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UNDERSTANDING NIH CLINICAL CASE DEFINITIONS FOR PEDIATRIC INTRATHORACIC TB BY APPLYING THEM TO A CLINICAL TRIAL

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Abstract

Setting and Objective—Currently, standardized clinical case definitions represent the best option for pediatric tuberculosis (TB) disease diagnosis and classification. We applied clinical case definitions for intrathoracic TB classification, developed by an expert panel for use in reporting diagnostic studies with passive case finding, to TB suspects from IMPAACT P1041, a trial of INH prophylaxis in healthy HIV-exposed, BCG vaccinated infants which employed active surveillance, to assess novel application of these guidelines in this setting.

Methods—P1041 TB suspects were retrospectively cross-classified by protocol-defined and NIH classifications and agreement assessed.

Results—Of 219 TB suspects, 166 had signs/symptoms (S/S), with 158 considered TB (21 confirmed, 92 probable, 45 possible) and 8 not TB (6 TB unlikely, 2 alternative diagnoses). Weight loss and failure to thrive represented the majority of observed S/S. Among those with S/S,

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agreement between definitions was poor. Additionally, 53 TB suspects were without S/S, including 33 classified by the P1041 protocol as TB.

Conclusion—The poor agreement between P1041 and NIH classifications reflects cases that are identified through active versus passive surveillance, the latter reflecting the intended use of NIH definitions. Given the interest in having standardized definitions for broader application, future efforts could focus on expanding TB disease classification for detection and classification of suspects identified through active surveillance.

Keywords

mycobacteria; guidelines; children

INTRODUCTION

Establishing a diagnosis of tuberculosis disease (TB) is challenging in children and is a major priority for pediatric TB research. Due to current lack of sensitive diagnostic tools, standardized clinical algorithms and case definitions represent the best available option for TB classification in children without microbiologically confirmed disease, which constitutes the majority of cases. Several guidelines and publications emphasize the usefulness of presenting symptoms for TB diagnosis. Marais' symptom-based approach, however, performed less well in HIV-uninfected children <3 years of age compared to older children. Their approach excluded a small percentage of HIV-infected children whose symptoms were of a shorter duration. Consensus clinical case definitions for use in reporting evaluation of TB diagnostics research in children were published following an NIH-sponsored workshop that convened an international expert panel (hereafter referred to as NIH classifications). They focus on diagnostic studies in children under 10 years of age with signs or symptoms (S/S) suggestive of intrathoracic TB, the most common manifestation of TB in children (approximately 75% of cases). Standardized case definitions for intrathoracic TB are important in clinical research and will also be highly valuable when evaluating results across studies. With interest in assessing the applicability of the NIH classifications to different research settings, such as in the context of active surveillance for TB, we retrospectively applied the NIH classifications to TB cases from a TB prevention trial. We assessed agreement between the NIH and protocol classifications and to describe the nature of the differences.

DESIGN

IMPAACT P1041 was a multi-center, Phase II-III, randomized, double-blind, placebo-controlled trial evaluating primary INH prophylaxis in healthy, bacille Calmette-Guérin (BCG) vaccinated, 3 to 4 months old infants. P1041 enrolled 804 HIV-exposed, uninfected and 547 HIV-infected infants who were followed for up to 4 years. Scheduled visits were quarterly for the first two years for all infants but were reduced to 6-monthly in years 3–4 for those HIV-exposed, uninfected. At each scheduled or unscheduled sick visit, participants were screened for TB exposure and signs and symptoms (S/S) of TB, using a score-based algorithm derived from South African guidelines to screen for and diagnose TB (Table 1). Participants with a score of 4 or more (excluding the tuberculin skin test (TST) were

evaluated further by means of a TST, chest radiograph (CXR) and sputum for microbiological confirmation. Participants were classified as definite, probable, possible, not TB or latent TB according to a protocol pre-established TB case definition (Table 2) and after review and adjudication by a blinded Endpoint Review Group (ERG). The ERG added an additional category 'not protocol-defined TB' to categorize symptomatic patients initiated on TB treatment by health care providers but not meeting protocol definitions of TB.

