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Original Contribution

Resistance and Susceptibility to *Mycobacterium tuberculosis* Infection and Disease in Tuberculosis Households in Kampala, Uganda

Catherine M. Stein*, Sarah Zalwango, LaShaunda L. Malone, Bonnie Thiel, Ezekiel Mupere, Mary Nsereko, Brenda Okware, Hussein Kisingo, Christina L. Lancioni, Charles M. Bark, Christopher C. Whalen, Moses L. Joloba, W. Henry Boom, and Harriet Mayanja-Kizza

* Correspondence to Dr. Catherine Stein, Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, 2103 Cornell Road, Cleveland, OH 44106 (e-mail: catherine.stein@case.edu).

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Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), remains a major public health problem. Household contact studies identify children and adults along the spectrum from Mtb exposure to disease. In the Kawempe Community Health Study (conducted in Kampala, Uganda), 872 culture-confirmed pulmonary TB cases and their 2,585 contacts were enrolled during 2002–2012 and followed for up to 2 years each. Risk factors identified by time-to-event analysis for secondary TB differed among children, women, and men. Younger age ($P = 0.0061$), human immunodeficiency virus (HIV) ($P = 0.0002$), thinness ($P = 0.01$), absent bacille Calmette-Guérin vaccination ($P = 0.002$), and epidemiologic risk score ($P < 0.0001$) were risks for children. For women, risks were HIV ($P < 0.0001$), thinness (World Health Organization criteria; $P < 0.0001$), and epidemiologic risk score ($P = 0.003$). For men, HIV ($P = 0.0007$) and low body mass index ($P = 0.008$) resulted in faster progression to TB. Tuberculin skin testing (TST) identified contacts with Mtb infection and those with persistently negative TST. Risks for faster time to Mtb infection were identified, and included age ($P = 0.0007$), baseline TST induration ($P < 0.0001$), and epidemiologic risk score ($P < 0.0001$) only in children. Those with persistently negative TST comprised 10% of contacts but had no unique epidemiologic characteristics among adults. The burden of Mtb infection and disease is high in TB households, and risk factors for progression from exposure to infection and disease differ among children, women, and men.

case-contact study; case finding; infectious disease epidemiology; Mtb infection; pediatric TB; resistance to infection

Abbreviations: BCG, bacille Calmette-Guérin; BMI, body mass index; HHC, household contact; HIV, human immunodeficiency virus; KCHS, Kawempe Community Health Study; LTBI, latent *Mycobacterium tuberculosis* infection; Mtb, *Mycobacterium tuberculosis*; PTST−, persistently negative tuberculin skin test; TB, tuberculosis; TST, tuberculin skin test.

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), remains a major public health problem globally (1). Failure of a recent TB vaccine in infants (2), limited new drug development, and increased drug resistance are roadblocks to battling the TB pandemic. Better biomarkers and pathogenic insight will allow identification of those at greatest risk for acute Mtb infection, development of latent Mtb infection (LTBI), and progression to tuberculosis disease, and household contact (HHC) studies are a means to identify risk factors for these 3 clinical states (3–6). The risk of Mtb infection and disease is greater among HHCs than in the community in TB-endemic settings (7). However, few TB HHC studies have used long-term follow-up to define when Mtb infection and disease occur, and whether some contacts resist developing LTBI. The Kawempe Community Health Study in Kampala, Uganda, was designed to follow-up an earlier TB HHC study focused on secondary TB (3). The present study analyzed risk factors for the natural history from Mtb exposure to infection to disease in adults and children in a human immunodeficiency virus (HIV)-endemic setting. Uganda is a high-burden TB setting with an annual risk of Mtb infection of 3% and annual incidence of new smear-positive TB cases of 159/100,000 population (8). This

number represents a national estimate; it almost certainly underestimates Mtb infection and TB rates in Kampala's urban setting (9). We enrolled 872 Ugandan households in which at least 1 member had confirmed TB and 2,585 adult and pediatric contacts during 2002–2012, and we followed them for 2 years. The longitudinal study design allowed examination of demographic and epidemiologic factors associated with Mtb exposure, acute Mtb infection, LTBI, and development of TB. Among those studied was a unique cohort of individuals who had persistently negative results from tuberculin skin tests (TSTs) for 2 years despite known Mtb exposure. We hypothesized that there would be differences in risk factors for Mtb infection and TB between children and adults as well as between women and men. In examining time to developing Mtb infection and TB, we identified clinically significant associations with age, sex, epidemiologic risk score, HIV, bacille Calmette-Guérin (BCG) vaccination scar, TST induration, and body composition.

METHODS

Study population

From April 2002 through April 2012, persons with culture-confirmed pulmonary TB and their HHCs were enrolled in a prospective cohort study of households in the Kawempe Division of Kampala, Uganda, called the Kawempe Community Health Study (KCHS). HHCs were defined as individuals who resided in the household of the TB index case for at least 7 consecutive days during the previous 3 months. HHCs were followed for up to 24 months. Adults with pulmonary TB, living in Kawempe, with 1 or more HHCs were recruited through 3 mechanisms: 1) clinics at the Uganda National TB and Leprosy Program treatment center at Mulago Hospital; 2) referral to the TB research clinic at Mulago Hospital; and 3) community sensitization efforts in the Kawempe division of Kampala. Diagnosis of TB was based on clinical presentation, a positive chest x-ray, and positive sputum culture for Mtb. Active TB was treated with standard short-course therapy with 2 months of isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin. TB treatment was extended when follow-up sputum cultures and/or smears remained positive. Sputum specimens were tested for drug sensitivity, and individuals with multidrug-resistant TB were provided with appropriate drug treatment. Treatment with 9 months of isoniazid was provided to HHCs less than 5 years old and to all HIV-infected and TST-positive HHCs. Mtb lineage was determined by genotyping 3 single nucleotide polymorphisms (10) and classified according to Gagneux (11, 12).

The study protocol was approved by the National HIV/AIDS Research Committee of Makerere University and the institutional review board at University Hospitals Cleveland Medical Center. Final clearance was given by the Uganda National Council for Science and Technology. Written informed consent was obtained from the head of household, all adults, and parents/guardians of children in the household, and assent was obtained from children over age 8 years.

