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***Mycobacterium tuberculosis* bacteremia in adults and children: A systematic review and meta-analysis**

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SUMMARY

Setting—Among HIV-infected adults living in tuberculosis (TB) endemic settings, *Mycobacterium tuberculosis* (MTB) is a common cause of bloodstream infections. Although children experience an increased propensity for MTB dissemination, MTB bacteremia is infrequently described in children.

Objective—To determine the prevalence of MTB bacteremia in adult and pediatric patients and to examine sources of heterogeneity between estimates.

Design—Systematic review and meta-analysis.

Results—Of 1077 reviewed abstracts, 27 publications met inclusion criteria, yielding 29 independent MTB bacteremia prevalence estimates (22 in adults, 6 in children, and 1 not stratified by age group). The random effects pooled MTB bacteremia prevalence in adults was 13.5% (95% CI: 10.8–16.2%) and in children was 0.4% (95% CI: 0–0.9%) (*p*-value for difference = 0.004). Restricting analyses to HIV-infected participants, pooled MTB bacteremia prevalence from 21 adult studies was 15.5% (95% CI: 12.5–18.5%) and 0.8% (95% CI: 0–1.8%) in 3 pediatric studies (*p*-value=0.001). Inclusion of pre-determined study-level confounders did not account for observed differences in MTB bacteremia prevalence between age groups.

Conclusion—While MTB bacteremia appears relatively common in adults, particularly those with HIV infection, bloodstream MTB appears to be rare in children.

Keywords

Mycobacterium tuberculosis bacteremia; mycobacterial sepsis; systematic review; adults and children

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CONFLICTS OF INTEREST

None of the authors have a commercial or other association that might pose a conflict of interest.

Tuberculosis (TB) remains a leading cause of death globally and HIV-infected individuals are at the highest risk of dying from the disease.¹ HIV-related immunosuppression is associated with poor containment of *Mycobacterium tuberculosis* (MTB) in the lungs, resulting in an increased risk of systemic dissemination.² Children under 5 years old are also at high risk of disseminated MTB disease, with the youngest children suffering from the highest risk of dissemination.^{3, 4, 5} Despite this, MTB bacteremia is reported predominantly in adults, even in high HIV prevalence areas. In HIV-infected adults living in high tuberculosis-burden settings, MTB is one of the most common causes of bloodstream infections with prevalence estimates as high as 20% and case-fatality ratios near 50%.^{6, 7, 8} However in children, including those with HIV, MTB bacteremia is rarely reported.^{9, 10, 11} Recency of Bacille de Calmette et Guérin (BCG) vaccine, limited available blood quantity for culture, degree of immunosuppression, quantity of blood drawn for MTB culture, and stage of TB disease (re-activation vs. primary infection) are hypothesized reasons for the discrepancy in the likelihood of detecting MTB bacteremia between adult and pediatric populations.^{9, 11} We conducted a systematic review and meta-analysis to compare the prevalence of MTB bacteremia in adult and pediatric patient populations and used meta-regression to explore sources of heterogeneity in pooled prevalence estimates between these two populations.

METHODS

Two independent reviewers, PP and EL, conducted a systematic literature review of all articles and conference abstracts presenting data on prevalence of MTB in blood samples from adult (≥ 18 years old) and pediatric (<18 years old) patient populations in longitudinal and cross-sectional studies published between January 1, 1980 and December 31, 2013. Titles and abstracts containing any of the terms ["tuberculosis bacteremia" OR "mycobacteremia" OR "TB bacteremia" OR "bloodstream tuberculosis" OR "disseminated TB" OR "disseminated tuberculosis" OR "tuberculosis bacteraemia"] were identified through MEDLINE and EMBASE searches. Studies were excluded if they included only cases of MTB bacteremia (case reports or case series), did not define the underlying population from which laboratory-confirmed MTB bacteremia cases were drawn, did not perform mycobacterial culture, were not in English, or if the publication was not a primary study (i.e., commentary or editorial). If a population was represented in two citations, we excluded the earlier citation.

Study and patient characteristics were abstracted from each included publication. For CD4 values, we accepted the unit of measure in the study (count, %, or % immunosuppressed based on CD4 % values). Median values of age, blood volume, and CD4 count/percent were abstracted when possible, and mean abstracted when median was not available. Actual collected blood volume was abstracted when available. If blood volume was not reported, the target volume was reported; if a range of volumes was reported, the midpoint was used. Studies were grouped according to the age of the included population (adult or pediatric). In instances when the age grouping differed more than the pre-specified cut-offs (for example a study may have defined "pediatrics" as <13 years rather than <18 years of age), we accepted the study age cut-off for adult vs. pediatric categories. If a given study included both adults and children, MTB bacteremia prevalence was abstracted separately by age-group.

