Title

The Association Between Social Network Characteristics and Tuberculosis Infection Among Adults in 9 Rural Ugandan Communities

Permalink

https://escholarship.org/uc/item/0174f17x

Journal

Clinical Infectious Diseases, 76(3)

ISSN

1058-4838

Authors

Marquez, Carina

Chen, Yiqun

Atukunda, Mucunguzi

et al.

Publication Date

2023-02-08

DOI

10.1093/cid/ciac669

Peer reviewed

The Association Between Social Network Characteristics and Tuberculosis Infection Among Adults in 9 Rural Ugandan Communities

Carina Marquez,[1,a] Yiqun Chen,[2,a] Mucunguzi Atukunda,[3] Gabriel Chamie,[1] Laura B. Balzer,[4] Joel Kironde,[3] Emmanuel Ssemmondo,[3] Florence Mwangwa,[3] Jane Kabami,[3] Asiphas Owaraganise,[3] Elijah Kakande,[3] Rachel Abbott,[1] Bob Ssekyanzi,[3] Catherine Koss,[1] Moses R. Kamya,[3,5] Edwin D. Charlebois,[6] Diane V. Havlir,[1] and Maya L. Petersen[4]

[1]Division of HIV, Infectious Diseases, and Global Medicine, Department of Medicine, University of California, San Francisco, California, USA; [2]Department of Biostatistics, University of Washington, Seattle, Washington, USA; [3]Infectious Diseases Research Collaboration, Kampala, Uganda; [4]Division of Biostatistics, School of Public Health, University of California, Berkeley, Berkeley, California, USA; [5]School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda; and [6]Center for AIDS Prevention Studies, School of Medicine, University of California, San Francisco, San Francisco, California, USA

Background. Social network analysis can elucidate tuberculosis transmission dynamics outside the home and may inform novel network-based case-finding strategies.

Methods. We assessed the association between social network characteristics and prevalent tuberculosis infection among residents (aged ≥15 years) of 9 rural communities in Eastern Uganda. Social contacts named during a census were used to create community-specific nonhousehold social networks. We evaluated whether social network structure and characteristics of first-degree contacts (sex, human immunodeficiency virus [HIV] status, tuberculosis infection) were associated with revalent tuberculosis infection (positive tuberculin skin test [TST] result) after adjusting for individual-level risk factors (age, sex, HIV status, tuberculosis contact, wealth, occupation, and Bacillus Calmette–Guérin [BCG] vaccination) with targeted maximum likelihood estimation.

Results. Among 3 335 residents sampled for TST, 32% had a positive TST results and 4% reported a tuberculosis contact. The social network contained 15 328 first-degree contacts. Persons with the most network centrality (top 10%) (adjusted risk ratio, 1.3 [95% confidence interval, 1.1–1.1]) and the most (top 10%) male contacts (1.5 [1.3–1.9]) had a higher risk of prevalent tuberculosis, than those in the remaining 90%. People with ≥1 contact with HIV (adjusted risk ratio, 1.3 [95% confidence interval, 1.1–1.6]) and ≥2 contacts with tuberculosis infection were more likely to have tuberculosis themselves (2.6 [95% confidence interval: 2.2–2.9]).

Conclusions. Social networks with higher centrality, more men, contacts with HIV, and tuberculosis infection were positively associated with tuberculosis infection. Tuberculosis transmission within measurable social networks may explain prevalent tuberculosis not associated with a household contact. Further study on network-informed tuberculosis case finding interventions is warranted.

Keywords. tuberculosis infection; social network analysis; tuberculosis case finding.

More than a quarter of the world's population is infected with tuberculosis [1]. In high-tuberculosis burden areas, an estimated 80% of these infections are acquired outside the home [2–4]. Household contact tracing is effective for identifying new cases; however, even if implemented at full scale, this approach is insufficient to reach global tuberculosis targets because much of tuberculosis transmission is thought to occur outside the household [5]. Social network– and venue-based strategies have the potential to complement household contact tracing and identify people who acquire tuberculosis infection in the community [6–10]. However, for such a strategy to succeed, formative data on the relationship of the sociospatial network—where and with whom one socializes—and risk of tuberculosis acquisition is needed to inform novel case finding and prevention interventions that address transmission outside the home.

Social network analysis is well suited to elucidate tuberculosis transmission in the community [8, 10–12]. It can map sources and patterns of person-to-person spread of infectious diseases and identify networks of people at high risk for a given disease by nature of shared behaviors and shared aggregate spaces (eg, bars, places of worship, schools, and workplaces) [3, 13–16]. In the context of tuberculosis, social network analysis has primarily been used to identify transmission networks of active

tuberculosis disease, but few studies include latent tuberculosis infection (LTBI) [10]. The few existing studies that include LTBI and social networks suggest a link between social network structure and tuberculosis infection and the possibility of enhanced efficiency and identification of new cases using social network informed case finding [8, 11, 17]. These studies, however, are predominantly from settings with a low tuberculosis burden and within the context of outbreak investigation.