Measurements

Household evaluation. HHCs were evaluated clinically at baseline and by standardized questionnaire for TB risk factors (Web Appendix 1, available at https://academic.oup.com/aje). Study visits were conducted upon enrollment, and after 3, 6, 12, 18, and 24 months. HIV-1 testing using enzyme-linked immunosorbent assay was conducted on samples from consenting adults and children >2 years old, and using polymerase chain reaction for samples from children under 2 years of age born to HIV-positive mothers. In Uganda, adolescents aged ≥15 years old are considered adults, so "children" in this study refers to those HHCs <15 years of age. Body mass index (BMI, calculated as weight (kg)/height $(m)^2$) was used as a continuous variable, and "thinness" as a binary variable, using the World Health Organization definition of grade 2 thinness (BMI <17 for adults (13)). Thinness in children was defined as weight-for-length z score cutoff of −2 standard deviations for children less than 5 years old, and BMI-for-age cutoff of −2 standard deviations for ages 5–15 years (14). BCG vaccination was ascertained by identifying the characteristic scar or by review of medical records, if available. Because metrics for body composition differ per age category in children, BMI was not analyzed on a continuous scale for children. Epidemiologic risk score for Mtb exposure was calculated for children (15) and adapted for adults (16) (Web Appendix 1).

Secondary TB in HHCs. All individuals were evaluated for TB, and contacts with signs and symptoms of TB were considered presumptive TB cases (Web Appendix 1). In addition to baseline chest x-ray and physical examination, presumptive TB cases had sputum or gastric lavage sent for Mtb microscopy and culture. HHCs presenting at scheduled follow-up visits, or at unscheduled times, with signs and symptoms of TB were considered presumptive TB cases and evaluated as described above.

Secondary TB cases were defined as cases in the household diagnosed in addition to the index case, and were classified as definite, probable, possible, or unlikely according to American Thoracic Society criteria (17) by trained clinicians in both Kampala and Cleveland, using results from sputum smear and culture, chest x-ray, symptoms, and response to TB treatment. Classification disagreements were resolved by consensus review. Secondary TB cases were those with "definite" or "probable" classifications, all having at least 1 specimen that was culture-confirmed for Mtb. Individuals who had TB diagnosed within 3 months of enrollment were considered coprevalent and those diagnosed later were considered incident. This definition of "incident" TB was based on data showing that TB risk in a close contact was highest in the first 3 months after identification of the index TB case (18) and was confirmed in our earlier contact study (3). Secondary TB cases were treated as described above.

Mtb infection in HHC according to TST. HHC were evaluated for LTBI by TST using the Mantoux method (0.1 mL of 5 tuberculin units of purified protein derivative, Tubersol; Connaught Laboratories Limited, Willowdale, Ontario, Canada). TST was administered on the left forearm and read after 48–72 hours as the diameter (mm) of palpable induration. Digital calipers were used to measure TST induration and histograms of

TST readings did not suggest digit bias (Web Figure 1). TST positivity was defined by a maximum induration of 10 mm or greater for individuals aged >5 years, or an induration of 5 mm or greater in children aged 5 years or younger or HIV-positive individuals (19). TST-positive HHCs at baseline received no further TST. TST conversion was defined by development of a positive TST based on those same criteria and increased increment (20) (Web Appendix 1). TST converters who remained asymptomatic and had a negative chest x-ray were offered 9 months of isoniazid preventive therapy.

HHC with persistently negative TST. HHC with negative baseline TST reactions who remained TST-negative upon repeat testing at 3, 6, 12, 18, and 24 months were considered persistently TST-negative (PTST−) (16). To be considered PTST− one needed at least 12 months, if lost to follow-up, and optimally 24 months of follow-up TSTs that were all negative, without evidence for disease (16). If an individual developed TB, that diagnosis superseded TST status in their final outcome classification (i.e., no PTST− subject could have TB).

Analytical strategy

We classified 4 clinical groups for analysis: 1) exposed and uninfected for up to 24 months (PTST−); 2) infected without disease based on baseline positive TST and no disease in 24 months; 3) acute Mtb infection based on TST conversion within 24 months; and 4) TB disease, either coprevalent (within 3 months of baseline visit) or incident (beyond 3 months of baseline visit).

Statistical analysis was performed using SAS (SAS Institute, Inc., Cary, North Carolina) and R (R Foundation for Statistical Computing, Vienna, Austria). *P* values of <0.05 were considered significant, and all are 2-sided. Mean or median estimates were