Additionally, we obtained World Health Organization (WHO) estimates of adult TB prevalence and percent BCG vaccine coverage for the year closest to the year of study enrollment.^{12, 13} If the study spanned over a two year period, WHO estimates were abstracted from the first of the two years and if more than two years, the midpoint year was used.

The prevalence of MTB bacteremia overall and in sub-groups of HIV-infected adults and children and 95% confidence intervals estimated assuming a binomial distribution were calculated for each citation. Meta-analyses were conducted to estimate the pooled MTB bacteremia prevalence in the adult and pediatric sub-populations, using fixed effects (weighted on sample size) and random effects when heterogeneity, as determined by $I^2 > 50\%$, was present between studies. Forest plots of MTB bacteremia prevalence were generated and pooled sub-group estimates calculated within adult and pediatric studies. Multivariable meta-regression using log-transformed prevalence estimates was used to test the hypothesis that age-group (adult vs. pediatric) of the study population was associated with heterogeneity in prevalence estimates between studies. Other potential sources of heterogeneity determined a priori (HIV prevalence of study population, average blood quantity drawn, African vs. non-African setting, BCG coverage, and adult TB prevalence estimates) were added stepwise to the model with age-group. Covariates were maintained in the model if the adjusted R^2 value, the between-study variance explained by the covariates, increased from the model including only age-group. Statistical analysis was performed using STATA version 11.2 (StataCorp, College Station, TX).

RESULTS

There were 1077 abstracts reviewed; 896 were identified through MEDLINE, 173 through EMBASE, and 8 through review of reference lists of included studies. The full text of 81 potentially included studies were reviewed and 27 met inclusion criteria (Figure 1).
6, 7, 8, 9, 10, 11, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 Full-text articles that were not primary studies (n=26), did not conduct mycobacterial blood culture testing (n=12), did not clearly define the population in whom mycobacterial blood culture was performed (n=9), contained data that was represented in a second, more recent citation (n=4), and that were not in English (n=3) were excluded. Of the 27 included studies, two included both adults and children and were counted as separate MTB bacteremia prevalence estimates and one study did not present MTB bacteremia prevalence separately by adults and children.^{11, 32, 33} A total of 4632 (3420 HIV-infected) adult and 1076 (545 HIV-infected) children were evaluated for MTB bacteremia prevalence.

The 27 included studies were published between 1989 and 2013 (median: 2003) and the median enrollment periods ranged from 1987–2013 (median 1998) (Table 1). The median BCG coverage and adult TB prevalence in the population corresponding to the study locations and median year of enrollment were 89% (range: 0%–96%) and 0.25% (range: 0.02% to 0.75%), respectively. Study objectives ranged widely, but fell into the two general categories of determining causes and consequences of fever or bloodstream infections (n=16) and evaluating the diagnostic utility of blood for TB diagnosis (n=11). The clinical symptoms and signs for study inclusion varied, ranging from fever alone to chronic fever,

cough, and wasting. Six (22.2%) of the 27 studies were conducted among TB suspects only and of the 22 studies in which admission status was specified, 17 (77.3%) were conducted solely among inpatients. Liquid culture (in 24 of 27 studies [85.2%]) was more common than solid media, with Bactec Myco F/lytic (Becton, Dickinson, and Company, Franklin Lakes, New Jersey, USA) and BacT/ALERT MB (bioMérieux, Durham, North Carolina) bottles most commonly used with Bactec or BacT/Alert 3D continuously monitored blood culture instruments. Duration of culture incubation ranged from 5–10 weeks and further descriptions of the diagnostic methods used in included studies are presented in Table 1.