Classification of TB endpoints using NIH classifications

We retrospectively reviewed the database for all potential intrathoracic TB cases reported by the study sites and reviewed by the ERG and classified cases using the NIH classifications. The aim of this study was to cross-classify potential intrathoracic TB cases in the P1041 cohort with the NIH classifications and estimate agreement between these classification schemes in order to understand the differences and applicability of the NIH classification to an active surveillance research setting. Table 2 shows the P1041 and NIH definitions used. Of note, because this was a retrospective study, requirements for NIH criteria could not be evaluated precisely and divergences in application to the P1041 data set are outlined in Table 3. The following diagnostic components included in the NIH definitions were assessed for each suspected TB case: microbial confirmation, clinical S/S suggestive of TB (persistent cough, weight loss/failure to thrive (FTT), persistent unexplained fever, persistent unexplained lethargy or reduced playfulness), interpretation of CXR, TB exposure, immunological evidence of *M. tuberculosis* (*M. tb*) infection, and response to anti-TB treatment. An additional aim was to describe those not classified by the NIH classifications.

Statistical Methods

Kappa statistics were used to estimate the agreement between the NIH and P1041 definitions for both the 5-category classification scheme and the binary TB vs. not TB classification, overall and by HIV status, after excluding those without S/S.

Discrepancies were examined to identify and understand how the NIH classification may apply to the active surveillance setting.

Frequencies and percentages of cases with each of the key diagnostic criteria included in the NIH classifications, with the addition of acid fast bacilli smear (AFB) results, were reported. Incidence of TB based on the NIH classifications was calculated overall and by HIV status (see Supplementary appendix). Among HIV-infected cases, the frequency and percentage on antiretroviral (ARV) drugs and the mean duration of ARV use were reported.

Study Oversight

The study was approved by the institutional review board of each site, the Medicines Control Council in South Africa, and the Division of AIDS and NIAID as documented in the original study. Good Clinical Practice Guidelines and the Declaration of Helsinki were followed. Written consent was obtained from the legal guardians of the children prior to randomization.

RESULTS

Classification of P1041 TB suspects reviewed

Of the 219 TB suspects in P1041, 148 cases were classified as TB and 71 as non-TB. Of the 148 TB cases, 24 were definite, 18 probable, and 106 possible TB. Of the 71 non-TB cases, 64 were 'not protocol-defined TB' and 7 had alternative diagnoses. One-hundred and sixty-six of 219 had TB S/S (Table 4).

Agreement between P1041 definitions and NIH classifications

Table 4 shows the cross-classification of the NIH and P1041 definitions as applied to the 219 potential TB cases in P1041. We excluded 53 (24%) without S/S in our assessment of agreement. Of the 166 children with S/S evaluated by the ERG, NIH criteria classified 21, 92, and 45 as confirmed, probable, and possible TB, respectively, and 6 and 2 as TB unlikely and 'not TB', respectively. Of the 166, P1041 classified 21, 15, and 79 as confirmed, probable and possible TB, respectively, and 44 and 7 as 'not protocol-defined TB' and alternative diagnosis, respectively. The Kappa-statistic showed poor agreement with an estimate of 0.07 (95% confidence interval (CI): -0.02, 0.16) for the 5-category classification and 0.17 (95% CI: 0.05, 0.29) for the TB vs. not TB classification. Twenty-one cases were classified as confirmed TB by both criteria. Ninety-three cases were classified as probable or possible by both P1041 and NIH criteria, with the latter ten times more likely to designate as probable. Of 44 P1041 not protocol-defined TB cases, 39 were NIH probable/possible. Of 7 cases with alternative diagnoses in P1041, 5 were probable/possible TB by the NIH classification. When the NIH classification designated a child as having TB but P1041 did not (44 children), 34 (77%) had CXRs consistent with TB, 14 (32%) were TST+, 10 (23%) were TB exposed, and 4 (9%) responded to TB treatment.

Table 5 lists the prevalence of criteria comprising the NIH classification overall and within each TB diagnostic category for classifiable patients. Twenty-one cases (13%) were culture positive for *M. tb*, and all were classified as having TB. Overall, the weight/FTT criteria accounted for the vast majority of the observed S/S, with cough, fever, and lethargy adding less than 1%. Eighty-three percent of potential cases had CXRs consistent with TB, the most common finding being soft tissue density suggestive of lymphadenopathy (perihilar, paratracheal or subcarinal) alone followed by the combination of suggestive soft tissue density and airspace disease. TST was positive in 56%, and response to anti-TB treatment was documented in only 23 (14%) cases. AFB smear results were positive in 17% of potential cases.

