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Low Prevalence of Tuberculin Skin Test Boosting among Community Residents in Uganda

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Abstract. Boosted tuberculin skin test (TST) reactions can be misclassified as new latent tuberculosis (TB) infection. To our knowledge, no study has evaluated the prevalence of TST boosting in a population-based sample in high TB burden settings. We determined the prevalence of TST boosting among urban residents in Uganda. We evaluated 99 participants with initial TST < 5 mm and repeated a skin test after 2 weeks. We found that only 2% had boosted TST reactions suggesting that most TST conversions could represent new TB infections in this high-burden setting.

INTRODUCTION

Tuberculosis (TB) remains a major global health problem with an estimated one-third of the world's population with latent tuberculosis infection (LTBI).[1] Most of the affected persons live in developing countries. Studies show that 5–20% with LTBI will progress to active TB disease, especially within 2–5 years of the initial infection.[2] Accurate identification and treatment of individuals with new LTBI is a key component of improved global TB control and elimination.[1–3]

The tuberculin skin test (TST) has been used to diagnose LTBI for more than a century but its specificity may be affected by Bacille Calmette–Guérin (BCG) vaccination or cross-reactivity with nontuberculous mycobacteria.[4] Interferon-gamma release assays (IGRAs) are newer and more specific for diagnosing LTBI but adoption for routine use is slow mainly because of high cost.[2]

One challenge in interpreting a TST reaction is the possibility of boosting. Boosting is believed to result from a recall of the immune response that occurs in subjects with past and remote exposure to mycobacterial antigens who have not been recently reexposed to an infectious case of TB.[5,6] In such a situation, the TST reaction may become negative but on a repeat TST, the size of the reaction may become boosted and meet criteria for a positive TST. This boosted reaction may be misinterpreted as a new TST conversion and result in unnecessary treatment.[5,7]

The prevalence of TST boosting in the general population in high-burden settings is not well documented. A few studies have evaluated boosting in high-risk populations in sub-Saharan Africa.[8,9] The aim of this study was to evaluate the prevalence of TST boosting in a population-based sample of participants in Kampala, Uganda.

METHODS

Study design, setting, and population. This was a prospective study that was conducted in Lubaga division in Kampala, Uganda, from January to February of 2016. Eligible participants were residents of Lubaga aged 18 years or older, who were willing to have a repeat TST with an initial test reading of less than 5 mm. Participants received a second TST within 2 weeks of the initial test. Individuals with baseline TST readings of 5 mm or greater were excluded from the study.

Ethics statement. Written informed consent was obtained from all eligible participants. The study was approved by the institutional review boards at the University of Georgia, Makerere University School of Public Health and the Uganda National Council for Science and Technology.

Definitions. Boosting was defined as a TST reaction of ≥ 10 mm on the second TST reading, with an increase of 6 mm over the first TST. Previous studies have also used this cutoff to define boosting.[10] Intermediary TST reaction was defined as repeat TST reading great or equal to 5 mm but less than 10 mm. Persistent TST-negative was defined as a repeated TST reaction of less than 5 mm.

Measurement and follow-up procedures. A two-step TST procedure was performed by trained research assistants to assess participants for boosting. Purified protein derivative TUBERSOL® (tuberculin purified protein derivative [Mantoux] 5 TU per 0.1 mL Statens Serum Institut, Copenhagen, Denmark) was placed in the right forearm. Using digital calipers, the TST induration was recorded in mm 48–72 hours later by two independent readers. If the induration was less than 5 mm, the participant was eligible for a repeat TST within 2 weeks of the initial placement. Rapid human immunodeficiency virus (HIV) testing was also performed according to the algorithm recommended by the Uganda national HIV testing policy. Participants were checked for a scar on the arm as evidence of previous BCG vaccination.

Statistical analysis. The proportion of participants who met the criteria for boosting was estimated with 95% confidence intervals (CI). Descriptive statistical analyses including means with SDs and proportions with corresponding 95% CI are presented.

RESULTS

Seven hundred ninety-five participants were screened in the community from January to February 2016. Of those screened, 510 (64%) individuals had a TST induration 5 mm or greater at baseline and hence were ineligible to participate in the study. Sixty-five (8%) participants either did not return after the initial TST or refused further participation (Figure 1). Of the 215 (27%) eligible TST-negative individuals, 135 (63%) had repeat TST placed. Of those, 99 (73%) returned or were followed-up for a second TST reading. The remaining 36 (27%)

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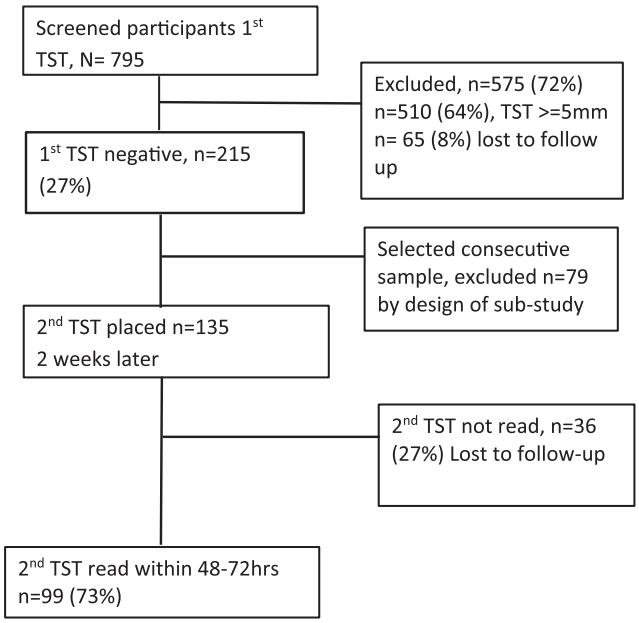

FIGURE 1. Flow chart showing participants enrolled in the study in Kampala, Uganda.

people missed the second TST reading because they were not found within the 48- to 72-hour window.