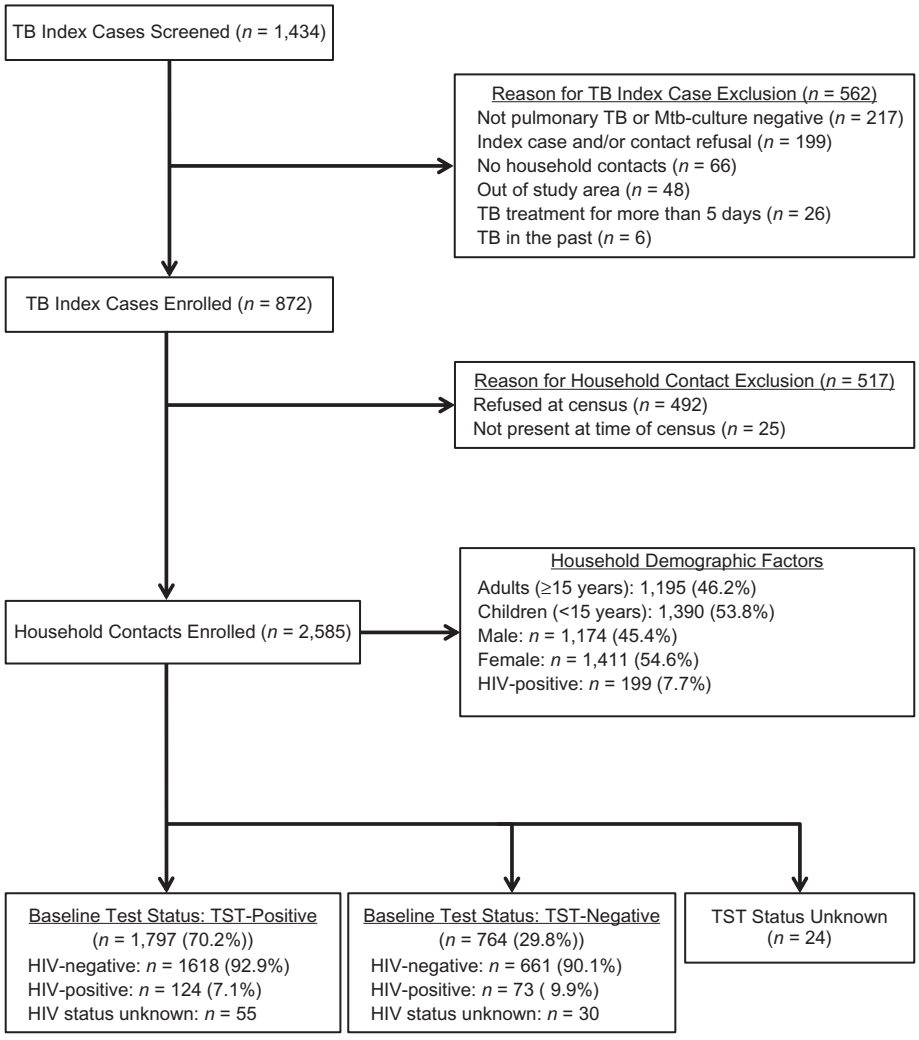

Figure 1. Tuberculosis (TB) household contact (HHC) study enrollment and demographic factors, Kawempe Community Health Study, Kampala, Uganda, 2002–2012. Among the HHCs enrolled, the mean number of contacts per household was 3.0 (range, 1–29), the mean number of adults per household was 1.4 (range, 0–17), and the mean number of children/household was 1.6 (range, 0–12). Mtb, *Mycobacterium tuberculosis*; HIV, human immunodeficiency virus; TST, tuberculin skin test.

Table 1. Baseline Tuberculin Skin Test and Human Immunodeficiency Virus Status of Household Contacts According to Age Group, Kawempe Community Health Study, Kampala, Uganda, 2002–2012

Baseline Status	Age Group, years									
	≤2 (*n* = 359)		3–5 (*n* = 330)		6–14 (*n* = 701)		≥15 (*n* = 1,195)		Total (*n* = 2,585)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Coprevalent TB[a]	62	17.6	26	8.0	18	2.6	36	3.0	142	5.5
TST-positive[a]	195	55.4	175	53.5	424	60.7	889	75.1	1,683	65.7
TST-negative[a]	95	27.0	126	38.5	257	36.8	259	21.9	737	28.8
HIV-positive[b]	13	4.4	9	2.8	20	3.0	148	12.4	190	7.6

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; TST, tuberculin skin test.

[a] Percentages are within column. TST status at baseline was missing for 23 subjects. The denominators for the coprevalent TB, TST-positive, and TST-negative rows were 352, 327, 699, 1,184 and 2,562 for the 4 age categories and total, respectively.

[b] Unknown baseline HIV status was inferred from follow-up HIV results when possible. HIV status remained missing for 92 subjects. The denominators for the HIV-positive row were 293, 322, 684, 1,194, and 2,493 for the 4 age categories and total, respectively.

compared using the parametric *t* test or nonparametric Wilcoxon-Mann-Whitney test, respectively. The χ^2 or Fisher's exact method was used to test for association between subject cohorts and categorical factors. The time-to-onset of secondary TB and time-to-TST conversion events were modeled using the Kaplan-Meier method, and survival models were assessed using Cox proportional hazards analysis. After each covariate was tested as a single predictor, multivariable analysis using stepwise regression was used to find the best model. We considered age, sex, and HIV as key covariates, and we evaluated interaction terms to explore potential effect modification. Parameter estimates were calculated under the independent working assumption with adjustment for clustering within household using a robust sandwich covariance estimator.

RESULTS

Study population at baseline

Between April 2002 and April 2012, 1,434 persons with pulmonary TB were screened for the present study, and 872 TB index cases (with a positive Mtb sputum culture, chest x-ray, and clinical syndrome consistent with pulmonary TB) enrolled along with their households (Figure 1).

Table 2. Outcomes of Household Contacts According to Age Group, Kawempe Community Health Study, Kampala, Uganda, 2002–2012

Outcome Status	Age Group, years									
	≤2 (*n* = 338)		3–5 (*n* = 305)		6–14 (*n* = 641)		≥15 (*n* = 1,097)		All ages (*n* = 2,381)[a]	
	No.	%	No.	%	No.	%	No.	%	No.	%
Secondary TB	67	19.8	27	8.9	29	4.5	50	4.6	173	7.3
LTBI	191	56.5	172	56.4	418	65.2	851	77.6	1,632	68.5
TST converter, month 3	27	8.0	36	11.8	61	9.5	109	9.9	233	9.8
TST converter, month 6	7	2.1	8	2.6	17	2.7	20	1.8	52	2.2
TST converter, month 12	7	2.1	1	0.3	6	0.9	3	0.3	17	0.7
TST converter, month 18	1	0.3	2	0.7	0	0.0	2	0.2	5	0.2
TST converter, month 24	0	0.0	5	1.6	7	1.1	3	0.3	15	0.6
PTST−, month 12	9	2.7	17	5.6	16	2.5	14	1.3	56	2.4
PTST−, month 24	29	8.6	37	12.1	87	13.6	45	4.1	198	8.3
Unclassifiable	21		25		60		98		204	

Abbreviations: LTBI, latent tuberculosis infection; PTST−, persistently negative tuberculin skin test; TB, tuberculosis; TST, tuberculin skin test.

[a] Percentages are by column and exclude unclassifiable subjects. Unclassifiable subjects (*n* = 204) were defined as TST-negative at baseline with no longitudinal TST placement (*n* = 133), TB in the past (*n* = 37), converter month unknown (*n* = 9), and otherwise unclassifiable due to missing clinical data (*n* = 25).

Exclusions of TB cases and HHCs are listed in Figure 1. Index cases were predominantly male, TST-positive, BCG-vaccinated, and HIV-negative (72%) (Web Table 1). Most index cases had a cough lasting longer than 12 weeks at presentation, and 88.6% had moderately or far advanced disease based on chest x-ray. There were 7 multidrug-resistant TB index cases, 3 of whom were HIV-positive, and no extensively drug-resistant TB cases. The number of individuals in a household was variable (mean = 4.0, range, 2–30). The breakdown of children (mean = 1.6, range, 0–12) and adults (mean = 2.4, range, 1–18) was also variable (Web Table 2).

