ORIGINAL ARTICLE

Well defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis

B J Marais, R P Gie, C C Obihara, A C Hesseling, H S Schaaf, N Beyers

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See end of article for authors' affiliations

Correspondence to: Dr B J Marais, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg, 7505, South Africa; bjmarais@sun.ac.za

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Background: The diagnosis of childhood pulmonary tuberculosis presents a major challenge as symptoms traditionally associated with tuberculosis are extremely common in children from endemic areas. The natural history of tuberculosis in children shows that progressive disease is associated with symptoms which have a persistent, non-remitting character. The aims of this study were to investigate whether improved symptom definition is possible in a clinical setting, and whether use of these well defined symptoms has improved value in the diagnosis of childhood pulmonary tuberculosis.
Methods: A prospective, community based study was conducted in two suburbs of Cape Town, South Africa. All children (<13 years) presenting to the local community clinic with a cough of >2 weeks duration, were referred to the investigator. Parents completed a symptom based questionnaire, whereafter reported symptoms were characterised in a standard fashion.
Results: Of the 151 children enrolled, 21 (15.6%) reported symptoms with a persistent, non-remitting character. Tuberculosis was diagnosed in 16 (10.5%) children, all of whom reported these symptom characteristics. A persistent, non-remitting cough was reported in 15/16 (93.8%) children with tuberculosis and in 2/135 (1.5%) children without tuberculosis, indicating a specificity of 98.5% (135/137). Persistent fatigue of recent onset was also sensitive (13/16, 81.3%) and specific (134/135, 99.3%). Persistent fever and/or chest pain were exclusively reported in children with tuberculosis, but were present in only 4/16 (25.0%) children with tuberculosis.
Conclusion: The use of well defined symptoms is feasible, even in resource limited settings, and may offer significantly improved value in the diagnosis of childhood pulmonary tuberculosis.

The diagnosis of childhood pulmonary tuberculosis presents a major challenge, because bacteriological confirmation is rarely achieved and radiological signs are often difficult to interpret.[1–3] Various symptom based diagnostic approaches have been developed, but these were mostly based on clinical experience and lack proper validation.[4]

Hospital based studies have reported widely varying results regarding the utility of a symptom based approach for the diagnosis of childhood pulmonary tuberculosis.[5–7] However, the selection bias inherent to these hospital based studies limits extrapolation to the community level. To our knowledge, only one study has documented the prevalence of symptoms traditionally associated with tuberculosis, such as a prolonged cough, night sweats, subjective weight loss, etc, in a random selection of children from an endemic area.[8] This community based survey found that these poorly defined symptoms were extremely common, even in children without tuberculosis.[8]

This finding prompted a careful re-evaluation of the symptoms associated with tuberculosis in children, which are best documented in the pre-chemotherapy literature that described the natural history of tuberculosis in children.[9] According to this literature, children can be categorised into two main risk groups: high risk children (<3 years of age and/or immune compromised children) and low risk children (immune competent children ⩾3 years of age).[9] In low risk children, progressive disease following primary infection with *Mycobacterium tuberculosis* was rare and was associated with persistent, non-remitting symptoms.[9] In high risk children, progressive disease occurred more frequently, but symptoms were also persistent and non-remitting, and sometimes had a more acute onset.[9] In the vast majority of children (>95%), disease progression occurred within 12 months of primary infection.[9 10] Careful review of these disease descriptions from the pre-chemotherapy literature identified previously unexplored symptom characteristics that may improve symptom specificity, namely persistent and non-remitting symptoms of recent onset.

The aims of this study were to investigate whether improved symptom definition is possible in a clinical setting, and whether the use of these well defined symptoms has improved value in the diagnosis of childhood pulmonary tuberculosis.

METHODS

A prospective, community based study was conducted from September through December 2003 in Cape Town, South Africa.

Setting

The study community is adjacent to the community where the previous symptom survey was carried out.[8] These communities are similar as regards ethnic and socio-economic parameters,[11] high tuberculosis incidence (>300/100 000 new smear positive cases per year), and relatively low prevalence of HIV infection (<8%).[12]

Study population

All children under the age of 13 years who presented to the local clinic with a cough of more than 2 weeks duration, not responding to first line antibiotic therapy (5 days of oral amoxacillin), were referred to the investigator. A standard symptom based questionnaire was completed and reported symptoms were individually characterised. A tuberculin skin test (TST) and chest radiograph (CXR) were performed in all children.

Abbreviations: CXR, chest radiograph; PCR, polymerase chain reaction; TST, tuberculin skin test

Questionnaire
The questionnaire was identical to that used in the previous community based symptom survey.[8] Parents were asked about the presence and duration of symptoms during the previous 3 months, including cough, shortness of breath, chest pain, haemoptysis, fever, fatigue, night sweats, anorexia, and weight loss. Reported symptoms were then characterised in a standard fashion to identify those with a persistent, non-remitting character.

