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Prevalence of Tuberculosis Risk Factors among Bacteriologically Negative and Bacteriologically Confirmed Tuberculosis Patients from Five Regional Referral Hospitals in Uganda

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Abstract. Understanding risk factors for tuberculosis (TB) and their prevalence helps guide early diagnosis. We determined their prevalence among bacteriologically negative and bacteriologically confirmed TB patients in five regional referral hospitals in Uganda. This cross-sectional study considered 1,862 adult presumptive TB participants. We performed fluorescent microscopy, Xpert MTB/RIF (Xpert), Lowenstein–Jensen culture, human immunodeficiency virus, and random blood sugar testing on recruited patients. Prevalence and prevalence ratios of risk factors were compared among bacteriologically negative and confirmed cases. Odds ratios and 95% confidence interval (CI) were determined for significant risk factors in bacteriologically confirmed patients. Of the 1,862 participants, 978 (55%) were male and the median age of the participants was 36 years (interquartile range: 27–48). Up to 273 (15%) had a positive result on all three TB tests. Most prevalent risk factors (prevalence ratio [PR] > 1.0) among bacteriologically negative and positive TB patients were cigarette smoking (9.3% versus 2.1%; PR = 2.1), biosmoke (24% versus 39.7%; PR = 1.7), contact (4.2% versus 6.5%; PR = 1.6), male gender (51.4% versus 72.5%; PR = 1.4), alcohol use (17.2% versus 24.4%; PR = 1.4), diabetes (0.7% versus 0.9%; PR = 1.3), and family history of TB (12.1% versus 13.7%; PR = 1.1). The risk factors and their adjusted prevalence rate ratios (95% CI) of being bacteriologically positive were male (1.8 [1.4–2.4]), biosmoke exposure (1.5 [1.2–2.0]), and history of cigarette smoking (1.6 [1.1–2.4]). Among bacteriologically confirmed patients in Uganda, cigarette smoking, biosmoke exposure, contact, male gender, alcohol use, diabetes, and family history of TB are important risk factors for TB. Interventions for TB control in people with these risk factors would help in TB control efforts.

INTRODUCTION

Tuberculosis (TB) remains a global disease burden, ranking alongside human immunodeficiency virus (HIV) infection as the leading cause of death worldwide.[1] Tuberculosis control efforts have been further complicated by the threat of multidrug-resistant tuberculosis and HIV infection. People living with HIV infection are 26 times more likely to fall sick with TB.[1]

The 2017 WHO global TB report lists Uganda as a high HIV/TB country. In 2016, the prevalence of bacteriologically confirmed TB per 100,000 population was 401 (292–509), whereas the incidence among all cases per 100,000 population was 201 (118–306).[2] The risk factors for TB could be exogenous or endogenous. There have been well-established risk factors such as HIV infection, malnutrition, and young age; however, a host of other risk factors has emerged. These include diabetes, indoor air pollution, use of alcohol, drugs that suppress immunity, and tobacco smoke.[3] The effect of these risk factors can be at either the individual or the population level. There are two possibilities in regard to the risk of TB. There is the risk of acquiring infection which depends on the prevalence of TB in the community, and the risk of an infected person progressing to TB disease, which most times is multifactorial.[4]

The various risk factors for TB include age, male gender, kitchen type, diabetes and low education level, being single or widowed, having a former episode of TB or having a family member who has had TB, cigarette smoking, alcohol and drug use, and indoor air pollution. Others include low accumulated wealth, consumption of unpasteurized milk, being unemployed, and living with a relative with TB.[5–12]

A previous study performed in Kampala[13] recommends a similar study on a bigger sample size and on a nationwide sample, and to the best of our knowledge, this is the only study on this topic in Uganda. A critical focus on risk factors for TB disease, their relative contribution, and development of interventions to reduce disease rates in these groups of people and improve the prognosis of patients with these risk factors goes a long way in contributing to efforts to TB control. More so, a better understanding of the risk factors and their prevalence shall allow preventive therapy to be given to those at greatest risk. This in the end helps in using the resources where they are most needed.

