

## NOVEL APPLICATION OF NIH CASE DEFINITIONS IN A PAEDIATRIC TUBERCULOSIS CONTACT INVESTIGATION STUDY

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**Summary:** We apply and compare recently proposed International Consensus (NIH) with protocol-specified case definitions for paediatric TB and describe the disease spectrum and severity in a community-based prospective cohort diagnostic TB study using household contact tracing.

1    **INTRODUCTION**

2    Tuberculosis (TB) in children reflects a broad spectrum of disease, ranging from asymptomatic  
3    infection through disseminated disease.<sup>1</sup> Although a higher proportion of young children develop  
4    disseminated forms of TB (miliary TB and TB meningitis),<sup>2,3</sup> primary childhood TB is typically more  
5    benign than adult-type TB. The majority (~75%) of disease is intrathoracic,<sup>4</sup> most commonly isolated  
6    mediastinal lymph node, Ghon focus or Ghon complex disease.<sup>5</sup> In mid-childhood, mediastinal lymph  
7    node disease predominates; adult-type disease with pleural effusions and cavitation  
8    typically emerges during adolescence.<sup>4,6</sup> The confirmation of TB in children is challenging due  
9    ~~pathobacillary~~ nature of the disease, challenges in specimen collection and the wide observed  
10   disease spectrum. In addition to informing clinical care, the use of standard case definitions is  
11   important to enable the adequate comparison of children in clinical research, where the yield of  
12   diagnostic tests, response to treatment, and the efficacy of new drugs or regimen and vaccines are  
13   evaluated. National Institute of Health (NIH) International Consensus Case Definitions for  
14   diagnostic research in childhood TB were proposed in 2012 by an expert panel.<sup>7</sup> These have not yet  
15   ~~been~~ applied to contact investigations.

16   The yield of diagnostic tests may correlate with disease spectrum and severity. For example, the  
17   yield of mycobacterial culture is considerably higher in children with extensive intrathoracic  
18   compared to limited disease.<sup>8</sup> We recently proposed a novel standard approach to describe the  
19   spectrum and severity of TB in children<sup>5</sup> which considers both the extent (containment) of disease  
20   and the presence of complications; resulting in a final assignation of “severe” or “nonsevere”  
21   disease, applicable to both intrathoracic and extrathoracic TB.<sup>5</sup>

22   The NIH case definition focuses on young children <10 years of age presenting with symptoms of  
23   intrathoracic TB, typically at the hospital or referral level (Table 1), and was thus expected to have  
24   limited applicability to active TB surveillance studies such as household contact tracing.

25 Prior to the publication of the NIH definition, we developed standard case definitions for use in a  
26 community-based household contact tracing study. We applied and compare the NIH and the  
27 protocol case definitions and describe the TB disease spectrum and severity <sup>5</sup> in our prospective  
28 community-based study . We hypothesized that our protocol case definition would better apply to  
29 our cohort, with anticipated limited disease spectrum and detected through active surveillance.

30

31

32 **STUDY POPULATION AND METHODS**

33 **Study design and setting**

34 We analysed data from a prospective community-based household contact tracing study aimed at  
35 determining the diagnostic utility of 2 commercial Interferon Gamma Release Assays (IGRAs) for  
36 detection of *Mycobacterium tuberculosis* (*M.tb*) infection and disease in HIV-infected and uninfected  
37 children. The study was conducted in three impoverished urban communities with high levels of TB  
38 and HIV<sup>9</sup> in Cape Town, South Africa, consisting of predominantly South African mixed race and  
39 Xhosa African populations. The adult TB case notification rate in Cape Town was 671 per 100 000  
40 and 315 per 100 000 in children aged 0-14 years in 2012 (Personal communication, Judy Caldwell,  
41 Cape Town City Health Department).

42

43 **Eligibility and recruitment**

44 HIV-infected and -uninfected children aged 3 months to 15 years with and without documented  
45 *M.tb* exposure were recruited between December 2007 and June 2012. Focusing on well children,  
46 the study excluded children under 5 kg, with laboratory-documented anemia (Hb < 9g/dL), on  
47 antituberculosis therapy, or where consent was not obtained. Infants below 5 kg were excluded due  
48 to blood volumes. Children on isoniazid preventive therapy (IPT) were not excluded. Enrolment was  
49 deferred if a Mantoux tuberculin skin test (TST) had been placed within 12 weeks, live attenuated  
50 vaccination had been given within 6 weeks, or if there was an acute severe respiratory, diarrheal or  
51 neurologic illness.

