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Mycobacterium tuberculosis Bacteremia among Acutely Febrile Children in Western Kenya

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Abstract. In children, *Mycobacterium tuberculosis* (*M. tuberculosis*) frequently disseminates systemically, presenting with nonspecific signs including fever. We determined prevalence of *M. tuberculosis* bacteremia among febrile children presenting to hospitals in Nyanza, Kenya (a region with high human immunodeficiency virus (HIV) and *M. tuberculosis* prevalence). Between March 2013 and February 2014, we enrolled children aged 6 months to 5 years presenting with fever (axillary temperature ≥ 37.5°C) and no recent antibiotic use. Blood samples were collected for bacterial and mycobacterial culture using standard methods. Among 148 children enrolled, median age was 3.1 years (interquartile range: 1.8–4.1 years); 10.3% of children were living with a household member diagnosed with *M. tuberculosis* in the last year. Seventeen percent of children were stunted (height-for-age z-score < −2), 18.6% wasted (weight-for-height *z*-score < −2), 2.7% were HIV-infected, and 14.2% were HIV-exposed uninfected. Seventeen children (11.5%) had one or more signs of tuberculosis (TB). All children had a Bacille Calmette-Guerin vaccination scar. Among 134 viable blood cultures, none (95% confidence interval: 0–2.7%) had *Mycobacterium* isolated. Despite exposure to household TB contacts, HIV exposure, and malnutrition, *M. tuberculosis* bacteremia was not detected in this pediatric febrile cohort, a finding consistent with other pediatric studies.

INTRODUCTION

Tuberculosis (TB) is a common cause of morbidity and mortality among children living in sub-Saharan Africa (SSA).[1,2] While *Mycobacterium tuberculosis* (*M. tuberculosis*) typically manifests as isolated pulmonary disease in immune-competent adults, in young children and in those who are immunosuppressed (with HIV or severe malnutrition), *M. tuberculosis* is more likely to disseminate.[3,4] Disseminated *M. tuberculosis* often presents with nonspecific signs and symptoms, including fever, weight loss, and general malaise, similar to the signs and symptoms of many other infections. Disseminated *M. tuberculosis* in children is associated with a very high case fatality rate, exceeding 50% in some reports.[5–7] Although prompt therapy likely reduces mortality, mycobacterial culture is not available and is cost-prohibitive in many settings leading to delays in diagnosis.

Among febrile, hospitalized adult populations in SSA, *M. tuberculosis* is a leading cause of bloodstream infection, with prevalence estimates ranging from 5.5% to 23.4%.[5,8–12] In this population, human immunodeficiency virus (HIV)-associated immunosuppression has emerged as the most important risk factor for *M. tuberculosis* bacteremia. However, studies assessing *M. tuberculosis* bacteremia in children are limited and the prevalence of *M. tuberculosis* bacteremia in children with acute febrile illness has not been described.[13–15] Given the difficulty in establishing the diagnosis of *M. tuberculosis* bacteremia in many settings and the need for prompt initiation of anti-tuberculosis therapy to reduce mortality, we sought to determine the frequency and correlates of *M. tuberculosis* bacteremia in Kenyan children aged 6 months to 5 years presenting with fever to one of three western Kenya hospitals.

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METHODS

Consecutive children aged 6 months to 5 years, without recent antibiotic use (defined as documented antibiotic use within the last 24 hours other than prophylactic cotrimoxazole for HIV exposure) were enrolled in a cross-sectional study evaluating bacterial causes of bloodstream infections. Children were enrolled from three health facilities (Kisii Teaching and Referral Hospital, Homa Bay District Hospital, and Migori District Hospital) in the Nyanza region of Kenya where the estimated adult prevalence of HIV and TB are 15.1% and 0.6%, respectively.[16,17] Children enrolled between February and August 2013 and between January and March 2014 were asked to provide additional blood for mycobacterial blood culture. The gap in enrollment in this substudy was due to unavailability of the appropriate mycobacteria culture bottles for the time period between September 2013 and December 2013. Written informed consent was obtained from primary caregivers of enrolled children. Study clinical officers examined children according to the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) guidelines, obtained height and weight, and assessed for presence of a Bacille Calmette-Guerin (BCG) scar.[18] Height-for-age (HAZ), weight-for-height (WHZ), and weight-for-age *z*-scores (WAZ) were calculated using the 2006 WHO reference populations for children under 5 years.[19] Stunting and wasting were defined as HAZ < −2 and WHZ < −2, respectively. A standardized questionnaire was used to obtain clinical history, signs and symptoms from the physical examination, and sociodemographic information.

