Performance of a Score to Characterize Adequate Contact among the Social Network of Persons with Tuberculosis

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Abstract

Background.

Exposure to an individual with tuberculosis is necessary for transmission to occur. Previously, we developed a score that measures contact between tuberculosis cases and their social networks in an African urban context. This score was built using exploratory factor analysis and identified contact as the conjunction of two domains – setting and relationship. Now, our aim is to determine whether this score covaries with the presence of tuberculous infection among social contacts of tuberculosis cases.

Methods.

This was a large cross-sectional study conducted in Kampala, Uganda from 2012-2016. Tuberculous infection was assessed in social contacts of adult tuberculosis cases. We estimated the prevalence of tuberculous infection in this population, overall and according to the setting and relationship domains. We calculated the prevalence ratio (PR) for the association between increasing scores in the setting and relationship domains and tuberculous infection, adjusted by other covariates, using modified Poisson regression models.

Results.

We enrolled 955 household and community contacts from 119 tuberculosis cases. The overall prevalence of tuberculous infection in the social networks was 52% (95% confidence interval [CI], 48-55). The prevalence of tuberculous infection in very low, low, medium, and high setting-contact quartiles was 44%, 40%, 53%, and 70% respectively ($P_{trend}<.0001$). By the relationship score, the prevalence of tuberculous infection in very low, low, moderate and high-contact groups was 41%, 47%, 53% and 66% respectively ($P_{trend}<.0001$). The effect of the setting score in the prevalence of tuberculous infection was higher among children between 5-14 years (PR=1.26; 95% CI 1.15-1.39) whereas the relationship score was associated with tuberculous infection in children of 0-4 years (PR=1.42; 95% CI 1.10-1.82)

Conclusion.

In this large observational study from an urban African setting, participants, especially children, with higher setting and relationship scores were more likely infected with *Mycobacterium tuberculosis* among contacts of a tuberculosis case.

Background

Tuberculosis remains an endemic disease in parts of Southeast Asia and Africa, despite optimizing treatment through directly observed therapy [1]. Tuberculosis persists in these regions because one infectious case is replaced by at least one other case over time [2]. An essential measure in the control of tuberculosis is to interrupt these chains of transmission. To achieve this end, we need to understand better the nature of transmission of *Mycobacteria tuberculosis*.
Household contact studies have provided a useful design for discovering factors from the index case or from the contact that can increase the risk of tuberculosis transmission, as measured by tuberculous infection. The age of the contact, sputum smear grade of the index case, cavitary lung disease, the number of people living in a household are just some of the factors that have been identified [3-5]. These factors by themselves, however, will not cause a transmission event unless there is adequate contact between the infectious case and a susceptible host. Previous studies have shown that the nature of the contact of an index case with a household contact can increase the likelihood of tuberculosis transmission [6, 7]. For example, spouses are at higher risk of tuberculous infection than other household members and daily contact can increase the risk of this infection in the household [8, 9].

Outside of the household, less is known about the transmission of $M.\ tuberculosi$s. From epidemiologic and molecular studies conducted in diverse settings, it appears that over 80% of $M.\ tuberculosi$s transmission occurs outside of the households of index cases [3, 10, 11]. From anecdotal reports of community outbreaks of tuberculosis [12-14], we know that some congregate settings are associated with transmission and the risk for tuberculosis disease, but the nature of interactions between infectious case and susceptible contact that define adequate contact for transmission in these settings are still not well understood. For this reason, there remains uncertainty about how best to implement public health strategies that detect detection and prevent transmission of tuberculosis in community-settings.

Methods

STUDY POPULATION

We enrolled tuberculosis index cases aged $\geq$15 years who were residents of Kampala, Uganda from 2012-2016. Index cases were microbiologically confirmed by a positive sputum smear and had signs and symptoms of pulmonary tuberculosis. We then ascertained their social networks including contacts within and outside of the household. These contacts were traced and enrolled; demographic and clinical information were collected from them using standardized interviews. More details of this study have been previously provided [11, 15].

