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Tuberculosis in Household Contacts of Infectious Cases in Kampala, Uganda

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Tuberculosis remains a serious threat to public health, especially in sub-Saharan Africa. To determine the host and environmental factors responsible for tuberculosis in African households, the authors performed a prospective cohort study of 1,206 household contacts of 302 index cases with tuberculosis enrolled in Uganda between 1995 and 1999. All contacts were systematically evaluated for active tuberculosis and risk factors for active disease. Among the 1,206 household contacts, 76 secondary cases (6%) of tuberculosis were identified. Of these cases, 51 were identified in the baseline evaluation, and 25 developed during follow-up. Compared with index cases, secondary cases presented more often with minimal disease. The risk for secondary tuberculosis was greater among young children than adults (10% vs. 1.9%) and among human immunodeficiency virus-seropositive than -seronegative contacts (23% vs. 3.3%). Host risk factors could not be completely separated from the effects of environmental risk factors, suggesting that a household may represent a complex system of interacting risks for tuberculosis.

cohort studies; disease transmission; risk; risk factors; tuberculosis

Abbreviations: BCG, Bacillus Calmette-Guérin; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

Since the discovery of the tubercle bacillus by Robert Koch in 1882, the study of household contacts of infectious tuberculosis cases has contributed substantially to our current understanding of tuberculosis and its transmission. In the era before effective antituberculous chemotherapy, studies of household contacts established that tuberculosis cases were most infectious when acid-fast bacilli were present in sputum (1–4). In these studies, young children were at great risk for developing tuberculosis, and the clustering of cases within families hinted at a familial susceptibility (5, 6). After the advent of effective antituberculous therapy, household studies demonstrated that proper treatment of tuberculosis was as effective as physical isolation in limiting further infection or disease in the household (7). Household studies were an effective way to estimate the efficacy of Bacillus Calmette-Guérin (BCG) vaccination (8, 9) and chemoprohylaxis of tuberculosis infection (10, 11). Since the emergence of the human immunodeficiency virus (HIV) pandemic, studies from Africa of household contacts have assessed the effect of HIV on transmission of *Mycobacterium tuberculosis* with variable results (12–15).

Previous studies of tuberculosis have shown that comorbidities such as HIV infection, lymphoma, and malnutrition increase the risk for active tuberculosis, yet except for HIV disease these conditions do not account for the burden of tuberculosis worldwide. Other studies have shown that environmental characteristics such as crowding and social factors (16, 17), including poverty, are associated with tuberculosis, but a causal link between environment and host factors for susceptibility has not been explicitly made. Finally, little is known about the virulence of different *M. tuberculosis* strains and whether it affects transmission or disease. These issues are rendered more complex where

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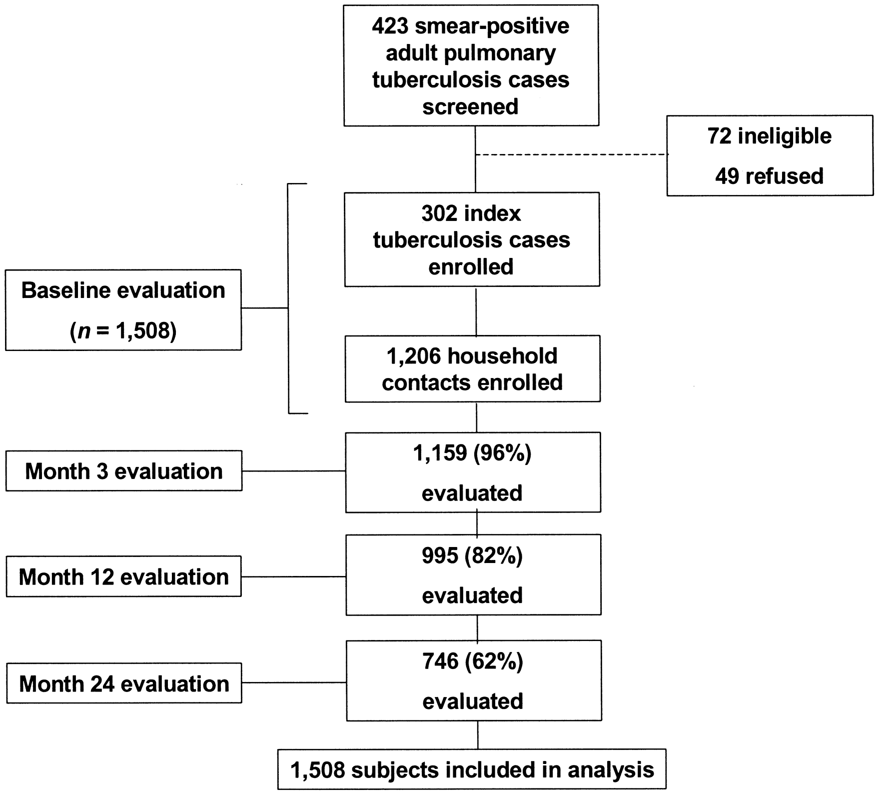

FIGURE 1. Study profile, Uganda, 1995–2001.

transmission of *M. tuberculosis* is high and recurrent exposure and reinfection may occur.

