Incident Tuberculosis Diagnoses in Children at High Risk for Disease

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We followed 35 children meeting a research definition for
unconfirmed tuberculosis (TB) but in whom a pediatric
pulmonologist did not diagnose or treat TB. After a median fol-
low-up of 16.4 months, most children were not diagnosed with
TB following a comprehensive evaluation. However, 2 were
diagnosed with TB, demonstrating high TB risk (6%; exact 95%
CI, 1%–19%). In some contexts, researchers may wish to sup-
plement these research definitions with clinical decision data
and longitudinal follow-up in order to improve specificity.

Keywords. case definition; diagnosis; pediatric
tuberculosis.

An estimated 400 children die each day of TB [1]. Timely diag-
nosis and treatment are critical to preventing mortality in this
group [2, 3]. However, challenges remain in diagnosing pediatric
TB [4]. Young children are often unable to produce sputum sam-
ples, and microbiological assays have low sensitivity in children
even when sputum is available [5]. This study aimed to trace a
cohort of children who met a standardized research case defini-
tion for unconfirmed TB, but in whom the disease was not diag-
nosed following a comprehensive evaluation. We quantified the
frequency of subsequent TB diagnoses in this group, either due to
existing undiagnosed TB (ie, a missed diagnosis) or incident TB.

METHODS

Context

This work was nested within a pediatric TB diagnostic study in
Lima, Peru [6–9]. From May 2015 through February 2018, the

study enrolled children <15 years of age who presented either
passively, or following household contact tracing, to a Ministry of
Health (MoH) primary-level facility. Eligible children had both
a close adult contact with TB in the previous 2 years and at least
1 TB symptom [10]. Children underwent routine TB diagnostic
procedures per Peruvian MoH guidelines, which include acid-fast
smear and mycobacterial culture of at least 2 respiratory speci-
mens (sputum or gastric aspirate), tuberculin skin testing (TST),
and chest radiography. A single MoH pediatric pulmonologist re-
viewed chest radiographs (frontal and lateral) for each child using
a standardized tool, noted the type and location of any abnormal-
ities, and made a determination of "normal," "abnormal, consistent
with TB," or "abnormal, not consistent with TB." The same pedi-
atric pulmonologist evaluated each case with respect to these re-
sults, exam findings, and clinical and epidemiologic history and
decided whether to treat for TB. Peruvian National TB Program
(NTP) guidelines define a case of probable (ie, bacteriologically
unconfirmed) TB as one in which at least 3 of the following criteria
are met: (1) presence of TB symptoms, (2) exposure to an infec-
tious active TB case, (3) positive TST, (4) chest radiography con-
sistent with TB, and (5) evidence from other supporting exams (ie,
for extrapulmonary TB) [11]. Among children in whom active TB
disease is ruled out, isoniazid preventive treatment is indicated for
those younger than 5 years old with a pulmonary TB contact and
for those 5 to 19 years old who have both a pulmonary TB contact
and a TST result ≥10 mm [11].

Participants

In this substudy, we enrolled children who met the National
Institutes of Health (NIH) research case definition for micro-
biologically unconfirmed pediatric TB [12], but in whom TB
was not diagnosed or treated by the pediatric pulmonary spe-
cialist overseeing the case, and conducted a re-evaluation for
TB disease. NIH case definitions for intrathoracic TB define
a case of unconfirmed pediatric TB as one in which bacterio-
logic confirmation was not obtained and that meets 2 of the fol-
lowing criteria: symptoms or signs suggestive of TB, abnormal
chest radiograph consistent with TB, close contact with a TB
case or immunologic evidence of infection with *Mycobacterium
tuberculosis*, or a positive response to TB treatment. Because
TB symptoms and close contact with an adult with TB were re-
quired for enrollment in the larger diagnostic study, all children
technically met the definition for unconfirmed TB. For the pur-
pose of this substudy, we required that children meet a third
NIH criterion, specifically that their chest radiograph was con-
sistent with TB. This approach aligns with Peruvian NTP pedi-
atric TB case definitions, which require that cases meet at least
3 criteria [11].

Data Collection

From September 2017 to September 2018, following informed consent, we conducted interviews with children and caregivers to determine whether children had experienced persistent TB symptoms in the previous 30 days. Children with symptoms received a chest radiograph. If a pediatric pulmonologist suspected TB based on the radiograph, a sample of sputum (or gastric aspirate if sputum could not be produced spontaneously) was collected for acid-fast smear and mycobacterial culture using BACTEC MGIT 960 (Becton-Dickinson, Franklin Lakes, NJ, USA). Following these procedures and a clinical evaluation, an MoH pediatric pulmonologist, who was not the physician who conducted the initial clinical evaluation, made a diagnostic determination. The pediatric pulmonologist had access to the initial chest radiograph for comparison purposes.

Patient Consent Statement

Written informed consent was obtained from a caregiver; written assent was obtained from children ≥8 years old. The design of the study was approved by the Ethics Committee of the National Health Institute of Peru (Lima, Peru) and the Human Research Ethics Committee of Harvard Medical School (Boston, MA, USA).