METHODS

Study participants. This was a nested cross-sectional study of all TB presumptive adults attending five regional referral hospitals (RRHs) in Uganda. We consecutively included adult presumptive TB patients aged 18 years and older. Excluded were patients too ill to speak and patients not consenting to the interview. The respondents were both HIV-positive and negative adults seeking care at these study sites (RRHs). The sites were well spread across the country, with some of the sites serving cross-border populations by virtue of being near or in border towns. The participants had at least one cardinal symptom for TB (i.e., cough of more than 2 weeks, night sweats, significant weight loss, persistent fevers, and hemoptysis). The study was conducted between October 2015 and August 2016.

A total of 1,862 presumptive TB cases were tested by fluorescent microscopy (FM), Xpert MTB/RIF, and Lowenstein–Jensen (LJ) culture as described in the main study.[14] Prevalence of the risk factors was ascertained in the bacteriologically negative and bacteriologically confirmed TB patients.

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Study procedures. All presumptive TB cases presenting to the study sites and meeting the study criteria were introduced to the study and their potential involvement and all procedures explained. Each consenting participant was tested for HIV infection and random blood sugar (RBS) testing was performed as well. Research assistants who underwent 1 week's training on the protocol and data tool used a piloted questionnaire to collect important patient and clinical data. The factors included male gender, history of contact with a known TB patient, family history of TB, overcrowding, alcohol use, cigarette smoking, diabetes, poverty, exposure to biosmoke, and absence of Bacillus Calmette–Guérin (BCG) scar. Contact in this study is where an individual had a contact with a TB patient within the past 1 year, whereas poverty cutoff was any individual living below US$1.9 a day.[15] Biosmoke exposure was defined as exposure to fumes arising from industrial sources, charcoal, and wood burning. Overcrowding was defined as two or more adult persons who are not of opposite gender sharing a bedroom.[13] The research assistants maintained a site register where they recorded all recruited participants after allocating them a unique study number. The study number was the same number used to label the participant's sputum sample. Each patient was asked to provide two samples of sputum (spot and early morning) and these were clearly labeled on whether they were spot or early morning on both the sputum mugs and laboratory forms. The laboratory personnel maintained a laboratory register for all the recruited participants. One sample was used for FM and Xpert MTB/RIF testing, whereas the other sample was shipped to the national TB reference laboratory for LJ and/or mycobacteria growth indicator tube culture as described earlier.[14] Shipment forms with patient unique identifiers were together with the labeled samples shipped to the national TB reference laboratory. The patients who were positive on any of the tests (FM, Xpert MTB/RIF, and/or culture) were initiated on TB treatment as per the national TB treatment guidelines. Human immunodeficiency virus infection and RBS testing were also performed according to the national guidelines. Human immunodeficiency virus infection rapid testing was used. We used a sequential rapid testing algorithm that included the Determine HIV-1/2 assay for screening (Abbott Laboratories, Chicago, IL), HIV-1/2 STAT-PAK Dipstick assay (Chembio Diagnostic Systems, Inc., New York, NY) for confirmatory testing, and the Uni-Gold test (Trinity Biotech, Wicklow, Ireland) as the tiebreaker. A negative test with the Determine assay was recorded as a negative result. A positive test with the Determine assay was confirmed using the STAT-PAK assay and later recorded as a positive result if both assays gave a positive result. If the Determine and STAT-PAK assay results were discordant, the sample was subjected to a third test using the Uni-Gold assay. The result was reported as positive if the Uni-Gold test result was positive and negative if both STAT-PAK assay and Uni-Gold test results were negative. Capillary blood was used for random blood glucose testing using a glucometer (LifeScan, Milpitas, CA). A value of 7.7 mmol/L was taken as no diabetes, 7.8 mmol/L–11.1 mmol/L as prediabetes, and 11.2 mmol/L and above as diabetes.

The FM and Xpert MTB/RIF assays were performed at the study sites according to standard operating procedures and as previously detailed in the previous work.[14] Culture results were communicated back to the sites electronically through emails and also relayed to the data center where the data manager merged filed data with culture results data using patient study numbers.