Symptom characterisation
Parents were asked the following standard questions to characterise reported symptoms: (i) Is your child symptomatic at present? and (ii) What is/was the uninterrupted symptom duration? This allowed differentiation between persistent, non-remitting symptoms and those that resolved spontaneously (without specific anti-tuberculosis treatment). Children not diagnosed with tuberculosis after initial screening were treated according to the most likely alternative diagnosis and followed up after 2–4 weeks. If symptoms persisted beyond 4 weeks of follow up, a repeat TST and CXR were performed. The uninterrupted symptom duration, until spontaneous symptom resolution or the onset of anti-tuberculosis chemotherapy, was recorded in weeks.

In addition, three distinct cough patterns were differentiated: (i) acute cough with delayed recovery, (ii) recurrent acute cough, and (3) persistent, non-remitting cough (fig 1). Parents were shown a graphic illustration of these three cough patterns and requested to identify the pattern that best described their child's condition. Questions were piloted in the community prior to the onset of the study.

Weight loss
Both subjective (reported) and objective weight loss were recorded. Objective weight loss was defined as crossing at least one centile line in the preceding 3 months or the loss of more than 10% of bodyweight (minimum 1 kg) over any time interval.

Tuberculin skin test
A TST, using intra-dermal injection of 2 tuberculin units of *M tuberculosis* PPD RT 23 (Statens Serum Institut, Copenhagen, Denmark) was performed on the volar aspect of the left forearm. The largest transverse diameter of induration was measured after 48–72 h.

Chest radiograph
Standard antero-posterior and lateral views were taken. Two independent experts, blinded to all clinical information, evaluated the CXRs and documented their findings on a standard report form.

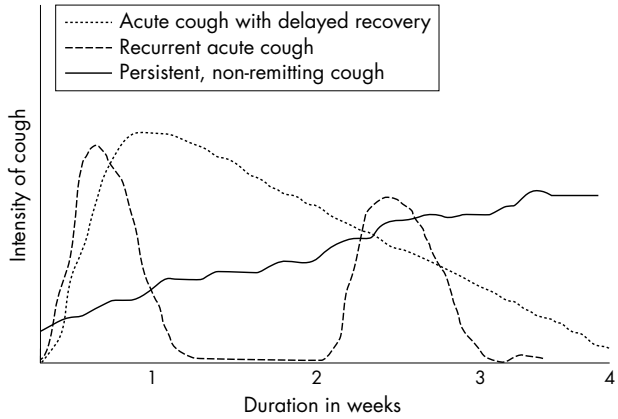

Figure 1 Differentiated cough patterns.

M tuberculosis culture
Children with a CXR suggestive of tuberculosis had sputum or gastric aspirate samples taken for culture. Samples were inoculated into Bactec 12B liquid medium (Becton Dickinson, Sparks, MD, USA). Positive cultures were confirmed as *M tuberculosis* by polymerase chain reaction (PCR).

Definitions used for clinical diagnoses
Probable tuberculosis was defined as a CXR indicative of tuberculosis, confirmed by two independent experts. Where the two objective experts disagreed, a third expert made the final decision. Confirmed tuberculosis was defined as isolation of *M tuberculosis* on culture. Viral infection was defined as a transient runny nose and/or fever at symptom onset, no clinical response to antibiotics, and no CXR signs suggestive of tuberculosis. Asthma was defined as recurrent cough episodes together with current and/or exercise induced wheeze with bronchodilator response, without CXR signs suggestive of tuberculosis.

Children diagnosed with probable or confirmed tuberculosis received anti-tuberculosis treatment and were offered a rapid HIV test (Determine HIV1/2; Abbott, Wiesbaden-Delkenheim, Germany) after appropriate counselling. All children not treated for tuberculosis were monitored for a period of 6 months to exclude subsequent treatment for tuberculosis. The study was approved by the Ethics Review Board of Stellenbosch University, the City of Cape Town Health Department, and local health committees.

Statistical analysis
Statistical analysis was carried out with SPSS for Windows version 11.0 (SPSS, Chicago, IL, USA). Symptom frequencies and symptom characteristics were compared between age groups and between different clinical diagnoses. Comparisons were performed using the Mantel-Haenszel χ^2 test and Fisher's exact test to determine two sided p values.

RESULTS
Of 156 referred children, 151 (96.8%) were enrolled in the study. Four children did not turn up for evaluation and study participation was refused in one child. A questionnaire and TST was completed in all 151 children and a CXR in 129 (85.4%). The 22 children who did not receive a CXR, all reported spontaneous symptom resolution before evaluation by the investigator. Table 1 describes the demographics and clinical diagnoses; 102 (67.6%) children were less than 5 years of age, viral infection (100, 66.2%) and asthma (24, 15.9%) were the most frequent clinical diagnoses.