The adult studies were from sub-Saharan Africa (n=13), south Asia (n=4), South America (n=5), and North America (n=1); all pediatric studies were from sub-Saharan Africa (Table 1). The median ages reported in adult studies ranged from 26–30 years and the ranges varied from 13 to 95 years. The median ages reported in pediatric studies ranged from 1.3–7.4 years, with the youngest at 2 months and oldest at 15 years. In adult studies, the median of median/mean blood volume collected for mycobacterial culture was 10mL (range: 2.5mL–45mL) whereas in children this value was 3mL (range: 1.3mL–5mL). Two studies reported the blood volume adequateness per manufacturer's recommendation.^{8, 9} Nine (39.1%) of the 23 adult studies included HIV-infected participants only whereas only one (16.7%) of the six pediatric studies included HIV-infected children alone. Among HIV-infected study participants, CD4 counts were reported variably, in terms of means and medians, counts and percentages, and either among the entire HIV-infected study population or separated by those with and without MTB bacteremia. Among the 9 adult studies that reported medians or means among the entire study population, the median CD4 count was 87 cells/ul and the lowest and highest values reported in these studies were 1 cells/ul to 1105 cells/ul. The median CD4 count was 62 cells/ul in adult patients with MTB bacteremia (reported in 8 studies) whereas in adults without MTB bacteremia (reported in 7 studies), the median was 104 cells/ul. In pediatric studies, CD4% was presented in two studies (ranging from 6–30%), and % immunosuppressed in a single study, reporting 61.5% to be severely immunosuppressed based on age-specific CD4%. While not reported in pediatric studies, the case-fatality ratio of adults with MTB bacteremia was high, ranging from 25.0% to 72.7%.

Across the 29 separate estimates, the pooled random effects MTB bacteremia prevalence was 11.4% (95%CI: 9.0%–13.8%). There was substantial heterogeneity between MTB bacteremia prevalence estimates within adult (I^2 -statistic 88.5%, p -value<0.001), but not pediatric studies (I^2 -statistic 21.3%, p -value = 0.27) therefore both random and fixed effects meta-analyses were performed. Using fixed effects, the pooled MTB bacteremia prevalence in adult studies was 12.5% (95% CI: 11.5–13.5%) versus 0.7% (95% CI: 0.7–1.4%) in pediatric studies (Figure 2). Using random effects, pooled TB bacteremia prevalence in adults was 13.5% [95%CI: 10.8–16.2%] and in children, was 0.4% [95%CI: 0.0–0.90%]. Restricting analyses to HIV-infected participants (studies that excluded HIV-uninfected participants or that presented results among the subset of HIV-infected participants) did not result in substantially different pooled MTB bacteremia prevalence estimates using fixed effects (adults: 15.5% [95%CI: 14.2%–16.8%]; pediatrics: 0.7% [95%CI: 0–4.8%]) (Figure 3) or random effects (adults: 15.5% [95%CI: 12.5%–18.5%]; pediatrics: 0.8% [95%CI: 0–1.8%] p -value for difference between adult and pediatric studies = 0.001).

In a univariate meta-regression model, age-group (adult vs. pediatric) explained more than 30% (adjusted $R^2=33.8\%$) of the between-study variance in MTB bacteremia prevalence (p -value=0.004). When study HIV prevalence was additionally included in a meta-regression model along with age-group, both were independently associated with variability in MTB bacteremia prevalence (p -value=0.001 and p -value =0.031, respectively; adjusted $R^2=39\%$). However the addition of other potential explanations of between-study sources of heterogeneity, average blood volume (p -value =0.68), % male (p -value =0.66), country-wide adult TB prevalence (p -value =0.17), country-wide BCG coverage (p -value =0.61), and study setting (Africa vs. non-African) (p -value =0.88), did not further explain heterogeneity between age group MTB bacteremia prevalence estimates. CD4 count could not be evaluated because measures of central tendency (mean and median) and units (count and %) differed within and between adult and pediatric studies.

DISCUSSION

The first case reports of MTB bacilli circulating in the bloodstream of patients with a clinical diagnosis of tuberculosis were described in the 19th century when researchers inoculated guinea pigs with blood from these patients.³⁵ Many MTB inoculated guinea pigs demonstrated transient bloodstream MTB, followed by a disappearance, and then a re-appearance of bacilli in the bloodstream up to 6 weeks thereafter. Since that time, researchers have also demonstrated the presence of circulating MTB in the bloodstream of adults and shown a high-risk of death associated with the disseminated disease. However, very rarely is bloodstream MTB described in children. In the present review, we summarized studies published since 1980 reporting the prevalence of MTB bacteremia in adult and pediatric populations. We demonstrated that bloodstream MTB is much more common in adult populations and this finding persisted despite accounting for many study-level factors, including HIV prevalence, average blood volume collected, country-wide TB prevalence and BCG coverage, and year of enrollment. HIV prevalence was the only additional independent predictor of MTB bacteremia, supporting the observation that MTB bacteremia tends to be a condition affecting mostly immunocompromised populations.

