

**Childhood intra-thoracic tuberculosis:  
addressing the diagnostic dilemma**

Dissertation presented by

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## **Declaration**

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any other university for a degree.

Signature

Date

## Summary

Children contribute little to disease transmission and the maintenance of the tuberculosis epidemic, but they constitute a significant proportion of the total tuberculosis (TB) caseload and experience considerable morbidity and mortality in endemic areas, despite the availability of cheap and effective treatment. The difficulty of diagnosing childhood tuberculosis is one of the major obstacles that hinder the provision of antituberculosis treatment to children in endemic areas.

The diagnosis of childhood tuberculosis is complicated by the lack of a practical gold standard, as bacteriologic specimens are difficult to collect and the yield is low. In non-endemic countries the diagnosis of childhood tuberculosis is based on the triad of: 1) exposure to an adult index case, 2) a positive tuberculin skin test, and 3) suggestive radiographic signs. However, the triad has limited value in endemic areas where exposure to and/or infection with *Mycobacterium tuberculosis* is common, and chest radiography is rarely available. The objective of this dissertation was to address the diagnostic dilemma faced by health professionals in endemic areas with limited resources, where children currently have poor access to chemoprophylaxis and antituberculosis treatment.

We first clarified basic disease concepts, through a critical review of the pre-chemotherapy literature that documented the natural history of childhood tuberculosis. Three central concepts were identified; 1) the importance of accurate case definition, 2) the relevance of risk stratification, and 3) the diverse spectrum of disease, which necessitates accurate disease classification. The importance of accurate case definition is illustrated by the fact that isolated hilar adenopathy, considered the principal radiographic sign of primary tuberculosis, becomes transiently visible in the majority of children following recent primary infection. Our analysis of the natural history of childhood tuberculosis allowed accurate quantification of the risk to progress to disease following primary infection with *M.tuberculosis*. This demonstrated that the risk depends mainly on the age and/or immune-status of the child, the time since primary infection occurred and the presence or absence of symptoms.

After analysing these historic studies, we proceeded to document the burden of childhood tuberculosis in an endemic area. We first conducted a retrospective study to describe current diagnostic practices and demonstrated almost exclusive reliance on chest radiography. We then calculated the burden of childhood tuberculosis in a prospective descriptive study. The corrected tuberculosis incidence rate in children was 407/100 000/year and children with severe forms of disease, such as disseminated (miliary) tuberculosis and/or tuberculous meningitis, were rarely recorded in the TB treatment register used for routine community-based surveillance.

An additional obstacle to progress in the field of childhood tuberculosis has been the lack of standard descriptive terminology. Following a careful review of the literature, we proposed a radiological classification of childhood intra-thoracic tuberculosis and explored the different pathologic mechanisms that underlie these diverse disease manifestations. We then conducted a prospective descriptive study to document the disease spectrum in children treated for tuberculosis in an endemic area. The disease patterns observed were consistent with those described in the pre-chemotherapy literature. In addition, we demonstrated that bacteriologic confirmation may be achieved in the majority of children with intra-thoracic tuberculosis, in highly endemic settings.

Finally we developed a novel symptom-based approach to diagnose pulmonary tuberculosis in children from endemic areas with limited resources. We followed a step-wise approach by first conducting a community-based survey to document the prevalence of symptoms traditionally associated with tuberculosis in a random selection of children from an endemic area. The survey demonstrated that poorly defined symptoms offer poor diagnostic value. The second step was to evaluate the diagnostic value of well-defined (persistent, non-remitting) symptoms in a small prospective study. Well-defined symptoms demonstrated good diagnostic value, but these promising results required further validation. As a final step, we validated the diagnostic value of a novel symptom-based approach in a large prospective, community-based study. In this study, a simple symptom-based approach diagnosed



childhood pulmonary tuberculosis with a remarkable degree of accuracy, particularly in HIV-uninfected children older than 3 years of age.