Statistical analysis. Data were double-entered in an electronic database (Epidata version 2.0/2007; Odense, Denmark), and where there were discrepancies, these were resolved by cross-checking with the source documents (raw data). Data were exported to Stata v13 (Stata Corp, College Station, TX) for analysis. Excluded from the analysis were respondents for whom a complete set of LJ and mycobacteria growth indicator tube results were available, contaminated results and results showing nontuberculous mycobacteria. Percentages and frequencies of important variables were generated. Poison regression was performed for variables with a prevalence of 50% and greater and also for variables with biological explanations, first doing bivariate analysis to obtain unadjusted odds ratios (ORs) and later multivariate analysis for bivariate variables with P-value < 0.2 using the backward elimination method to obtain adjusted ORs. Variables with adjusted ratio having a P-value less than 0.05 at 95% confidence interval (CI) were considered significant.

Ethics statement. Approval for the study was granted from Makerere School of Public Health Institutional Review Board and national approval granted by the Uganda National Council for Science and Technology. All participants gave written informed consent.

RESULTS

The characteristics of the respondents are presented in Table 1. Of the 1,859 eligible participants, 1,014 (54.6%) were male. More than half of the respondents (1,056; 56.8%) were in the age group 18–38 years.

Bacteriological test result. The results of each of the bacteriological tests are presented in Figure 1, with Xpert MTB/RIF detecting up to 26.7% (497) of the TB patients. Smear microscopy picked the least number of cases (398; 21.4%).

Prevalence of TB risk factors among the respondents. Table 2 shows the prevalence of the risk factors in the bacteriologically negative and bacteriologically positive patients. In the bacteriologically negative respondents, the most prevalent factor was exposure to poverty (607; 53.6%), followed by being male (788; 51.4%), absent BCG scar (46.8%), and overcrowding (39.2%), whereas in the bacteriologically positive group, the most prevalent factors were exposure to poverty (53.0%), being male (72.5), absent BCG scar (51.3%), exposure to biosmoke (39.7%), and overcrowding (35.1%).

Risk factors for bacteriologically confirmed TB among presumptive TB patients. Table 3 shows the risk factors for bacteriologically confirmed TB among presumptive TB patients in Uganda. The risk factors and their adjusted prevalence rate ratios (adjPRR) (95% CI) were being male (1.8 [1.4–2.4]), exposure to biosmoke (1.5 [1.2–2.0]), and any history of cigarette smoking (1.6 [1.1–2.4]).

DISCUSSION

This study carried out across Ugandan referral hospitals highlights the prevalence of the main TB risk factors. The prevalence of known TB risk factors among all bacteriologically negative patients in descending order is poverty, male gender, absence of BCG scar, overcrowding, and exposure to biosmoke.

TABLE 1
Characteristics of all study participants (n = 1,859)

Demographic characteristics		
Characteristic	All, *n* (%)	Bacteriologically confirmed, *n* (%)
Age group (years)		
18–38	1,056 (56.8)	413 (66.0)
39–59	593 (31.9)	164 (26.2)
60+	210 (11.3)	49 (7.8)
Gender		
Male	1,014 (54.6)	401 (64.1)
Female	845 (45.4)	225 (35.9)
Human immunodeficiency virus infection status		
Human Immunodeficiency virus positive	445 (24.1)	161 (25.8)
Human Immunodeficiency virus negative	1,402 (75.9)	462 (74.2)
Diabetes status		
No diabetes	1,519 (93.3)	494 (93.0)
Prediabetes	96 (5.9)	32 (6.0)
Diabetes	13 (0.8)	5 (1.0)
Alcohol use		
Yes	337 (18.3)	122 (19.5)
No	1,521 (81.7)	504 (80.5)
History of cigarette smoking		
Yes	204 (11.0)	87 (13.9)
No	1,651 (89.0)	537 (86.1)
Tuberculosis treatment category		
Previously treated	195 (10.5)	59 (9.4)
Never been treated	1,643 (88.4)	562 (89.8)
Missing	21 (1.1)	5 (0.8)
Overcrowding		
Yes	715 (38.5)	241 (38.5)
No	1,144 (61.5)	385 (61.5)
Occupation		
Unemployed	392 (20.4)	141 (22.1)
Self-employed	1,092 (56.7)	342 (53.6)
Civil servant	79 (4.1)	24 (3.8)
Others	361 (18.8)	131 (20.5)
Education level		
Tertiary	150 (8.1)	46 (7.4)
Secondary	678 (36.6)	252 (40.4)
Primary	822 (44.4)	282 (45.2)
None	202 (10.9)	44 (7.0)
Marital status		
Married	1,110 (57.5)	349 (54.7)
Unmarried	728 (37.8)	271 (42.5)
Unknown	86 (4.5)	18 (2.8)

Self-employed = 1,092 (56.7%): builder 80 (4.3%), peasant farmer 390 (21.0%), farmer 102 (5.5%), market vendor 153 (8.2%), business 367 (19.8%). Employed: health worker 10 (0.5%). Civil servant 69 (3.7). Others 292 (15.7).