Viral infection was the most common diagnosis in all age groups, particularly in children less than 2 years of age (45/54, 83.3%). The frequency of asthma peaked in the 5–9 year age group (16/38, 42.1%), where it rivalled viral infection as the most common clinical diagnosis. Tuberculosis was diagnosed in a total of 16/151 (10.6%) children, of whom nine (56.2%) were less than 5 years of age. The two radiology experts disagreed in two cases judged to have tuberculosis; one had culture confirmation, while the other was less than 2 years of age, had a TST of 18 mm, and showed excellent clinical response to treatment. Bacteriological confirmation was achieved in 10/16 (62.5%) children with tuberculosis. The bacteriological yield was highest in children with cavitating disease (4/4, 100%) and in those with alveolar consolidation (4/6, 66.7%). None of the children had clinical signs indicative of AIDS. All 16 diagnosed with tuberculosis were tested for HIV and none were HIV infected.

Figure 2 shows the association between specific cough patterns and clinical diagnoses. An acute cough with delayed recovery was most common in children under 2 years of age and was associated with a diagnosis of viral infection.

Table 1 Demographics and clinical diagnoses of all children enrolled (n = 151)

	Number (%)
Demographics	
Gender	
Male	79 (52.3)
Female	72 (47.7)
Age	
<2 years	54 (35.8)
2–4 years	48 (31.8)
5–9 years	38 (25.2)
10–12 years	11 (7.2)
Clinical diagnoses	
Viral infection	100 (66.2)
Bacterial infection (good antibiotic response)	10 (6.6)
Asthma	24 (15.9)
Tuberculosis	16 (10.6)
Other	1 (0.7)

A total of 156 children were referred of whom 151 (96.8%) were enrolled.

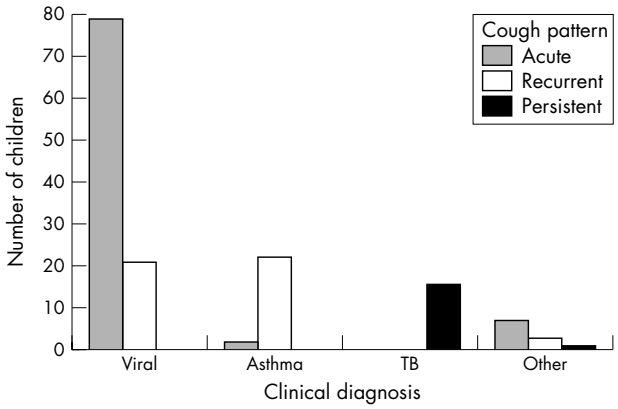

Figure 2 The frequency of specific cough patterns associated with different clinical diagnoses (n = 151).

Recurrent cough episodes were most common in children aged 2–10 years, and were associated with either recurrent viral infections or asthma. A persistent, non-remitting cough was uncommon in all age groups and was almost exclusively (16/18, 88.9%) associated with tuberculosis. Only two children without tuberculosis reported a persistent cough beyond 4 weeks of follow up. One was a previous premature baby with bronchiectasis whose symptoms were not of recent (<12 months) onset, and the other a child with atypical pneumonia in whom the cough resolved over a period of 2 months. No child who reported spontaneous symptom resolution was diagnosed with tuberculosis in the 6 months subsequent to the study.

Table 2A shows the frequency of the five most relevant symptoms (cough, chest pain, weight loss, fatigue, and fever) in children with and without tuberculosis. In agreement with the inclusion criteria, all children reported a cough. Additional symptoms were common: chest pain (33, 21.9%), weight loss (40, 26.5%), fatigue (37, 24.5%), and fever (50, 33.1%). Only weight loss and fatigue were significantly more frequent in children with tuberculosis. The results for difficult breathing, haemoptysis, poor appetite (anorexia), and night sweats are not reported as parents showed variable symptom interpretation. Difficult breathing was interpreted as either dyspnoea at rest or exercise induced wheezing. Haemoptysis was uncommon, being reported in only two children, neither of whom had tuberculosis, but it was frequently confused with nose bleeds or haematemesis. Night sweats were frequently reported (37/151, 24.%), especially in children less than 2 years of age (20/54, 37%) who shared a bed with their parents; it was generally not associated with a tuberculosis diagnosis.

Table 2B focuses on symptoms of recent onset with a persistent, non-remitting character. These well defined symptoms were uncommon: cough (16, 10.6%), chest pain (4, 2.6%), objective weight loss (9, 6.0%), fatigue (14, 9.3%), and fever (4, 2.6%), and were all significantly associated with tuberculosis. A persistent, non-remitting cough was reported in 15/16 (93.8%) children with tuberculosis and in 2/135 (1.5%) children without tuberculosis, indicating a specificity of 98.5% (135/137). Persistent fatigue of recent onset was also sensitive (13/16, 81.3%) and specific (134/135, 99.3%). Persistent fever and/or chest pain were exclusively reported in children with tuberculosis but were present in only 4/16 (25.0%) children with tuberculosis, two of whom had a pleural effusion.