This novel diagnostic approach offers the exciting prospect of extending antituberculosis treatment to children in endemic areas with limited resources, where current treatment access is poor.

## Opsomming

Tuberkulose beheer programme plaas feitlik geen klem op die behandeling van kinders nie, omdat kindertuberkulose selde aansteeklik is en die persepsie bestaan dat kinders slegs in raar gevalle ernstig siek word. Tuberkulose lewer egter 'n betekenisvolle bydrae tot kindermorbiditeit en mortaliteit in endemiese areas, terwyl dit 'n maklik behandelbare siekte is. Kindertuberkulose is moeilik om te diagnoseer en dit is 'n belangrike faktor wat daartoe bydra dat kinders dikwels nie antituberkulose behandeling ontvang wanneer hulle dit nodig nie.

Die diagnose van kindertuberkulose is moeilik, omdat die organisme selde aangetoon kan word. In nie endemiese areas word kindertuberkulose dikwels gediagnoseer na aanleiding van: 1) blootstelling aan 'n volwasse indeks geval, 2) 'n positiewe tuberkulien veltoets, en 3) die teenwoordigheid van radiologiese tekens suggestief van tuberkulose. Hierdie benadering het definitiewe tekortkominge in endemiese areas, waar blootstelling aan en infeksie met *Mycobacterium tuberculosis* algemeen is. Gevolglik berus die diagnose van kindertuberkulose hoofsaaklik op die subjektiewe interpretasie van die borskasplaat, wat welbekende tekortkominge het en verder is radiologiese toetse dikwels nie beskikbaar in hierdie areas nie. Die doel van die navorsingsprojek was om die dilemma rondom die diagnose van kindertuberkulose in endemiese areas aan te spreek.

Eerstens is basiese siektekonsepte uitsorteer deur 'n kritiese oorsig van studies uit die pre-chemoterapie era. Hierdie kosbare studies het die natuurlike verloop van tuberkulose in kinders beskryf, nog voordat antituberkulose middels beskikbaar was. Drie sentrale konsepte is geïdentifiseer; 1) die belang van akkurate siekte definisie, 2) die relevansie van risiko stratifikasie en 3) die diverse spektrum van patologie wat akkurate siekte klassifikasie noodsaak. Die belang van akkurate siekte definisie word geïllustreer deur die feit dat geïsoleerde hilêre adenopatie 'n verbygaande verskynsel is in die meerderheid van kinders kort na primêre infeksie. Ons analyse het daarop gefokus om die risiko om siekte te ontwikkel nadat primêre infeksie met *M.tuberculosis* plaasgevind het, te kwantifiseer. Die hoof risiko

faktore was; 1) die ouderdom en/of immuunstatus van die kind, 2) die tydsverloop sedert infeksie, en 3) die teenwoordigheid van simptome al dan nie.

Hierna het ons die siektelas wat tuberkulose vandag op kinders in endemiese areas plaas gedokumenteer. Ons het eers die huidige diagnostiese praktyke geëvalueer in 'n retrospektiewe studie en toe 'n prospektiewe beskrywende studie gedoen om die siektelas so akkuraat as moontlik te meet. Die insidensie van kindertuberkulose was hoog ( $>400/100\,000$ /jaar), selfs na korreksie vir kinders wat ontoepaslik behandeling ontvang het. Verder is gevind dat die meerderheid van kinders met ernstige siekte toestande soos miliêre tuberkulose en/of meningitis, nie in roetine moniterings data reflekteer word nie.

'n Bykomende struikelblok in kindertuberkulose is die gebrek aan standaard beskrywende terminologie. Om dit te bevorder ontwikkel ons 'n nuwe radiologiese klassifikasie van intra-torakale kindertuberkulose en beskryf ons die verskillende patologiese meganismes onderliggend tot hierdie uiteenlopende siektebeelde. Daarna dokumenteer ons die volledige spektrum van kindertuberkulose in 'n endemiese area en demonstreer dat die siektepatrone wat ons vandag observeer soortgelyk is aan die wat in die pre-chemoterapie literatuur beskryf is. Ons toon ook dat bakteriologiese bevestiging moontlik blyk te wees in die meerderheid van kinders wat vir intra-torakale tuberkulose behandel word in endemiese areas.