DERIVED RISK SCORE

The study exposure was a derived score between tuberculosis cases and their contacts. The development of this score have been previously described [15]. Briefly, index cases answered questions related to the social mixing between them and each of their social networks. A factor analysis was conducted among these variables, which identified two main domains. The setting domain comprised six variables: nature of ventilation at usual place of meeting, frequency of sleeping in same room/same bed, most recent meeting was indoors or outdoors, frequency of shared meals since onset of cough, place of usual meeting (home versus other location) and frequency and duration of contact over the past month. The relationship domain also included six variables: case trusted contact, case shared tuberculosis diagnosis
with contact, case was provided care by the contact in the past 3 months, length of knowing contact, how well does the case knows the contact, means of transportation used most often with contact-none/walking versus a type of transportation. Factor analyses results provided weights to each of these variables. We then took the sum of these weights to obtain a setting and a relationship score for each interaction case-contact. We have previously shown that these domain scores reliably measure the extent and nature of the contact between an infectious case and susceptible contact [15].

**OUTCOME**

The study outcome was tuberculous infection in contacts, either latent tuberculous infection or active disease. Latent tuberculous infection was determined using the tuberculin skin test (TST). A positive TST result was defined as an induration ≥ 10 millimetres as it has shown to be an adequate cut-off in the Ugandan setting [6]. Active tuberculosis was defined either as: the presence of at least one smear positive for acid fast bacilli, positive culture for *Mycobacterium tuberculosis*, positive molecular result for *Mycobacterium tuberculosis* and history of previous tuberculosis disease, informed by the social contact.

**ANALYTICAL STRATEGY**

The main objective of this analysis was to estimate and compare the prevalence of tuberculous infection according to the contact scores. We included in the analysis contacts with complete exposure and outcome data.

We explored the probability of tuberculous infection against setting and relationship scores, using a loess (locally weighted scatterplot smoothing) model to obtain a nonparametric smoothed curve [16, 17]. Next, we created a matrix of infection prevalence according to setting and relationship score combinations. We rounded scores to the nearest integer for presentation.

We explored the association of the twelve individual variables that comprised the setting and relationship factors with the prevalence of tuberculous infection in the social contacts of tuberculosis cases. The prevalence of tuberculous infection according to each of the responses is shown with 95% confidence intervals (CI).

We categorized the setting and relationship scores as very low, low, moderate, and high contact according to quartiles and estimated the prevalence and 95% CI of tuberculous infection in each category, overall and stratifying by household status (household or extra-household) and smear grade. We used the Cochran-Armitage Trend Test to assess for trends across setting and relationship quartiles.

We used Poisson regression models with a robust variance to estimate the prevalence ratio for the association between increasing scores in setting and relationship domains and tuberculous infection [18-20]. This technique allows the analysis of clustered data [21]. Final models included the setting or relationship score and pre-selected potential confounders: age, sex, HIV status, body mass index (BMI)
and smear grade of the index case, and the age, sex, BCG, and HIV status of contacts [6, 22-29]. We also included independent social factors that were shown to be associated with tuberculous infection. The final models are presented stratified by age of contact: 0-4 years, 5-14 years, and ≥15 years, as the stratified analysis and regression models suggested age of contact was an effect modifier of the association.

In the Appendix, we showed the results of an overall combined score, considering both the setting and relationship score.

All analyses were conducted using SAS software v 9.4 (SAS Institute, Cary, NC, US) and R v3.6.0 (R Foundation for Statistical Computing, Vienna, Austria, 2016).

**Results**

Contacts of 123 index cases were enrolled in the study. Complete data for this analysis were available for 955 of 1006 contacts (95%), including 119 index cases (Figure S1). The median age of index cases was 28 years (IQR, 23–36) while 82% were men. Almost one in five index cases were living with HIV (17%). Contacts were similarly distributed in terms of sex (52% female). The median age was 23 years (IQR, 13–31) (Table 1). Almost two-thirds of contacts were from outside the household (61%).
Table 1
Characteristics of the enrolled contacts of 119 tuberculosis cases from Kampala, Uganda that answered the social network survey.