The current study was performed to examine the relative contribution of host and environmental factors to the risk of tuberculosis in African households. The household is a natural setting in which to study tuberculosis because the epidemiology of infection and disease can be characterized. In this article, we describe in detail the epidemiology of tuberculosis disease and factors associated with it in Ugandan households.

MATERIALS AND METHODS

Study population

Between October 1995 and February 1999, tuberculosis cases and their household contacts were enrolled in a prospective cohort study. The study recruited sputum smear-positive pulmonary tuberculosis cases who were aged 18 or more years and who had one or more household contacts living with them. Cases were identified at the Uganda National Tuberculosis and Leprosy Program treatment center at Old Mulago Hospital in Kampala, Uganda. On the initial home visit made within 2 weeks of diagnosis for index cases, home health visitors informed household contacts about the study and provided health education about tuberculosis. Written informed consent was obtained from the head of the household, all adults, and parents or guardians of children in the household aged less than 18 years. The study was approved by institutional review boards in both the United States and Uganda.

A household was defined as a group of people living within one residence who share meals together and identified a head of family who made decisions for the household. An index case was defined as the first tuberculosis case identified in the household. A household contact was defined as an individual who had resided in the household for at least 7 consecutive days during the 3 months prior to the diagnosis of tuberculosis in the index case. Secondary cases were defined as tuberculosis cases among household contacts of the index case. Secondary cases were classified as "coprevalent" if active tuberculosis was present at the time of the baseline household investigation or as "incident" if active tuberculosis was absent at the time of the baseline household investigation and developed during follow-up.

Measurements

Index cases were evaluated with a medical history and physical examination performed by Ugandan medical officers. Sputum samples were collected for microscopic examination and mycobacterial culture. Chest radiographs were taken, and HIV serology and tuberculin skin testing

TABLE 1. Baseline demographic and environmental characteristics of households, Uganda, 1995–1999

Characteristic	Summary measure	
	No.	%*
No. of households	302	
Household member	1,508	100
Index tuberculosis cases	302	20
Household contacts	1,206	80
Median family size (range, 2–18)	5	
Household size distribution		
2–3 persons	89	30
4–5 persons	113	37
≥6 persons	100	33
Household composition (last 3 months)		
Unchanged	259	86
Changed	43	14
New member	11	4
Member who moved away	28	9
Recent death	4	1
Household characteristics		
Geographic location of household		
Urban	3	1
Trading center near paved road	10	3
Trading center near dirt road	31	10
Rural	60	20
Semiurban/suburb	114	38
Slum	84	28
Type of residence		
Muzigo with walls not reaching ceiling	40	13
Muzigo with walls reaching ceiling	135	45
Single family house	120	40
Other	7	2
Inside cooking		
Firewood/charcoal	62	21
Electricity	14	5
Household amenities		
Potable water inside household	155	51
Electricity inside household	117	39
Family use of own toilet or latrine	78	26
Indicators of crowding		
Median no. of habitable rooms per household (range, 1–7)	2	
Median no. of outside windows per house (range, 0–8)	1	
Median no. of persons per habitable room (range, 0–9)	3	

* Percentages were rounded to the nearest integer so they may not add to 100%.

were performed. Index cases were treated with standard self-administered, short-course tuberculosis chemotherapy (18). Home visitors evaluated eligible household contacts at baseline with standardized questionnaires, a limited physical examination including height and weight (19), and tuberculin skin testing.

Children aged 5 years or less, HIV-seropositive contacts older than 5 years, and contacts with signs or symptoms of tuberculosis were considered tuberculosis suspects. These suspects were evaluated for active tuberculosis with a medical examination, specimen microscopy, mycobacterial culture, and chest radiograph. Children aged 5 years or less and HIV-seropositive adults without active tuberculosis were offered a 6-month course of isoniazid treatment. All confirmed secondary tuberculosis cases were treated with short-course therapy (18).

After the baseline evaluation, contacts were evaluated at 3, 12, and 24 months for active tuberculosis. Study participants were instructed to attend the study clinic at any time in case of illness. Patients not attending scheduled appointments were traced by home visitors to enhance follow-up and to determine their vital status.

Tuberculin skin testing was performed on all study subjects by placing 0.1 ml of 5 tuberculin units of purified protein derivative (Tubersol; Connaught Laboratories, Limited, Toronto, Canada) on the left forearm using the Mantoux method. After 48–72 hours, the diameter of palpable induration was recorded by home visitors using standardized procedures (20). A tuberculin skin test was considered positive if it was 5 mm or greater (21).

A posteroanterior chest radiograph was taken on all study subjects at baseline and on tuberculosis suspects. The extent of disease on these radiographs was graded on a four-category ordinal scale by experienced physicians (22).

Three sputum samples were collected from index cases and tuberculosis suspects. A sputum smear grade of acid-fast bacilli was recorded on a four-point ordinal scale (23). In children and patients unable to produce a sputum sample, gastric lavage was performed. Specimens were cultured on Lowenstein-Jensen slants at 37°C and examined weekly for 8 weeks.

HIV testing by enzyme-linked immunosorbent assay (Cambridge BiosScience, Worcester, Massachusetts) was performed with counseling on all consenting study subjects. For children 5 years of age or younger, HIV testing was done when the mother was seropositive or when the child was diagnosed with active tuberculosis; otherwise, a child was considered HIV seronegative if the mother tested negative.