AFB smear results

Among participants with S/S, 29 cases were acid fast bacilli smear positive (AFB+). Of these, 10 (34%) were definite TB (culture-confirmed), 8 probable TB, 8 possible TB, and 3 'not protocol-defined TB', and with none categorized as 'not TB' by NIH criteria. Of the 3 AFB+ cases designated as 'TB unlikely' by NIH criteria, all had FTT but no other criteria contributing to a TB diagnosis.

HIV status

When stratifying TB classification by HIV status, agreement was higher among the 74 in the HIV-exposed, uninfected group than among the 92 in the HIV-infected group for the 5-category classification scheme (Kappa=0.14 vs. 0.00, respectively) but was similar for the binary classification scheme (Kappa=0.15 vs. 0.18, respectively).

Of the 92 cases among HIV-infected participants, 62 (67.4%) were taking ARVs at the time of TB endpoint. Of those on ARVs, the average length of time on treatment prior to TB diagnosis was 6.5 months. Among HIV-infected participants agreement between the two classification schemes was not better among those on ARVs than those not receiving ARVs (Kappa= -0.02 vs 0.03, respectively).

Cases without TB Signs/Symptoms

Of the 219 potential cases retrospectively reviewed, 53 (24%) did not have S/S suggestive of TB as defined by the NIH classifications. Of the 53 reviewed without S/S, the P1041 ERG also rejected 20 as 'not TB'. Of the 33 that were considered TB by P1041 criteria: three had a positive culture, with two also having a CXR suggestive of TB, while the third had a negative CXR but had documented TB exposure. All three of the P1041 probable cases without S/S were AFB positive (required), and had a CXR suggestive of TB and documented TB exposure; 2 of the 3 were also TST+. Of the 27 P1041 possible cases without S/S, all had a CXR suggestive of TB (required) and in addition, 8 were both TB exposed and TST+, and 18 were either TB exposed or TST+ but not both. Of the 20 P1041 TB unlikely cases, 12 met at least two TB diagnostic criteria shown in Table 5, while 8 met fewer than 2. (See supplemental appendix Table 6)

By expanding the diagnostic evaluation to include exposure in the absence of S/S, 23 of these would have been classified as TB cases, including 14 classified as TB and 9 classified as TB unlikely in P1041.

DISCUSSION

We observed poor agreement in classification of TB suspects between NIH classifications intended for reporting diagnostic studies with suspects identified through passive surveillance and study-specific criteria in the P1041 study which used active surveillance, much of it accounted for by differing application of S/S, CXR and AFB. Among those with S/S, NIH classifications on average gave diagnoses a higher certainty level. When categorizing suspects by whether they were classified as TB or not, agreement improved but remained poor.

While many researchers have misinterpreted the consensus recommendations to require strict symptom entry criteria, even with the application of broad symptoms entry criteria as they intended, some children with microbiologic confirmation of *M.tb* without symptoms or with less persistent symptoms than defined may be missed in the active surveillance setting.

Notably, of the potential pulmonary TB cases retrospectively evaluated using the NIH classifications, we found that 53 (24.2%) did not have well-defined S/S suggestive of TB.

With active surveillance, prolonged symptoms such as cough may not be observed, noted by the WHO guidelines for infants whose symptoms may be more acute. In a study by Jeena et al, 43% presented with symptoms of less than 10 days duration, seen equally in HIV-infected and HIV-uninfected children. Marais et al. found that those who were actively screened based on household contacts were less likely to be symptomatic and may represent infection rather than disease. Furthermore, data from the pre-chemotherapy era suggest that many ostensible cases of *M.tb* identified shortly after TB exposure without symptoms may represent TB infection with transient excretion of *M.tb* bacilli rather than active TB disease. Although still subject to debate, caution may dictate that such infants be managed as having TB disease. A recent publication by Wiseman et al in which the NIH case definitions were applied to a contact investigation study, indicated that asymptomatic patients with bacterial confirmation of TB represent a continuum of disease that do warrant further evaluation. CXR while useful for diagnosing intrathoracic TB, is limited by poor inter-rater agreement. Refinement of NIH definitions to be sensitive to early disease might warrant consideration. An ability to classify disease in these children would be helpful for earlier treatment with better treatment outcomes, and may be more applicable to patients followed closely on clinical trials.

As with studies evaluating TB diagnostics, TB studies in children with TB disease outcomes urgently need harmonized clinical case definitions and data harmonization. A number of papers highlight difficulties in comparing results across studies.” Whether the NIH definitions can be broadened to be applicable to settings of clinical research with active surveillance requiring it to capture a wide spectrum of TB disease requires expert consideration.