| Characteristic                              | N   | %   |
|---------------------------------------------|-----|-----|
| Contacts enrolled                           | 1006| 100 |
| Contacts enrolled with complete data        | 955 | 95  |
| Gender                                      |     |     |
| Male                                        | 462 | 48  |
| Female                                      | 493 | 52  |
| Type of contact                             |     |     |
| Household                                   | 369 | 39  |
| Extra-household                             | 586 | 61  |
| Age, years, median [IQR]                    | 23  | [13–31] |
| Age group, years                            |     |     |
| 0–4                                         | 110 | 12  |
| 5–14                                       | 141 | 15  |
| ≥ 15                                        | 704 | 74  |
| Residence                                   |     |     |
| Lives in Rugaba                             | 920 | 96  |
| Do not live in Rugaba                       | 34  | 4   |
| No information available                    | 1   | 0   |
| HIV Result                                  |     |     |
| Positive                                    | 71  | 7   |
| Negative                                    | 874 | 92  |
| Not done/refusals                           | 10  | 1   |
| BCG vaccine                                 |     |     |
| Yes¶                                        | 816 | 85  |
| No                                          | 80  | 8   |

Abbreviations: HIV, human immunodeficiency virus. BCG, Bacillus Calmette–Guérin. TST, tuberculin skin test. IQR, interquartile range

¶ Reported by verbal communication or by proof of immunization card.
| Characteristic                                      | N  | %  |
|----------------------------------------------------|----|----|
| Don’t know/Missing                                 | 59 | 6  |
| Tuberculous infection                              |    |    |
| Yes                                                | 493| 52 |
| TST Result ≥ 10 mm                                 | 431| 45 |
| Previous history of TB/current TB disease          | 62 | 6  |
| No (TST Result < 10 mm)                            | 462| 48 |

Abbreviations: HIV, human immunodeficiency virus. BCG, Bacillus Calmette–Guérin. TST, tuberculin skin test. IQR, interquartile range

¶ Reported by verbal communication or by proof of immunization card.

Sex assortment with cases differed by sex; one-third of female contacts were exposed to a female index case whereas 73% of male contacts were exposed to a male index case.

The overall prevalence of tuberculous infection in social networks was 52% (95% CI, 48–55). Both setting and relationship scores were positively associated with tuberculous infection in contacts (Figure S2). Contacts who had setting scores ≥ 14 units and relationship scores ≥ 11 units had a higher prevalence of tuberculous infection than other contacts (77% versus 49%, respectively; P < 0.0001) (Fig. 1; also Figure S3).

When we categorized contact scores into quartiles, we found a rise in the risk of infection with each increasing quartile. In very low, low, medium, and high setting-contact quartiles, the prevalence of tuberculous infection was 44%, 40%, 53% and 70%, respectively (Table 2, P trend < .0001). This corresponded to a crude prevalence ratio of 1.0 (95% CI 0.81–1.24), 1.30 (95% CI 1.04–1.63) and 1.64 (95% CI 1.33–2.01) for each quartile compared to the very low quartile. As for the relationship score, in very low, low, medium, and high-contact groups, the prevalence of tuberculous infection was 41%, 47%, 53%, and 66%, respectively (P trend < .0001). This corresponded to a crude prevalence ratio of 1.13 (95% CI 0.93–1.37), 1.24 (95% CI 1.01–1.52) and 1.62 (95% CI 1.35–1.96) for each quartile compared to the very low quartile.
Table 2
Prevalence and crude prevalence ratio (95% CI) for tuberculous infection among social contacts of tuberculosis cases by the setting and relationship scores.