The prevalence of the same risk factors among the bacteriologically confirmed TB patients in descending order is male gender, poverty, absence of BCG scar, exposure to biosmoke, and overcrowding.

Exposure to biosmoke at 24% and 39.7% in bacteriologically negative and bacteriologically confirmed TB cases, respectively, emerged as a big risk factor. This is hardly surprising as most of the African population relies on biomass

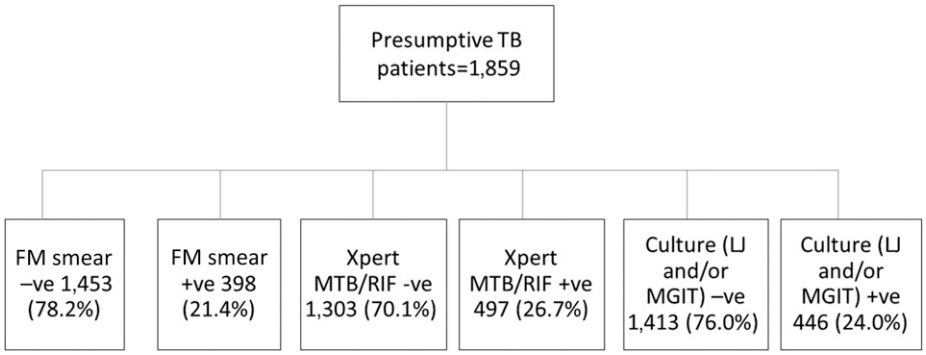

FIGURE 1. Bacteriological test results.

TABLE 2
Prevalence of TB risk factors among the respondents

Variable	Bacteriologically negative: Number with risk factor (%)	Bacteriologically positive: Number with risk factor (%)	Prevalence ratio
Absent Bacillus Calmette–Guérin scar	715 (46.8)	134 (51.3)	1.1
Alcohol use	263 (17.2)	64 (24.4)	1.4
Contact	65 (4.2)	17 (6.5)	1.6
Diabetes	10 (0.7)	2 (0.9)	1.3
Exposure to biosmoke	368 (24.0)	104 (39.7)	1.7
Family history of TB	186 (12.1)	36 (13.7)	1.1
Human immunodeficiency virus positive	369 (24.2)	60 (23.0)	1.0
Male	788 (51.4)	190 (72.5)	1.4
Overcrowding	601 (39.2)	92 (35.1)	0.9
Poverty	607 (53.6)	114 (53.0)	1.0
Prediabetes	85 (6.3)	7 (3.1)	0.5
Previous TB treatment	173 (11.3)	18 (6.9)	0.6
Cigarette smoking	143 (9.3)	52 (19.9)	2.1

TB = tuberculosis.

as their source of fuel for cooking and on frequent burning of grass during farming, which is the main activity in Uganda. The prevalence among the TB cases is closely similar to findings of an Indian study on the contribution of biomass to the prevalence of TB which found 51% of the TB was attributable to biomass fuels for cooking. Indoor air pollution has been found to be associated with increased risk of TB.[16–18]

Absence of BCG scar was very prevalent in both bacteriologically negative and bacteriologically confirmed TB patients at 46.8% and 51.3%, respectively. This is way below the BCG vaccination coverage of 95% for Uganda.[19] Interestingly, another report rates Uganda as the country with the lowest immunization coverage in the region.[20] The effect of BCG is up to 10 years[21] and the fact that it protects against severe forms of TB calls for improved immunization coverage. A West African study found the presence of a BCG scar to be protective,[5] whereas a study carried out in Gambia did not find an association between tuberculin skin test positivity and the presence of a BCG scar.[8] The BCG scar in this study was used as a proxy indicator of immunization coverage, and as the protective effect of the vaccine wanes after 10 years, the finding could help strengthen TB control in children for whom most of the times adults are the source of TB infection.