We found that weight loss and FTT accounted for the vast majority of observed signs/symptoms and that diagnosis of FTT was somewhat sensitive to the interpretation of the definitions. For future studies, it will be important to understand the role of using weight as a driving force in defining tuberculosis, particularly in light of type of observation (active vs passive). The possibility of malnutrition secondary to other diseases, including HIV, also a consideration in many high TB burden countries.

The rate of response to TB treatment was lower than expected and was likely underestimated as it was not captured prospectively as part of P1041 original endpoints. P1041 recorded resolution of TB diagnoses but not improvements short of resolution, and FTT was primarily captured through changes in anthropometric measurements especially since the extent of FTT is less likely when disease is diagnosed earlier. The limited availability of data on TB improvement and the relatively short window (3 months) for observing TB resolutions may have contributed to the low response to treatment rate as noted in a recent study.

This study includes a number of limitations. While P1041 clinical criteria were prospectively captured, retrospective application of NIH classifications to the P1041 database required some adaptation (Table 3). Because of the retrospective nature of this study we were only able define signs/symptoms criteria based on what was captured in the data base (fever >1 week, cough >2 weeks, etc.) which did not capture nuances such as whether they were persistent and therefore entry and classification criteria were not

distinguishable. Our need to adapt the NIH criteria for this evaluation highlights the usefulness of harmonization of data collection across all TB studies that include diagnosis. Moreover, children who would have been evaluated by NIH criteria but not evaluated by the P1041 study could not be identified.

The TB suspects studied here may represent a broader spectrum of TB disease, particularly less severe disease compared to what would be observed under passive surveillance. Had passive surveillance been employed, some of the children who did not have S/S as defined by the NIH classification criteria or who were classified as not having TB may have eventually met the NIH TB definition. While the NIH classification scheme was not intended for use in active surveillance, this work provides insight into the domains in which definitions need to be expanded in order for them to be applicable to that setting.

CONCLUSIONS

Poor agreement in protocol and NIH classifications for children evaluated for TB in the P1041 study, including a substantial proportion of infants investigated for TB without sign/symptoms highlight differences in their intended uses but provides insight into how the definitions could be expanded for use in active surveillance. Revisions or additions to NIH classifications that allow for harmonized definitions for use in both passive and active surveillance could be beneficial to TB researchers. While a single set of broadly applicable definitions is desirable, distinct definitions for passive and active monitoring might be warranted. Criteria for categorizing TB disease in studies employing active surveillance, such as TB contact investigations or prevention trials, will need to be less restrictive to capture the broad continuum of TB disease presentation and severity, including microbiologic confirmation without symptoms or with acute symptoms of short duration that would likely be observed with active surveillance. As with TB disease classification for use in diagnostic studies with passive case finding, harmonized data collection will be critical for active surveillance settings to facilitate the conduct of high quality meta-analyses across studies and for applying revised definitions as new evidence comes to light.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Algorithm for screening and diagnosing clinical tuberculosis during IMPAACT P1041^{*}

Feature	Score			
	0	1	2	4
Weeks of illness (including cough)	<2	2–4		
Nutrition (% weight for age)/malnutrition	>80%	60–80%	<60%/drop 2 lines	>4
Family history of TB	None	Reported by family		Sputum proven
Tuberculin skin test [†]				Reactive [†]
Fever not responding to treatment for >2 weeks			X	
Confirmed or suspected extrapulmonary tuberculosis				X

^{*}The South African National Tuberculosis Control Programme Practical Guidelines, 2004, Study participants with a score of 4 or more (excluding the tuberculin skin test) during screenings at their routine visits every 3 months were screened further by means of a tuberculin skin test and a chest radiograph.

[†]Reactive TST is defined as ≥ 5 or ≥ 10 mm for HIV-infected and HIV-uninfected, respectively.