RESULTS

Forty-nine children met eligibility criteria (Figure 1). Among them, 5 (10%) could not be located. Of 44 invited to participate, 35 (80%) enrolled. The remaining 9 did not participate due to having moved outside the country (n = 1), time constraints (n = 6), refusal (n = 1), and a recent TB diagnosis (n = 1). The median age (range, interquartile range [IQR]) of the 35 participants was 3.6 (0.8–12.7, 1.8–9.1) years, and there was a median (IQR) of 16.4 (12.2–21.8) months between the initial and follow-up evaluations. Table 1 describes characteristics of those who did and did not participate. The frequency of isoniazid preventive therapy was low in both groups (17% and 8%, respectively). Participants were generally similar to those diagnosed with unconfirmed TB by a study clinician, with the exception that TST positivity tended to be higher among those with an unconfirmed diagnosis (67%, vs 47% among participants).

At the time of re-evaluation, 14 children (40%) had at least 1 symptom of TB and underwent chest radiograph. Of these, 5 (36%) had abnormal chest radiograph findings consistent with TB, including interstitial changes (n = 2), nodular infiltrates (n = 2), calcification (n = 2), and perihilar lymphadenopathy (n = 3). All 5 children had negative smear and culture results. Two of these 5 children, 6% of all those re-evaluated (exact 95% CI, 1%–19%), were diagnosed with TB based on their re-evaluation, one 10 and the other 30 months post–initial evaluation. Both children—a 10-year-old male and an 11-year-old female—had productive cough and unexplained fatigue that had
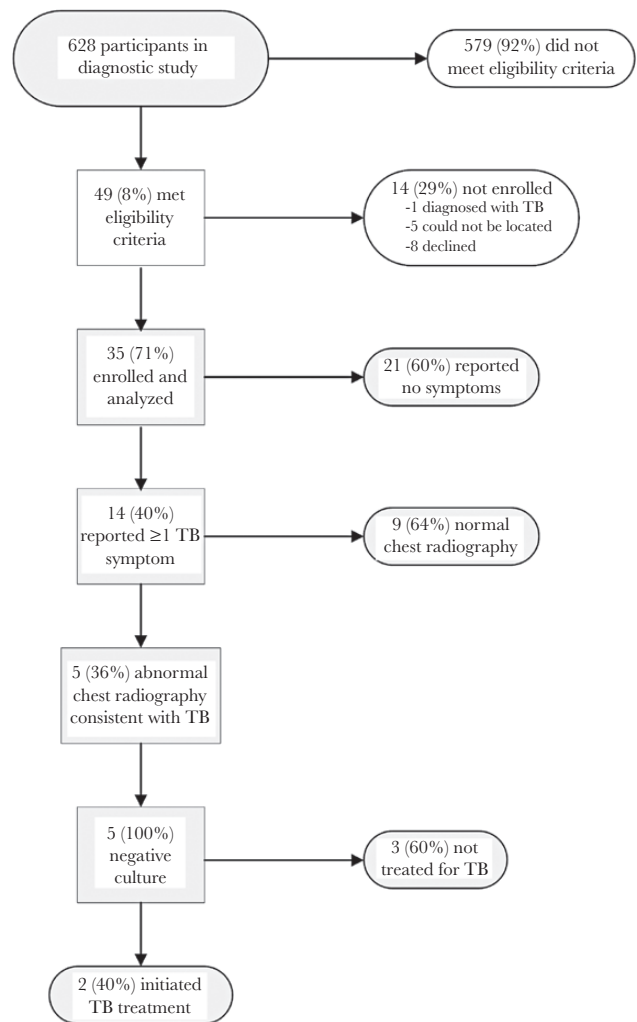

Figure 1. Flowchart of study enrollment and follow-up. Abbreviation: TB, tuberculosis.

resolved after the initial evaluation but then returned. On chest radiograph, 1 had nodular infiltrates and perihilar lymphadenopathy, and the other had calcification and perihilar lymphadenopathy. A pulmonologist from the primary-level health facility discontinued TB treatment in 1 of the 2 children after 1 week and initiated antibiotics for "bronchitis."

DISCUSSION

Our study illustrates a number of practical challenges to diagnosing and researching pediatric TB. The first relates to the application of NIH case definitions. We identified children with TB symptoms, a household contact, and chest radiograph consistent with TB (ie, a case of unconfirmed TB according to NIH case definitions) who were not diagnosed with TB by a pediatric pulmonary specialist. A median of 16.4 months after initial evaluation, TB was ruled out for a second time in the majority of children who were located and screened. This

Table 1.   Descriptive characteristics of participants, non-participants, and children in whom unconfirmed tuberculosis was diagnosed

