of contacts. Most contact investigation studies sample contacts within geographically located family units, such as households [22–25] or family compounds [26], and do not include concurrent community samples. Our sampling frame was based on social relationships that included household and community contacts. We thereby reduced the selection bias inherent in contact investigation studies. Other epidemiologic studies have used social networks to delineate chains of transmission among patients with culture-confirmed disease [27–29], but this approach greatly underestimates transmission of *M. tuberculosis* because only a fraction of newly infected contacts ever develop disease during observation. Our study uses TB infection as the outcome of interest, thereby avoiding the effect of variable latency.

We further refined the design to include a contemporaneous, local set of control networks to estimate TB in the community. This feature was critical because it allowed us to estimate prevalence differences, which accounted for background prevalence of infection in the population, and thereby estimated the additional, or excess, risk associated with exposure to the index case. Although we believe our estimates to be valid, it is possible that the selected control group was not representative of TB infection in the population. We believe this issue to be minimal because the age- and sex-specific prevalence in our study aligns with previous studies from Kampala [4, 30]. It is also possible that there is residual confounding, despite frequency matching on age category, sex,

Table 2. Comparison of Demographic and Social Characteristics of First-degree Social Network Contacts of Tuberculosis Index Cases and Index Controls, Stratified by Age Category

	Age <15 y			Age ≥15 y		
Variables	Contacts of Cases	Contacts of Controls	*P* Value	Contacts of Cases	Contacts of Controls	*P* Value
Sex						
Male	142 (53.2)	82 (47.7)	.303	341 (46.1)	496 (56.9)	<.001
Female	125 (46.8)	90 (52.3)		398 (53.9)	376 (43.1)	
HIV status						
Positive[a]	5 (1.9)	3 (1.7)	1.000	77 (10.4)	63 (7.2)	.029
Negative	260 (97.4)	169 (98.3)		660 (89.3)	808 (92.7)	
Refused/not done	2 (0.7)	0 (0.0)		2 (0.3)	1 (0.1)	
Marital status						
Married	3 (1.1)	4 (2.3)	.554	425 (57.5)	522 (59.9)	.403
Not married	264 (98.9)	168 (97.7)		311 (42.1)	349 (40.0)	
Unknown	0 (0.0)	0 (0.0)		3 (0.4)	1 (0.1)	
Religion						
Christian	153 (57.3)	117 (68.0)	.003	469 (63.5)	612 (70.2)	.010
Muslim	81 (30.3)	49 (28.5)		180 (24.4)	186 (21.3)	
Other	33 (12.4)	6 (3.5)		88 (11.9)	73 (8.4)	
Unknown	0 (0.0)	0 (0.0)		2 (0.3)	1 (0.1)	
Education						
None	144 (53.9)	84 (48.8)	.413	24 (3.2)	39 (4.5)	.093
Primary	107 (40.1)	73 (42.4)		254 (34.4)	333 (38.2)	
Postprimary	16 (6.0)	15 (8.7)		459 (62.1)	499 (57.2)	
Unknown	0 (0.0)	0 (0.0)		2 (0.3)	1 (0.1)	
Income, USD/mo						
<80	261 (97.8)	169 (98.3)	1.000	504 (68.2)	555 (63.6)	.054
≥80	1 (0.4)	0 (0.0)		231 (31.3)	314 (36.0)	
Unknown	5 (1.9)	3 (1.7)		4 (0.5)	3 (0.3)	
Exposure status						
Household	180 (67.4)	115 (66.9)	.987	202 (27.3)	99 (11.4)	<.001
Extra-household	87 (32.6)	57 (33.1)		537 (72.7)	773 (88.6)	

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; USD, United States dollars.

[a] Among the 148 HIV-seropositive contacts in the study, 74 were already in care and 74 were newly diagnosed in the study and referred for care.

and parish. To address this issue, we adjusted for potential confounders and compared crude and adjusted estimates of risk.