Among 2,585 HHCs, the median age was 13 years; 1,390 (54%) HHCs were less than 15 years of age, and included 689 (27%) children aged 5 years or younger (Web Table 3). HHCs were predominantly women, BCG-vaccinated, HIV-negative (8%), and first-degree relatives, and often shared the same bedroom or bed with the index case. Thinness was present in 3% of HHCs. The majority of HHCs were TST-positive at baseline, with the prevalence of LTBI increasing with age (Tables 1 and 2); additional descriptive statistics on TST induration are shown in Web Table 4.

Classification of HHCs along the spectrum of Mtb exposure, infection, and disease

Classification occurred at baseline and after follow-up of up to 2 years, based on TST status and active disease status (definite or probable) (Table 1). In the present study, 173 HHCs met the criteria (17) for "definite" or "probable" TB, with 142 coprevalent and 31 incident cases. Ninety-four children under age 5 years were diagnosed with TB (a subset of these children was described earlier (21)). Six (4%) secondary TB cases were extrapulmonary, and only 1 occurred in a child. No multidrug resistant TB cases occurred in HHCs.

Of 737 HHCs who were TST-negative at enrollment, 322 became TST-positive during the study, with most TST conversions (88.8%) occurring within the first 6 months. Among those who did not convert their TST, 2 groups were identified: those who remained TST-negative for 12 months and were lost to follow-up and those who remained TST-negative for the entire 24 months, together comprising 10.7% of classifiable HHC (Table 2).

Secondary TB and factors associated with progression

TB incidence rate over the course of the study was 0.0074/person-year, or 740/100,000. Most coprevalent TB and incident cases before 6 months occurred in children and adolescents aged <15 years (Table 2, Figure 2), while most TB cases occurring >6 months after enrollment were in adults. In univariate analyses, coprevalent TB was more likely to occur in younger and first-degree relatives when compared with incident cases. In children, the risk score was significantly higher in coprevalent versus incident TB (Table 3).

To examine risk factors associated with time to developing TB in children, women, and men, we conducted separate models for those aged ≥15 years. This also improved the analytical approach because many variables (e.g., BMI, smoking, alcohol intake) were confounded by age. Adults also were stratified by sex, because of significant interactions between sex and other variables. The mean time to TB for adults was 3.13 (standard deviation, 5.3) months, and for children 1.61 (standard deviation, 4.1) months. In multivariable models, HIV was associated with more rapid progression to TB in both sexes (male, $P = 0.0007$; female, $P < 0.0001$), while low BMI was associated with more rapid development of TB in males ($P = 0.008$), and thinness and epidemiologic risk score were associated with more rapid development in females ($P < 0.0001$ and $P = 0.003$, respectively) (Table 4). In children, younger age ($P = 0.0061$), HIV positivity ($P = 0.0002$), thinness ($P = 0.01$), absence of BCG scar ($P = 0.002$), and higher epidemiologic risk score ($P < 0.0001$) were all associated with more rapid development of TB (Table 4).

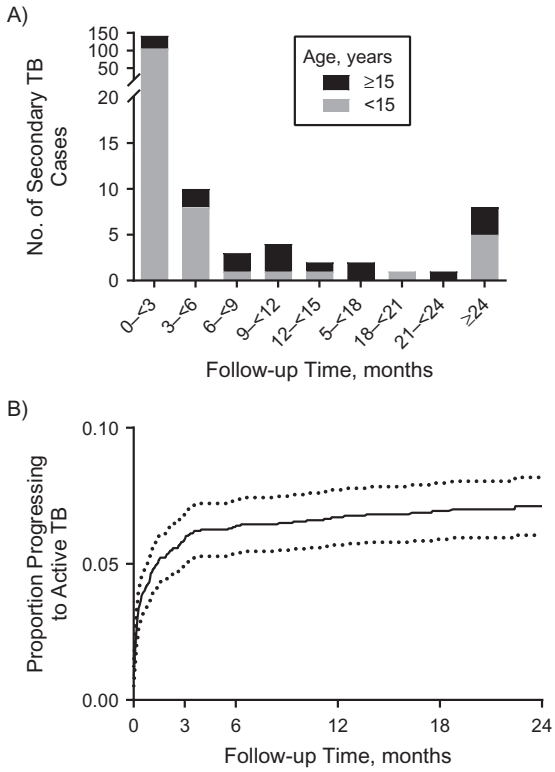

Figure 2. Study of tuberculosis (TB) household contacts, Kawempe Community Health Study, Kampala, Uganda, 2002–2012. A) Secondary TB events grouped according to age and binned according to the number of months of follow-up. B) Plot of the cumulative cases over the 24-month follow-up period with 95% confidence interval. The number of secondary TB cases and number at risk are shown in Web Table 6.

Factors associated with TST conversion and PTST−

We compared TST converters with PTST− HHCs and found that converters were older ($P < 0.0001$), had a slightly larger TST induration at baseline ($P < 0.001$), and, among children, had a higher epidemiologic risk score ($P = 0.008$) (Table 5). Besides age, no other characteristics differentiated those

Table 3. Comparison of Baseline Measures Between Incident and Coprevalent Tuberculosis Stratified by Age, Kawempe Community Health Study, Kampala, Uganda, 2002–2012