52

53 A three-pronged approach was employed, recruiting children via either community TB clinics as  
54 household contacts of adult TB cases (who started treatment within preceding 3 months; i.e from

55 "TB households"), or from neighbouring households ("community controls") or from community  
56 paediatric HIV clinics (HIV-infected children with and without documented *M.tb* exposure).

57

58 All symptomatic adult household members were screened for TB and if diagnosed with TB, that  
59 household was reclassified. Children were investigated at enrolment and follow-up for *M.tb*  
60 infection and disease, using standard protocols.<sup>10,11</sup>

61

## 62 **Study measures**

63 Using methods previously described,<sup>12</sup> the larger study enrolled 1093 children with median follow-  
64 up duration of 15 months.<sup>13</sup> Children were seen at baseline (enrolment), months 3, 6, 15, and in the  
65 case of HIV-infected children, 27 months' follow-up. From the total enrolled, a dataset was compiled  
66 of all potential TB cases, detected at any (scheduled and unscheduled) study visits.

67 Children were included in analysis of potential TB cases if they were documented as having  
68 Confirmed, Probable or Possible TB (protocol definition), reported by the study team, parent or  
69 healthcare provider (TB clinic or referral hospital), or if there was laboratory evidence of *M.tb*, at any  
70 time during the study period. Data sources included the study database, clinic, hospital, and routine  
71 laboratory surveillance data.

72 Standard methods were used to define TB symptoms,<sup>11</sup> *M.tb* contact history, chest radiograph  
73 interpretation<sup>14</sup> and bacteriology. TB disease spectrum and severity were described;<sup>5</sup> the most  
74 severe manifestation was reported.

75 HIV testing was completed on all children with unknown or negative status (Abbott Determine HIV-  
76 1/2 rapid test followed by DNA PCR or HIV ELISA depending on whether they were younger or older  
77 than 18 months, respectively, in the case of a positive or indeterminate test). All HIV-infected  
78 children had access to combination anti-retroviral therapy (cART).

79 *TB exposure history* was captured using information including the presence of contact with a known  
80 adult (> 18 years old) household or other TB source case (person currently receiving TB treatment  
81 regardless of sputum smear status or disease type), the level of exposure and the number of TB  
82 cases in the household. The level of exposure was reported as a contact score of 1-10 derived from  
83 combined data assuming that the level of exposure was a product of proximity, duration and  
84 infectivity of exposure.<sup>12</sup>

85

86 *Measures of TB infection* included the TST and IGAs. The TST (2 TU PPD RT 23, Statens Serum  
87 Institute) was administered intradermally and read using the ballpoint method and callipers at 48-72  
88 hours. TST was completed at all study visits except at month 6, in the case of a previous reported  
89 TST adverse event, or TST administered within the preceding 3 months. A positive TST was defined  
90 as an induration of ≥10 mm in HIV-uninfected and ≥5 mm in HIV-infected children. The T-SPOT.TB  
91 (Oxford Immunotec, UK)<sup>15</sup> and the Quantiferon-TB Gold In Tube (QTF-IT, Cellestis, Australia)<sup>16</sup> were  
92 completed at all study visits..<sup>17</sup> IGRA results were reported at the visit closest to the TB episode as  
93 positive (if either QTF or T-SPOT.TB was positive), negative (both tests negative or only 1 available  
94 result, which was negative), indeterminate or not done. *M.tb* infection was defined as either a  
95 positive TST and/or IGRA.

96

97 *TB symptoms and signs* were classified at the time of the TB episode (Table 1).<sup>7,11,13,18,19</sup>

98

99 *Bacteriological* data included specimen type, number of specimens sent, number of positive  
100 specimens, result of direct smear microscopy for acid-fast-bacilli (AFB), liquid mycobacterial culture  
101 (mycobacterial growth indicator tubes; MGIT, Becton Dickinson, Sparks, MD, USA),<sup>20-28</sup> histology,  
102 speciation and drug susceptibility test (DST) pattern using the Genotype® MTBDRplus line probe  
103 assay (Hain Lifescience, Nehren, Germany).<sup>29</sup> Gastric aspirates were collected in all children younger  
104 than 5 years<sup>13</sup> and expectorated sputum samples in all older children at baseline and at subsequent