The rarity of MTB bacteremia identified in children could reflect a unique pathology of the disease in pediatric compared to adult populations. Recency of the primary infection may make re-activation TB less likely. If sustained and therefore detectable MTB bloodstream infection is a manifestation of re-activation TB, with MTB entering the bloodstream only transiently during primary infection, it follows that MTB bacteremia is more rare in children who have had less opportunity for re-activation. A related explanation is that recency of BCG vaccine may prolong the time to reactivation or prevent the dissemination of the initial infection. It is well-established that BCG vaccine is particularly efficacious against TB meningitis and miliary TB.³⁶ Prior to the 1920's when the BCG vaccine was first tested in humans, case reports of MTB bacteremia included children.^{35, 37} While BCG vaccine likely plays a substantial role in preventing MTB bacteremia in children, there may be circumstances where BCG vaccine may not be given or efficacious. BCG vaccine efficacy is reduced in HIV-infected infants because the vaccine requires a T-cell response.^{36, 38, 39} Concern about disseminated BCG disease among HIV-infected children led to a World Health Organization recommendation that BCG vaccine be avoided in confirmed HIV-

infected infants.^{40, 41} Therefore if BCG vaccination was the sole explanation for why MTB bacteremia is uncommon in children, then it is plausible that MTB bacteremia could still be observed in HIV-infected children who did not receive, or mount a response to, the vaccine.

While blood volume did not emerge as a key predictor of MTB bacteremia prevalence, blood volume likely plays a major role in the likelihood of recovering MTB bacilli from blood samples. The concentration of MTB bacilli in the blood of adults has been shown to be as low as 0.4 CFU/ml.⁴² In children with paucibacillary disease, the concentration of MTB bacilli in the bloodstream may be lower than in adults, thereby requiring a larger quantity of blood to achieve growth.⁴³ The minimum volume of blood required to detect mycobacteria in the bloodstream of children is largely unknown. Increased blood volume is associated with increased sensitivity in bacterial bloodstream infections.^{44, 45} Although not explicitly evaluated in this review, the duration of culture incubation, the number of cultures performed, and the culture media/system used may also have contributed to likelihood of MTB bacilli recovery.^{42, 44, 46}

In addition to age-group, study HIV prevalence was a key predictor of MTB bacteremia prevalence. The inter-relationship between HIV-infection and MTB bacteremia in adults is well-established, and is likely modulated by T-cells as evidenced by the inverse relationship between CD4 count and MTB bacteremia in HIV-infected adults.^{6, 8} However, even in immunocompromised HIV-infected children, MTB bacteremia appears to be very rare.⁹ Among the 1076 children assessed across the included pediatric studies, only eight had culture-confirmed MTB bloodstream infection. All but one of these eight children were HIV-infected, and all presented with a severe illness (AIDS-defining conditions, suspected disseminated TB, or drug resistant TB suspect).^{11, 23, 33} A recent review of cause of death in HIV-infected adults and children found prevalence of TB to be substantially higher in adult than pediatric populations confirming that even in the presence of HIV, adults are more likely to have TB.⁴⁷

Although understanding the difference in risk or identification of MTB bacteremia in adult compared to pediatric populations provokes interesting scientific questions about the immunology and pathogenesis of this disease, in practice, culture-confirmation of MTB bacteremia may not be available when key clinical management decisions need to be made. A mycobacterial culture can take up to 6 weeks to grow, even longer in children with characteristically paucibacillary disease, and recent data suggests that approximately 50% of HIV-infected adults with MTB bacteremia die within 30-days of their hospital presentation.^{6, 8} Ideally, molecular-based methods could be used for such diagnoses but they have not shown great promise in getting quicker results from blood samples due to low sensitivity, even with high volume extraction.^{20, 48} Urine samples may be an alternative; a recent study found that urine Xpert MTB/RIF and urine lipoarabinomannan (LAM) identified 32 (78%) and 27 (66%), respectively, of the 41 MTB culture positive blood samples in a population of HIV-infected inpatient adults in South Africa.^{49, 50} These diagnostic tools using samples from children need to be explored.

The current review was limited by the number of pediatric studies and variability in the inclusion criteria of participants, ranging from suspected sepsis and suspected TB, to fever.