Nadat ons duidelikheid verkry het oor die basiese siektekonsepte, siekte klassifikasie en die siektelading in ons omgewing, kon ons op die ontwikkeling van 'n simptoombaseerde benadering tot die diagnose van kindertuberkulose fokus. Ons het 'n stapsgewyse benadering gevolg. Die eerste stap was om die voorkoms van simptome wat gebruiklik met tuberkulose vereenselwig word te dokumenteer in 'n ewekansige groep kinders. Die gemeenskapsopname het getoon dat swak gedefiniëerde simptome swak diagnostiese waarde bied. Die tweede stap was om vas te stel of verbeterde simptoomb definisie die diagnostiese waarde kan verbeter. 'n Klein prospektiewe studie het getoon dat goed gedefiniëerde simptome (persisterende simptome van onlangse aankoms) goeie diagnostiese waarde bied. Die finale stap was om hierdie belowende benadering formeel te toets in 'n

groot prospektiewe, gemeenskapsgebaseerde studie. Hierdie studie het getoon dat 'n eenvoudige simptoom-gebaseerde benadering pulmonale tuberkulose met goeie akkuraatheid kan diagnoseer, veral in HIV-ongeïnfekteerde kinders wat ouer is as 3 jaar.

Hierdie nuwe diagnostiese benadering bied die moontlikheid om antituberkulose behandeling te voorsien aan kinders in endemiese areas wat tans feitlik geen behandeling ontvang nie.

## **Dedication**

To my wife for her patience and support, to my children despite their lack of patience, and to the children of Africa who need our support

“It is a struggle of the African people, inspired by our own suffering and our own experience. It is a struggle for the right to live..... I have cherished the ideal of a democratic and free society in which all persons live together in harmony and with equal opportunities”

Nelson Mandela at the Rivonia trial 1964

From “Higher than Hope”, Fatima Meer 1988

“The resilience of the community of life and the well-being of humanity depend upon preserving a healthy biosphere with all its ecological systems, a rich variety of plants and animals, fertile soils, pure waters, and clean air. The global environment with its finite resources is a common concern of all peoples. The protection of the Earth’s vitality, diversity, and beauty is a sacred trust”

From the preamble of “The Earth Charter”, [www.earthcharter.org](http://www.earthcharter.org)

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## Chapter 1.

### Introduction

Tuberculosis (TB) is an old disease that has affected humankind since the earliest times. Suggestive spinal changes have been recorded in neolithic man, while tuberculosis has been confirmed in mummified remains from Egypt, dating back to 3400 BC.<sup>1</sup> Hippocrates (460-377 BC) introduced the ancient Greek term, *phthisis*, which became better known as consumption; later renamed tuberculosis. Tuberculosis flourished in Europe during the time of industrialization, causing an estimated 20% of all deaths in the British Isles during the 17<sup>th</sup> century;<sup>2</sup> John Bunyan declared tuberculosis “The captain of all these men of death”, in 1680. During the 20<sup>th</sup> century the prevalence of tuberculosis in Europe decreased to such an extent that it was commonly regarded a conquered foe in the developed world. However, during the later half of the 20<sup>th</sup> century the prevalence of tuberculosis escalated to epidemic proportions in many developing countries.