To address these knowledge gaps, we sought to assess whether the characteristics of nonhousehold social networks in 9 rural communities in Uganda, a country with a high tuberculosis burden, were associated with prevalent tuberculosis infection, after adjustment for individual-level tuberculosis risk factors. We hypothesized that individuals with a dense social network and those who are more central within their network would have a higher risk of tuberculosis infection, because a greater overall number of contacts would result in higher chances of encountering a contact with tuberculosis infection. We also hypothesized that persons with first-degree contacts who have a higher individual-level risk of tuberculosis (men, people with human immunodeficiency virus [HIV], people with LTBI) would themselves have an increased risk of tuberculosis infection, independent of their own risk factors. This hypothesized association could be due to due to direct person-to-person time between close contacts or could be a marker of shared behaviors or time spent in venues where the risk of acquiring tuberculosis from a casual contact is high.

METHODS

Study Design and Setting
This cross-sectional study was nested within the Sustainable East Africa Research in Community Health (SEARCH) trial (NCT01864603). The parent study, the SEARCH trial, was a 32-community cluster-randomized trial of a "universal HIV test and treat" model in Uganda and Kenya, conducted from 2013 to 2017. The trial's procedures and outcomes have been described elsewhere [18].

The nested TB Infection Survey was conducted in a sample of households from 9 communities participating in the SEARCH trial in Eastern Uganda. Survey procedures have been described elsewhere [19]; briefly, in each community we randomly selected 100 households with an adult with HIV and 100 households without an adult with HIV (leveraging the household enumeration and 90% HIV testing coverage in the parent trial). Household members received a tuberculin skin test (TST), a tuberculosis history and symptom screen, and assessment of Bacillus Calmette–Guérin [BCG] vaccination. For this analysis, the study population included all participants in the nested TB Infection Survey aged ≥15 years who had a TST placed and read, and who had ≥1 nonhousehold social network contact.

Study Measures and Definitions
Social Networks
During the SEARCH baseline survey in 2013–2014, all participants aged ≥15 years were asked to name up to 6 contacts in each of 5 social domains with whom, over the last 12 months, they had (1) shared food with outside their household, (2) spent free time, (3) discussed money matters, (4) discussed health issues, or (5) went to for emotional support.

This name generator was adapted to the local context from approaches previously used in low- and middle-income countries [9]. The name, village, and ages of contacts were collected by field staff on tablet computers. Sociocentric networks of nonhousehold contacts for each community were separately constructed using a semisupervised record linkage algorithm that matches contacts named by each participant ("ego") to other enumerated residents ("alter"), as described in prior work [20, 21]. Networks were visualized with Gephi software using the Force Atlas2 algorithm for layout [21], with "nodes" corresponding to individual community residents and "edges" corresponding to ≥1 matched contact across social domains.

Tuberculosis Infection Measures
Tuberculosis infection was measured in the nested Household TB Infection Survey by means of TSTs and results were defined as positive if the TST induration was ≥10 mm, or ≥5 mm for people with HIV. Receipt of BCG vaccination was defined as the presence of a BCG vaccine scar on the deltoid region of the arm or proof by a vaccination record. Throughout this analysis, we define tuberculosis infection as inclusive of LTBI and active tuberculosis disease, because tuberculosis disease is underreported and undiagnosed in rural Uganda and cannot be fully excluded by a negative tuberculosis symptom screen [22]. The Household TB Infection Survey also collected demographics (including sex, age, and occupation), personal history of tuberculosis disease, history of a household contact with tuberculosis disease, and mobility (living outside the community for ≥6 months). HIV status and household wealth index were measured during the SEARCH baseline survey. Household wealth was assessed based on ownership of livestock and household assets (clock, radio, television, and refrigerator), analyzed using principal component analysis, and categorized into the lowest, middle and highest tertiles of the household wealth index [23, 24].

Statistical Analysis
Demographic variables and network characteristics were described overall and stratified by tuberculosis infection status. Network metrics were assessed on an undirected graph (with a first-degree contact in a dyad defined as ≥1 member matched to the other). Network metrics evaluated as exposures included the number of first-degree connections (ie, number of "friends"), eigen centrality (a node with high centrality is one

with many first- and second-degree connections), hub centrality (a variant of eigen centrality that weighs connections differently), betweenness centrality (a node with high betweenness is one that is most likely to be included on the shortest path between any 2 other nodes in the network), and transitivity (proportion of any 3 individuals who all know each other in the network) [23]. We further evaluated as exposures the sex, HIV, and tuberculosis infection status of first-degree contacts.