| Score range     | N   | Prevalence tuberculous infection | Crude prevalence ratio (95% CI) |
|-----------------|-----|----------------------------------|---------------------------------|
| Category        |     | N                               | % (95% CI)                      |
| Overall         | 955 | 493                             | 52 (48–55)                      |
| Setting score (continuous) | 5.3–18.6 | 955 |                                 | 1.05 (1.03–1.07) |
| Setting score (categorical) |     |                                 |                                 |
| Very low        | 5.3-7.0 | 239 | 105                           | 44 (38–50)                      |
| Low             | 7.0-10.3 | 238 | 95                            | 40 (34–46)                      |
| Medium          | 10.3–13.7 | 239 | 126                           | 53 (46–59)                      |
| High            | 13.7–18.6 | 239 | 167                           | 70 (64–76)                      |
| Relationship score (continuous) | 4.0-14.8 | 955 |                                 | 1.08 (1.05–1.10) |
| Relationship score (categorical) |     |                                 |                                 |
| Very low        | 4.0-6.4 | 242 | 99                            | 41 (35–47)                      |
| Low             | 6.4–7.7 | 236 | 111                           | 47 (41–53)                      |
| Medium          | 7.7–10.1 | 238 | 126                           | 53 (46–59)                      |
| High            | 10.2–14.8 | 239 | 157                           | 66 (60–72)                      |

The relationship between the 12 component variables of the two factors and tuberculous infection prevalence followed a similar pattern as the overall factor scores (Table 3). In the setting score, indoor meetings with reduced ventilation resulted in higher prevalence of infection for contacts of index cases as compared with outdoor meetings or rooms with ventilation. Similarly, the prevalence of infection was higher among contacts spending more than 66.5 hours/week with the case (74%) and individuals who shared meals daily with the index case (64%). Contacts who slept in the same room and/or same bed as the index case had a higher prevalence of tuberculous infection (62–75%) than contacts who did not sleep in the same room as the index case (48%) (Table 3).
Table 3
Association between individual variables that comprised the setting and relationship domains and prevalence of tuberculous infection among contacts of tuberculosis cases.

| Variable                                                                 | Prevalence TBI * |
|--------------------------------------------------------------------------|-----------------|
|                                                                          | N ¥  | n    | Prop % (95% CI) † |
| **SETTING DOMAIN**                                                       |      |      |                  |
| Nature of ventilation at usual meeting place                              |      |      |                  |
| Full ventilation                                                         | 459  | 209  | 46 (41–50)       |
| Fair ventilation                                                         | 188  | 100  | 53 (46–60)       |
| Minimal ventilation                                                      | 154  | 100  | 65 (57–72)       |
| Poor ventilation                                                        | 154  | 84   | 55 (47–62)       |
| Frequency of sleeping in the same room and bed                           |      |      |                  |
| No slept in same room, nor bed                                           | 748  | 358  | 48 (44–51)       |
| Slept same room, but not same bed                                       | 139  | 91   | 65 (57–73)       |
| Slept same room and same bed, not daily                                  | 16   | 12   | 75 (54–96)       |
| Slept same room and same bed, daily                                     | 52   | 32   | 62 (48–79)       |
| Most recent meeting was indoor or outdoor                                |      |      |                  |
| Mostly meeting outdoors                                                  | 452  | 201  | 44 (40–49)       |
| Equally indoors/outdoors                                                | 251  | 132  | 53 (46–59)       |
| Mostly meeting indoors                                                  | 252  | 160  | 63 (58–69)       |
| Frequency of sharing meals with contact                                  |      |      |                  |
| Not shared meals                                                         | 365  | 168  | 46 (41–51)       |
| Shared meals, less than a day per week                                   | 83   | 32   | 39 (28–49)       |
| Shared meals 1–3 days/week                                               | 134  | 62   | 46 (38–55)       |
| Shared meals 4–6 days/week                                               | 59   | 31   | 52 (40–65)       |

¥ N represents the number of contacts in that category, n indicates the number of contacts with tuberculous infection.