Baseline Characteristic	Incident TB			Coprevalent TB			*P* Value[a]
	No.	%	Median (min, max)	No.	%	Median (min, max)	
Adults ≥15 years	14			36			
Age in years			32.5 (15.0, 42.0)			26.5 (16.0, 56.0)	0.8
Male sex	7	50		21	58		0.7
HIV-negative	9	64		20	56		0.7
TST size, mm			18.2 (0, 23.6)			16.1 (0, 24.5)	0.2
BCG scar present	8	73		24	75		1.0
BMI[b]			20.3 (17.1, 31.4)			19.9 (14.2, 28.2)	0.6
Relationship to index							
First-degree relative	5	36		15	43		
Second-degree relative	2	14		2	6		0.7
Unrelated	7	50		18	51		
Risk score for infection[c]			7.0 (5.0, 10.0)			8.0 (5.0, 10.0)	0.3
Alcohol consumption (age ≥18 years)	6	50		7	22		0.1
Children <15 years	17			106			
Age in years			6.0 (0.2, 14.0)			2.0 (0.1, 14.0)	0.009
Male sex	9	53		52	49		0.8
HIV-negative[d]	16	94		89	91		1.0
TST size, mm			10.2 (0, 17.5)			13.4 (0, 23.1)	0.1
BCG scar present	11	79		63	68		0.5
Body mass[b]							
BMI-for-age *z* score (age 5–15)			0.1 (−1.3, 1.6)			−0.6 (−6.5, 1.8)	0.3
Weight-for-length *z* score (age 0–5)			1.0 (0.1, 1.9)			0.3 (−3.8, 3.2)	0.08
Relationship to index							
First-degree relative	8	47		90	85		
Second-degree relative	8	47		9	8		0.0004
Unrelated/spouse	1	6		7	7		
Risk score for infection[c]			7.0 (5.0, 9.0)			8.0 (5.0, 9.0)	0.0002
Adults and children	31			142			
Thinness[e]	0	0		14	10		0.06
Index Mtb lineage[f]							
Euro-American Ugandan (sublineage 4.6.1)	19	70		58	54		
Euro-American other than Ugandan (lineage 4 other)	6	22		37	26		
India/East African lineage (lineage 3)	2	7		12	11		0.3

Abbreviations: BCG, bacille Calmette-Guérin; BMI, body mass index; HIV, human immunodeficiency virus; Mtb, *Mycobacterium tuberculosis*; TB, tuberculosis; TST, tuberculin skin test.

[a] Categorical frequencies were compared between incident and coprevalent groups using the Fisher's exact or χ^2 test. Medians were compared using the Wilcoxon-Mann-Whitney test, and means were compared using the *t* test.

[b] BMI was calculated as weight (kg)/height $(m)^2$. Values are expressed as mean (standard deviation). BMI-for-age and weight-for-length *z* scores were calculated based on World Health Organization growth standards for healthy children and adolescents.

[c] Risk score was computed separately for children and adults (see text for definitions).

[d] Eight children in the coprevalent group were missing HIV status at baseline.

[e] Thinness was defined as having a BMI-for-age or weight-for-length *z* score below −2 standard deviations in children or grade 2 thinness in adults (BMI <17).

[f] Lineage results were missing for 39 index cases.

Table 4. Cox Proportional Hazards Model for Time to Secondary Tuberculosis Stratified by Age, Kawempe Community Health Study, Kampala, Uganda, 2002–2012

Baseline Measure	Single Variable Model			Multivariable Model		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Men Aged ≥15 Years (n = 451)[a]						
Age, years	1.01	0.98, 1.03	0.3	1.01	0.99, 1.04	0.3
HIV status, positive	4.33	1.82, 10.31	0.0009	4.39	1.87, 10.36	0.0007
TST size, mm	1.01	0.93, 1.10	0.8			
BCG scar absent	0.89	0.35, 2.24	0.8			
BMI[b]	0.69	0.55, 0.87	0.002	0.68	0.52, 0.91	0.008
Thinness (BMI <17)[c]	4.04	1.21, 13.46	0.023	1.09	0.26, 4.62	0.9
Relationship to index						
First-degree relative	0.96	0.41, 2.21	0.9			
Second-degree relative	0.67	0.18, 2.43	0.5			
Unrelated	1.00	Referent				
Risk score for infection	1.30	1.00, 1.70	0.053			
Mtb lineage of index case[d]						
EA Non-Ugandan (LN 4 other)	1.50	0.62, 3.62	0.4			
IEA (LN 3)	0.54	0.07, 4.20	0.5			
EA Ugandan (SLN 4.61)	1.00	Referent				
Women Aged ≥15 years (n = 714)[a]						
Age, years	1.01	0.99, 1.03	0.4	1.01	0.97, 1.06	0.5
HIV status, positive	16.02	6.21, 41.32	<0.0001	10.43	3.76, 28.96	<0.0001
TST size, mm	1.04	0.96, 1.13	0.3			
BCG scar absent	0.75	0.36, 1.53	0.4			
BMI[b]	0.89	0.79, 1.02	0.09			
Thinness (BMI <17)[c]	10.49	2.27, 48.41	0.003	17.35	6.43, 46.79	<0.0001
Relationship to index						
First-degree relative	0.42	0.15, 1.17	0.1			
Unrelated	1.00	Referent				
Risk score for infection	2.29	1.52, 3.45	<0.0001	1.97	1.27, 3.07	0.003
Mtb lineage of index case[d]						
IEA (LN 3)	3.13	1.08, 9.01	0.03			
EA Ugandan (SLN 4.61)	1.00	Referent				
Children Aged <15 years (n = 1,383)[a]						
Age, years	0.81	0.76, 0.86	<0.0001	0.88	0.81, 0.96	0.0061
Sex, male	0.97	0.68, 1.39	0.8	0.79	0.52, 1.18	0.25
HIV status, positive	3.58	1.85, 6.91	0.0001	4.24	1.97, 9.09	0.0002
TST size, mm	1.03	1.01, 1.06	0.004	1.03	0.99, 1.06	0.11
BCG scar absent	1.93	1.27, 2.92	0.002	2.05	1.31, 3.20	0.002
BMI-for-age *z* score for ages 5–15 years[b]	0.95	0.64, 1.42	0.8			
Weight-for-length *z* score for ages 0–5 years	0.83	0.70, 0.99	0.03			
Thinness[c]	2.56	1.31, 5.03	0.01	2.21	1.18, 4.14	0.01
Relationship to index						
First-degree relative	1.62	0.79, 3.33	0.2			
Second-degree relative	0.97	0.41, 2.27	0.9			
Unrelated	1.00	Referent				
Risk score for infection	3.71	2.89, 4.77	<0.0001	3.23	2.28, 4.58	<0.0001

Table continues

Table 4. Continued

Baseline Measure	Single Variable Model			Multivariable Model		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Mtb lineage of index case[d]						
EA Non-Ugandan (LN 4 other)	1.18	0.74, 1.88	0.5			
IEA (LN 3)	1.34	0.71, 2.51	0.4			
EA Ugandan (SLN 4.6.1)	1.00	Referent				

Abbreviations: BCG, bacille Calmette-Guérin; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; Mtb, *Mycobacterium tuberculosis*; TB, tuberculosis; TST, tuberculin skin test.