Fuelled by the immune-compromise that results from human immunodeficiency virus (HIV) infection, Sub-Saharan Africa currently has the highest tuberculosis incidence rates in the world and is worst affected by the dual TB-HIV epidemic.<sup>3,4</sup> As the gravity of the problem became apparent, a global tuberculosis emergency was declared by the World Health Organization (WHO) in 1993. At the start of the new millennium it was estimated that a third of the world's population is infected with *M. tuberculosis*; 8.3 million people develop tuberculosis annually and 1.8 million people die every year from tuberculosis.<sup>3</sup> However, the prevalence of tuberculosis varies greatly between countries, with poor developing countries carrying the bulk of the disease burden, while tuberculosis has become a disease of immigrant and marginalized populations in the developed world.<sup>5</sup>



The common perception is that children are not severely affected by tuberculosis, that they get mild forms of disease and that the main contribution of anti-tuberculosis chemotherapy in children is to eradicate the pool of latent infection, from which future reactivation disease may result. From a tuberculosis control point of view, the argument concludes that as children rarely become seriously ill and do not transmit the organism, their treatment is not a priority in highly endemic areas, and the best way to help children in these areas is to treat and prevent adult tuberculosis. Unfortunately, the almost exclusive emphasis placed on the treatment of adults with sputum smear-positive disease in endemic areas undermines service delivery to children.<sup>6</sup>

In reality, children contribute a substantial proportion of the tuberculosis disease burden, particularly in endemic areas such as sub-Saharan Africa. Of the estimated 8.3 million new tuberculosis cases diagnosed in 2000, 884 019 (11%) were children less than 15 years of age.<sup>4</sup> More recent estimates indicate that children contribute approximately 15% of the tuberculosis disease burden in low-income countries,<sup>4</sup> and this may be even higher in endemic areas.<sup>7,8</sup> Childhood tuberculosis results from recent transmission within a community, and therefore the number of diseased children reflects the level of epidemic control achieved in a particular setting. This explains the severe disease burden imposed on African children, where the epidemic is poorly controlled. Proof that African children suffer severe tuberculosis-related morbidity and mortality is provided by an autopsy study done in Zambia.<sup>9</sup> This study found that tuberculosis rivals acute pneumonia as a major cause of death from respiratory causes in children older than 1 year of age, particularly in HIV-uninfected children.<sup>9</sup> The two most common respiratory causes of death reported were; 1) in HIV-uninfected children 12-17 months of age, acute pyogenic pneumonia 57.9% and tuberculosis 36.8%, 2) in HIV-uninfected children 18 months to <16 years, tuberculosis 39.1% and acute pyogenic pneumonia 34.8%, 3) in HIV-infected children 12-17 months of age, acute pyogenic pneumonia 45.5% and tuberculosis 31.8%, 4) in HIV-infected children 18 months to <16 years, acute pyogenic pneumonia 52.0% and tuberculosis 20.0%.<sup>9</sup>

The majority of children who suffer from tuberculosis develop intra-thoracic disease. This is a more inclusive term than pulmonary tuberculosis, which is often defined as sputum smear-positive disease only. We used the terms intra-thoracic disease and childhood pulmonary tuberculosis interchangeably. A small percentage of children do develop sputum smear-positive disease, but they are usually older than 10 years of age and pose a major transmission risk in congregate settings such as schools.<sup>10</sup> Children with sputum smear-negative intra-thoracic tuberculosis do not pose a high transmission risk, but they suffer significant morbidity and mortality from a readily treatable disease.

The worldwide role-out of the Directly Observed Therapy Short course (DOTS) strategy has created an excellent treatment infrastructure, extending to the most resource-limited settings. However, despite the existence of this excellent infrastructure few children receive antituberculosis treatment at present.<sup>6</sup> Multiple factors contribute to the poor service delivery, but three of the main factors are 1) a lack of political commitment, 2) the almost exclusive emphasis on adults with sputum smear-positive disease, and 3) the difficulty of diagnosing childhood tuberculosis, especially in resource-limited endemic areas.