The prevalence of HIV infection in the bacteriologically negative and bacteriologically confirmed TB patients was 24.2% and 23.0%, respectively. This is lower than the quoted 2016 figure of 34% for the African region.[22] This value is also lower than that found in a similar study in Kampala.[13] The difference in prevalence could be because of the strengthening of HIV–TB collaborations that have been encouraged, leading to more HIV-positive individuals being routinely screened for TB in HIV clinics and also others being started on isoniazid preventive therapy. It is also possible that the prevalence rates of HIV infections have decreased overtime.

TABLE 3
Risk factors among bacteriologically positive TB patients

Risk factors	Bacteriologically confirmed: PRR (95% CI)	*P*-value	Bacteriologically confirmed diagnosis: adjPRR (95% CI)	*P*-value
Female	Reference			
Male	2.2 (1.7–2.9)	< 0.001	1.8 (1.4–2.4)	< 0.001
Exposure to biosmoke				
No	Reference			
Yes	1.8 (1.4–2.4)	< 0.001	1.5 (1.2–2.0)	0.001
Above poverty level	Reference			
Below poverty level	0.98 (0.7–1.3)	0.882	–	–
Presence of BCG scar	Reference			
Absence of BCG scar	1.2 (0.9–1.5)	0.212	–	–
Alcohol consumption				
No	Yes			
Yes	1.5 (1.1–1.9)	0.010	1.0 (0.7–1.4)	0.869
No history of household contact	Reference			
History of household contact*	1.5 (0.9–2.4)	0.139	–	–
No diabetes	Reference			
Diabetes	1.1 (0.3–4.6)	0.849	–	–
Prediabetes	0.5 (0.3–1.1)	0.091	–	–
No family history of TB	Reference			
Family history of TB	1.1 (0.8–1.6)	0.502	–	–
Human immunodeficiency virus negative	Reference			
Human immunodeficiency virus positive	0.9 (0.7–1.3)	0.693	–	–
No history of cigarette smoking	Reference			
Any history of cigarette smoking	2.0 (1.5–2.8)	< 0.001	1.6 (1.1–2.4)	0.007

adjPRR = adjusted prevalence rate ratios; BCG = Bacillus Calmette–Guérin; CI = confidence interval; TB = tuberculosis.
* Contact with a TB patient within the past 1 year.

There was a substantial risk associated with cigarette smoking at 9.3% among the bacteriologically negative respondents and 19.9% among bacteriologically confirmed TB patients. Previous studies have proved a positive association between smoking and TB and there was a dose-dependent association.[23,24] A Hong Kong study found that smoking accounted for 18.7% of the TB risk among a cohort of elderly clients.[24] There is an increase in TB case rates of up to 2- to 4-fold in people who smoke in excess of 20 cigarettes a day. The likely explanation for the increased risk of TB is that nicotine turns off the production of tumor necrosis factor-α in the lungs by the macrophages. This in turn makes the patient more susceptible to develop active disease from a reactivation of the latent TB infection. The association between cigarette smoking and TB is dependent on pack-years, with those with more pack-years being more likely to have TB. Those with more than 15 pack-years have the highest risk. Smokers are more likely to develop pulmonary TB and more cavitary lesions.[25–27] This study found a prevalence similar to that found in the Hong Kong study. It was, however, lower than that found in the Kampala study.[13] This could be because of the differences in personal behavior associated with cigarette smoking and alcohol consumption being more common in cities than rural areas. Also, the high income levels in the urban dwellers could be linked to increased expenses on alcohol and cigarette smoking.[28]