Table 2

NIH and P1041 TB classification definitions and correlation as listed

NIH definitions and classification of TB endpoints	P1041 protocol-defined classification of TB endpoints
Confirmed TB cases will be children with at least 1 sign or symptom* suggestive of TB and microbiologically confirmed TB, defined as at least 1 positive culture with <i>M. tb</i> speciation from a specimen representative of intrathoracic disease.	Definite Pulmonary TB cases must have <i>M. tb</i> isolated on gastric washing and/or induced sputum.
Probable TB cases will include children with at least 1 sign or symptom suggestive of TB and a chest radiograph (CXR) consistent with intrathoracic TB and at least 1 of the following: (1) positive clinical response to anti-TB therapy, (2) documented exposure to a household or close contact with a TB case, or (3) immunologic evidence of infection with <i>M. tb</i> infection by a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA).	<p>Probable Pulmonary TB cases must have positive AFB (auramine fluorochrome, most commonly used in South Africa, or Ziehl Neelson (ZN)) stain on a specimen obtained by gastric washings or induced sputum in a child who fulfills at least one of the following:</p> <p>1 Presence of at least 2 clinical criteria:</p> <ul style="list-style-type: none"> • Cough > 2 weeks duration • Family history of PTB in the prior 24 weeks • Reactive TST (>5 mm in an HIV +, >10 mm in HIV-) • Weight <3rd percentile for age or a decrease in weight that has crossed 2 major growth percentiles since the last documented weight • Fever of unknown origin >2 weeks duration <p>OR</p> <p>2 Abnormal chest x-ray with at least one of the following:</p> <ul style="list-style-type: none"> • Hilar lymphadenopathy • Paratracheal lymphadenopathy • Alveolar consolidation • Miliary pattern • Lung parenchymal breakdown/cavitation • Ghon focus
Possible TB cases will include children with at least 1 sign or symptom suggestive of TB and who have either: (1) a CXR that is consistent with intrathoracic TB or (2) at least 1 of the following: (a) positive clinical response to anti-TB therapy, (b) documented exposure to a household or close contact with a TB case, or (c) immunologic evidence of infection with <i>M. tb</i> (TST or IGRA positivity).	<p>Possible TB cases will have both:</p> <p>1 Abnormal chest x-ray (see criteria above)</p> <p>2 One of the following:</p> <ul style="list-style-type: none"> a. Positive TST (≥ 5mm in HIV-infected and ≥ 10 mm in HIV-uninfected), OR b. Scores ≥ 6 on the algorithm to diagnose clinical TB (see Table 1)
Tuberculosis unlikely cases are symptomatic but not fitting the above definitions and no alternative diagnosis established.	See footnote ** Not protocol defined TB or clinical TB
Not tuberculosis cases fit the diagnosis for tuberculosis unlikely but with an established alternative diagnosis.	Not TB are those cases evaluated for TB but with an established alternative diagnosis. Latent TB infection are those cases have positive TST (as defined above) but do not meet any of the above definitions. ***

* **NIH: Clinical signs/symptoms suggestive of TB (i.e. entry points/criteria):**

- A.** Persistent (>2 weeks), nonremitting cough.
- B.** Weight loss/failure to thrive: unexplained weight loss: >5% reduction in weight compared with the highest weight recorded in last 3 months, or failure to thrive: Clear deviation from a previous growth trajectory and/or documented crossing of 1 or more major percentile lines in the preceding 3 months and/or weight-for-age z score of -2 in the absence of information on previous/recent growth trajectory and/or weight-for-height z score of -2 in the absence of information on previous/recent growth trajectory and not responding to nutritional rehabilitation (or antiretroviral therapy if HIV-infected).

- C. Persistent (>1 week), unexplained fever (>38°C) reported by a guardian or objectively recorded at least once.
- D. Persistent, unexplained lethargy or reduced playfulness reported by the parent/caregiver.

Not protocol defined TB cases are those cases that were evaluated by the P1041 ERG but did not meet protocol defined definitions of TB. These cases were prescribed anti-TB therapy by an attending physician who was not a member of the study team.

Note, we will not evaluate LTBI cases that were determined at week 96 or beyond, because these were not TB suspects. They have a diagnosis based on TST done per protocol schedule of evaluations rather than due to clinical suspicion of TB disease.