The household environment was assessed for dwelling type, number of people in the household, number of habitable rooms, and number of windows in the house. A house was classified as a “muzigo” if it was a multifamily housing unit on the same building block, usually with one or two rooms per family.

Tuberculosis was classified as definite, probable, and possible tuberculosis (24) by investigators using clinical, radiographic, and microbiologic findings in tuberculosis suspects. Response to therapy was defined by improvement of radiographic abnormalities and weight gain with treatment. For this analysis, active tuberculosis was defined as definite or probable tuberculosis. In three incident cases, review of baseline chest radiographs indicated subtle abnormalities in the area of subsequent disease; these cases were reclassified as coprevalent instead of incident cases in this analysis.

TABLE 2. Baseline demographic and clinical characteristics of household contacts, Uganda, 1995–1999

Characteristic	Summary measure	
	No.	%
No. of subjects	1,206	
Median age in years (range, 0–70)*	11	
Age distribution in years		
0–5	335	28
6–15	439	36
16–25	226	19
26–35	119	10
>35	87	7
Female sex	672	56
Marital status in 460 adults (≥15 years)		
Never married	193	42
Married in monogamous relationship	201	44
Other	66	14
Religion		
Catholic	465	39
Anglican	441	37
Muslim	266	22
Other	34	2
Educational level		
None/preprimary	432	36
Primary school	549	46
Secondary school	209	17
Degree or more	12	1
Ethnicity (tribe)		
Ganda	885	73
Soga	60	5
Nyankole	40	3
Other	221	19
Biologic relationship to index case		
Spouse	181	15
Parent	34	3
Son/daughter	579	48
Sibling	91	8
Unrelated	123	10
Other	198	16
Intimacy of contacts with index case		
Share same bed	213	18
Share bedroom but not bed	522	43
Different bedroom	456	38
Unknown	15	1

Table continues

TABLE 2. Continued

Characteristic	Summary measure	
	No.	%
z scores for 814 subjects aged <18 years		
Weight for age and height for age > –2	634	78
Weight for age < –2	27	3
Height for age < –2	95	12
Both	58	7
Body mass index (kg/m²) for 386 subjects aged ≥18 years†		
Median (range, 15–43)	22	
Body build		
Contacts aged <18 years with weight-for-age *z* score of <–2.0	86	11
Contacts aged ≥18 years with body mass index of <19 kg/m²	40	10
Previous history of tuberculosis	7	1
Exposure to other known tuberculosis case	86	7
BCG‡ vaccination		
Scar present	878	73
Vaccination record available	363	30
Vaccination recorded, scar absent	20	6
PPD‡ skin test		
Positive (≥5 mm)	963	80
Positive (≥10 mm)	801	66
Positive (≥15 mm)	544	45
Median induration in mm (range, 0–40)	13	
HIV‡ status		
Positive	123	10
Negative	840	70
Unknown	243	20
Treatment of latent tuberculosis infection		
Children aged ≤5 years		
Eligible subjects§	272	
Accepted	209	77
Completed (5 or 6 months)	163	78
HIV-infected contacts		
Eligible for treatment§	105	
Accepted treatment	27	26
Completed treatment	22	81

* The youngest contact was 4 days of age.

† Body mass index was calculated in contacts aged 18 years or more, and "weight-for-age" *z* scores were used in contacts aged less than 18 years. Six children did not have information to calculate *z* scores.

‡ BCG, Bacillus Calmette-Guérin; PPD, purified protein derivative; HIV, human immunodeficiency virus.

§ Not all patients were eligible for preventive therapy (i.e., suspected or confirmed active tuberculosis).

Analytical strategy

The goal of the analysis was to determine whether characteristics of the index case, household contact, and environment were associated with active tuberculosis in household contacts. The main outcome was active tuberculosis in a household contact; separate analyses were performed for coprevalent and incident tuberculosis. To determine factors associated with active tuberculosis in contacts, we performed a univariate analysis with secondary tuberculosis as the outcome. Predictor variables included clinical and epidemiologic characteristics of the index case and household contacts, as well as environmental factors. Variables associated with tuberculosis in the univariate analysis ($p <$

0.15) were retained for the multivariable analysis. A series of logistic regression models were fit using the generalized estimation equation method (SAS version 8.0, PROC GENMOD; SAS Institute, Inc., Cary, North Carolina) to adjust for household correlations (25). No two-way interaction effects were found. Crude and adjusted odds ratios and 95 percent confidence intervals are reported.

RESULTS

Between October 1995 and February 1999, 423 consecutive cases of smear-positive pulmonary tuberculosis patients were screened at the study center. Of these, 302 were enrolled as index cases into the study. Patients who were not enrolled were either ineligible ($n = 72$) or refused participation in the study ($n = 49$). Among the 302 index cases, 1,206 household contacts were eligible and enrolled into the study. Follow-up proportions at 3, 12, and 24 months were 96 percent, 82 percent, and 62 percent, respectively (figure 1).