Characteristic	Participants (N=35)	Non-participants (eligible but not enrolled, N=13)[a]	Unconfirmed TB (N=103)
Age in years, median (IQR)	3.6 (1.8–9.1)	4.0 (1.9–5.2)	4.7 (2.3–8.5)
Age group, n (%)			
0–4 years	20 (57)	9 (69)	52 (50)
5–10 years	11 (31)	3 (23)	42 (41)
11–14 years	4 (11)	1 (8)	9 (9)
Female, n (%)	15 (43)	1 (8)	55 (53)
Symptoms at initial evaluation, n (%)			
fever	2 (6)	1 (8)	13 (13)[b]
weight loss	5 (14)	1 (8)	19 (19)[b]
night sweats	2 (6)[c]	1 (8)	5 (5)[b]
cough	22 (63)	5 (38)	63 (63)[b]
Contact was child's mother, n (%)	13 (37)	6 (46)	32 (33)[d]
BMI, median (IQR)	16.5 (15.7–18.4)	17.5 (17.0–18.6)	16.6 (15.4–18.6)
Socioeconomic score, median (IQR)[e]	−0.40 (-0.81–0.42)	0.44 (-1.57–1.38)	−0.16 (-1.60–1.05)
Positive TST result, n (%)[f,g]	16 (47)	5 (42)	66 (67)
Chest radiography consistent with TB	35 (100)[h]	13 (100)[h]	88 (88)[b]
BCG (self-report), n (%)[i]	26 (96)	12 (100)	93 (98)
HIV, n (%)	0 (0)	0 (0)	0 (0)[b]
Received isoniazid preventive treatment	6 (17)	1 (8)	Not applicable

Abbreviations: BCG, Bacillus Calmette-Guérin; BMI, body mass index; IQR, interquartile range; TB, tuberculosis; TST, tuberculin skin testing.

[a]We excluded from this column the child who did not participate because he was diagnosed with TB.

[b]N=100.

[c]N=34.

[d]N=97.

[e]Based on principal component analyses [18].

[f]N=34, N=12, N=98 for children who did and did not enroll and who had unconfirmed TB, respectively.

[g]Skin reactions with an induration of 10 mm or greater were considered positive.

[h]Required for participation.

[i]N=27, N=12, and N=95 for children who did and did not enroll and who had unconfirmed TB, respectively.

raises the possibility that these case definitions may overcall TB in some settings, which has important implications for the studies using them. When appropriate, investigators may wish to improve specificity by combining these case definitions with data from a clinical evaluation or prescription of treatment. One potential contributor to the observed discrepancies between NIH case definitions and clinical decision-making is that the NIH case definitions were not designed for the setting of active case finding [13, 14], and some of children presented to health facilities following contact tracing activities. Another consideration is that NIH case definitions apply equal weight to each criterion, while clinicians may implicitly or explicitly weigh factors differently or consider factors beyond those noted in case definitions (eg, access to care). Future work could build on these research case definitions to expand their use in different contexts (eg, active case finding). Weighting of criteria and differentiation between an absence of data vs the explicit absence of a finding are just 2 potential pathways that could be explored to optimize performance in different settings.

A second important finding is that while most children did not have TB on follow-up, 2 (6%) were diagnosed with TB as a result of the study's active follow-up, suggesting either missed diagnoses or incident TB. Our small sample size resulted in wide 95% CIs, indicating that this frequency may be anywhere from 1% to 19%. If we count the third child who was eligible for enrollment but not enrolled because he was diagnosed with TB after the initial study evaluation but before our active follow-up, the frequency of TB in this group was 8% (3/36; 95% CI, 2%–22%). Thus, children who meet the NIH case definition for unconfirmed TB are at high risk for TB and should be closely monitored even if TB is initially ruled out. Of note, a sizable proportion (27% (13/49)) of children eligible for inclusion could not be located or their caregivers declined to participate. On the whole, participants and nonparticipants were similar; however, if nonparticipants had a risk of TB that was higher or lower than those who were enrolled, results would be biased.

Last, we highlight the child diagnosed at follow-up, but in whom TB treatment was suspended after 1 week by a different pulmonologist. This scenario exemplifies the uncertainty of diagnosing TB in the absence of an accurate test, even among experienced specialists. Inter-rater reliability of chest radiography readings is suboptimal [15], and hesitation and conflicting diagnostic opinions among health providers may lead to delays in prescribing effective treatment [16], including IPT. Appropriately, providers may hold off on IPT if there

is uncertainty about whether a child has TB. In our cohort, this was evidenced by a lower frequency of IPT among these children relative to a programmatic cohort in Lima, Peru, from the same time period [17].

A limitation of this study is that were unable to determine whether new TB diagnoses were initially missed or represent incident TB. A second limitation is the lack of additional follow-up among children enrolled in this substudy who were not treated for TB, including the 1 in whom TB treatment was discontinued. Data were collected as part of a research study and within a well-functioning NTP; children had access to pulmonologists and a broad range of diagnostic tools, including liquid culture, gastric aspiration, chest radiography, and tuberculin skin testing. Therefore, these results may represent a "best case" scenario in which a relatively small percentage of TB cases would be expected to have been missed. In the absence of an accurate diagnostic tool for TB, regular longitudinal monitoring of children at high risk will be essential to prompt diagnosis and treatment.

Acknowledgments

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