We calculated deciles for each network-based exposure metric and compared (1) persons in the top 10% with those in the remaining 90% and (2) persons in the bottom 10% with those in the remaining 90%. Deciles were selected a priori to assess the association between tuberculosis infection and social network characteristics in the most connected (top decile), given prior use of this method in social network analyses including evaluation of dose responses to connectivity [8, 21]. Given the sparsity of first-degree contacts who were TST positive or had HIV, rather than using deciles, we encoded these exposures as having ≥1 TST-positive (or HIV-positive) first-degree contact or having ≥2 TST-positive (or HIV-positive) first-degree contacts.

We estimated relative risk of tuberculosis infection for each of these network-derived exposures, with and without adjustment for individual-level tuberculosis risk factors, including age, sex, wealth status, mobility, HIV status, household tuberculosis contact, BCG vaccination status, and occupation, using targeted maximum likelihood estimation performed with the ltmle R package, which allows for flexible nonparametric adjustment for covariates while maintaining valid statistical inference [25]. All analyses accounted for clustering by community in standard error estimates and incorporated weights to account for household sampling and TST placement within sampled households. In a sensitivity analysis, we also explored alternative modeling of the relationships between network-derived exposure measures (as linear, continuous variables) and tuberculosis infection risk using generalized estimating equations with corrections for a small number of clusters.

Because network-based case finding strategies may be efficacious, we also assessed whether people cluster by their TST status. The extent of first-degree clustering was quantified by the proportion of all pairs that were TST status concordant (number of ego-alter pairs that have the same TST status); P values were computed by randomly permuting individuals' TST status within each community.

Ethical Considerations

The Makerere University School of Medicine Research and Ethics Committee (Uganda), the Uganda National Council on Science and Technology (Uganda), and the University of California, San Francisco, Committee on Human Research (United States) approved the study protocol and consent procedures. Participants in the TB Infection Survey provided written informed consent, and those in the SEARCH baseline survey provided verbal informed consent with fingerprint biometric confirmation of agreement.

RESULTS

Demographics and Individual-Level Predictors of Prevalent Tuberculosis Infection

The TSTs were completed in 3335 of the 6118 persons (55%) registered to the 1380 households in the tuberculosis infection survey at the time of the baseline census. Among the 3351 participants who had a TST completed, 32% had a positive TST result and 71% had ≥1 connection to the social networks of nonhousehold contacts (Supplementary Figure 1). The mean age of participants who had a TST placed was 39.5 years (standard deviation, 17.0 years), 60% were women, 26% had HIV, and 3.5% had a known household tuberculosis contact (Table 1). Tuberculosis infection was positively associated with older age, male sex, BCG vaccination, and household tuberculosis contact and negatively associated with HIV (Table 2).

Network Visualization and Characteristics

Overall, the social network contained 2395 participants with TSTs placed and 15 328 first-degree nonhousehold contacts. A sample visualization of a network from one community, colored by the participants' TST status, is included as Figure 1. The network structure is described in Table 3, and the summary of top and bottom deciles in Supplementary Table 1. The average number of first-degree contacts [standard deviation] was higher among TST-positive people (7.4 [12.1]) than among TST-negative people (5.8 [5.8]). TST-positive people also had more first-degree contacts who were male (mean [standard deviation], 3.6 [6.0] vs 2.6 [3.3]) and who were TST positive (1.2 [0.5] vs 0.1 [0.4]) (Table 3).

Association Between Prevalent Tuberculosis Infection and Social Network Characteristics

Adjusting for individual-level risk factors, people in the most central networks had a higher risk of prevalent tuberculosis (adjusted risk ratio [aRR], 1.3 [95% confidence interval (CI), 1.1–1.6] for eigen centrality and 1.3 [1.0–1.7] for betweenness centrality) than those in the bottom 90%. Individuals with more first-degree contacts (top decile; ≥13 first-degree connections) had a higher risk of prevalent tuberculosis infection (aRR, 1.2 [95% CI, 1.0–1.5]) than those with fewer connections (although not significant at an α value of 5%). Persons with the most men in their first-degree contacts (top decile; ≥8 men) had a higher risk of prevalent tuberculosis (aRR, 1.5 [95% CI, 1.1–1.9]) than those with fewer male connections (Table 4). Results from our sensitivity analysis, which treated the network-derived exposures as linear, continuous variables. yielded similar results (Supplementary Table 2).