The median family size was five, but one third of households had six or more members (table 1). The study population was stable, as 259 (86 percent) households had not experienced changes in family composition in the 3 months before the baseline study evaluation. Most households were located in rural or semiurban areas of Kampala and were part of multifamily housing units called muzigos. Households were crowded with a median of three persons per room. Ventilation was minimal in most houses as there was typically only one window per house; 67 houses (22 percent) had no windows.

Household contacts

Among the 1,206 household contacts, the median age was 11 years, including 335 (28 percent) children aged 5 years or less (table 2). Among the contacts, 672 (56 percent) were women, and 885 (73 percent) were from the Ganda tribe. Most adult contacts were self-employed or held multiple jobs, and most school-age children attended school. First-degree relatives accounted for 59 percent of the contacts living with index cases. Contacts often shared either the same bedroom or the same bed with the index case. Slim body build was present in 86 children younger than 18 years (11 percent) and in 40 adults (10 percent).

BCG vaccination was evident in 898 (79 percent) of the contacts; 878 contacts (73 percent) had a characteristic scar, whereas 20 contacts (6 percent) had no discernible scar but BCG vaccination was recorded on the medical record. BCG vaccination varied with age: 622 (83 percent) children aged less than 15 years had a scar or record, whereas 276 (60 percent) adults had evidence of vaccination. Tuberculin skin test reactions of 5 mm or more were present in 963 contacts (80 percent) and of 10 mm or more in 801 contacts (66 percent). Of 963 contacts who consented to HIV testing, 123 contacts were HIV seropositive; 243 contacts were not tested. Of the 123 HIV-seropositive contacts, 27 (22 percent) were younger than 15 years.

Tuberculosis patients

As shown in table 3, among the 302 index cases, there was a 1:1 male:female ratio, only 54 percent had BCG scars, and 49 percent were HIV seropositive. Cough was present in all the cases, and it had lasted more than 90 days in half of the patients. The chest radiograph at diagnosis indicated either moderately advanced or far advanced disease in 86 percent of the index cases. All index cases were smear positive, most with high smear grades and positive mycobacterial cultures.

Secondary tuberculosis cases

A total of 76 secondary tuberculosis cases were identified among 530 household contacts suspected of active tuberculosis. Among the 1,206 contacts, 51 contacts (4.2 percent) had coprevalent tuberculosis, and 25 contacts (2.1 percent) had incident tuberculosis. In most coprevalent cases, the diagnosis was made within 3 months of the baseline household evaluation, but in nine coprevalent cases (18 percent), the diagnosis was made between 5 and 21 months after their baseline evaluation (figure 2). The diagnosis in these contacts was delayed because they initially presented with nonspecific symptoms and subtle radiographic findings that were appreciated only after active disease had developed. Except for three cases, incident tuberculosis occurred after 6 months of observation. The median time to diagnosis of coprevalent tuberculosis was 27 days, while the median time to diagnosis of incident tuberculosis was 16 months.

Of the 51 coprevalent cases (table 3), 34 were found among 335 contact children aged 5 years or less (10.1 percent). Children with coprevalent disease were more likely to have received BCG vaccination than were adult coprevalent or index cases (68 percent vs. 53 percent, $p = 0.09$). These children presented with short-lived disease compared with index cases, as chronic cough was less common in children than in index cases (74 percent vs. 100 percent, $p = 0.0001$). Minimal disease, or normal chest radiograph, was more common among children (56 percent vs. 13 percent, $p = 0.0001$). Among 83 children with suspected tuberculosis, 216 gastric aspirates were performed (range, 1–3 gastric aspirates per child). Of the 34 children with coprevalent disease, nine (27 percent) had positive mycobacterial cultures, all obtained through gastric aspirate, and seven (21 percent) had positive microscopy with negative cultures. The diagnosis of tuberculosis was based solely on clinical presentation in 18 children.

Coprevalent cases aged more than 5 years were more likely to be female or HIV infected when compared with index cases. Like children with coprevalent disease, older coprevalent cases had a shorter duration of symptoms and less advanced disease on chest radiograph than did index cases. Unlike children, 13 of 17 coprevalent cases aged more than 5 years (77 percent) were confirmed through culture.

Children aged 5 years or less and HIV-seropositive contacts carried the highest risk for active tuberculosis (table 4). In this logistic regression model, age was the only confounder of the association between HIV infection and tuberculosis. In stratified analyses, the proportion of tuberculosis cases was lower in BCG-vaccinated versus nonvacci-