Also, we were limited by varying blood volumes in studies, and variable reporting of true, instead of intended, blood volume collected. With only 6 pediatric studies we were underpowered to detect factors that were driving the significant difference in MTB bacteremia prevalence between the two populations. However, HIV prevalence did emerge as an independent predictor of MTB bacteremia prevalence, which suggests that age and HIV-status are key drivers of likelihood of MTB bacteremia. Larger cohorts of children with equivalent immunocompromise, clinical presentation, blood volumes, and diagnostic methods to adults are needed to determine whether there are biological differences between TB disease progression in these two populations.

Recent commentaries highlight the importance of MTB bacteremia in adult HIV-infected populations and emphasize the need for diagnostic tools.^{50, 51} This review confirms the relatively high prevalence of MTB bacteremia in immunocompromised adults living in high HIV-prevalence settings and demonstrates a low prevalence, with current diagnostic methods, of MTB bacteremia in children. Given the cost, difficulty, and extremely low yield of MTB from blood cultures, current methods of mycobacterial blood culture are unlikely to be informative for TB diagnoses in children. Equipped with better diagnostic tools, probing differences in risk of MTB bacteremia between adult and pediatric populations may provide insight into the pathophysiology of this frequently fatal manifestation of MTB.

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Figure 1.

Flow chart of systematic review of *M. tuberculosis* bacteremia prevalence studies among children and adults worldwide, 1980–2013

i. Abstract identified through MEDLINE (n=896), Embase (N=173), and expert consultation/reference lists (N=8)

Figure 2. Forest plot of MTB bacteremia prevalence estimates (and 95% confidence intervals) by age group using fixed effects meta-analysis weighted by sample size

Figure 3. Forest plot of MTB bacteremia prevalence estimates (and 95% confidence intervals) by age group among HIV-infected participants using fixed effects meta-analysis weighted by sample size

Characteristics of eligible studies of *M. tuberculosis* bacteremia among children and adults worldwide, 1980–2013

Table 1

First Author, Year of publication	Country	Study Enrollment Period	Inclusion Criteria	Sample Size *	Median Age (years)	Age Range (years, IQR)	% HIV-infected	CD4 count (cells/ul) or % among HIV-infected	% Male	% ART at baseline	Blood Quantity for Culture (mL)	Culture Media and System Used for Culture Positivity	Adult TB Prevalence [†]	Country's BCG Coverage (%) [‡]
STUDY POPULATION: ADULTS														
Archibald 1998 ^{1,4}	Tanzania	2005	Admitted to hospital, fever 37.5°C, age 15 years	517	38.0	15–95 (NR)	54.5	NR	54.0	NR	10.0	Myco-Check biphasic mycobacteria bottle, Middlebrook 7H11 agar, heated blood (chocolate), and inhibitory mold agar slants manually monitored for up to 8 weeks. System not specified.	254	88.0
Archibald 1999 ^{1,5}	Thailand	1997	Fever (38°C) within 12 hours of admission to hospital, age 15 years	246	32.0	15–87 (NR)	74.0	NR	69.5	NR	10.0	Myco-Check biphasic bottle, Middlebrook 7H11 agar, heated blood (chocolate), and inhibitory mold agar slants manually monitored for up to 8 weeks. System not specified.	276	99.0
Arthur 2001 ^{1,6}	Kenya	1988–1989; 1992; 1997	TB suspected and/or fever (38°C)	411 ^{\$}	NR	NR	52.1 ^{**}	NR	57.2 ^{††}	NR	2.0–3.0	Kirschner medium manually monitored for up to 6 weeks.	225	46.0
Bacha 2004 ^{1,7}	Brazil	2001–2002	Fever (37.8° C) > 30 days, HIV+, CD4 count < 200 cells/mL, age >18 years	44	33.0	21–59 (NR)	100.0	Mean: 0.058	65.9	11.6 ^{‡‡}	5.0	BacT/Alert mycobacterial bottles or Bactec Myco/F lytic bottles continuously monitored using MB/Bact or Bactec systems, respectively	80	99.0
Bell 2001 ^{1,8}	Malawi	1998	Fever (35.5° C), age 14 years	238	29.0	14–61 (NR)	72.7	NR	42.4	NR	15.0	Bactec Myco F/Lytic bottles and ISOLATOR10 tubes inoculated in a Sept-Check AFB biphasic bottles manually monitored for up to 8 weeks.	400	99.0
Crump 2012 ⁸	Tanzania	2006–2010	Mar 2006–Aug 2008; Admitted with	508	37.4	13.6–104.8 (NR)	46.5	Median: 111 (Range: 1–1105)	56.2	35.6	15.0	BacT/Alert mycobacterial bottles continuously monitored in BacT/Alert	201	89.0