Age was an effect modifier of the excess risk of infection among household contacts but not among extra-household contacts. The effect modification was evident within the household contacts as the excess risk was larger among younger contacts compared with older ones. We interpret this effect modification to indicate age assortment whereby children mix with other children and infrequently mix with

Table 3. Prevalence of Tuberculosis Infection Among Contacts of 123 Tuberculosis Index Cases and 124 Index Controls According to Household or Extra-household Contact

	Case Contacts (n = 1006)		Control Contacts (n = 1044)	
	Household (n = 382)	Extra-household (n = 624)	Household (n = 214)	Extra-household (n = 830)
Outcome	No. (%) [95% CI]			
Tuberculosis infection	235 (61.5) [56.6–66.4]	280 (44.9) [41.0–48.8]	54 (25.2) [19.4–31.1]	342 (41.2) [37.9–44.6]
No tuberculosis infection	145 (38.0) [33.2–42.8]	329 (52.7) [48.8–56.6]	154 (72.0) [65.9–78.0]	476 (57.3) [54.0–60.7]
Refused test	2 (0.5) [.1–1.2]	15 (2.4) [1.2–3.6]	6 (2.8) [.6–5.0]	12 (1.4) [.6–2.2]

Abbreviation: CI, confidence interval.

Table 4. Stratified Analysis of Crude and Adjusted[a] Risk Difference by Age Category

		Contacts of Cases		Contacts of Controls			
Characteristics	Age Category, y	No.	TB Infection, No. (%)	No.	TB Infection, No. (%)	Crude Risk Difference (95% CI)	Adjusted Risk Difference (95% CI)
Contact status							
Household	<15 y	180	103 (57.2)	115	12 (10.4)	46.8 (37.6–56.0)	47.2 (35.3–59.0)
	<5 y	81	41 (50.6)	40	1 (2.5)	48.1 (36.0–60.2)	NE[b]
	5–14 y	99	62 (62.6)	75	11 (14.7)	48.0 (35.4–60.5)	48.8 (32.6–65.0)
	≥15 y	202	132 (65.3)	99	42 (42.4)	22.9 (11.1–34.7)	31.7 (18.1–45.3)
Extra-household	<15 y	87	9 (10.3)	57	2 (3.5)	6.8 (−1.2 to 14.9)	NE[b]
	<5 y	39	8 (20.5)	18	0 (0)	20.5 (7.4–33.6)	NE[b]
	5–14 y	48	1 (2.1)	39	2 (5.1)	−3.0 (−11.2 to 5.1)	−5.6 (−36.8 to 25.5)
	≥15 y	537	271 (50.5)	773	340 (44.0)	6.5 (.1–12.0)	7.6 (.7–14.5)

Abbreviations: CI, confidence interval; NE, no estimate; TB, tuberculosis.

[a] Adjusted by continuous age (within category), sex, human immunodeficiency virus serostatus of contact, and clustering according to index case.

[b] Model did not converge.

adults, except parents [31]. As a result, young children were more likely to acquire infection in the household than by encounters outside the household.

In extra-household first-degree network members, we found that the excess risk of infection from exposure to an index case was modest (5.4%), and substantially lower than in the household setting. In contrast to household exposure, we did not observe effect modification by age in the extra-household setting. As expected, the prevalence of latent infection among older contacts exceeded the prevalence among younger contacts 5-fold, but the age-specific excess risk estimates were similar by age category.

The extra-household adult contacts were not a homogeneous group as regards risk of infection. A subset of case network members had a prevalence of infection that was similar to the prevalence in the household contacts, indicating that they may have experienced adequate contact with the index case to transmit *M. tuberculosis* [32]. This subset of contacts was defined by social closeness both with kin and work associates. The remaining first-degree network members lacked the social closeness and had a prevalence of infection resembling the community prevalence, suggesting previous exposure to 1 or more undetected, infectious cases.

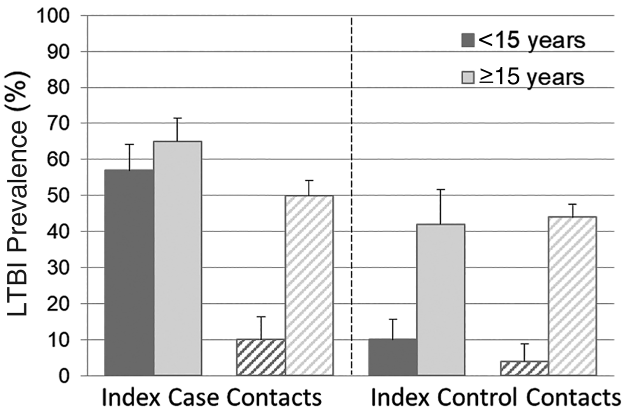

Figure 2. Prevalence of latent tuberculosis infection (LTBI) among household and extra-household contacts of 123 index tuberculosis cases and 124 index controls, stratified by age category.