For 99 participants included in this analysis, the mean age was 26 (SD ± 7) years. Sixty-seven (68%) were female, 49 (50%) were single or never married, 40 (41%) worked outside of the home, 88 (90%) had a BCG scar, and 2 (2%) were HIV-infected.

Of the 99 participants, 2 (2%) had a boosted TST reaction of 10 mm or greater, 5 (5%) had a TST between 5 and 10 mm, and 92 (93%) had a TST less than 5 mm (Table 1). The two participants with TST boosting were female, had BCG scars, and were HIV seronegative. Of the 5 participants with intermediary reactions, all were female and HIV seronegative, three had BCG scars.

DISCUSSION

We evaluated the prevalence of TST boosting in an urban community in Uganda. We found that 2% of participants with a TST reaction of less than 5 mm at baseline had a boosted TST within 2 weeks. To our knowledge, we present the first findings on TST boosting in the general population in a high-burden African setting. Two published studies assessed TST boosting in Africa.[8,9,11] One study focused on HIV-infected persons in Uganda[8] whereas the other study was performed among health care workers and medical students volunteers in South Africa.[9]

Outside Africa, studies done to evaluate the TST boosting focused on specific high-risk populations, and levels of TST boosting varied widely among studies. For example, prevalence of boosting ranged from 6% to 8.4% in Brazilian household contacts and medical students, respectively,[7,12] 13% among international adoptees in the U.S.,[10] and to 31% in foreign-born persons in Canada.[5] The higher levels of TST boosting in these studies could be explained by the relatively higher risk of prevalent latent TB in the study populations. In addition, slight differences in the cutoffs used to define boosting could explain these results.[5]

Previous BCG vaccination can sometimes lead to false-positive TST reactions, and thus could bias the estimation of TST boosting,[5] but the BCG effect tends to wane by 10 years of age.[4] Our study included only adults aged 18 years or older, therefore, the confounding effect of BCG on TST results should be less of a concern. In our study, the prevalence of BCG scars was 90% but the level of TST boosting observed in this general urban population was relatively low. Previous studies have shown a correlation between LTBI prevalence and level of boosting,[5] but we did not find this relationship.

In the presence of HIV infection, the level of TST boosting can be low because of false-negative TST readings, especially with advanced immunosuppression.[8] Although HIV is endemic in Uganda, the prevalence of HIV infection in the study population was 2% compared with the 6.7% estimated HIV prevalence for Kampala. Selection bias in favor of healthier participants could explain the differences we observed in our study.

Intermediary TST reactions remain a gray area for further exploration. These intermediary reactions, where the repeat TST readings were above 5 mm but less than 10 mm occurred in 5% of the participants. None of the studies published thus far have explicitly reported on this subgroup of participants; therefore, we do not know how frequently this phenomenon has been observed. The intermediary reactions could be explained by failure to mount a strong enough immune response to reach the prespecified cutoff for a positive TST within the limited time of observation. Use of IGRA as second test in the case of intermediary results could improve the specificity of the TST in the diagnosis of LTBI.[9]

This study is one of the first to measure the level of TST boosting in a population-based sample in a high-burden African setting. We believe that this will provide a baseline context for interpretation of the incidence of latent TB infection in future studies in sub-Saharan Africa.

Our study had some limitations. We used a convenience sample of volunteer participants in urban Uganda. Differences in participants and nonparticipants could have led to selection bias that could affect the accurate estimation of boosting. The small sample size and attrition of TST-negative participants who failed to return for enrollment or TST reading 48–72 hours

TABLE 1
Characteristics of study participants by boosting status in Kampala, Uganda

Characteristics	Overall *N* = 99	Boosting present (TST ≥ 10 mm)	Intermediary reactions (TST ≥ 5–<10 mm)	Persistent negatives (TST < 5 mm)
Age (mean, SD)	26 (±7)	29.5 (±16)	24 (±8)	26 (±6)
Number [%, 95% CI]		2 [2%, 0.4–8%]	5 [5%, 1.9–12%]	92 [93%: 86–97%]
			n (%)	
Female sex	67 (68)	2 (3)	5 (7)	62 (93)
BCG scar present	88 (89)	2 (2)	3 (3)	83 (94)
HIV seropositive	2 (2)	0	0	2 (100)

BCG = Bacille Calmette–Guérin; CI = confidence intervals; HIV = human immunodeficiency virus; TST = tuberculin skin tests.

could have led to underestimation of the prevalence of boosting in this population. Nonetheless, our preliminary conclusion is that the level of TST boosting was relatively low. This could suggest that most of the TST reactions we observe are likely to be new TB infections in this largely BCG-vaccinated urban African population.

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