TABLE 3. Clinical characteristics of tuberculosis cases, Uganda, 1995–2001*

Characteristic	Index cases	Coprevalent cases		Incident cases
		≤5 years	>5 years	
Demographic				
No. of cases	302	34	17	25
Age in years				
Median	30	2	24	31
Range	18–60	0–5	7–40	1–59
Age distribution (years)				
0–5		34 (100)		3 (12)
6–15			3 (18)	2 (8)
16–25	81 (27)		6 (35)	5 (20)
26–35	123 (41)		7 (41)	8 (32)
>35	98 (32)		1 (6)	7 (28)
Male sex	158 (52)	19 (56)	6 (35)	13 (52)
Biologic relationship to index case				
Spouse			8 (47)	14 (56)
First-degree relative		31 (91)	4 (24)	11 (44)
Other relative		3 (9)	3 (18)	0 (0)
Unrelated		0 (0)	2 (12)	0 (0)
Clinical				
BCG† vaccination	164 (54)	23 (68)	9 (53)	13 (52)
PPD† skin test				
≥5 mm	269 (89)	27 (79)	12 (71)	23 (92)
≥10 mm	240 (79)	23 (68)	10 (59)	20 (80)
Induration in mm				
Median	15	13	15	15
Range	0–30	0–22	0–23	0–27
Nutritional status				
Mean weight-for-age *z* score		–1.13 (1.24)‡		–1.69 (0.18)‡
Mean body mass index (kg/m^2)	19.2 (2.7)‡		22 (4.7)‡	22 (3.7)‡
Comorbid illnesses	18 (6)	0 (0)	0 (0)	1 (4)
Symptoms				
Cough present for >3 weeks	302 (100)	25 (74)	13 (76)	16 (64)
Duration of cough in days				
Median	90	14	45	30
Range	1–730	3–365	4–300	7–252

Table continues

nated contacts, among not only children (8 percent vs. 19 percent; odds ratio (OR) = 0.41, 95 percent confidence interval (CI): 0.19, 0.89) but also older contacts (3.5 percent vs. 7.2 percent; OR = 0.46, 95 percent CI: 0.25, 0.86). A similar association between BCG vaccination and disease was seen in HIV-seropositive (17 percent vs. 34 percent; OR = 0.45, 95 percent CI: 0.18, 1.09) and HIV-seronegative (9 percent vs. 12 percent; OR = 0.62, 95 percent CI: 0.33, 1.15) contacts. Cavitary disease in the index case, prolonged contact with an index case (>18 hours/day), and muzigo residence were independently associated with coprevalent disease (table 4). Other host factors were not significantly associated with active tuberculosis in the contacts.

Of the 25 incident tuberculosis cases, 80 percent were aged 15 or more years, and 52 percent were HIV infected (table 3). Incident cases were either the spouse of the index case or a first-degree relative. At baseline, 23 incident cases (92 percent) had purified protein derivative reactions of 5 mm or more, and 20 cases (80 percent) had reactions of 10 mm or more. When compared with index cases, incident cases were identified at an early stage of disease as indicated by the short duration of symptoms, preserved body mass (19.2 vs. 22 kg/m^2, p = 0.007), and minimal disease or normal chest radiographs at presentation (13 percent vs. 56 percent, p = 0.0001). Sixteen incident cases (64 percent) presented with negative, scanty, or grade 1 acid-fast bacilli

TABLE 3. Continued

Characteristic	Index cases	Coprevalent cases		Incident cases
		≤5 years	>5 years	
Weight loss	264 (87)	7 (21)	9 (53)	8 (32)
Fever	205 (68)	12 (35)	9 (54)	8 (32)
Chest radiograph findings§				
Normal	11 (4)	1 (3)	3 (18)	8 (32)
Minimal	28 (9)	18 (53)	10 (59)	6 (24)
Moderately advanced	98 (32)	15 (44)	2 (12)	8 (32)
Far advanced	164 (54)	0 (0)	2 (12)	3 (12)
HIV† status				
Positive	147 (49)	4 (12)	11 (65)	13 (52)
Negative	155 (51)	30 (88)	6 (35)	12 (48)
Unknown/indeterminate	0	0	0	0
Diagnostic microbiology				
Criteria				
Definite	299 (99)	9 (26)	13 (76)	18 (72)
Probable	3 (1)	25 (74)	4 (24)	7 (28)
Specimen results				
AFB† positive and culture positive	299 (99)	2 (6)	11 (65)	12 (48)
AFB negative and culture positive	0 (0)	7 (21)	2 (12)	6 (24)
AFB positive and culture negative or unknown	3 (1)	7 (21)	2 (12)	5 (20)
AFB negative and culture negative	0 (0)	14 (41)	2 (12)	1 (4)
Missing information	0 (0)	4 (12)	0 (0)	1 (4)
Sputum AFB grade				
Negative		21 (62)	4 (24)	7 (28)
Scanty	0 (0)	5 (15)	1 (6)	3 (12)
1	23 (8)	4 (12)	4 (24)	6 (24)
2	30 (10)	0 (0)	3 (18)	4 (16)
3	249 (82)	0 (0)	5 (29)	4 (16)
Missing information	0	4 (12)	0	1 (4)

* Values are no. and % unless indicated otherwise.
† BCG, Bacillus Calmette-Guérin; PPD, purified protein derivative; HIV, human immunodeficiency virus; AFB, acid-fast bacilli.
‡ Values in designated parentheses, standard deviation.
§ One chest radiograph from an index case not reviewed.

smears, and 18 incident cases (72 percent) were culture positive.

At the time of baseline household investigation, HIV infection and the presence of chronic cough in the contact were associated with the development of incident tuberculosis (table 5). The rate of tuberculosis tended to be lower in 236 contacts treated with isoniazid compared with 925 contacts not treated (1.7 percent vs. 2.2 percent; OR = 0.75, 95 percent CI: 0.26, 2.24). Of the 236 contacts that received isoniazid treatment, 185 contacts completed 5–6 months of treatment, and tuberculosis occurred in three of these contacts.