Since the extra-household risk of infection was modest, our findings raise the question whether community exposure within the social network of infectious index cases can account for the high prevalence of LTBI found among adults in the community. It is plausible that community prevalence of infection is maintained through transmission to contacts not identified as part of reported social networks but instead as part of unspecified contact networks. It may also be the product of slow transmission dynamics of TB [33] or of casual transmission [34] in settings outside of the household, such as schools [8, 35], hospitals and clinics [36, 37], and transportation hubs [8, 38].

Other explanations, however, are plausible. Recent research has shown that cases of TB can produce aerosols containing *M. tuberculosis* through normal tidal respiration [39, 40], implying that cough may not be necessary for transmission. We are also beginning to understand better the prehistory of TB when cough is absent, or a minor symptom, and how cases may be infectious before overt clinical disease is detected [41, 42]. Based on this emerging line of research, we postulate that transmission from occult infectious cases may be the driving force behind epidemics of TB in African cities.

The ascertainment of our social networks was incomplete. We believe this limitation is minor because our estimates of infection are in line with previous household contact studies [6] and community infection surveys [30]. Because the study was cross-sectional, we did not directly measure the incidence of TB infection. Instead, we inferred incidence using the prevalence difference among contacts of cases and controls, or the excess risk attributable to exposure to an index case. This approach is used to estimate the annual risk of TB infection [43] and the secondary attack rates of TB infection in households [4]. In this analysis, we made steady-state

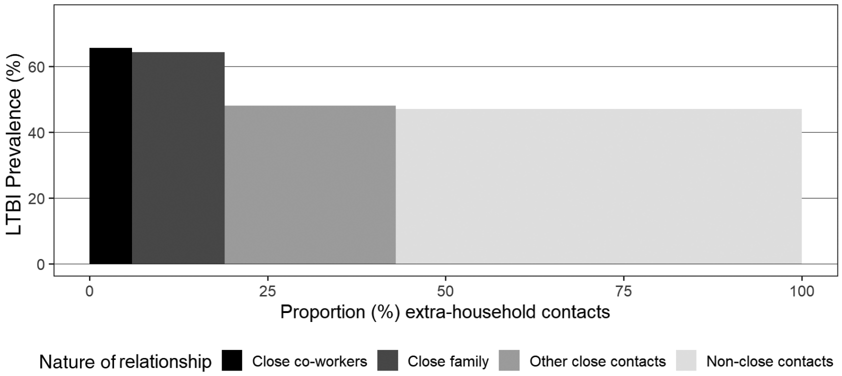

Figure 3. Prevalence of latent tuberculosis infection (LTBI) among extra-household contacts 15 years and older according to nature of their relationship to index case.

assumptions about the incidence of infection and migration of infected persons to and from the study population [44]. Finally, we confined our epidemiologic analysis to first-degree contacts in the social networks of index participants, though a more expansive study of community networks is underway in Lubaga Division.

Given these caveats, we conclude that most social network members of TB cases do not experience additional risk of infection from exposure to that case but instead acquire infection through unrecognized exposures with infectious cases in the community. These undetected and infectious cases, possibly without cough, may be the hidden drivers of transmission in ongoing, local epidemics. Since community transmission of *M. tuberculosis* was not fully captured using the social network framework, further research is needed to map "hotspots" of ongoing transmission [45, 46] to geographic locations so that public health interventions, such as active case finding and community-based preventive therapy, may be targeted to areas where it is most needed [47, 48]. Only when transmission of *M. tuberculosis* is mitigated will there be fewer new infections and lower rates of TB disease.

Notes

Acknowledgments. The authors thank the Uganda National Tuberculosis and Leprosy Control Programme, Lubaga Hospital, the municipal leaders of Lubaga Division of Kampala, and the Kampala Capital City Authority for their cooperation and support of the field work needed to complete this study. The authors also acknowledge the home health visitors for their invaluable contributions to the science of this study and the Epidemiology in Action research group of the Global Health Institute, University of Georgia, for their critical insights.