First Author, Year of publication	Country	Study Enrollment Period	Inclusion Criteria	Sample Size *	Median Age (years)	Age Range (years, IQR)	% HIV-infected	CD4 count (cells/ul) or % among HIV-infected	% Male	% ART at baseline	Blood Quantity for Culture (mL)	Culture Media and System Used for Culture Positivity	Adult TB Prevalence [†]	Country's BCG Coverage (%) [‡]
3D Microbial Detection system, Myco/F Lytic bottles manually monitored, & Wampole ISOLATOR10 tubes inoculated onto Middlebrook 7H10 agar manually monitored for up to 6 weeks.														
David 2004 ¹⁹	India	1994–1995	Confirmed or suspected TB	93	36.2	15.0–76.0 (NR)	59.1	NR	88.2	NR	10.0	Lowenstein-Jensen (LJ) and Kirchner's medium manually monitored for 8 and 5 weeks, respectively.	467	99.0
Feasey 2013 ²⁰	Malawi	2011	Fever (38.5° C) and a cough 1 weeks, HIV + adults	104	37.0 ^{\$\$}	NR	100.0	Median: 94 ^{***}	67.0	NR	10.0	Bactec Myco/F lytic bottles manually monitored for up to 6 weeks.	156	99.0
Gilks 1995 ²¹	Kenya	1992	1 month of diarrhea and/or fever and/or cough, clinically wasted, HIV+	48	Men: 24; Women: 31	NR	100.0	Among TB+: Mean: 15 (Range: 0–100)	56.0	NR	8.0	ISOLATOR10 tubes inoculated to Middlebrook 7H10 agar manually monitored for up to 6 weeks.	225	46.0
Gopinath 2008 ²²	India	2005–2006	Suspected TB	79	HIV +: 31; HIV -: 24 ^{\$\$}	HIV+: 20–47 HIV -: 19–34	66.0	Among MTB+: Mean 173.6 (SD: 49.2); Among MTB -: Mean 274.1 (SD: 32.8)	89.0	NR	5.0	BacT/ALERT MB bottles continuously monitored in MB/BacT system.	365	99.0
Grinsztejn 1997 ²⁴	Brazil	1992–1994	HIV+ and Fever, hepatomegaly, splenomegaly, or lung infiltrates	50	35.4 ^{\$\$}	NR	100.0	Among MTB+: Mean: 80 (SD: 110); Among MTB -: Mean: 80 (SD: 90)	86.0	NR	45.0	Sediment form Becton inoculated onto Middlebrook 7H9 biorth and Lowenstein-Jensen media and manually monitored.	116	95.0
Hernandez 2010 ²⁵	Colombia	2006–2007	Suspected TB, HIV+	47	37.0 ^{\$\$}	NR	100.0	NR	88.0	NR	10.0–13.0	Bactec Myco/F Lytic bottle continuously monitored in Bactec 9050 system and Saponin-treated and control WBC were cultured in MGIT 960, Middlebrook 7H9, and Middlebrook 7H11-	57	96.0

First Author, Year of publication	Country	Study Enrollment Period	Inclusion Criteria	Sample Size *	Median Age (years)	Age Range (years, IQR)	% HIV-infected	CD4 count (cells/ul) or % among HIV-infected	% Male	% ART at baseline	Blood Quantity for Culture (mL)	Culture Media and System Used for Culture Positivity	Adult TB Prevalence [†]	Country's BCG Coverage (%) [‡]
TLA and monitored (manually for all but MGT) for up to 8 weeks.														
Heysell 2010 ³³	South Africa	2006–2008	Suspected drug-resistant TB and advanced HIV, prior history of TB, and/or persistent symptoms despite 1 month of drug resistant TB treatment	122	31.5 ^{†††}	NR (27–38) ^{†††}	88.0 ^{†††}	Median: 100 (IQR: 28–190) ^{†††}	56.0 ^{†††}	47.0 ^{†††}	5.0	Bactec Myco/F Lytic bottles continuously monitored in Bactec 9240 system for up to 6 weeks.	753	77.0
Jacob 2013 ⁶	Uganda	2008–2009	Suspected infection with 2 of following: fever (<35.5 or 37.5° C), heart rate >90 bpm, respiratory rate >20 breaths/min, SBP 100mmHg, whole blood lactate concentration >2.5mmol/L, or Karnofsky Performance Scale 40	368	34	27–40 (NR)	100.0	Median: 46 (IQR: 13–128.8)	47.0	23.4	3.0–5.0	Bactec Myco/F Lytic bottles continuously monitored in Bactec 9120 system. Time unspecified.	234	86.0
Lewis 2002 ⁷	Malawi	2000	Fever (37.4° C) or in shock (heart rate >120 bpm and SBP<100mmHg) or afebrile at visit but history of high fever within last 4 days	344	31.5	15–64 (NR)	83.0	NR	44.0	NR	5.0	Bactec 13A blood culture bottles examined manually for up to 8 weeks.	365	83.0
Munseri 2011 ²⁶	Tanzania	2007–2008	Hospitalized with history of cough or fever for 2 weeks, HIV+, age 18 years	258	TB+: 35; TB–: 36	TB+: 22–64, TB –: 18–65 (NR)	100.0	Among TB patients: ^{†††} Median: 44 (range: 1–534); Among patients without TB: Median: 99 (range 2–1016)	33.0	32.6	40.0,\$\$\$	Wampole ISOLATOR tubes inoculated in Lowenstein-Jensen agar manually monitored for up to 8 weeks and Bactec bottles continuously monitored in MB BacT/Alert system for up to 8 weeks.	195	89.0