Among the host characteristics for tuberculosis, the age of 5 years or less was associated with all other risk factors except cavitary disease in the index case (table 6). Children were more likely than adults to be vaccinated with BCG, to be a first-degree relative of the index case, and to be thin, but they were less likely to be HIV seropositive. Children lived in crowded settings, often in muzigos, and had prolonged daily exposure to the index case.

DISCUSSION

In this household contact study from Kampala, Uganda, active tuberculosis was common among household contacts of infectious index cases, occurring in 6 percent of contacts. Most secondary cases were present at the time of baseline household evaluation, although some incident disease did occur despite treatment of latent tuberculous infection in children and HIV-infected adults.

The presentation of the secondary tuberculosis cases differed from that of the index cases and posed challenges to the diagnosis of tuberculosis in the household contacts. These challenges were imposed partly by the young age of the contacts and the inherent difficulty in making the diagnosis of active disease in children (26, 27). The diagnostic

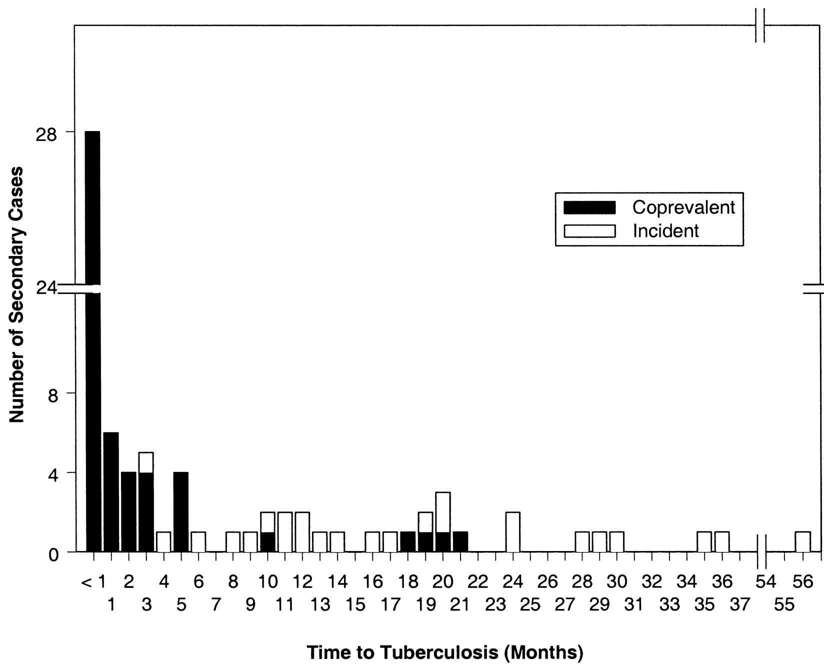

FIGURE 2. Timing of diagnosis of coprevalent and incident tuberculosis cases following diagnosis in the index case, Uganda, 1995–2001.

criteria for pediatric tuberculosis used in the study were conservative, requiring either culture or smear evidence of disease and weight gain or improvement in chest radiograph appearance with treatment. Children with minimal extent of disease on chest radiograph were not often considered to have disease unless additional signs or symptoms of tuberculosis were present.

The challenge of diagnosis was also imposed by the early stage of tuberculosis at presentation. Although no formal staging system for active tuberculosis exists, many of the secondary cases presented with pauci-bacillary, minimal disease. This presentation differed markedly from that of the index cases, who often had advanced signs and symptoms, moderate or advanced disease on chest radiograph, and positive sputum microscopy or mycobacterial culture. Further, many incident cases had a chronic cough at the time of the baseline household evaluation but no other evidence of active tuberculosis despite a detailed clinical evaluation, sputum examination and culture, and chest radiography. If these persons with cough at baseline had subclinical, active disease and were misclassified, then conventional methods for diagnosis were inadequate. Finally, the presentation of secondary cases may have been affected by the prevalence of HIV infection in the population (approximately 10 percent) and the atypical presentation of tuberculosis seen in HIV-infected persons. The methods for diagnosis of tuberculosis in advanced disease are, for the most part, satisfactory, but the findings from our study emphasize the need for diagnostic tools that identify tuberculosis in its early stages.

Because secondary cases often present with subtle manifestations of disease, one may ask how best to identify these cases in the context of household investigation. The risk of transmission of *M. tuberculosis* has been correlated with the clinical characteristics of the index case (4, 28, 29) and behaviors that promote contact with infectious cases (16, 29). Once infection has occurred, the risk for disease is attributed to the duration of infection (30) and intrinsic characteristics such as age (31), body build (32), BCG vaccination (33), HIV infection (34), and host genetic susceptibility (35, 36).

In the current study, we found that young age and HIV infection were associated with increased risk for active tuberculosis at the time of contact evaluation, whereas BCG vaccination reduced the risk. Ten percent of children aged less than 5 years had active tuberculosis at the time of the contact investigation. The findings in children must be interpreted with caution because culture-confirmed cases were few (26 percent), giving rise to the possibility of misclassification and overestimation of disease status in the young children. Of the 123 HIV-seropositive contacts, 23 percent had or developed active tuberculosis, indicating the high risk for tuberculosis faced by these individuals, as seen in other studies (12, 13, 37, 38).