105 scheduled or unscheduled study visits where clinically indicated (e.g. new TB symptoms, new  
106 reported TB contact, or previous reported abnormality).<sup>13</sup> Samples were collected, transported and  
107 processed following standard guidelines and standard cross-contamination prevention measures  
108 were taken.<sup>30</sup> PCR identification of *M.tb* on any culture-positive specimen defined bacteriological  
109 confirmation, while caseating necrosis/granulomas with or without positive microscopy for AFB on  
110 cytology or histology specimens defined histological confirmation.

111 *Radiological data* included all available chest radiograph (CXR) reports. Antero-posterior and lateral  
112 CXR were done at all initial visits and at subsequent study visits as clinically indicated. CXRs were  
113 reviewed by two experienced independent blinded reviewers using a standard classification.<sup>14</sup>  
114 Where discrepancies arose, a third blinded, independent reviewer was used. Reviewers reported  
115 CXRs as being “Certain TB,” “Uncertain TB”, “Not TB” or “Normal”. A final radiological classification  
116 was assigned as either “Compatible with TB,” “Abnormal but not compatible with TB” or “Normal”.  
117 In the case of an abnormal CXR deemed not to be compatible with TB, an alternative clinical  
118 diagnosis, where possible, was assigned.

119

## 120 **TB disease definitions**

121 The NIH consensus definition<sup>7</sup> and protocol case definition were used (Table 1). The NIH case  
122 definition classified disease as Confirmed, Probable, Possible, Unlikely or Not TB.<sup>7</sup> Protocol-specified  
123 case definitions assigned these same case definitions as a function of bacteriological confirmation,  
124 well-defined symptoms/signs, TB-compatible CXR, and TB exposure (Table 1). Tests of infection were  
125 purposefully excluded since they were the index test under evaluation in the study.

126

127 TB episodes were classified as “prevalent” (detected within 6 weeks of enrolment) or “incident” (detected  
128 after 6 weeks’ enrolment).

129 All protocols were approved by the Health Research Ethics Committee, Stellenbosch University, and  
130 the institutional review boards of Case Western Reserve University, USA, Baylor College of Medicine,  
131 USA and the Charite Institute, Berlin, Germany and local health authorities. All **well** children with  
132 *M.tb* contact or positive TST who were HIV-infected or below 5 years of age were referred for IPT, as  
133 per local and international guidelines.<sup>31,32</sup> All cases of suspected TB were referred for treatment.

134 **Data management and analysis**

135 Agreement between diagnostic approaches was measured using the Kappa statistic with 95% confidence  
136 intervals (CI). All cases with a potential TB diagnosis in our cohort were included in analysis, regardless of  
137 age. Odds ratios (OR), calculated with Chi-squared or Fisher's exact tests, were used to compare disease  
138 severity in HIV-infected vs. uninfected children and in different age and TB exposure groups. The TB disease  
139 spectrum was described. TB incidence rates were calculated by age, HIV and TB exposure status. Data was  
140 analysed using STATA/SE version 12.0 (StataCorp LP, Texas, USA).

141

142    **RESULTS**

143    Of 1093 children enrolled, 169 were HIV-infected and 924 were HIV-uninfected; 671 (61%) were  
144    enrolled from TB households, 242 (22%) from neighbouring households, 180 (16%) children from  
145    community HIV clinics, of whom 163 were HIV-infected and 17 were uninfected siblings. Of the  
146    remaining 6 HIV-infected children, 5 were recruited from TB households and 1 from a neighbouring  
147    household.

148

149    There were 111 potential TB disease episodes documented in 109 children, of whom 23 (21%) were  
150    HIV-infected. 62 (56%) were prevalent and 49 (44%) incident cases. There was known TB exposure in  
151    82 (74%) episodes. The median *M.tb* contact score at enrolment in the 109 children was 5 (0-10). Of  
152    prevalent cases eligible for IPT according to programme criteria, only 5/40 (12.5%) children were on  
153    IPT at the time of TB diagnosis; whilst 5 of 18 (28%) of incident cases had received IPT at diagnosis. A  
154    further 6 (33%) were referred but either failed to attend the clinic or defaulted therapy. 16/22 (72%)  
155    children with a potential TB episode had documented TB exposure but were not referred for IPT  
156    based on programme criteria (HIV-uninfected and older than 5 years of age). Of HIV-infected  
157    children, 83% were on cART at the time of TB diagnosis.