First Author, Year of publication	Country	Study Enrollment Period	Inclusion Criteria	Sample Size *	Median Age (years)	Age Range (years, IQR)	% HIV-infected	CD4 count (cells/ul) or % among HIV-infected	% Male	% ART at baseline	Blood Quantity for Culture (mL)	Culture Media and System Used for Culture Positivity	Adult TB Prevalence [†]	Country's BCG Coverage (%) [‡]
Oplustil 2001 ²⁷	Brazil	1995–1997	HIV + and 1 of: fever, hepatic and/or spleen enlargement, diarrhea, abdominal pain, weight loss, lymphadenopathy	254	NR	NR	100.0	Among MTB+; Median 0.234 (Range: 0.001 – 0.097)	NR	NR	10.0	Bactec 13A vials manually monitored in Bactec 460TB system for up to 8 weeks.	98	99.0
Rosas 2003 ²⁸	Brazil	1997–1999	HIV+ with CD4+ <200, unexplained fever (38.0° C), age 13 years	111	33.0	NR	100.0	Mean: 0.064 (Range: 0.001 to 20.1)	68.0	69.4	20.0	ISOLATOR10 tubes inoculated to blood agar, chocolate agar, brain-heart infusion, Sabouraud dextrose agar, and Lowenstein-Jensen media and manually monitored for up to 45 days.	91	99.0
Shafer 1989 ²⁹	United States	1997–1998	Suspected TB	59	35 ^{*****}	29–63 (NR)	61.4 ^{*****}	NR	88.9 ^{*****}	NR	16.0	Inoculated Middlebrook 7H11 agar and LJ medium manually monitored for up to 8 weeks.	15	0.0
Ssali 1998 ³⁰	Uganda	1997	Admitted to hospital, fever (38.0° C), age 15–65	305	30.0	15–64 (NR)	76.0	NR	53.0	NR	20.0	Bactec 13A bottles and biphasic brain-heart infusion bottles monitored for 6 weeks. System not described	412	88.0
von Gottberg 2001 ³¹	South Africa	1998–1998	Suspected TB (fever, cough with weight loss, or night sweats 2 weeks)	71	36.0 ^{§§}	18–57	81.7	Mean: 125.7 (Range: 0–818)	56.3	NR	5.0	Bactec 13A bottles in Bactec 460 system manually read for up to 10 weeks.	443	95.0
Waddell 2001 ¹¹	Zambia	1996–1998	HIV+ or suspected HIV+, age >15 years	355	32.0	15–77	96.9	NR	65.0	NR	10.0 (mean 8.3)	Wampole isolator tubes inoculated onto Middlebrook 7H10 and 7H11 agar and manually monitored for up to 8 weeks.	574	81.0
STUDY POPULATION: PEDIATRIC														
Archibald 2003 ¹⁰	Malawi	1998	Newly admitted, TB suspected, age <15	517	2.7	1 month–13 years (NR)	28.0	NR	56.0	NR	3.0	Becton Myco-F-Lytic bottles manually monitored for up to 8 weeks. System not described.	400	97.0