BCG vaccination was the only factor that reduced the risk for tuberculosis among contacts of all ages, even in this setting of acute transmission. For contact cases, the magnitude of protection based on the adjusted logistic regression model was 49 percent and is consonant with published studies (33, 39). These findings support the continued use of BCG vaccination in Uganda where transmission of *M. tuberculosis* is high and where HIV infection is endemic. Isoniazid treatment of latent tuberculosis infection reduced the risk of incident tuberculosis, but the magnitude of protective effect, 25 percent, was less than the protective effect of

TABLE 4. Crude and adjusted odds ratios for characteristics associated with coprevalent tuberculosis in household contacts of adult infectious index cases with tuberculosis, Uganda, 1995–1999

Characteristic	No.	Active tuberculosis		Crude odds ratio	95% confidence interval	Adjusted odds ratio*	95% confidence interval
		No.	%				
HIV serostatus of contact							
Positive	123	15	12.2	4.03	2.16, 7.53	6.40	3.14, 13.03
Negative	1,083	36	3.3	1.00		1.00	
Age							
≤5 years	335	34	10.1	5.80	3.16, 10.65	6.88	3.61, 13.14
>5 years	871	17	1.9	1.00		1.00	
BCG vaccination							
Yes	878	32	3.6	0.61	0.34, 1.12	0.51	0.27, 0.96
No	327	19	5.8	1.00		1.00	
Contact with index case							
≥18 hours/day	105	14	13.3	4.42	2.29, 8.52	2.39	1.23, 4.63
<18 hours/day	1,101	37	3.4	1.00		1.00	
House type							
Muzigo	567	36	6.3	2.85	1.58, 5.15	2.12	1.13, 3.95
Other	639	15	2.3	1.00		1.00	
Chest radiograph of index case							
Cavitary	670	36	5.4	1.97	1.05, 3.71	2.23	1.14, 4.35
Noncavitary	536	15	2.8	1.00		1.00	

* Logistic regression analysis using generalized estimating equations adjusting for Bacillus Calmette-Guérin (BCG) vaccination, human immunodeficiency virus (HIV) serostatus in the household contact, age less than 5 years, duration of daily contact with the index case, type of house, and presence of cavitary disease in the index case.

77 percent seen in clinical trials (11). This attenuated effect may result from incomplete adherence with treatment, as it was self-administered, or from the short duration of treatment. Revised guidelines for the treatment of tuberculosis infection recommend 9 instead of 6 months of treatment (40). The moderate effect observed with the shorter regimen provides support for longer periods of isoniazid treatment in this setting.

In this study, host characteristics were not the only factors associated with secondary tuberculosis in households. Cavitary disease in the index case, duration of daily contact with the index case, and type of housing were also associated with the risk for disease. In previous household contact studies, the presence of acid-fast bacilli in the sputum of the index case was a consistent predictor of active disease in household contacts (3, 4, 6, 28). Because we enrolled only patients with smear-positive tuberculosis, it was not possible to examine the effect of smear-negative disease on tuberculosis in the household. Among smear-positive patients, the presence of cavitary disease in the index case was found to be

TABLE 5. Characteristics associated with incident tuberculosis in household contacts of adult infectious index cases of tuberculosis, Uganda, 1995–2001

Characteristic	No.	Active tuberculosis		Crude odds ratio	95% confidence interval	Adjusted odds ratio*	95% confidence interval
		No.	%				
HIV serostatus of contact							
Positive	123	13	10.6	11.87	5.25, 26.83	4.43	1.55, 12.64
Negative or unknown	1,083	12	1.1	1.00		1.00	
Chronic cough							
Present	166	16	9.4	16.17	6.84, 38.23	15.47	5.21, 45.95
Absent	1,038	9	0.9	1.00		1.00	

* Logistic regression analysis using generalized estimating equations adjusting for age, human immunodeficiency virus (HIV) serostatus in the household contact, and presence of cough for more than 3 weeks at the time of initial evaluation.

TABLE 6. Relations among host and environmental characteristics associated with tuberculosis among household contacts, Uganda, 1995–1999*

Characteristic associated with tuberculosis present (yes) or absent (no)	No. of contacts in each group	Host characteristics†					Environmental characteristics†			
		Age ≤5 years	HIV+	BCG‡	Slim body build	First-degree relative	Cavity in index	Contact > 18 hours/day	Crowded household	Muzigo house
Age ≤5 years										
Yes	335		5§	81§	14§	74§	58	19§	42§	56§
No	871		12	70	9	52	55	5	25	44
HIV+										
Yes	123			15§	11	31§	49	11	29	61§
No	1,083			29	10	62	56	8	30	45
BCG vaccination										
Yes	878				10	60¶	56	7§	30	49¶
No	327				11	54	55	12	29	42
Slim body build										
Yes	126					60	63	13¶	37	46
No	1,079					58	55	8	29	47
First-degree relative										
Yes	704						54	10	34§	50§
No	502						57	8	25	43
Cavity in index										
Yes	670							8	30	45
No	536							9	29	50
Contact > 18 hours/day										
Yes	105								42§	58¶
No	1,101								28	46
Crowded household										
Yes	360									86§
No	846									30