[a] Fifteen subjects reported having TB in the past and were not considered included in the analysis for secondary TB.

[b] BMI was calculated as weight (kg)/height (m)^2.

[c] Thinness was defined as having a BMI-for-age or weight-for-length *z* score below −2 standard deviations in children or grade 2 thinness in adults (BMI <17).

[d] EA Ugandan (SLN 4.61): Euro-American Ugandan (sublineage 4.6.1); EA Non-Ugandan (LN 4 other): Euro-American other than Ugandan (lineage 4 other); IEA (LN 3): India/East African lineage (lineage 3). There were too few female secondary TB cases to evaluate the EA Non-Ugandan (LN 4 other) category.

with PTST− from other clinical groups. In particular, adults did not differ ($P > 0.05$) in epidemiologic risk score, confirming our earlier observation that those who are PTST− do not have lower risk of exposure (16). Stratified analysis of children by age group showed that risk score was significantly different in those with PTST− versus TST converters and LTBI in age groups 2–4 and 5–14 years, and among those who were <2 years of age (data not shown).

TST conversion rate for HHCs was 326 conversions per 590 person-years of observation or 56% per year (95% CI: 0.49, 0.61). For HIV-negative HHCs, the conversion rate was 301 converters/536.7 person-years of observation or 56% per year (95% CI: 0.50, 0.62). For HIV-positive HHCs, the conversion rate was 18 converters/42 person-years of observation or 43% (95% CI: 0.23, 0.63) (7 individuals had missing HIV status). Most TST conversions occurred within 6 months, and most of those within 3 months of enrollment (Table 2, Figure 3). HIV status did not affect determination of PTST− state or TST conversion (Web Table 4).

When examining risk factors for time to TST conversion using a Cox proportional hazards model, several factors were significantly associated in a univariate model, including older age ($P < 0.0001$), larger TST induration at baseline ($P < 0.0001$), and for children, higher epidemiologic risk score ($P = 0.0006$). In a multivariable model, these variables remained significant (Table 6). There was also a significant interaction between risk score and age ($P = 0.0065$). Follow-up analyses (Web Table 5) showed that risk score was a significant predictor of progression to active Mtb infection only in those aged 5–15 years.

DISCUSSION

The present study in Kampala was one of the largest TB HHC studies with long-term follow-up, which allowed us to rigorously characterize distinct phases along the spectrum from Mtb exposure to disease, including exposure, resistance to Mtb infection, acute and latent Mtb infection, and secondary TB. Epidemiologic parameters and samples collected in this study allowed examination of genetic, environmental, nutritional, microbiologic, and immunologic factors associated with Mtb susceptibility (4, 22). In our previous HHC study (3), as well as in other analyses of this cohort (23), we identified factors associated with the occurrence of secondary TB and LTBI within the household, including clinical characteristics of the index case, proximity to the index case, and clinical features of the contacts themselves. At least half of these secondary cases were due to direct transmission from the index case, based on restriction-fragment-length-polymorphism analysis (7), which was confirmed with our Mtb lineage data (data not shown). Our new analyses extended to the identification of factors associated with the timing of secondary TB, acute Mtb infection (TST conversion), and resistance to Mtb infection in children and adults. The strengths of this study were the HHC design, careful characterization of clinical phenotypes, longitudinal follow-up, and consideration of confounders. The study revealed novel insights into risks for children, women, and men of progression to acute Mtb infection and TB. Risk factors associated with progression to acute Mtb infection included age and larger TST induration at baseline, but epidemiologic risk score was associated only in children aged 5–15 years. On the other hand, factors associated with progression to active TB in children were HIV, epidemiologic risk score, thinness, and lack of BCG-vaccination scar. For women, these factors were HIV, thinness, and epidemiologic risk score, and for men, HIV and BMI. Thus there were different risks for children, women, and men.

Secondary TB cases in households were predominantly in children, and all pediatric TB cases were pulmonary with no extrapulmonary disease (21). Secondary TB was most likely to occur within a few months of the index case's diagnosis, and HIV, epidemiologic risk score, thinness, and absence of BCG-vaccination scar were associated with time-to-developing TB. BCG scar has been reported to be protective against TB disease, as well as associated with improved survival from non-TB related illness during early childhood (3). Pediatric TB cases were more likely to be coprevalent than incident, in contrast with adults, consistent with other studies (5, 24), although other studies found older individuals progressing more rapidly to TB (6, 25). These disparate observations can be partially explained by differences in timing of clinical visits and definitions of

Table 5. Comparison of Baseline Factors Between Persons With Positive Tuberculin Skin Tests, Tuberculin Skin Test Converters, and Those With Persistently Negative Tuberculin Skin Tests, Kawempe Community Health Study, Kampala, Uganda, 2002–2012