Up to 5 mL of blood was collected aseptically and separated for bacterial culture, HIV testing, malaria testing, and up to 3 mL for mycobacterial culture. Maximum allowable blood draw volumes (2 mL/kg) were set based on those used at Seattle Children's Hospital and additional blood for mycobacterial blood culture was drawn only when an additional 1–3 mL could be drawn from the child. Children were tested

for HIV using antibody testing (Abbott Determine™ rapid test kit and confirmed using Uni-Gold™) or HIV RNA polymerase chain reaction if < 18 months of age. Maternal HIV-status was ascertained by self-report if the mother reported being HIV-infected and confirmed by antibody testing if the mother was unsure of her infection status or reported being HIV uninfected. Malaria was assessed at the study site using both rapid diagnostic testing (RDT) (Paracheck Pf® Orchid Biomedical Services, India) and microscopy.

For mycobacteria blood culture, 1–3 mL of blood inoculated in Bactec™ Myco F/lytic bottles were shipped daily to the nearby Kenya Medical Research Institute (KEMRI)/Center for global health research (CGHR) TB laboratory in Kisian, Kenya where they were immediately placed in a Bactec 9120 machine for incubation. The transit time to the laboratory was less than 24 hours. Flagged bottles were removed, mixed gently, and subcultured to blood agar plates and Ziehl–Neelsen (ZN) smears. Positive ZN smears were subcultured onto Löwenstein-Jensen solid medium and evaluated for an additional 3 weeks. Flagged bottles that were ZN negative and positive on brain heart infusion agar were deemed contaminated. Unflagged bottles at 42 days were considered negative. Bacterial blood cultures were performed at the U.S. Army Medical Research Unit Microbiology Hub laboratory in Kericho, Kenya. Methods and results of bacterial culture for the parent study are presented elsewhere.[20]

Frequencies and percentages of clinical and sociodemographic characteristics were calculated and the 95% confidence interval (CI) around the *M. tuberculosis* bacteremia prevalence estimated assuming a binomial distribution. Analyses were conducted using Stata 11.1 (Stata Corp., College Station, TX). The University of Washington Institutional Review Board and the KEMRI Ethical Review Committee approved the study.

RESULTS

Of 375 children enrolled, 148 (39.5%) agreed to participate in the *M. tuberculosis* substudy and met weight standards for maximum blood draw quantity after blood for bacterial culture, malaria, and HIV testing was collected. Enrolled children were a median of 3.1 years of age (interquartile range [IQR]: 1.8–4.1 years), 54.7% were male, and 43.9% lived in a household with two or more people per room (Table 1). All children had a BCG scar. Reflective of the underlying population of children seeking care for acute illness in the study settings, malnutrition was relatively common; 17.0% of children were stunted and 18.6% wasted. In addition, 2.7% of children were HIV-infected and 14.2% were HIV-exposed uninfected. The median temperature at presentation was 38.6°C (IQR: 38.2–39.3°C). One third of the children (28.4%) presented with at least one IMCI-defined general danger sign and 11.5% had signs and symptoms suggestive of *M. tuberculosis* (5.4% with 2 or more weeks of night sweats, 5.4% with 2 or more weeks of cough, and 1.4% with 1 or more weeks of fever). Over a third (36.5%) of children had a positive malaria RDT result and 36.4% had parasitemia.