* Values are the % with the characteristic.
† The columns labeled "Host characteristics" and "Environmental characteristics" indicate the proportions of contacts with those characteristics. For example, among 335 contacts of age ≤5 years, 5% were human immunodeficiency virus seropositive (HIV+), whereas among 871 contacts of age >5 years, 12% were HIV seropositive.
‡ BCG, Bacillus Calmette-Guérin.
§ $p \leq 0.01$ (chi-square test).
¶ $p \leq 0.05$ (chi-square test).

important. Cavitary disease has been associated with a greater burden of organisms and greater grade of acid-fast bacilli (41). These two clinical measures were highly correlated in our study, suggesting that patients with cavitary disease had a high burden of organisms and were highly infectious.

Among the many environmental factors explored, only the duration of contact with the index case and the muzigo type of housing were associated with disease. These factors likely measured the nature of contact with the index case. Of the variables included to assess the intensity of contact with the index case, contact of more than 18 hours per day was associated with the presence of active tuberculosis. In many instances, prolonged contact occurred when the caregiver of a dependent child had active tuberculosis, most often the mother. A muzigo is a building with multiple rooms that often share air space. These dwellings have limited ventilation, usually with only one door or window, and are often crowded, so they are an efficient type of setting for transmission of tuberculosis.

Why would these environmental factors, usually associated with transmission of *M. tuberculosis* and tuberculous infection, be associated with development of disease? The results of the study are consistent with at least two possible explanations. First, recent infection with *M. tuberculosis* confers a high risk for developing progressive primary tuberculosis (30). Second, environmental features could be markers for or determinants of risk for tuberculosis (16, 29). This explanation is likely because the environmental factors and host characteristics were correlated in this study. Indeed, there was a web of connectedness among the many factors associated with tuberculosis (figure 3), consistent with a multicausal model for tuberculosis (42–44). In this web, young children appear most vulnerable. For example,

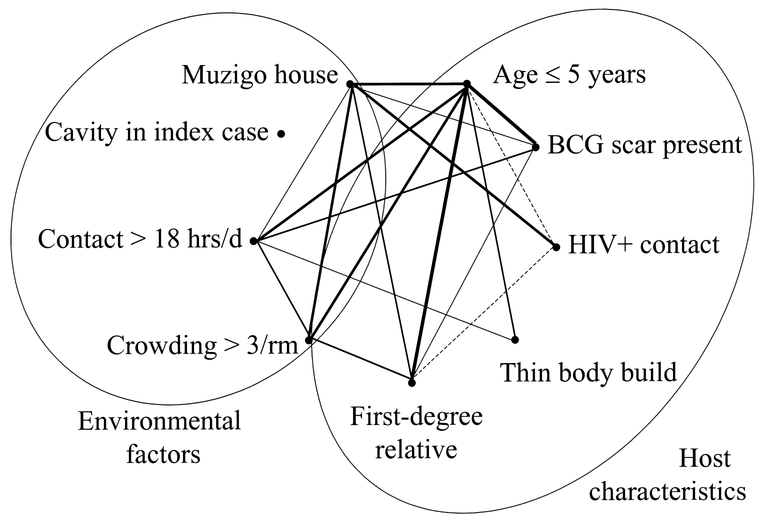

FIGURE 3. Interrelations among environmental and host factors associated with tuberculosis, Uganda, 1995–1999. These interrelations are consistent with a multicausal model of disease. Lines connecting points represent a statistically significant association. The thickness of the line represents the strength of the association between two points. Solid lines represent factors with direct correlation; dashed lines represent inverse correlation. BCG, Bacillus Calmette-Guérin; HIV+, human immunodeficiency virus seropositive; rm, room; hrs/d, hours/day.

although young children were more often vaccinated with BCG, they more often lived in crowded muzigos and had more contact-hours with infectious cases. The only factor not linked with the other risk factors was cavitary disease in the index case. Although each factor was independently associated with the risk of tuberculosis, thereby conferring unique information about the risk for disease, the web of connections between these host and environmental factors suggests that the household may function more like a complex system of risk than a collection of individuals at risk.

In Uganda, many household contacts were related to the index case, but in a culture of extended families, the contact network extends beyond the nuclear family. The current study focuses attention only on the well-defined social network of a household and does not delineate contact networks outside the household. Transmission of tuberculosis does occur in the community (45), but the balance of tuberculosis transmission—whether it occurs mostly in households or in the community at large—is not known and may differ from region to region depending on the prevalence of tuberculosis and mixing patterns of infectious cases. Knowing where tuberculosis is transmitted can have important implications for tuberculosis control strategies.

In conclusion, tuberculosis is common among household contacts of index cases in Africa, especially among young children and HIV-infected contacts. Host risk factors cannot, however, be completely distinguished from the effects of environmental risk factors, suggesting that a household may represent a complex system of interacting risks for disease. Household evaluation of contacts is hindered by shortcomings of current diagnostic methods for early or minimal disease. New approaches to household contact tracing will require improved diagnostic methods and assessment of household environmental risks. Further efforts to improve living conditions and to control HIV infection are essential in reducing household risk for tuberculosis in Africa.

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