Table 1. Demographic and Health Characteristics of Adult Residents in the Tuberculosis Infection Survey in Rural Uganda Who Were Connected to Community Social Networks of Nonhousehold Contacts

Characteristic	Participants, No. (%)[a]		
	TST Negative (n = 1602)	TST Positive (n = 793)	Overall (N = 2395)
Age			
Mean (SD), y	38.9 (17.3)	40.7 (16.4)	39.5 (17.0)
<20 y	242 (15.1)	88 (11.1)	330 (13.8)
>50 y	412 (25.7)	234 (29.5)	646 (27.0)
Sex			
Male	608 (38.0)	359 (45.3)	967 (40.4)
Female	994 (62.0)	434 (54.7)	1428 (59.6)
Wealth tertile			
Low	309 (19.3)	168 (21.2)	477 (19.9)
Middle	556 (34.7)	270 (34.0)	826 (34.5)
High	713 (44.5)	340 (42.9)	1053 (44.0)
Data missing	24 (1.5)	15 (1.9)	39 (1.6)
Mobile residents			
Yes	230 (14.4)	119 (15.0)	349 (14.6)
No	1372 (85.6)	674 (85.0)	2046 (85.4)
Data missing	0	0	0
HIV			
Yes	485 (30.3)	141 (17.8)	626 (26.1)
No	1117 (69.7)	652 (82.2)	1769 (73.9)
Data missing	0	0	0
Household tuberculosis contact (ever)			
Yes	34 (2.1)	51 (6.4)	85 (3.5)
No	1381 (86.2)	657 (82.8)	2038 (85.1)
Data missing	187 (11.7)	85 (10.7)	272 (11.4)
BCG vaccinated (scar or record)			
Yes	1257 (78.5)	650 (82.0)	1907 (79.6)
No	159 (9.9)	59 (7.4)	218 (9.1)
Data missing	186 (11.6)	84 (10.6)	270 (11.3)
Occupation[b]			
Formal	320 (20.0)	139 (17.5)	459 (19.2)
Informal low risk	1191 (74.3)	605 (76.3)	1796 (75.0)
Informal high risk	25 (1.6)	10 (1.3)	35 (1.5)
Other	62 (3.9)	33 (4.2)	95 (4.0)

Abbreviations: BCG, Bacillus Calmette–Guérin; HIV, human immunodeficiency virus; SD, standard deviation; TST, tuberculin skin test.

[a]Data represent no. (%) of participants unless otherwise specified.

[b]Occupation classification based on HIV and tuberculosis risk category (high vs low) and type of sector (formal vs informal). Formal occupations included teacher, student, government worker, military worker, health worker, and factory worker; informal high risk, fishmonger, fisherman, bar owner, bar worker, and worker in transportation and tourism industry; informal low risk, farmer, shopkeeper, market vendor, hotel worker, household worker, construction worker, and mining worker. "Other" included participants with no job, those who were disabled, clerical workers, and manual laborers; data were missing in 20 participants (0.1%).

Having ≥2 first-degree contacts with tuberculosis was strongly associated with an increased risk of tuberculosis infection (aRR, 2.6 [95% CI, 2.2–3.0]) (Table 4). In addition, we detected first-degree clustering by TST status in 5 of the 9 communities at a 5% significance level and 6 of 9 at a 10% significance level (Table 5). Persons who had first-degree contacts with HIV were more likely to have tuberculosis infection (aRR,

Table 2. Unadjusted and Adjusted Associations of Baseline Individual Covariates and Prevalent Tuberculosis Infection (N = 2395)[a]

Covariate	RR (95% CI)	aRR (95% CI)
Age group		
≤20 y	0.77 (.62–.95)	0.74 (.59–.93)
>20 y	Reference	Reference
≥50 y	1.13 (1.00–1.28)	1.10 (.97–1.23)
<50 y	Reference	Reference
Sex		
Male	1.22 (1.09–1.37)	1.36 (1.20–1.54)
Female	Reference	Reference
Alcohol use		
Yes	1.11 (.96–1.23)	0.91 (.81–1.10)
No	Reference	Reference
Wealth tertile		
Low	1.08 (.94–1.24)	1.14 (.97–1.35)
Middle or high	Reference	Reference
Mobile residents		
Yes	1.03 (.88–1.21)	1.15 (.94–1.40)
No	Reference	Reference
HIV status		
Person with HIV	0.57 (.48–.68)	0.52 (.47–.57)
Person without HIV	Reference	Reference
BCG vaccinated (scar or record)		
Yes	1.26 (1.00–1.58)	1.25 (1.02–1.51)
No	Reference	Reference
Household tuberculosis contact (ever)		
Yes	1.86 (1.71–2.27)	1.97 (1.71–2.27)
No	Reference	Reference

Abbreviations: aRR, adjusted risk ratio; BCG, Bacillus Calmette–Guérin; CI, confidence interval; HIV, human immunodeficiency virus; RR, risk ratio.

[a]Targeted maximum likelihood was used to estimated unadjusted RRs and aRRs, accounting for clustering by community; aRRs were adjusted for age, sex, alcohol use, wealth tertile, resident mobility, HIV status, BCG vaccination, and household tuberculosis contacts.