DISCUSSION

The results of this study demonstrate that it is possible to identify symptoms with a persistent, non-remitting character at primary health care level, even in resource limited settings. It may be difficult to distinguish between the different cough patterns at the initial evaluation, but clinical follow up after 2–4 weeks proved to be a valuable diagnostic tool. Only two children without tuberculosis reported a non-remitting cough that persisted beyond 2–4 weeks of follow up.

Table 2 Symptoms reported in children without TB compared to children with TB

Symptoms	No TB (n = 135)	TB (n = 16)	OR (95% CI)	p value
A. Symptoms reported in children without TB compared to children with TB				
Cough	1335 (100%)	16 (100%)	NA	NA
Chest pain	29 (21.8%)	4 (25.0%)	1.2 (0.4–4.1)	0.752
Weight loss	30 (22.6%)	10 (62.5%)	5.8 (2.0–17.4)	0.001
Fatigue	23 (17.3%)	14 (87.5%)	34.1 (7.3–160.3)	<0.001
Fever	45 (33.8%)	5 (31.3%)	0.9 (0.3–2.8)	1.000
B. Persistent, non-remitting symptoms reported in children without TB compared to children with TB				
Cough	2 (1.6%)	15 (93.8%)	2010.0 (119.5–33812.9)	<0.001
Chest pain (confirmed by child)	0 (0.0%)	4 (25.0%)	NA	<0.001
Weight loss (objective)	3 (2.6%)	6 (37.5%)	25.0 (3.4–184.5)	0.001
Fatigue	1 (0.8%)	13 (81.3%)	580.7 (56.3–5990.1)	<0.001
Fever	0 (0.0%)	4 (25.0%)	NA	<0.001

CI, Confidence interval; OR, odds ratio; NA, not applicable (2A: all children coughed; 2B: no children without TB reported persistent chest pain or fever); TB, tuberculosis.

What is already known about this topic

- Current symptom based diagnostic algorithms are poorly validated; symptoms traditionally associated with tuberculosis are too common in children from high burden communities to be of real diagnostic value
- There is a need to reassess the value of symptom based approaches for the diagnosis of childhood pulmonary tuberculosis, especially in high burden settings with limited resources

What this study adds

- Well defined symptoms, including only persistent, non-remitting symptoms of recent onset, are uncommon and offers potentially excellent diagnostic value in HIV uninfected children in high burden tuberculosis settings
- Prospective, community based studies are required to validate the diagnostic value of these well defined symptoms in communities with a high burden of tuberculosis

In this study, well defined symptoms had excellent diagnostic value. Both a persistent cough and/or persistent fatigue of recent onset were highly sensitive and specific. Persistent chest pain, confirmed by the child, was the presenting symptom in both children with tuberculous pleural effusion, which correlates with the typical clinical picture described in children with this disease manifestation,[9] although it was present in only 25% of all children diagnosed with tuberculosis. Subjective and objective weight loss showed poor correlation with each other, but both were significantly associated with tuberculosis. In endemic tuberculosis settings, the diagnostic value of weight loss may be enhanced by first eliminating other common causes of poor weight gain, such as worm infestation and food insecurity.

The study had several limitations. It was questionnaire driven and thus subject to recall bias and reporter subjectivity. Recall bias was limited by focusing on current symptoms. Reporter subjectivity was reduced by standard symptom characterisation. Investigator bias was limited, as symptom characterisation was done before the TST or CXR results were known. The study population was a very select group; only those presenting with a cough of more than 2 weeks duration, not responding to first line antibiotics, were recruited. The use of a therapeutic trial of broad spectrum antibiotics is widely advocated,[13 14] but is controversial, as patients with tuberculosis may show some symptomatic response, and anti-tuberculosis treatment of infectious patients may be delayed.[14–16] However, first line antibiotics should not lead to complete symptom resolution in children with tuberculosis. In this study, antibiotics were given before referral and thus did not prolong diagnostic delay. Furthermore, none of the children with complete symptom resolution required anti-tuberculosis treatment in the subsequent 6 months, indicating that they did not have tuberculosis.

In conclusion, the use of well defined symptoms is feasible, even in resource limited settings, and may offer significantly improved value in the diagnosis of childhood pulmonary tuberculosis. A large prospective, community based study is required to validate the diagnostic value of this symptom based approach.

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Authors' affiliations

B J Marais, R P Gie, C C Obihara, A C Hesseling, H S Schaaf, N Beyers, Desmond Tutu TB Centre and the Department of Paediatrics and Child Health, Tygerberg Children's Hospital and the Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa

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