158    Based on NIH case definitions,<sup>7</sup> there were 8 episodes of confirmed (Table 3), 12 of probable, 17 of  
159    possible, 3 of unlikely and 2 of not TB disease. Applying protocol-defined case definitions, there were  
160    23 episodes of confirmed (Table 3), 36 of probable, 27 of possible, 0 of unlikely and 21 of not TB. Of  
161    the 111 potential TB disease episodes, 69 were unclassifiable (4 due to insufficient data and 65 due  
162    to lack of symptoms), of whom 18 (26%) had no documented TB exposure, using the NIH definition.  
163    Four TB episodes were unclassifiable using the protocol case definition due to insufficient data; **2**  
164    (50%) who had no documented TB exposure. Agreement between the NIH and protocol-defined  
165    approach was 0.30 (95% CI: 0.23; 0.38).

166

167 Using the protocol case definition and excluding the episodes classified as “not TB,” and “unlikely TB,” there  
168 were 62 episodes (72%) of nonsevere and 24 episodes (28%) of severe disease. Of those with severe disease,  
169 all had intrathoracic disease, 2 (6%) had cavities/adult-type disease, 4 (13%) had expansive pneumonia; and 1  
170 (4%) had disseminated disease (miliary TB) [Table 4]. HIV-infected children were more likely to have severe  
171 disease than HIV-uninfected children (OR: 3.87; 95% CI 1.26; 11.81, p=0.0056) Children with a documented  
172 TB source case were less likely to have severe disease than those without known exposure (21% vs. 44%; OR:  
173 0.34, 95%CI: 0.12; 1.01, p=0.025). When stratifying by TB exposure and HIV status, proportions with severe  
174 disease remained unchanged, making it challenging to elucidate whether HIV infection or the lack of  
175 documented TB exposure determined TB disease severity. The proportion of children with severe disease  
176 was similar in children below 2 years of age vs. older children (27% vs. 22%; OR: 0.93, 95%CI: 0.29; 2.71,  
177 p=0.88).9 of the 24 children with severe disease were eligible for IPT based on programme criteria; only 3 of  
178 these had received IPT. Children with known TB exposure at enrolment were more likely to have prevalent  
179 TB (OR: 1.48, 95%CI: 0.55; 3.96, p=0.38) than those without exposure.

180

181 TB incidence rates (per 1000 patient years) were 109/1000 and 76/1000 in HIV-infected versus uninfected  
182 children; 106/1000 and 76/1000 in children under versus over two years; 111/1000 and 53/1000 in children  
183 under versus over five years old, and 86/1000 and 74/1000 in those with versus without known *M.tb*  
184 exposure.

185 **DISCUSSION**

186 This is the first published application of the NIH diagnostic definition for intrathoracic childhood  
187 TB, published in 2012.<sup>7</sup> In our community-based diagnostic study, we found that almost two-thirds  
188 of children could not be classified using this definition, despite the presence of severe disease in almost  
189 a third. In contrast, almost all children could be classified using the protocol case definition, which  
190 did not rely on the presence of presenting symptoms.

191 This is most likely explained by the emphasis in the NIH approach on diagnosing TB in symptomatic  
192 children, not typically seen in contact investigation studies, where the majority of diseased children  
193 are expected to have limited disease and thus more limited symptomatology. The NIH approach  
194 would thus have limited applicability to paediatric TB studies using active surveillance, e.g. TB  
195 contact investigation, and vaccine trials.<sup>33</sup> We propose the use of our protocol definition as more  
196 relevant to contact investigation studies.