1.3 [95% CI, 1.1–1.6] for ≥1 contact and 1.3 [1.0–1.6] for ≥2 contacts (Table 4).

DISCUSSION

In this cross-sectional study of residents (aged ≥15 years) living in rural communities in Uganda and their social networks of nonhousehold contacts, we found that people who are more central (eigen and betweenness centrality) in their nonhousehold social networks had a higher risk of tuberculosis infection than those who were less central, even after adjustment for individual-level tuberculosis risk factors. In addition, the characteristics of one's close contacts are predictive of tuberculosis. Specifically, people whose immediate social networks contain more men, more people with HIV, and more persons with tuberculosis infection have a higher risk of prevalent tuberculosis infection. Although we cannot disentangle whether the association is directly related to person-to-person spread between friends or frequenting shared spaces with high risks, such as bars, these results highlight the fact that tuberculosis infection
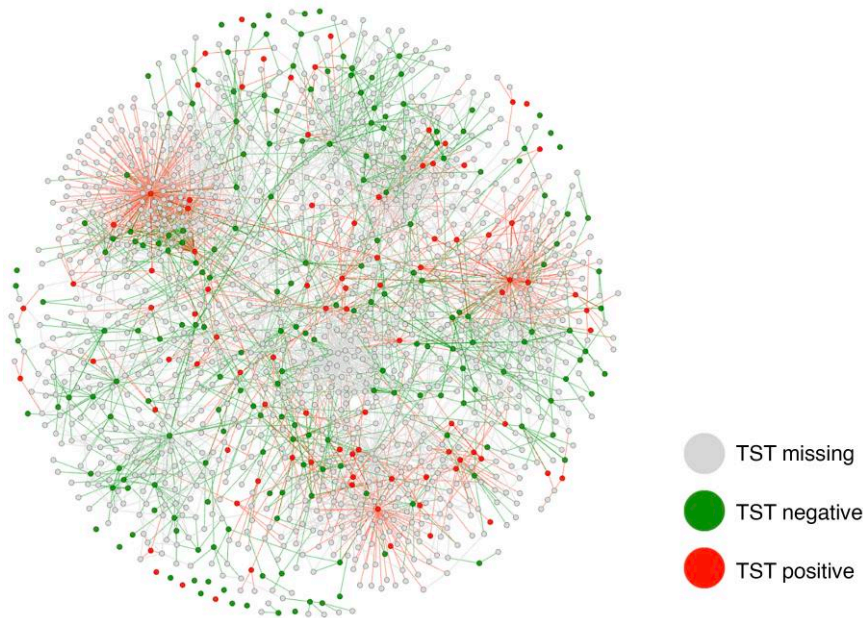
Figure 1. Visualization of a social network in one rural community in Eastern Uganda, by tuberculin skin test (TST) status. Only individuals included in the tuberculosis infection survey and their first-degree nonhousehold contacts were plotted; colors correspond to individual TST results.

risk differs depending on the characteristics of one's nonhousehold contacts within measurable social networks—a finding consistent with the observation that most tuberculosis transmission in settings with high prevalence occurs outside the household.

In sub-Saharan Africa, men have a higher tuberculosis burden than women [26, 27]. We found that not only do men have a higher individual-level risk of tuberculosis, but this risk extends to their social networks. In this study, individuals whose first-degree social networks contained more men (top decile) had nearly a 50% higher risk of tuberculosis infection than those with fewer men in their network. We hypothesize that this relationship is driven by (1) a higher likelihood of contact with someone with infectious tuberculosis, because men have a higher risk of tuberculosis disease compared to women, and (2) a higher likelihood of being in shared venues where the risk of acquiring tuberculosis is high owing to poor ventilation and casual or close contacts in the venue who have a higher individual-level risk for tuberculosis disease.

Our findings are consistent with modeling and social mixing studies from Zambia and South Africa that attributed 57% and 67% of tuberculosis infections, respectively, to contact with adult men [28, 29]. A study from Kampala, Uganda, found sex-assortative mixing patterns in both people with tuberculosis (cases) and controls and a higher proportion of male contacts in the egocentric networks of cases compared with controls. These data suggest that sex-assortative mixing patterns may amplify sex disparities in tuberculosis disease. Social network strategies that focus on engaging men and their networks for tuberculosis

prevention and case finding may be high yield and could reduce sex disparities in tuberculosis infection.