*TBI = tuberculous infection

†Prop = Proportion of contacts (%) with tuberculous infection. 95% CI = 95% Confident interval of the proportion.
| Variable                                                                 | Prevalence TBI *                                      |
|-------------------------------------------------------------------------|------------------------------------------------------|
|                                                                         | N ¥ | n   | Prop % (95% CI) † |
| Shared meals daily                                                      | 314 | 200 | 64 (58–69)       |
| Location of usual meeting with contact                                  |     |     |                  |
| Outside home of tuberculosis case                                      | 415 | 49  | 49 (44–53)       |
| Home of tuberculosis case                                              | 540 | 54  | 54 (50–58)       |
| Frequency and duration of contact over the past month                   |     |     |                  |
| Less than 3.5 hours/week                                               | 276 | 107 | 39 (33–44)       |
| Between 3.5–28 hours/week                                              | 378 | 187 | 49 (44–54)       |
| Between 28–66.5 hours/week                                             | 216 | 136 | 63 (56–69)       |
| Greater 66.5 hours/week                                                | 85  | 63  | 74 (65–83)       |
| RELATIONSHIP DOMAIN                                                     |     |     |                  |
| Case discuss and confide important life issues with contact             |     |     |                  |
| No discuss nor confide                                                 | 410 | 186 | 45 (40–50)       |
| Discuss but not confide                                                | 293 | 150 | 51 (45–57)       |
| Discuss and confide                                                    | 252 | 157 | 62 (56–68)       |
| Case shared tuberculosis diagnosis with contact                         |     |     |                  |
| No                                                                      | 537 | 245 | 46 (41–50)       |
| Yes                                                                     | 418 | 248 | 59 (55–64)       |
| Frequency of care provided by contact in the past three months          |     |     |                  |
| No care by contact                                                     | 800 | 394 | 49 (46–53)       |
| Care provided, less than a day per week                                 | 35  | 18  | 51 (35–68)       |
| Provided care 1–3 days/week                                             | 41  | 25  | 61 (46–76)       |
| Provided care 4–6 days/week                                             | 15  | 7   | 47 (21–72)       |

¥ N represents the number of contacts in that category, n indicates the number of contacts with tuberculous infection.

*TBI = tuberculous infection

†Prop = Proportion of contacts (%) with tuberculous infection. 95% CI = 95% Confident interval of the proportion.
| Variable                                      | N  | n  | Prop % (95% CI) † |
|----------------------------------------------|----|----|--------------------|
| Provided care daily                          | 64 | 49 | 76 (66–87)         |
| Length knowing the contact                   |    |    |                    |
| Less than 2 years                            | 375| 164| 44 (39–49)         |
| 2–4 years                                    | 165| 83 | 50 (43–58)         |
| 5–6 years                                    | 190| 109| 57 (50–64)         |
| More than 6 years                            | 225| 137| 61 (54–67)         |
| How well does the case knows contact         |    |    |                    |
| Not well/almost do not know                  | 15 | 1  | 7 (0–19)           |
| Somewhat well                                | 131| 53 | 40 (32–49)         |
| Moderately well                              | 229| 100| 44 (37–50)         |
| Very well                                    | 580| 339| 58 (54–62)         |
| Means of transportation used most often with contact. |    |    |                    |
| None/walking                                 | 782| 398| 51 (47–54)         |
| Another type of transportation               | 173| 95 | 55 (47–62)         |

‡ N represents the number of contacts in that category, n indicates the number of contacts with tuberculous infection.

*TBI = tuberculous infection

† Prop = Proportion of contacts (%) with tuberculous infection. 95% CI = 95% Confident interval of the proportion.

For each variable in the relationship score, there was a monotonic increase in proportion of infection as the extent of exposure increased within each category, except in care of contact (Table 3). The highest prevalence of tuberculous infection occurred in contacts who discuss and confide with the case (62%), knew the tuberculosis diagnosis of the case (59%), provided daily care to the case (76%), known each other for more than 6 years (61%) and were known very well by their index case (58%).

Since the nature of exposure may differ according to household or extra-household exposure (Figure S4), we stratified the analysis by each category. Among household contacts, the majority had setting scores in the medium and high quartiles and the prevalence of tuberculous infection was highest in the highest quartile (70%, \( P_{\text{trend}} < 0.0001 \)). Similarly, for the relationship score, the prevalence of tuberculous infection increased with increasing quartile in the contact score, from 41% in the very low quartile to 68% in the
high quartile ($P_{\text{trend}}=0.0052$). Among extra-household contacts, the prevalence of tuberculous infection tended to increase across quartiles from very low (44%), low (42%) medium (54%), to high (70%) ($P_{\text{trend}}=0.0713$). For the relationship score, the prevalence of tuberculous infection in extra-household contacts was 41%, 42%, 50 and 60% in the very low, low, middle, and high relationship-contact quartiles, respectively ($P_{\text{trend}}=0.0048$).