Baseline Characteristic	TST-positive/LTBI (n = 1,632)			TST Converter (n = 331)			PTST− (n = 254)			*P* Value Overall[a]	*P* Value Pairwise[a] PTST− Vs. LTBI, PTST− Vs. Converter
	No.	%	Median (min, max)	No.	%	Median (min, max)	No.	%	Median (min, max)		
Age in years			15.0 (0.2, 89)			13.0 (0.1, 78)			8.0 (0.1, 75)	<0.0001	<0.0001, 0.0004
Male sex	744	46		139	42		115	45		0.4	
HIV-negative	1,493	94		306	94		228	92		0.2	
TST size, mm			15.4 (4.7, 33.4)			0 (0, 9.4)			0 (0, 8.5)	<0.0001	<0.0001, <0.0001
BCG scar present	1,121	76		230	78		156	72		0.2	
BMI[b]											
Adults ≥15 years			23.2 (4.3)			22.6 (4.3)			22.0 (3.3)	0.06	
BMI-for-age, 5–15 years			−0.38(0.89)			−0.37 (1.08)			−0.43 (0.89)	0.9	
Weight-for-length, 0–5 years			0.47 (1.30)			0.41 (1.17)			0.51 (0.97)	0.8	
Thinness[c]	43	2.6		9	2.7		5	2.0		0.8	
Adult HHC relationship to index										0.5	
First-degree relative	334	40		64	45		29	50			
Second-degree relative	125	15		21	15		7	12			
Unrelated	372	45		56	40		22	3			
Child relationship to index										0.04	0.09, 0.07
First-degree relative	562	74		119	66		124	66			
Second-degree relative	129	17		46	26		43	23			
Unrelated	67	9		15	8		20	11			
Risk score for infection											
Children <15 years			7.0 (4.0, 9.0)			6.5 (4.0, 9.0)			6.0 (4.0, 8.0)	<0.0001	<0.0001, 0.008
Adults ≥15 years			7.0 (4.0, 10.0)			7.0 (4.0, 10.0)			6.0 (5.0, 9.0)	0.06	
Mtb lineage of index case[d]										0.1	
EA Ugandan (SLN 4.6.1)	704	66		120	57		98	65			
EA Non-Ugandan (LN4 other)	262	25		62	30		37	24			
IEA (LN3)	96	9		27	13		17	11			
Alcohol consumption (age >18 years)	206	30		23	23		10	26		0.2	

Abbreviations: BCG, bacille Calmette-Guérin; BMI, body mass index; HHC, household contact; HIV, human immunodeficiency virus; LTBI, latent *Mycobacterium tuberculosis* infection; Mtb, *Mycobacterium tuberculosis*; PTST−, persistent TST negative; TST, tuberculin skin test.

[a] The *t* test was used to compare means, the Wilcoxon-Mann-Whitney test was used to compare medians and the χ^2 or Fisher's exact test was used to compare frequencies between groups.

[b] BMI is calculated as weight (kg)/height $(m)^2$. Values are expressed as mean (standard deviation).

[c] Thinness was defined as having a BMI-for-age or weight-for-length *z* score below −2 standard deviations in children or grade 2 thinness in adults (BMI <17).

[d] EA Ugandan (SLN 4.61): Euro-American Ugandan (sublineage 4.6.1); EA Non-Ugandan (LN 4 other): Euro-American other than Ugandan (lineage 4 other); IEA (LN 3): India/East African lineage (lineage 3).

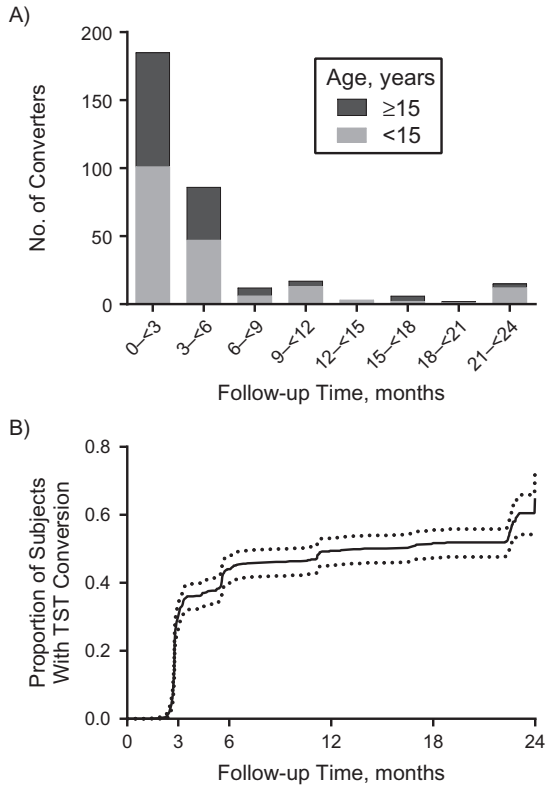

Figure 3. Study of tuberculosis (TB) household contacts, Kawempe Community Health Study, Kampala, Uganda, 2002–2012. A) Tuberculin skin test (TST) conversion events grouped according to age and binned according to the number of months to conversion. B) Plot of the cumulative proportion of converters over the 24-month follow-up period with 95% confidence interval. The number of conversions and number at risk are shown in Web Table 6.

"coprevalent" versus "incident" TB (4–6, 24, 25). How quickly index cases in these different studies sought care was unknown, and this influences length of first Mtb exposure. Our findings emphasize the susceptibility of young children to Mtb infection and disease following household exposure to an adult with pulmonary TB, and the importance of active case finding in children in TB households; all had early pulmonary disease without dissemination or central nervous system involvement (21).

Expanding on previous studies (26–28), we found body composition to differ between adult men and women as a risk for TB. Ugandan women have higher fat content than men, and with TB disease onset, preferential fat loss relative to lean tissue loss (28); our thinness variable reflects this, because BMI doesn't distinguish muscle versus fat loss (26). Among adults, risk score was significant only in women, which likely reflects their roles as caretakers and greater presence in the home. As in other studies, we found that time to TB was associated with HIV (6), sleeping with the index case (6), and closer contact with the index case (5). Our findings suggest TST induration may be a simple risk factor to identify individuals at risk for progression to TB. Epidemiologic risk score, unlike categorical representations of contact with an index case, represents an accumulation of risk factors, including clinical factors in the index case as well as proximity to the index case. This is noteworthy because this risk score was originally developed to capture LTBI (15, 16), and here we show that it is also associated with risk of progressing to TB. Last, factors associated with time to TST conversion or development of TB disease differed from those associated with TST positivity and/or coprevalent TB at baseline, consistent with our previous work (3, 23), where HIV serostatus of the index case was significant. In other words, factors associated with baseline presentation versus long-term outcome can differ.

A small yet significant proportion of HHCs had persistently negative TSTs, despite living with an infectious TB case in a TB-endemic setting, indicating that these individuals appear resistant to developing latent Mtb infection. The prevalence of TST-positive individuals is higher in households with active TB cases than in the community, and TST positivity increases with age (7). To our knowledge, we are the first research group to prospectively characterize such a large group of presumed LTBI resisters in a household setting. Epidemiologic risk score did not differentiate those with PTST− from TST converters in adults, suggesting an innate mechanism to LTBI resistance (16). In children, there was an association between epidemiologic risk score and TST conversion, even if the median values were similar. Longer residence in a TB-endemic setting likely increases the likelihood of detecting true LTBI resistance. Smoking and cooking method were not associated with LTBI or TST conversion (data not shown). We have found that genetic (29, 30) and immunologic (31) factors are associated with the PTST− state. This suggests that there may be host and as-yet-unidentified epidemiologic factors resulting in (relative) resistance to or clearance of Mtb infection and no evidence of development of LTBI.