197 There was, understandably, poor agreement between the case definitions. Despite the fact that the  
198 protocol case definition did not consider tests of TB infection, almost all children were classifiable  
199 using well quantified *M.tb* exposure as a proxy for tests of infection. Well quantified exposure was  
200 previously shown to correlate well with tests of infection and suggested as a possible replacement  
201 for tests of infection in resource-poor settings to guide targeted IPT delivery.<sup>12</sup> A major difference  
202 resulting from the use of the NIH and protocol case definitions lies in the number of confirmed  
203 cases detected (Table 3). Using the protocol definition, there were almost threefold the number of  
204 confirmed cases than with the NIH definition. Only 8 of these 23 cases (with at least bacteriological  
205 confirmation) had “well-defined symptoms”<sup>18</sup>, although most had symptoms of more acute  
206 duration with or without abnormal CXR. We agree that all 23 children may not have had overt  
207 disease, however, all were treated as TB by the program. Recent well-documented *M.tb* exposure  
208 with isolated bacteriological confirmation may be described as “acute TB infection” as supported by  
209 natural history studies, where positive mycobacterial cultures were obtained in children with

210 normal chest radiographs and a positive TST or history of *M.tb* exposure.<sup>4</sup> We appreciate that whilst  
211 the clinical relevance in children with bacteriological confirmation without well-defined TB  
212 symptoms remains unknown and an area of ongoing discussion, it is not imprudent to regard such  
213 cases with high suspicion due to the risk of dissemination in very young or HIV-infected children,  
214 given that laboratory contamination can be excluded. Management should be on a case-by-case  
215 basis until consensus is reached.

216 The site of TB disease seen in our cohort was almost exclusively intrathoracic, but with a wide  
217 observed disease spectrum and severity, ranging from uncomplicated intrathoracic lymph node  
218 disease to uncontrolled intrathoracic disease with complications (lymph node or other) [Table 4].  
219 Despite this being a predominantly (62%) asymptomatic (i.e. no “well-defined” symptoms<sup>18</sup>) cohort  
220 of children recruited through active surveillance, 28% of children had severe intrathoracic disease.  
221 HIV-infected children had the highest proportion of severe disease (48%), followed by children  
222 without documented TB source exposure (44%). Possible explanations for the unexpectedly high  
223 rate of severe disease are the high HIV prevalence and the high proportion of young children in our  
224 study (Table 2), both risk factors for severe disease.<sup>2,3,34,35</sup> HIV infection is associated with a higher  
225 incidence of severe intrathoracic disease including cavities<sup>34</sup> although not more disseminated  
226 disease.<sup>34</sup> HIV-infected children recently started on cART may however be prone to more severe  
227 disease manifestations including TB Immune Reconstitution Inflammatory Syndrome (IRIS).<sup>36</sup> High TB  
228 incidence rates have been reported in HIV-infected children<sup>37,38</sup> despite the availability of IPT and  
229 improved immunological function on cART,<sup>39</sup> consistent with our findings.

230 Diagnostic and treatment delay in adults<sup>40</sup> may also have led to delayed presentation of children  
231 resulting in disease progression, especially in children without known TB exposure, where TB may  
232 not have been readily suspected in the absence of a known source case.<sup>41</sup> Lastly, poor IPT uptake  
233 may be reflected in the high TB rates seen here in HIV-infected and –uninfected under-five year olds,  
234 despite IPT recommendations. Although IPT would not have prevented the majority of our TB cases,

235 which were diagnosed within 6 weeks of enrolment, IPT at the time of source case identification by  
236 the program could have prevented a substantial proportion of disease in child contacts. Active  
237 contact tracing and routine IPT delivery in these communities was documented as limited with no  
238 structured IPT adherence support offered by the TB program.<sup>42,43</sup>We have subsequently supported  
239 the implementation of structured IPT delivery tools to improve uptake and adherence.<sup>44</sup>

240

241 **CONCLUSIONS**

242 The current NIH case definition for paediatric intrathoracic TB has limited applicability to household  
243 contact studies where, as shown in this study from a high-TB burden setting, a surprisingly wide  
244 spectrum of TB disease was observed in HIV-infected and uninfected children. Further work is  
245 needed to develop paediatric TB case definitions to ensure that the wide spectrum of relevant  
246 paediatric TB observed in clinical research is captured, including in contact investigation studies.