Disclaimer. The sponsors of this study played no role in the design, conduct, analysis, or interpretation of the study.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases and the Fogarty International Center of the National Institutes of Health (grant numbers R01 AI093856, NO1-AI95383, D43-TW01004); and the Schlumberger Foundation Faculty for the Future Fellowship.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. World Health Organization. Global tuberculosis report 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1. Accessed 28 September 2020.
2. Ho J, Fox GJ, Marais BJ. Passive case finding for tuberculosis is not enough. Int J Mycobacteriol **2016**; 5:374–8.
3. Wingfield T, Verguet S. Active case finding in tuberculosis-affected households: time to scale up. Lancet Glob Health **2019**; 7:e296–8.
4. Whalen CC, Zalwango S, Chiunda A, et al. Secondary attack rate of tuberculosis in urban households in Kampala, Uganda. PLoS One **2011**; 6:e16137.
5. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J **2013**; 41:140–56.
6. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis **2008**; 8:359–68.
7. McCreesh N, White RG. An explanation for the low proportion of tuberculosis that results from transmission between household and known social contacts. Sci Rep **2018**; 8:5382.
8. Andrews JR, Morrow C, Walensky RP, Wood R. Integrating social contact and environmental data in evaluating tuberculosis transmission in a South African township. J Infect Dis **2014**; 210:597–603.
9. Middelkoop K, Mathema B, Myer L, et al. Transmission of tuberculosis in a south African community with a high prevalence of HIV infection. J Infect Dis **2015**; 211:53–61.
10. Verver S, Warren RM, Munch Z, et al. Transmission of tuberculosis in a high incidence urban community in South Africa. Int J Epidemiol **2004**; 33:351–7.
11. Guerra-Assunção J, Crampin A, Houben R, et al. Large-scale whole genome sequencing of *M. tuberculosis* provides insights into transmission in a high prevalence area. Elife **2015**; 4:e05166.
12. Martinez L, Shen Y, Mupere E, Kizza A, Hill PC, Whalen CC. Transmission of *Mycobacterium tuberculosis* in households and the community: a systematic review and meta-analysis. Am J Epidemiol **2017**; 185:1327–39.
13. McElroy PD, Southwick KL, Fortenberry ER, et al. Outbreak of tuberculosis among homeless persons coinfected with human immunodeficiency virus. Clin Infect Dis **2003**; 36:1305–12.
14. Kline SE, Hedemark LL, Davies SF. Outbreak of tuberculosis among regular patrons of a neighborhood bar. N Engl J Med **1995**; 333:222–7.
15. Chaves F, Dronda F, Cave MD, et al. A longitudinal study of transmission of tuberculosis in a large prison population. Am J Respir Crit Care Med **1997**; 155:719–25.
16. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. N Engl J Med **1992**; 326:1514–21.
17. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol **1990**; 43:87–91.
18. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep **2000**; 49(RR-6):1–51.
19. Rothman KJ, Greenland S, Lash T. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, **2008**.
20. Nelder JA, McCullaugh P. Generalized linear models. 2nd ed. London: Chapman & Hall/CRC, **1898**.
21. Hill PC, Ota MO. Tuberculosis case-contact research in endemic tropical settings: design, conduct, and relevance to other infectious diseases. Lancet Infect Dis **2010**; 10:723–32.