Rates of TST conversion were not significantly different between HIV-positive and HIV-negative persons. When TST conversion occurred, TST responses were similarly robust in both those who were HIV-positive and those who were HIV-negative. Although anergy is an issue in HIV-positive TST-negative individuals (32), our results suggest that resistance to Mtb infection may also occur in HIV-infected individuals. Future studies will examine the impact of CD4 count and antiretroviral treatment (ARV) on the PTST− state. Since this study started many years before the availability of antiretroviral treatment in Uganda, CD4 counts and antiretroviral-treatment uptake in many HIV-positive contacts was unknown. TST boosting was unlikely for several reasons. There were at least 3 months between TST to avoid boosting. TST induration increments were robust in converters, and in a previous study, no increase in interferon-gamma responses to Mtb antigens was noted at 1 month among nonconverting HHCs (31).

Limitations of this study include the following: All children less than 5 years old, HIV-positive subjects, and TST-positive subjects were offered isoniazid preventative therapy. This may have decreased the number of secondary TB cases and TST conversions. This was not a clinical trial, and thus we offered preventive therapy, but we did not monitor adherence to it. The ratio of incident to coprevalent TB in this study (1:4.6) was lower than the ratio (1:2.6) in our earlier HHC study (3), in which isoniazid was offered only to young children and HIV-positive HHCs. Broader administration of isoniazid in this

Table 6. Cox Proportional Hazards Modeling of Baseline Risk Factors for Tuberculin Skin Test Conversion in Household Contacts Who Were Tuberculin Skin Test–Negative at Baseline ($n = 718$)[a], Kawempe Community Health Study, Kampala, Uganda, 2002–2012

Baseline Characteristics	No.	Single Variable Model			Multivariable Model		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, 1-year units	718	1.02	1.01, 1.03	<0.0001	1.07	1.03, 1.12	0.0007
Age, 5-year units	718	1.10	1.05, 1.15	<0.0001	1.44	1.16, 1.78	0.0007
Sex, male	718	0.89	0.72, 1.11	0.3	0.92	0.74, 1.14	0.4
HIV status, positive	690	0.77	0.48, 1.22	0.3			
TST size, mm	718	1.13	1.09, 1.17	<0.0001	1.11	1.08, 1.15	<0.0001
BMI[b] (≥15 years)	252	1.03	0.99, 1.06	0.2			
BMI-for-age *z* scores (5–15 years)	248	1.00	0.78, 1.28	1.0			
Weight-for-length *z* scores (0–5 years)	216	0.97	0.79, 1.18	0.8			
Thinness[c]	718	1.47	0.70, 3.10	0.3			
BCG scar present vs. none	626	1.18	0.89, 1.56	0.2			
Relationship to index	692						
First-degree relative vs. unrelated		0.84	0.64, 1.11	0.2			
Second-degree relative vs. unrelated		0.82	0.59, 1.16	0.3			
Risk score for infection	718						
Children <15 years		1.25	1.10, 1.42	0.0006	1.37	1.19, 1.58	<0.0001
Adults ≥15 years		1.06	0.93, 1.20	0.4			
Mtb lineage of index case[d]	462						
EA Non-Ugandan (LN 4 other)		1.27	0.95, 1.70	0.2			
IEA (LN 3)		1.31	0.85, 2.02	0.1			
EA Ugandan (SLN 4.6.1)		1.00	Referent				
Risk score-by-age interaction	718				1.08[e]	1.03, 1.12	0.0065

Abbreviations: BMI, body mass index; BCG, bacille Calmette-Guérin; CI, confidence interval; HHC, household contact; HIV, human immunodeficiency virus; HR, hazard ratio; Mtb, *Mycobacterium tuberculosis*; TST, tuberculin skin test.

[a] The time-to-conversion analysis included 718 baseline TST-negative HHCs. Participants not at risk for conversion were removed, including coprevalent, incident, reported TB in the past, and unclassifiable.

[b] BMI was calculated as weight (kg)/height $(m)^2$.

[c] Thinness was defined as having a BMI-for-age or weight-for-length *z* score below −2 standard deviations in children or grade 2 thinness in adults (BMI <17).

[d] EA Ugandan (SLN 4.61): Euro-American Ugandan (sublineage 4.6.1); EA Non-Ugandan (LN 4 other): Euro-American other than Ugandan (lineage 4 other); IEA (LN 3): India/East African lineage (lineage 3).

[e] Age effect at risk score = 6.

study may have had an impact. The availability of antiretroviral treatment later in the study may have affected HIV-associated TB. As in any epidemiologic study, there was loss to follow-up, but that was accounted for in the analysis.

Our findings have implications for TB public health and design of clinical studies. First, this HHC study illustrates the heavy burden of Mtb infection and disease that is present in households in which at least 1 member has TB. HHC tracing can have a major impact on identifying and treating individuals with risk factors for Mtb infection and TB, thereby preventing progression to the advanced TB seen in children and the HIV-infected. Second, careful clinical characterization of HHCs allows ready linkage with multiple biologic approaches to understanding protective and failing host responses to Mtb (33, 34). Third, HHC studies should include well-characterized index cases, thus providing an identifiable point source to epidemiologically characterize and opportunity to utilize more high-tech methods to measure aerosolized Mtb exposure. Fourth, HHC studies are optimal to gain insight into Mtb infection and disease in children, given children's susceptibility to Mtb. Finally, TB household studies are well-suited to identify individuals who are resistant to latent Mtb infection (e.g., PTST−). Although the percentage of those with PTST− is small, it is a novel population important for understanding biologic factors associated with resistance to latent Mtb infection and thus TB.

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Author affiliations: Department of Population and Quantitative Health Sciences, Case Western Reserve University School of Medicine, Cleveland, Ohio (Catherine M. Stein, Ezekiel Mupere); Center for Proteomics and

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