Among contacts exposed to index cases with a high-smear grade, the prevalence of tuberculous infection increased from 42% in the lowest quartile of the setting score to 69% in the highest quartile ($P_{\text{trend}}<0.0001$) (Figure S5). Among contacts of index cases with a low smear grade, this pattern was not found. Instead, the prevalence of tuberculous infection did not differ markedly among contacts in the lowest three quartiles (40%, 46%, 32%, respectively), and was highest among contacts in the highest quartile of the setting score (75%) ($P_{\text{trend}}=0.0716$). For the relationship score, both contacts of index cases with low or high smear grade results showed an increase in the prevalence of tuberculous infection according to the relationship quartiles (Figure S5).

After adjustment for covariates, the setting and relationship scores continued to be associated with the prevalence of tuberculous infection in contacts (Fig. 2). This association was most pronounced in children. In the contacts 0–4 years old, the prevalence ratio for infection was 1.11 (95% CI, 1.04–1.19) for the setting score, meaning that with each increment of one unit in the score, the risk of infection was 11% higher. Similarly, for the relationship score where the prevalence ratio for infection was 1.42 (95% CI, 1.10–1.82). For contacts 5–14 years old, the adjusted prevalence ratio was 1.26 (95% CI, 1.15–1.39) for the setting score and 1.14 (95% CI, 1.06–1.23) for the relationship score. Among adults, both scores were associated with infection, but magnitude of effect of the score was less. When analysed by quartiles, the results were like the ones of the crude prevalence ratio. For the setting score, the adjusted prevalence ratios were 1.00 (95% CI 0.82–1.22), 1.33 (95% CI 1.07–1.65) and 1.81 (95% CI 1.47–2.23) for each quartile compared to the very low quartile. For the relationship score, these values were 1.10 (95% CI 0.91–1.34), 1.22 (95% CI 1.0–1.49) and 1.47 (95% CI 1.21–1.79).

### Discussion

Ongoing transmission of *M. tuberculosis* is the central reason for persistence of tuberculosis in the world today. Transmission of any pathogen is difficult to observe and therefore measure but defining adequate contact for transmission is more feasible. To this end, in a large observational study from an East African city with endemic tuberculosis, we developed a scoring method that used exploratory factor analysis as an agnostic approach to identify ways in which tuberculosis index cases interact with their social network contacts [15]. The factor analysis identified two factors that described the setting and relationship between index cases and their contacts.
Here, we found that scores from each factor were consistently associated with tuberculous infection, especially in young children. We found consistent performance of the factors scores across different scenarios, such as household or extra-household exposure, and infectiousness of the index case as measured by sputum microscopy. These integrated analyses provide strong support for the overall validity of the scores in assessing adequate contact for transmission.

The validity of the factor scores is further supported by the component variables that describe the settings of the interactions and the relationships between the cases and contacts. In the setting factor, three component variables have been identified as risk factors for tuberculous infection in prior studies [30–32]. These variable included ventilation in the usual meeting place, sleeping with the index case, and interaction predominantly indoors or outdoors For instance, it is known that higher ventilation rates decrease quanta concentration in inspired air, which in turn reduces the number of new incident cases [33], and prolonged and repeated exposures as happens during sleep is associated with new infections and disease [8, 30, 34]. Thus, the inclusion of these variables in our setting domain supports its strong content validity.

Importantly, our setting-specific score disaggregated contacts with and without *M. tuberculosis* infection both in household and community contacts. For example, in community contacts, the prevalence of tuberculous infection was greatest (70%) among the quartile with the highest setting score. The prevalence of tuberculous infection was almost 30% lower in the lowest quartile (44%). Most transmission in high-burden settings occurs outside the household [10]. However, efficient tools to identify high-risk individuals in the community are lacking. Potentially, an approach targeting community members with high setting or relationship scores may be a viable approach to both improve efficiency when screening the community and improve cost-effectiveness.