Social network–informed interventions may be an efficient strategy to reach people with tuberculosis infection not identified through traditional case finding methods, such as household contact investigation [10, 11]. Centrality and network density have been associated with tuberculosis infection in outbreaks in settings with a low tuberculosis burden. In an outbreak investigation in Japan, contacts with higher network betweenness scores (top 90%) were more likely to have tuberculosis infection diagnosed than contacts with lower scores [8], and in contact investigation in outbreak settings in the United States and Canada, tuberculosis contacts in denser portions of sociospatial networks had a higher risk of LTBI [11]. In the United States, network-informed contact investigations yielded 7.8-fold more persons with a positive TST result compared with standard contact tracing methods [30]. We identified an association between eigen centrality and tuberculosis infection. Focusing tuberculosis contact tracing efforts on contacts and community members with high eigen centrality may be a high-yield approach, as they have a high number of connections to other highly central people.

Data on social network-based case finding and the association with tuberculosis infection are sparse; however, studies of sociospatial network techniques have successfully identified "hidden" nonhousehold transmission links between people with active tuberculosis, including in healthcare venues in a study from South Africa [31, 32], bars in a study from Uganda [16], and cinemas, marketplaces, schools, and

Table 3. Social Network Characteristics of Nonhousehold Contacts of Adult Residents (N = 2395) in the Tuberculosis Infection Survey in Rural Uganda, Stratified by Prevalent Tuberculosis Infection Status

Characteristic[a]	TST Result Negative (n = 1602)	TST Result Positive (n = 793)	Overall (N = 2395)
No. of 1st-degree contacts			
Mean (SD)	5.8 (5.8)	7.4 (12.1)	6.4 (8.4)
Median (IQR)	4 (2–8)	5 (3–9)	4 (2–8)
Eigen centrality, mean (SD)	0.01 (0.04)	0.01 (0.06)	0.01 (0.05)
Transitivity, mean (SD)	0.16 (0.22)	0.15 (0.21)	0.15 (0.22)
Betweenness centrality, mean (SD)	9818 (19 039)	16 605 (63 490)	12 012 (39 458)
Hub centrality, mean (SD)	0.007 (0.035)	0.008 (0.045)	0.007 (0.038)
No. of 1st-degree male contacts			
Mean (SD)	2.6 (3.3)	3.6 (6.0)	2.9 (4.4)
Median (IQR)	2 (1–4)	3 (1–6)	2 (1–5)
No. of 1st-degree female contacts			
Mean (SD)	3.3 (3.8)	3.8 (6.5)	3.5 (4.9)
Median (IQR)	3 (1–5)	3 (1–5)	3 (1–5)
No. of 1st-degree TST-positive contacts			
Mean (SD)	0.1 (0.4)	1.2 (0.5)	0.5 (0.7)
Median (IQR)	0 (0–0)	1 (1–1)	0 (0–1)
No. of 1st-degree HIV-positive contacts			
Mean (SD)	0.5 (0.8)	0.4 (0.8)	0.5 (0.8)
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation; TST, tuberculin skin test.

[a]Eigen centrality, transitivity, betweenness centrality, and hub centrality are all defined in the Statistical Analysis section.

Table 4. Unadjusted and Adjusted Associations Between an Individual's Prevalent Tuberculosis Infection Status and the Characteristics of Their Social Network, With and Without Adjustment for the Individual's Risk Factors (N = 2395)[a]

Characteristic[b]	RR (95% CI)	aRR (95% CI)
No. of 1st-degree contacts		
First (most connected) decile[c]	1.33 (1.09–1.51)	1.22 (.98–1.51)
Last (least connected) decile	0.81 (.64–1.02)	0.78 (.62–.99)
Transitivity		
First (most transitive) decile	0.92 (.68–1.23)	0.94 (.71–1.26)
Last (least transitive) decile	0.91 (.79–1.06)	0.91 (.78–1.06)
Eigen centrality		
First (most central) decile	1.38 (1.14–1.66)	1.32 (1.07–1.61)
Last (least central) decile	0.88 (.69–1.12)	0.89 (.67–1.18)
Betweenness centrality		
First (most central) decile	1.36 (1.11–1.66)	1.31 (1.03–1.67)
Last (least central) decile	0.86 (.66–1.13)	0.76 (.57–1.02)
Hub centrality		
First (most central) decile	1.25 (1.02–1.55)	1.13 (.90–1.42)
Last (least central) decile	1.01 (.78–1.31)	0.93 (.69–1.25)
Male contacts		
First (most male contacts) decile	1.58 (1.32–1.89)	1.47 (1.13–1.91)
Last (fewest male contacts) decile	0.81 (.66–.98)	0.93 (.82–1.06)
TST-positive contacts		
≥2 TST-positive 1st-degree contacts	2.58 (2.28–2.92)	2.56 (2.22–2.97)
<2 TST-positive 1st-degree contacts	Reference	Reference
Contacts with HIV		
≥1 1st-degree contact with HIV	1.25 (1.07–1.46)	1.33 (1.13–1.57)
No 1st-degree contacts with HIV	Reference	Reference
HIV-positive contacts		
≥2 1st-degree contacts with HIV	1.11 (.84–1.47)	1.25 (.96–1.62)
<2 1st-degree contacts with HIV	Reference	Reference

Abbreviations: aRR, adjusted risk ratio; BCG, Bacillus Calmette–Guérin; CI, confidence interval; HIV, human immunodeficiency virus; RR, risk ratio; TST, tuberculin skin test.