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Table 3

Diagnostic components included in NIH definition and corresponding criteria applied to the P1041 data base

Diagnostic components	Summary of NIH definitions	Criteria applied to P1041 data base
Microbiologic confirmation	At least one positive culture (with confirmed <i>M. tb</i> speciation) from sputum	At least one positive culture, defined as <i>M. tb</i> isolated on gastric washing and/or induced sputum
Clinical signs and symptoms suggestive of tuberculosis ¹	Persistent cough (>2 weeks, unremitting)	Any cough (>2 weeks) present at TB diagnosis
	Persistent unexplained fever (>1 week, >38°C)	Any fever (>1 week) present at TB diagnosis
	Persistent, unexplained lethargy or reduced playfulness	Any lethargy present at TB diagnosis
	Unexplained weight loss >5% reduction in weight compared to the highest weight recorded in the last 3 months	Any weight loss >5% reduction in weight compared to the highest weight recorded in the last 3 months, assessed at TB diagnosis or closest prior visit within 3 months. ¹
	One of following indicators of FTT: (1) clear deviation from a growth trajectory, (2) documented crossing of percentile lines in preceding 3 months, (3) weight-for-age z-score -2 in the absence of previous/recent growth trajectory or weight-for-height z-score -2 in the absence of previous/recent growth trajectory. In addition, not responding to nutritional rehabilitation (or ARV if HIV infected).	One of the following: (1) documented diagnosis of FTT present at TB diagnosis, (2) weight-for-age or weight-for-height that crossed one major percentile line (3, 10, 25, 50, 75, 90, 97) within a 3-month period, recorded in the preceding 3 months ¹ , (3) weight-for-age z-score or weight-for-height z-score -2 in the preceding 3 months. ¹ Data on response to nutritional rehabilitation was not available.
	Additional signs and symptoms suggestive of TB for infants 0–60 days include (a) neonatal pneumonia, (b) unexplained hepatosplenomegaly, or (c) sepsis-like illness	Data not available. All infants in P1041 were at least 91 days of age at enrollment.
Interpretation of CXR	CXR reading and reporting procedure: minimum of 2 independent and blinded readers, a third expert reader in case of discordant reading, overall quality of CXR indicated, and standardized forms. CXR is classified as “consistent with tuberculosis” if there is a positive response for any 1 of the following radiographic features at the same location, by at least 2 expert reviewers: airway compression and/or tracheal displacement, soft tissue density suggestive of lymphadenopathy, air space opacification, widespread bilateral nodular picture, either miliary or larger lesions, pleural effusion, cavities, ghon focus, or vertebral spondylitis.	CXRs not required to be read by more than one reader. Acceptable quality of CXR indicated. Positive response for any 1 of the following radiographic features: airway compression and/or tracheal displacement, soft tissue density suggestive of lymphadenopathy, air space opacification, widespread bilateral nodular picture, either miliary or larger lesions, pleural effusion, cavities, or ghon focus, within 3 months of TB diagnosis.
Tuberculosis exposure	History of exposure to <i>M. tb</i> was defined as reported exposure to a case of TB (household/close contact with documented or verbal report of smear positive and/or culture positive TB or TB treatment), within preceding 24 months	Reported exposure to a case of TB (household or non-household contact with a positive TB result or receipt of TB treatment), within preceding 24 months.
	Immunologic evidence of <i>M. tb</i> infection was defined as either (1) a positive tuberculin skin test (using 5TU PPD or 2TU RT23) defined as ≥10 mm if HIV uninfected or ≥5 mm if HIV-infected or severely malnourished or (2) a positive IGRA test	TST of ≥10 mm for HIV-uninfected or ≥5 mm for HIV-infected or severely malnourished patient, within 3 months ¹ of TB diagnosis. IGRA testing was not conducted as part of the diagnostic work up for TB in P1041.
Response to anti-tuberculosis treatment	Appropriate anti-TB treatment should meet the following criteria: treatment with standard regimens in accordance with local or international treatment guidelines and satisfactory adherence proposed as 80% adherence by pill count or self-reported. Response to anti-TB treatment should be evaluated at 2 months after anti-TB treatment has commenced using standardized forms with tick-box options for recording. Response to anti-TB therapy was defined as clinical features suggestive of TB disease that were present at baseline have improved, and there is no new clinical feature suggestive of TB.	TB patients in P1041 were not evaluated specifically for response to anti-TB treatment, as described in the NIH consensus guidelines. Response to treatment was based on resolution of sign/symptoms, diagnoses and changes in anthropometric measurements. A positive response to anti-tuberculosis treatment was defined as 1) resolution or improvement in all clinical signs/symptoms (as defined above) that contributed to the TB diagnosis or documentation that TB diagnosis resolved within 3 months ¹ after

Diagnostic components	Summary of NIH definitions	Criteria applied to P1041 data base
		treatment initiation, and 2) no new clinical signs/symptoms within 3 months ¹ after treatment initiation. Data on adherence to anti-TB treatment was not available.