22. Guwatudde D, Nakakeeto M, Jones-Lopez EC, et al. Tuberculosis in household contacts of infectious cases in Kampala, Uganda. Am J Epidemiol **2003**; 158:887–98.
23. Fox GJ, Nhung NV, Marks GB. Household-contact investigation for detection of tuberculosis in Vietnam. N Engl J Med **2018**; 378:221–9.
24. Jackson-Sillah D, Hill PC, Fox A, et al. Screening for tuberculosis among 2381 household contacts of sputum-smear-positive cases in The Gambia. Trans R Soc Trop Med Hyg **2007**; 101:594–601.
25. Rutherford ME, Hill PC, Maharani W, et al. Risk factors for mycobacterium tuberculosis infection in Indonesian children living with a sputum smear-positive case. Int J Tuberc Lung Dis **2012**; 16:1594–9.
26. Egere U, Togun T, Hill PC, et al. Identifying children with tuberculosis among household contacts in The Gambia. Int J Tuberc Lung Dis **2017**; 21:46–52.
27. Hoang TTT, Nguyen VN, Dinh NS, et al. Active contact tracing beyond the household in multidrug resistant tuberculosis in Vietnam: a cohort study. BMC Public Health **2019**; 19:241.
28. Gardy JL, Johnston JC, Ho Sui SJ, et al. Whole-genome sequencing and social-network analysis of a tuberculosis outbreak. N Engl J Med **2011**; 364:730–9.
29. Klovdahl AS, Graviss EA, Yaganehdoost A, et al. Networks and tuberculosis: an undetected community outbreak involving public places. Soc Sci Med **2001**; 52:681–94.
30. Kizza FN, List J, Nkwata AK, et al. Prevalence of latent tuberculosis infection and associated risk factors in an urban African setting. BMC Infect Dis **2015**; 15:165.
31. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med 5:0381–91.
32. Castellanos ME, Zalwango S, Kakaire R, et al. Defining adequate contact for transmission of *Mycobacterium tuberculosis* in an African urban environment. BMC Public Health **2020**; 20:892.
33. Blower SM, McLean AR, Porco TC, et al. The intrinsic transmission dynamics of tuberculosis epidemics. Nat Med **1995**; 1:815–21.
34. Golub JE, Cronin WA, Obasanjo OO, et al. Transmission of *Mycobacterium tuberculosis* through casual contact with an infectious case. Arch Intern Med **2001**; 161:2254–8.
35. Mathema B, Andrews JR, Cohen T, et al. Drivers of tuberculosis transmission. J Infect Dis **2017**; 216(Suppl 6):S644–53.
36. Sekandi JN, Zalwango S, Martinez L, et al. Four degrees of separation: social contacts and health providers influence the steps to final diagnosis of active tuberculosis patients in urban Uganda. BMC Infect Dis **2015**; 15:361.
37. Chamie G, Wandera B, Marquez C, et al. Identifying locations of recent TB transmission in rural Uganda: a multidisciplinary approach. Trop Med Int Health **2015**; 20:537–45.
38. Izumi K, Ohkado A, Uchimura K, et al. Detection of tuberculosis infection hotspots using activity spaces based spatial approach in an urban Tokyo, from 2003 to 2011. PLoS One **2015**; 10:e0138831.
39. Patterson B, Wood R. Is cough really necessary for TB transmission? Tuberculosis (Edinb) **2019**; 117:31–5.
40. Williams CM, Abdulwhhab M, Birring SS, et al. Exhaled *Mycobacterium tuberculosis* output and detection of subclinical disease by face-mask sampling: prospective observational studies. Lancet Infect Dis **2020**; 20:607–17.
41. Onozaki I, Law I, Sismanidis C, Zignol M, Glaziou P, Floyd K. National tuberculosis prevalence surveys in Asia, 1990–2012: an overview of results and lessons learned. Trop Med Int Health **2015**; 20:1128–45.
42. Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. Clin Microbiol Rev **2018**; 31:e00021–18.
43. Rieder HL. Methodological issues in the estimation of the tuberculosis problem from tuberculin surveys. Tuber Lung Dis **1995** ; 76:114–21.
44. Kleinbaum D, Kupper L, Morgenstern H. Epidemiologic research: principles and quantitative methods. New York: Von Nostrand Reinhold, **1982**.
45. Dowdy DW, Golub JE, Chaisson RE, Saraceni V. Heterogeneity in tuberculosis transmission and the role of geographic hotspots in propagating epidemics. Proc Natl Acad Sci U S A **2012**; 109:9557–62.
46. Tiwari N, Adhikari CM, Tewari A, Kandpal V. Investigation of geo-spatial hotspots for the occurrence of tuberculosis in Almora district, India, using GIS and spatial scan statistic. Int J Health Geogr **2006**; 5:33.
47. Dowdy DW, Azman AS, Kendall EA, Mathema B. Transforming the fight against tuberculosis: targeting catalysts of transmission. Clin Infect Dis **2014**; 59:1123–9.
48. Cudahy PGT, Andrews JR, Bilinski A, et al. Spatially targeted screening to reduce tuberculosis transmission in high-incidence setting. Lancet Infect Dis **2019**; 19:e89–95.