Fourteen children (10.3%) lived in the same household as someone diagnosed and treated for TB in the last year. The identified household TB case was the mother for four children, the father for three children, both the mother and father for one child, and other household members for the remaining six. Only one of the 14 (7.1%) TB-exposed children was being treated with isoniazid preventive therapy per caregiver report.

A bacterial pathogen was isolated from blood culture in 5 (3.4%) of the 148 children, 4 had non-typhoidal *Salmonella* and 1 *Staphylococcus auerus,* and 3 (2.0%) had a potential bacterial contaminant (*Staphylococcus epidermidis* was isolated in one sample and *Micrococcus* in two). Fourteen of the mycobacterial cultures (9.5%) were not evaluable for mycobacteria due to overgrowth of bacteria or contamination, 5 (35.7%) of which were from children who had positive

TABLE 1
Characteristics of enrolled children ($N = 148$)

Characteristic	*n* Median (IQR)
Sociodemographic	
Median age (years)	3.1 (1.8–4.1)
Male	81 (54.7%)
Site	
Kisii	72 (48.7%)
Homa Bay	67 (45.3%)
Migori	9 (6.1%)
Monthly household income < 5,000 Kenyan Shilling	72 (48.7%)
Crowding*	65 (43.9%)
Parent/caregiver married	126 (85.2%)
Clinical history	
Household TB†	14 (10.3%)
BCG scar	148 (100%)
Median number of months exclusively breast-fed	6 (4–6)
Currently breast-feeding‡	24 (55.8%)
Hospitalized in the last year	15 (10.1%)
Malaria§	54 (36.5%)
HIV-exposed uninfected‖	20 (14.2%)
HIV-infected¶	4 (2.7%)
HIV-associated immunosuppression**	1 (25%)
Enrolled in care	1 (25%)
Taking cotrimoxazole	1 (100%)
Taking antiretroviral therapy	0 (–)
Clinical presentation	
Any IMCI danger sign	42 (28.4%)
Unable to drink or breast-feed	16 (10.8%)
Excessive vomiting	30 (20.3%)
Convulsions	6 (4.1%)
Lethargy/unconscious	3 (2.0%)
Any pneumonia sign	25 (17.2%)
Chest in-drawing	0 (–)
Stridor in calm child	0 (–)
Fast breathing	25 (17.2%)
Any TB sign	17 (11.5%)
2 + weeks of night sweats	8 (5.4%)
2 + weeks of cough	12 (8.1%)
1 + week of fever	2 (1.4%)
Stunted†† (HAZ < −2)	24 (17.0%)
Wasted‡‡ (WHZ < −2)	26 (18.6%)
Acute malnutrition (MUAC < 12.5 cm)	7 (4.7%)

BCG = Bacille Calmette-Guerin; HAZ = height-for-age z-score; HIV = human immunodeficiency virus; ICMI = Integrated Management of Childhood Illness; IQR = interquartile range; RDT = rapid diagnostic test; TB = tuberculosis; WHZ = weight-for-height z-score.

*≥ 2 people per room living in house.

†Member of household diagnosed or treated for TB in last year.

‡Among 43 children under ≤ 24 months of age.

§Diagnosed by malaria RDT or smear microscopy (54/148 positive by RDT; 52/143 positive by microscopy).

‖Among 141 children who were HIV-uninfected and accompanied by their biological mother.

¶Three out of four children were diagnosed with HIV as part of this study.

**Defined in terms of CD4% (age ≤ 11 months: < 25%, 12–35 months: < 20%, 36+ months: < 15%) or, in absence of CD4% data, in terms of CD4 count (age ≤ 11 months: < 1,500 cells/mm^3, 12–35 months: < 750 cells/mm^3, 36^+ months < 350 cells/ mm^3).

††HAZ less than −6 and greater than 6 were considered to be implausible values and set to missing.

‡‡WHZ less than −6 and greater than 6 were considered to be implausible values and set to missing.

bacterial cultures (2 *Salmonella* O Poly A, 1 *Salmonella choleraesuis,* and 2 *Micrococcus* spp.). No *Mycobacterium* (0%) was identified in the remaining 134 samples (95% CI: 0–2.7%).