[a]Targeted maximum likelihood was used to estimated unadjusted RRs and aRRs, accounting for clustering by households and incorporating sampling weights to account for (1) household sampling and (2) TST placement in sampled households. The adjustment set included age, sex, alcohol use, wealth tertile, resident mobility, HIV status, BCG vaccination, and household tuberculosis contacts.

[b]Transitivity and eigen, betweenness, and hub centrality are all defined in the Statistical Analysis section.

[c]Unless otherwise stated, the reference category is the other 90% of the population.

transport venues in Peru [15]. The current study is the first of its kind to look at social network links and tuberculosis infection on a population level outside of an outbreak setting. Our findings highlight a potential role for network-informed case finding because they demonstrate that individuals with ≥2 nonhousehold contacts with positive TST results have a higher likelihood of tuberculosis infection themselves. Further study is needed to assess the yield of network-based case finding for both tuberculosis disease and latent infection in high-tuberculosis burden settings.

Our findings are subject to limitations. First, we were unable to assess transmission chains directly, or to differentiate transmissions between casual contacts from shared environmental risk (eg, social network contacts frequent similar locations together or independently). However, both mechanisms support the potential for network-based case ascertainment approaches to identify new TST-positive cases. Second, not all named contacts were matched, and every matched connection is given the same weight regardless of its strength; this might bias the reported associations, particularly if network assessment differed by TST status, as well as potentially affecting sample representativeness. Third, there is no reference standard for

ascertainment of tuberculosis infection, and TSTs may have false-positive results owing to BCG vaccination and false-negative results owing to HIV. To partially account for this, we adjusted for HIV and BCG vaccination and used a lower TST positivity cutoff for people with HIV (induration ≥5 mm). Finally, we likely had differential missingness among people who had a TST performed, but a well-characterized cohort allowed us to do a 2-stage adjustment to account for sampling weights and probability of a TST being performed.

Although the majority of tuberculosis infections are acquired outside the home, community-based tuberculosis transmission dynamics remain elusive, especially in rural, high-tuberculosis settings in East Africa. In the current study, we examined the relationship between tuberculosis infection and social networks of nonhousehold contacts. Our data suggest that drivers of

Table 5.   Results of Permutation Tests for Clustering on Tuberculin Skin Test Status

Community	P Value[a]
Nsiinze	.07
Nankoma	.44
Kiyunga	<.001
Kamuge	.36
Bugono	.07
Muyembe	<.01
Merikit	<.01
Kiyeyi	.02
Kadama	.06

[a]P values were computed based on 10 000 random permutations.