First Author, Year of publication	Country	Study Enrollment Period	Inclusion Criteria	Sample Size *	Median Age (years)	Age Range (years, IQR)	% HIV-infected	CD4 count (cells/ul) or % among HIV-infected	% Male	% ART at baseline	Blood Quantity for Culture (mL)	Culture Media and System Used for Culture Positivity	Adult TB Prevalence [†]	Country's BCG Coverage (%) [‡]
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Gray 2013 ⁹	Tanzania	2010–2011	Age <16 years, HIV +, and 2 of the following: fever (37.5° C), cough 2 weeks, wasting, presence of adult TB case in patient's home, immunosuppression based on CD4 count	91	7.4	0.2–15.7	100.0	Percent severely immunosuppressed: 61.5% ^{††††}	57.1	51.0	Median: 4.1 (range: 1.9–6.7)	BioMérieux Mycobacteria blood tubes continuously monitored in the BacT/Alert 3D Microbial Detection system for up to 6 weeks.	190	99.0
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Grewal 2013 ²³	South Africa	2007–2008	Age 13 years, suspected disseminated TB	35	NR	NR	36.4	NR	NR	NR	NR	Bactec Myco/F Lytic bottles subcultured into Lowenstein Jensen agar and manually monitored for up to 6 weeks.	753	77.0
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Heysell 2010 ³³	South Africa	2006–2008	Suspected drug-resistant TB and advanced HIV, prior history of TB, and/or persistent symptoms despite 1 month of drug resistant TB treatment	8	NR	<12 (NR)	88.0 ^{†††}	Reported for three children: Median: 7%	56% ^{†††}	47.0 ^{†††}	5.0	Bactec Myco/F Lytic bottles continuously monitored in Bactec 9240 system for up to 6 weeks	753	77.0
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Pavlinac 2015 ³⁴	Kenya	2013–2014	Fever (37.5°C) and no antibiotic use (other than prophylactic cotrimoxazole)	148	3.1	0.6–5.4 (1.8–4.1)	2.7	CD4% reported in 1 child: 30%, CD4 count reported in 3 children: Median: 443 (IQR: 384–1389);	54.7	0.0	1.0–3.0	Bactec Myco/F bottles continuously monitored in BD 9120 system for up to 8 weeks.	299	84.0
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Waddell 2001 ¹¹	Zambia	1996–1998	Suspected HIV infection, age <15 years	583	15 months	4 days–15 years	66.4	NR	35.0	NR	1.5	Wampole isolator tubes inoculated onto Middlebrook 7H10 and 7H11 agar and manually monitored for up to 8 weeks.	574	81.0
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STUDY POPULATION: ADULT & PEDIATRIC														
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Dubey 2013 ³²	India	2011–2012	Suspected TB (clinical symptoms)	130	29	5–82 (NR)	0.0	n/a	30.8	n/a	5.0	Ethylenediaminetetraacetic acid anticoagulated tubes continuously monitored in	249	99.0

First Author, Year of publication	Country	Study Enrollment Period	Inclusion Criteria	Sample Size *	Median Age (years)	Age Range (years, IQR)	% HIV-infected	CD4 count (cells/ul) or % among HIV-infected	% Male	% ART at baseline	Blood Quantity for Culture (mL)	Culture Media and System Used for Culture Positivity	Adult TB Prevalence [†]	Country's BCG Coverage (%) [‡]
BacT/Alert 3D system. Time not specified.														

* Of enrolled subjects with MTB bacteremia results available

[†] Per 100,000 population during year closest to the year of study enrollment or midpoint if more than one year (WHO Data Repository)

[‡] BCG vaccine coverage for the year closest to the year of study enrollment or midpoint if more than one year (WHO Data Repository)

[§] 1988–1989: n=19, 1992: n=53, 1997: n=239

^{**} 1988–1989: 42.1% 1992: 57.5%, 1997: 49.4%

^{††} 1988–1989: 59.5%, 1992: 59.1%, 1997: 53.5%

^{†††} Regularly taking ART

^{§§} Mean age

^{***} Among 89 individuals with results available

^{††††} Estimated for entire population (pediatric and adult)

^{†††††} With or without MTB + blood culture

^{§§§§} Patients randomized to get one 40mL draw or two 20mL draws 12–24 hours apart

^{*****} Among TB positive only (n=9)

^{††††††} Severe Immunosuppression defined differently by age: 11 months=CD4 <25%; 12–35 months=CD4% <20%; 36–59 months=CD4% <15%; 5 years=CD4 <200 or CD4% <15%.