For the relationship factor, we found a strong association between the score and tuberculous infection in children under 15 years of age. This effect was especially pronounced among young children less than five years because the component variables measure the close relationship with household members, especially their parents who must care for them. The relationship domain likely reflected this intimate relationship and showed its utility in establishing *M. tuberculosis* transmission. Previous studies have used similar methods [8, 35] to measure exposure to tuberculosis and the risk of tuberculous infection and disease among child household contacts [35]. Acuna-Villaorduna and colleagues modified this methodology to include adult household contacts in Brazil [8]. Both studies found an association between the score and infection.

Our approach refines these approaches in important ways. First, we included both household and extra-household contacts in developing the factors that underly the score, whereas the earlier studies included only household contacts. Furthermore, we validated the performance of our scores separately for household and extra-household contacts. It has been established for a long time that the household is an environment for likely transmission of *M. tuberculosis*, especially to resident children. Our approach takes a step further to validate partially the use of the factors scores in the community. Moreover, the results
from these prior studies may not be directly comparable because they did not use social science methods to ascertain networks and social networks are distinct from place-to-place [36]. In addition, the background tuberculosis burden in Brazil is much lower than Uganda while South Africa has a higher prevalence of tuberculous infection and disease [1]. Local transmission dynamics should be considered when evaluating such scores and validation of our methods should be performed in other settings.

Our study has limitations. First, in our definition of tuberculous infection we included contacts with latent and active tuberculosis. As this is a cross-sectional study, we cannot establish the directionality of the transmission for the latter category. Nevertheless, the large majority (87%) of our contacts had latent tuberculosis suggesting it is unlikely that our findings would differ if we excluded contacts with active tuberculosis. Second, setting and relationship characteristics were reported by the index case, so recall bias is possible. Third, social mixing and behaviour is context-dependent [26]; our findings might not be applicable in other settings. Nevertheless, we developed the factors through and agnostic and unbiased approach to describe contact between the index case and social network member. We further validated the relationship between the factor scores and infection among contacts. As with any predictive tool, further development and testing should be done in other locations. This score was developed to quantitively measure one of the components that drives tuberculosis transmission, adequate contact.

Based on our analyses, we propose that the setting and relationship domains can contribute to characterize adequate contact among tuberculosis cases and their contacts. All infectious tuberculosis cases have a contact network that comprises both known (household members, friends, workmates) and unknown members with whom the index case may have a single contact. A previous study has suggested that causal contacts might represent more than 60% of the total contacts of the index cases [37] indicating that the household network is only partially defined through the social network.

**Conclusions**

In conclusion, relationship and setting-specific grouped characteristics identified contacts with *M. tuberculosis* infection. These factor scores were especially apparent in children, a group at high-risk to develop tuberculosis once infected. These factors may be useful in prioritizing contact investigations of tuberculosis index cases, not only in the households of cases but in the community as well.

**Abbreviations**

PR=prevalence ratio, CI= confidence interval, TST= tuberculin skin test, HIV= human immunodeficiency virus, BMI= body mass index

**Declarations**

**Ethics approval and consent to participate.**
Written informed consent was obtained from all participants prior to study inclusion. For all participants 18 years or younger we obtained written parental or guardian informed consent. In Uganda, the age of assent is eight years, so for all participants between the ages of 8 and 17 (inclusive), we obtained an assent. Institutional review board clearance was obtained from the Higher Degrees Research and Ethics Committee at Makerere University School of Public Health and approved by the Uganda National Council for Science and Technology in Uganda and the Institutional Review Board at University of Georgia. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available on request from the senior author, CCW. The data are not publicly available due to containing information that could compromise the privacy of research participants.

Competing interests

The authors declare that they have no competing interests.

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Author’s contributions

Conception and design: MEC, CCW; data collection: SZ, RK, NK, CCW, data analyses: MEC, TQ, interpretation of the study results: MEC, SZ, TQ, RK, LM, MHE, KKD, NK, CCW. Review and edit of the manuscript: MEC, SZ, TQ, RK, LM, MHE, KKD, NK, CCW. All authors approved the final version of the manuscript.

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