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**Table 1. Definition and comparison between NIH and protocol case definitions for pediatric tuberculosis**

Disease categories	NIH Case definition <sup>7</sup>	Protocol Case definition	Key differences
Confirmed TB	≥1 symptom/sign <sup>7</sup> together with microbiological confirmation of <i>Mycobacterium tuberculosis</i> ( <i>M.tb</i> )	Bacteriological or histological <sup>1</sup> confirmation of <i>M.tb</i> , either 1.alone, <sup>2</sup> (with/without TB exposure/ alternative (non-TB) CXR diagnosis), or with 2. either a TB-compatible CXR, or 3. well-defined symptoms/signs <sup>3,4</sup>	Bacteriological confirmation alone considered and symptoms not mandatory in protocol case definition. Additional symptoms and signs considered in the protocol case definition.
Probable TB	≥1 symptom/sign and a TB-compatible CXR and: 1.either a positive treatment response, or 2.documented exposure to <i>M.tb</i> , or 3. immunological evidence of <i>M.tb</i> infection	1. Nonspecific histology <sup>5</sup> with 1.1. a TB-compatible CXR, or 1.2. symptoms/signs, or 2. A TB-compatible CXR with 2.1. symptoms/signs, or 2.2. TB exposure	Symptoms/signs not mandatory in protocol definition; tests of infection and treatment response not considered in protocol case definition. Additional symptoms and signs considered in the protocol case definition.
Possible TB	≥1 symptom/sign and either 1.a positive treatment response or documented exposure to <i>M.tb</i> or immunological evidence of	Either of the following: 1. nonspecific histology, or 2. a TB-compatible CXR, or 3. symptoms/signs with or without TB exposure	Symptoms/signs not mandatory in protocol definition; TB-compatible CXR alone is defined as possible TB in protocol

	<i>M.tb</i> infection, or: 2. A TB-compatible CXR		case definition; tests of infection and treatment response not considered in protocol case definition.  Additional symptoms and signs considered in the protocol case definition.
Unlikely TB	≥1 symptom/sign but not fitting any of above definitions, but with no alternative established diagnosis	Abnormal, TB-incompatible CXR with no alternative radiological or clinical diagnosis, with or without TB exposure	Symptoms/signs not mandatory in protocol case definition, otherwise similar.  Additional symptoms and signs considered in the protocol case definition.
Not TB	≥1 symptom/sign, not fitting any of the above definitions, and with an established alternative diagnosis	Abnormal, TB-incompatible CXR with an alternative radiological or clinical diagnosis, with or without TB exposure	Symptoms/signs not mandatory in protocol definition, otherwise similar

<sup>1</sup>Histological confirmation implies Ziel Nielsen Stain (Zn) positive with granulomatous inflammation and/or caseating necrosis

<sup>2</sup>Area of ongoing clinical debate/discussion

<sup>3</sup> Symptoms/signs include any or more than one of the following

*Cough:* persistent, non-remitting cough for more than 2 weeks, not responding to a course of antibiotics

*Weight loss/failure to thrive:* unexplained weight loss of >5% vs. the highest recorded weight /clear deviation from previous growth trajectory ±documented crossing of centile lines in preceding 3 months± weight for age z-score of ≤-2 with no previous/recent growth trajectory information, not responding to nutritional rehabilitation/cART

*Persistent unexplained fever:* subjectively reported by guardian and a temperature of >38 degrees Celsius for more than one week objectively recorded at least once.

*Persistent, unexplained reduced playfulness or activity:* perceived and reported by the parent or caregiver.

<sup>4</sup>Protocol defined symptoms and signs are any of the above as well as or any of the following, in isolation:

*Neck nodes/visible neck swelling:* defined as noticed by the parent/caregiver in the preceding month

*Night sweats:* reported by caregiver of a drenching nature, requiring a change of clothing.

*Convulsions, lethargy or a decreased level of consciousness:* defined as reported by the caregiver in the preceding two weeks

<sup>5</sup>Zn- with granulomatous inflammation and/or caseating necrosis

**Table 2. Characteristics of children enrolled in a community-based diagnostic study (N=1093 children) at enrolment and at the time of diagnosis of a potential disease episode (N=109)**