DISCUSSION

We did not identify *M. tuberculosis* from the bloodstream of febrile children presenting to several hospitals in western Kenya despite the relatively high prevalence of HIV, *M. tuberculosis*, and malnutrition in this region.[17,21] Several studies in Africa have reported that in acutely ill HIV-infected adults, *M. tuberculosis* bacteremia is common and is found primarily in those with profound immunosuppression and severe illness.[9,10] The lack of *M. tuberculosis* bacteremia identified in children observed in this study is consistent with previous pediatric studies, which have demonstrated the absence or extremely low prevalence of *M. tuberculosis* bacteremia in children.[13–15] Although our study included relatively few children with HIV, a known risk factor for disseminated TB, a recent study in Tanzania also reported no evidence of *M. tuberculosis* bacteremia among 93 HIV-infected infants and children with frequent severe immunosuppression (over 60%) and presenting with severe illness; however, only 25% had fever.[13]

Although young age is a risk factor for the most severe forms of TB, including disseminated TB, available evidence suggests that *M. tuberculosis* bacteremia is uncommon among young children.[4,22] For bacterial bloodstream infections, blood volume and number of samples correlate with yield.[23,24] Therefore, it is possible that *M. tuberculosis* bacteremia is missed in children due to inadequate detection tools and blood volume limits. However, it should be noted that *M. tuberculosis* bacteremia was identified in a number of adult studies that reported inoculation volumes of 5 mL or less.[10,25,26] Children with TB are also more likely to have paucibacillary disease, which, when combined with low blood volumes, may also limit the ability to detect circulating TB.[27] Given these diagnostic limitations, more sensitive methods may be needed to detect *M. tuberculosis* bacteremia in children, although molecular methods have had mixed diagnostic utility in adults.[28–30] Widespread use of BCG vaccine may be another reason why TB bacteremia is rarely seen in children. BCG vaccine has demonstrated protection against TB meningitis and disseminated TB during infancy, but this protection wanes by adulthood.[31–34]

This study had several notable strengths. The inclusion of young, febrile children from areas of high *M. tuberculosis* and HIV prevalence yielded a cohort with plausible risk for *M. tuberculosis* bacteremia. The use of standardized mycobacterial culture techniques in the CGHR laboratory was also a strength. The study also had several limitations. First, we included all children with fever, including those without HIV, malnutrition, or immunosuppression, who may have had lower risk for *M. tuberculosis* bacteremia. However, because the clinical presentation of children with *M. tuberculosis* bacteremia is largely unknown, this nonspecific inclusion criteria could have led to identification of novel signs and symptoms of *M. tuberculosis* bacteremia in children. By excluding children with recent antibiotic use (because of the parent study's goal of identifying bacterial causes of bloodstream infections) we may have excluded some children who were failing antibiotic therapy due to *M. tuberculosis* disease. *M. tuberculosis* bacteremia may be more likely to be detected in a cohort restricted to HIV-infected, immunosuppressed, and febrile children who fail antibiotic therapy.[35] Although 3 mL was the targeted amount of blood to be inoculated, as little as 1 mL was accepted in cases when the volume blood limits prohibited collecting the optimal volume. Actual blood volume collected was not recorded, however, the importance of obtaining 3 mL when possible was emphasized throughout all study trainings. A final limitation is that potentially useful clinical data (such as the presence of lymphadenopathy or hepatosplenomegaly) from the physical examination were not captured, prohibiting reporting these potential indicators of TB in children.

In this study of febrile children in areas of high HIV and TB prevalence, we did not find evidence of *M. tuberculosis* bacteremia. Although children make up as much as 21% of the global tuberculosis burden, detection of *M. tuberculosis* disease remains a major challenge in this population.[36,37] This study adds to the body of evidence suggesting *M. tuberculosis* bacteremia is either very rare or undetectable in pediatric populations. Given the increased risk and high case fatality of disseminated TB in children, more sensitive methods for detection are needed to exclude *M. tuberculosis* bacteremia in children presenting with fever in high TB- and HIV-prevalence settings.

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