¹ A 4-week allowance was added to the 3 month windows during which S/S and response to anti-TB treatment were evaluated for consistency with the P1041 study visit schedule and to allow for late visits.

Table 4

Cross-classification of P1041 and NIH consensus definition event certainties

		NIH Classification							
		TB disease			No TB disease				
		Confirmed	Probable	Possible	Unlikely	Alternative diagnosis			
P1041 Classification	TB disease	Confirmed	21	0	0	0	0	21	3
		Probable	0	7	7	1	0	15	3
		Possible	0	71	8	0	0	79	27
	No TB disease	Unlikely	0	13	26	5	0	44	20
		Alternative diagnosis	0	1	4	0	2	7	0
		Total	21	92	45	6	2	166	53

¹Those lacking signs or symptoms are not classifiable by the NIH criteria.

Table 5

TB diagnostic criteria by NIH classification of intrathoracic TB disease for those with NIH signs or symptoms suggestive of TB

TB disease characteristic	NIH classification							Total (N=166)	P-Value ¹
	Confirmed TB (n=21)	Probable TB (n=92)	Possible TB (n=45)	Sub-total TB (N=158)	TB unlikely (n=6)	Alternative Diagnosis (n=2)	Sub-total Not TB (N=8)		
Culture positive	21 (100%)	0 (0%)	0 (0%)	21 (13%)	0 (0%)	0 (0%)	0 (0%)	21 (13%)	0.60
Persistent cough (>2 weeks)	0 (0%)	0 (0%)	2 (4%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	>0.999
Persistent fever (>1 week)	0 (0%)	0 (0%)	2 (4%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	>0.999
Lethargy	0 (0%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	>0.999
Any weight-related symptom ²	21 (100%)	92 (100%)	43 (96%)	156 (99%)	6 (100%)	2 (100%)	8 (100%)	164 (99%)	>0.999
Weight loss >5%	3 (14%)	4 (4%)	5 (11%)	12 (8%)	0 (0%)	0 (0%)	0 (0%)	12 (7%)	>0.999
Met at least one definition of FTT ³	21 (100%)	92 (100%)	43 (96%)	156 (99%)	6 (100%)	2 (100%)	8 (100%)	164 (99%)	>0.999
Crossed at least 1 weight for age or weight for height major percentile	19 (90%)	76 (83%)	34 (76%)	129 (82%)	5 (83%)	2 (100%)	7 (88%)	136 (82%)	>0.999
Weight for age or weight for height Z-score < -2	6 (29%)	31 (34%)	21 (47%)	58 (37%)	3 (50%)	0 (0%)	3 (38%)	61 (37%)	>0.999
FTT diagnosis recorded on comprehensive diagnosis form	8 (38%)	16 (17%)	10 (22%)	34 (22%)	4 (67%)	0 (0%)	4 (50%)	38 (23%)	0.082
CXR consistent with TB	14 (67%)	92 (100%)	32 (71%)	138 (87%)	0 (0%)	0 (0%)	0 (0%)	138 (83%)	<0.001
Soft tissue density (STD) suggestive of lymphadenopathy	10 (48%)	76 (83%)	21 (47%)	107 (68%)	0 (0%)	0 (0%)	0 (0%)	107 (64%)	<0.001
Both STD suggestive of lymphadenopathy and air space opacification	6 (29%)	38 (41%)	18 (40%)	62 (39%)	0 (0%)	0 (0%)	0 (0%)	62 (37%)	0.026
TB exposure in preceding 24 months	5 (24%)	25 (27%)	6 (13%)	36 (23%)	0 (0%)	0 (0%)	0 (0%)	36 (22%)	0.20
TST positive	9 (43%)	75 (82%)	9 (20%)	93 (59%)	0 (0%)	0 (0%)	0 (0%)	93 (56%)	0.001
Response to anti-TB therapy	1 (5%)	20 (22%)	2 (4%)	23 (15%)	0 (0%)	0 (0%)	0 (0%)	23 (14%)	0.60
AFB positive result	10 (48%)	8 (9%)	8 (18%)	26 (16%)	3 (50%)	0 (0%)	3 (38%)	29 (17%)	0.145

¹ Fisher's Exact Test comparing TB vs not TB groups

² Weight loss >5% or met at least one definition of FTT

³ Crossed at least 1 weight for age or weight for height major percentile, weight for age or weight for height Z-score < -2, or FTT diagnosis recorded on comprehensive diagnosis form