Characteristics	Total cohort (N =1093)	Children with potential TB (N=109)
Age at enrolment (months: median, range)	61 (3-190)	39 (5-184)
Age at TB episode	N/A	41 (5-188)
Under 2 years of age [N (%)]	197 (18)	26 (23)
Under 5 years age [N (%)]	534 (49)	74 (67)
HIV-infected [N (%)]	169 (15)	23 (21)
Median CD4 count at enrolment: Absolute (range), % (range)	1400 (35-4200), 28.5 (3-47)	1450 (35-3700), 27 (3-44)
Median CD4 count at TB episode: Absolute (range), % (range)	N/A	1232 (35-2601), 27 (3-47)
Follow-up - HIV-infected children (months: median, range)	15 (0-29)	15 (3-28)
Follow-up HIV-uninfected children (months: median, range)	15 (0-21)	15 (0-21)
Ethnicity: Mixed race [N (%)]	717 (66)	73 (67)
Ethnicity: Xhosa [N (%)]	365 (33)	35 (32)
Ethnicity: Other [N (%)]	11 (1)	1 (1)
Community A [N (%)]	355 (32)	28 (26)
Community B [N (%)]	359 (33)	45 (41)
Community C [N (%)]	379 (35)	36 (33)
Recruited from TB household [N]	671 (61)	76 (70)

(%)]		
Recruited from neighbouring household [N (%)]	242 (22)	13 (12)
Recruited from community HIV clinic [N (%)]	180 (16)	20 (18)

**Table 3. Comparison of diagnostic features in children with confirmed tuberculosis as classified by the NIH and protocol case definitions**

<b>Confirmed TB based on the NIH definition (N=8)</b>	<b>N (%)</b>
Bacteriological confirmation and symptoms	2 (25.0)
Bacteriological confirmation, symptoms and a lobar pneumonia on CXR	1 (12.5)
Bacteriological confirmation, symptoms and documented TB exposure	3 (37.5)
Bacteriological confirmation, symptoms, TB exposure together with interstitial pneumonia on CXR	1 (12.5)
Bacteriological confirmation, symptoms, TB exposure and a TB-compatible CXR	1 (12.5)
<b>Confirmed TB based on the protocol definition (N=23)</b>	<b>N (%)</b>
Bacteriological confirmation alone	1 (4)
Bacteriological confirmation ( <i>MDR M.tb</i> ) with multiple palpable cervical lymph nodes (1.5 cm diameter)	1 (4)
Bacteriological confirmation with interstitial pneumonia on CXR	1 (4)
Bacteriological confirmation with, lobar pneumonia and acute respiratory symptoms	1 (4)
Bacteriological confirmation and TB exposure (“acute infection”)	6 (26)
Bacteriological confirmation, TB exposure and an interstitial pneumonia on CXR	1 (4)
Bacteriological confirmation, TB exposure, lobar pneumonia on CXR and acute respiratory symptoms	1 (4)
Bacteriological confirmation, TB exposure and a TB-compatible CXR	3 (13)
Bacteriological confirmation and well-defined symptoms	2 (9)
Bacteriological confirmation, well-defined symptoms and interstitial pneumonia on CXR	1 (4)
Bacteriological confirmation, well-defined symptoms and documented TB	3 (13)

exposure

Bacteriological confirmation, well-defined symptoms, documented TB exposure      1 (4)

and interstitial pneumonia on CXR

Bacteriological confirmation, well-defined symptoms, documented TB exposure      1 (4)

and a TB-compatible CXR

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**Table 4. Tuberculosis disease spectrum observed in children with confirmed, probable and possible tuberculosis based on the protocol case definition (N=86)**

	N (% of N=86)
<i>Intrathoracic tuberculosis</i>	
-Isolated uncomplicated intrathoracic lymph node disease	28 (32)
-Controlled, uncomplicated intrathoracic (parenchymal) disease (n=29) and 3 with additional uncomplicated intrathoracic lymph node disease	32 (37)
-Pleural effusion with uncomplicated intrathoracic lymph node disease	1 (1)
-Complicated intrathoracic lymph node disease (8 in isolation); 2 had additional controlled uncomplicated intrathoracic (parenchymal) disease	10 (12)
-Uncontrolled uncomplicated intrathoracic (parenchymal) disease, of which 2 had additional uncomplicated intrathoracic lymph node disease	7 (8)
-Disseminated disease (miliary TB) with bilateral small pleural effusions and uncomplicated intrathoracic lymph node disease	1 (1)
-Uncontrolled complicated intrathoracic disease (complications were mostly lymph node related)	7 (8)
<i>Extrathoracic tuberculosis</i>	
-Controlled uncomplicated cervical adenitis	1 (1)

Note: Entities listed show where there was overlap between more than one disease entity. Disease extent (controlled vs. uncontrolled) and the presence of complications are described using a standard approach used to describe disease spectrum and severity.<sup>11</sup>