The prevalence of alcohol use in this study was found to be 17.2% in the bacteriologically negative respondents and 24.4% among the bacteriologically confirmed TB patients. Alcohol intake has been documented in previous literature as a risk factor for TB and the risk is markedly higher in people who take more than 40 g of alcohol per day.[29] This was, however, lower than that found in the Kirenga et al. study in Kampala.[13] The reason could be the disposable income available to spend among dwellers in big cities. Possible explanation for the increased risk of TB associated with alcohol use includes the social mixing patterns witnessed in the alcohol consumers, reduced immunity as a result of breakdown of the immune system through the toxic effects of alcohol, or the result of micro- and macronutrient deficiencies.[29] A systematic review found that heavy alcohol consumption or alcohol use disorder is a risk factor for the incidence and reinfection of TB.[30] It is hypothesized that reduction in alcohol consumption is associated with reduced risk of TB. The reversibility effect of removal of alcohol exposure is supported by evidence from Ukraine and Russia where when the alcohol use went back to old lower levels, a reduction in the TB mortality was noted.[30] Alcohol use is not only a risk factor for TB, but it also presents challenges in TB management. It is associated with nonadherence and poor treatment outcomes in TB patients.[31] A North Carolina study found excess alcohol use to be associated with pulmonary TB and presence of cavities on chest radiographs, and these patients were found to be more infectious. This study found the prevalence of alcohol use among TB patients at 23.8%.[32]

Poverty in this study was found to be very prevalent at 53.6% among the bacteriologically negative respondents and 53.0% among the bacteriologically confirmed TB patients. This is in agreement with previous studies which showed the socioeconomic gradient associated with the risk of TB where the poorest were found with the highest risk.[7] Kirenga et al. in their study of prevalence of TB risk factors found a prevalence of 39.5% among TB cases.[13] The high prevalence found in this study could be attributed to two reasons. One, the previous study used a cutoff of $1.25 per day, whereas the present study used the revised poverty level of less than $1.9. The second reason could be differences in the study settings; Kampala by virtue of being the capital has people who earn much more than the average Ugandan. However, this is more than the population below the poverty line in Uganda, where 21.4% of the population live below the poverty line.[33]

The prevalence of contact to a TB case was 4.2% and 6.5% among the bacteriologically negative respondents and bacteriologically confirmed TB patients, respectively. This is in agreement with studies carried out that have shown contact to be a risk factor for TB. In one study carried out in children, it was discovered that the prevalence of TB infection and TB disease among children who had household contact with adult patients was higher than that in the general population.[34,35] This calls for more rigorous contact-tracing efforts.

The prevalence of diabetes in this study was found to be 0.7% among the bacteriologically negative respondents and 0.9% among the bacteriologically confirmed TB patients. This was lower than that in the Kirenga et al. study which was carried out in the capital, Kampala, which found the prevalence of diabetes to be 5%.[13] The difference in prevalence of diabetes could be explained by the lifestyle differences of people in both studies. People in most developing cities tend to take on sedentary lifestyles and diets that predispose them to diabetes, and thus diabetes is more prevalent in the cities.

Family history of TB as a risk factor was seen in 12.1% of the bacteriologically negative respondents and 13.7% of the bacteriologically confirmed TB patients. Family history is a risk factor for TB as was found out in a study carried out in West Africa.[5] Our finding is, however, lower than that found in a West African study where family history was found to be a risk factor in 24% of West African TB cases,[35] but slightly lower than findings from the Kirenga et al. study[13]

Findings from this study reveal that most of the respondents had been exposed to biosmoke. Those respondents who had not had any form of biosmoke exposure were more likely to have a positive bacteriological test as opposed to those with exposure. On the contrary, the respondents who had a positive history of cigarette smoking were more likely to have a positive TB result than those who did not have a history of cigarette smoking. The reasons for this discrepancy warrant a research into the effect of biosmoke exposure and cigarette smoking on bacteriological positivity of the specimens. It is possible that biosmoke and cigarettes exert their effects in different ways on the respiratory system.

LIMITATIONS

A potential limitation in our study is that we were not able to use pack-year to assess cigarette smoking and also to quantify the alcohol intake among the respondents who used alcohol. Areas for further research would include exploring the mechanisms under which biosmoke and cigarette smoking exert their effects on the respiratory system, thereby affecting the bacteriological test results.

CONCLUSION

Among bacteriologically confirmed TB patients in Uganda, cigarette smoking, biosmoke exposure, contact with TB

patients, being male, alcohol use, diabetes mellitus, and family history of TB are vital risk factors for TB. Interventions aimed at TB control in people with these risk factors would contribute tremendously to TB control efforts.

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