tuberculosis risk extend beyond the individual to the individual's social network—the people with whom one socializes, shares space, and shares behaviors. These data support the potential for network-informed case finding and prevention strategies to identify cases acquired in the community in high-tuberculosis burden settings. Further study is needed to assess the efficiency and acceptability of these approaches.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. G. C. reports participation on a data safety monitoring board or advisory board as a member of a data monitoring committee for an National Institutes of Health (NIH)–funded clinical trial (TB Screening Improves Preventive Therapy Uptake [TB SCRIPT] trial). E. D. C. reports support from the NIH (grant 1R01AI151209-01 [paid to institution]) and consulting fees from the Infectious Diseases Research Collaboration, Kampala, Uganda (paid to the author for Integrated HIV & Hypertension Study consulting). D. V. H. reports nonfinancial support from Gilead (drug donation for an NIH study) and Abbott (diagnostic test donation). All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Houben RMGJ, Dood PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med **2016**; 13:e1002152.
2. 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.
3. 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.
4. Middelkoop K, Bekker LG, Morrow C, Lee N, Wood R. Decreasing household contribution to TB transmission with age: a retrospective geographic analysis of young people in a South African township. BMC Infect Dis **2014**; 14:221.
5. Dodd PJ, Yuen CM, Becerra MC, Revill P, Jenkins HE, Seddon JA. Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study. Lancet Glob Health **2018**; 6:e1329–38.
6. Cudahy PGT, Andrews JR, Bilinski A, et al. Spatially targeted screening to reduce tuberculosis transmission in high-incidence settings. Lancet Infect Dis **2019**; 19: e89–95.
7. 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.
8. Kawatsu L, Izumi K, Uchimura K, Urakawa M, Ohkado A, Takahashi I. Can social network analysis assist in the prioritisation of contacts in a tuberculosis contact investigation? Int J Tuberc Lung Dis **2015**; 19:1293–9.
9. Perkins JM, Subramanian SV, Christakis NA. Social networks and health: a systematic review of sociocentric network studies in low- and middle-income countries. Soc Sci Med **2015**; 125:60–78.
10. Nagarajan K, Das B. Tuberculosis and social networks: a narrative review on how social network data and metrics help explain tuberculosis transmission. Curr Sci **2019**; 116:1068.
11. Cook VJ, Sun SJ, Tapia J, et al. Transmission network analysis in tuberculosis contact investigations. J Infect Dis **2007**; 196:1517–27.
12. Kakaire R, Kiwanuka N, Zalwango S, et al. Excess risk of tuberculosis infection among extra-household contacts of tuberculosis cases in an African city. Clin Infect Dis Off Publ Infect Dis Soc Am **2021**; 73:e3438–45.
13. Nagarajan K, Muniyandi M, Palani B, Sellappan S. Tracing the potential extra-household contacts of TB patients: findings from a personal social network survey in a high TB burden setting in India. Trans R Soc Trop Med Hyg **2022**; 116:190–2.
14. Nagarajan K, Palani B, Basha L, Jayabal L, Muniyandi M. A social networks-driven approach to understand the unique alcohol mixing patterns of tuberculosis patients: reporting methods and findings from a high TB-burden setting. Humanit Soc Sci Commun **2022**; 9:1–8.
15. Bui DP, Oren E, Roe DJ, et al. A case-control study to identify community venues associated with genetically-clustered, multidrug-resistant tuberculosis disease in Lima, Peru. Clin Infect Dis **2019**; 68:1547–55.
16. 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.
17. Munang ML, Browne C, Evans JT, et al. Programmatic utility of tuberculosis cluster investigation using a social network approach in Birmingham, United Kingdom. Int J Tuberc Lung Dis **2016**; 20:1300–5.
18. Havlir DV, Balzer LB, Charlebois ED, et al. HIV testing and treatment with the use of a community health approach in rural Africa. N Engl J Med **2019**; 381:219–29.
19. Marquez C, Atukunda M, Balzer LB, et al. The age-specific burden and household and school-based predictors of child and adolescent tuberculosis infection in rural Uganda. PLoS One **2020**; 15:e0228102.
20. Chen Y, Zheng W, Brown LB, et al. Semi-supervised record linkage for construction of large-scale sociocentric networks in resource-limited settings: an application to the SEARCH study in rural Uganda and Kenya. [Preprint: not peer reviewed]. 24 August 2019. Available from: https://arxiv.org/abs/1908.09059.
21. Chen YT, Brown L, Chamie G, et al. Social networks and HIV care outcomes in rural Kenya and Uganda. Epidemiol Camb Mass **2021**; 32:551–9.
22. World Health Organization. WHO consolidated guidelines on tuberculosis module 2: screening—systematic screening for tuberculosis disease. Available at: https://www.who.int/publications-detail-redirect/9789240022676. Accessed 22 July 2022.
23. Balen J, McManus DP, Li YS, et al. Comparison of two approaches for measuring household wealth via an asset-based index in rural and peri-urban settings of Hunan province, China. Emerg Themes Epidemiol **2010**; 7:7.
24. Vyas S, Kumaranayake L. Constructing socio-economic status indices: how to use principal components analysis. Health Policy Plan **2006**; 21:459–68.
25. Lendle SD, Schwab J, Petersen ML, van der Laan MJ. ltmle: An R package implementing targeted minimum loss-based estimation for longitudinal data. J Stat Soft **2017**; 81:1–21.
26. World Health Organization. Global tuberculosis report 2019. World Health Organization, Available at: http://www.who.int/tb/publications/global_report/en/. Accessed 1 March 2020.
27. Boum Y, Atwine D, Orikiriza P, et al. Male gender is independently associated with pulmonary tuberculosis among sputum and non-sputum producers people with presumptive tuberculosis in Southwestern Uganda. BMC Infect Dis **2014**; 14: 638.
28. Dodd PJ, Looker C, Plumb ID, et al. Age- and sex-specific social contact patterns and incidence of *Mycobacterium tuberculosis* infection. Am J Epidemiol **2016**; 183:156–66.

29. Shaweno D, Horton KC, Hayes RJ, Dodd PJ. Assortative social mixing and sex disparities in tuberculosis burden. Sci Rep 2021; 11:7530.

30. Andre M, Ijaz K, Tillinghast JD, et al. Transmission network analysis to complement routine tuberculosis contact investigations. Am J Public Health 2007; 97: 470–7.

31. Shah NS, Auld SC, Brust JCM, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. N Engl J Med 2017; 376:243–53.

32. Gandhi NR, Weissman D, Moodley P, et al. Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. J Infect Dis 2013; 207:9–17.