### ***Diagnostic dilemma***

The diagnosis of childhood tuberculosis is complicated by the absence of a practical gold standard. Bacteriological confirmation, the gold standard used in adults, is problematic as culture yields in children are considered to be low and collecting an adequate specimen is difficult. Acid-fast smears, often the only diagnostic test available in endemic areas, is positive in less than 10-15% of children with probable tuberculosis,<sup>11,12</sup> while *M. tuberculosis* can be isolated from less than 30-40% of children,<sup>11</sup> despite using optimal methods for specimen collection such as induced sputum.<sup>12</sup>

Due to the difficulty of achieving bacteriologic confirmation, the diagnosis of childhood tuberculosis in non-endemic areas is based upon; 1) known contact with an adult index case (usually within the household), 2) a positive tuberculin skin test (TST), and 3) suggestive signs on the chest radiograph. This triad provides a fairly accurate diagnosis in settings

where exposure to *M. tuberculosis* is rare and well documented. However, the diagnostic value of this triad is greatly reduced in endemic areas where exposure to *M. tuberculosis* is common and often undocumented as the majority of exposure occurs outside the household.<sup>13,14</sup> Infection with *M. tuberculosis*, as measured by a positive TST is also common. Consequently, the diagnosis of tuberculosis in endemic areas depends mainly on clinical features and the subjective interpretation of the chest radiograph,<sup>15</sup> which has well known limitations that result in both under- and over-diagnosis of tuberculosis.<sup>16,17</sup> In addition, chest radiography is rarely available in areas with limited resources.<sup>18</sup>

The tuberculin skin test (TST) was adapted from Robert Koch's failed attempt to treat tuberculosis using purified protein derivative (PPD). A positive TST provides a fairly accurate indication of infection with *M. tuberculosis*, although specificity is a concern with BCG vaccination or exposure to environmental mycobacteria,<sup>19</sup> and sensitivity is poor in HIV-infected and/or immune compromised children.<sup>20</sup> Recent advances in identifying *M. tuberculosis* infection include the development of T-cell based assays (T-spot and Quantiferon gold), which use a combination of *M. tuberculosis* specific antigens (ESAT-6 and CFP-10) that provide improved specificity and sensitivity in comparison to the traditional TST.<sup>19,21</sup> These new tests may offer particular value in HIV-infected and or immune compromised children,<sup>21</sup> where the TST performs poorly and the diagnosis of latent *M. tuberculosis* infection is highly relevant. However, current T-cell based assays do not differentiate latent *M. tuberculosis* infection from active disease, which is the major diagnostic challenge in endemic areas.

Current serological tests are unable to diagnose childhood tuberculosis with accuracy,<sup>22</sup> while sputum-based polymerase chain reaction (PCR) tests showed variable results and limited utility.<sup>23</sup> Good results were recently reported with the use of a heminested PCR technique, but the study used uninfected children as the control group and could therefore not evaluate the ability of this novel PCR-based test to differentiate latent infection from active disease.<sup>24</sup>

A variety of clinical diagnostic approaches, which include the use of symptoms, have been developed. A recent critical review evaluated all 16 clinical diagnostic approaches that have been published and concluded that they are limited by a lack of standard symptom definitions and adequate validation.<sup>25</sup> Recommendations were that symptom characteristics should be standardized, that novel diagnostic approaches should be developed for use in endemic areas with limited resources and that these approaches should be adequately validated. In addition, hospital-based studies have reported widely variable results regarding the utility of symptom-based approaches to diagnose tuberculosis in children. However, hospital-based studies are limited by extensive selection bias, which complicates interpretation and extrapolation of results to the community level.

The validation of novel diagnostic approaches is problematic, due to the absence of a gold standard case definition. Bacteriological confirmation is mainly limited by poor bacteriologic yields, but it is restricted by two other factors as well. Firstly, amongst diseased children, those with bacteriologic confirmation may represent a select sub-population that does not represent the full disease spectrum. Secondly, the ability to culture *M.tuberculosis* in healthy children shortly after primary infection indicates that the presence of a positive culture, in the absence of signs or symptoms suggestive of tuberculosis, does not necessarily represent disease. The alternative case definition that is frequently used is the presence of suggestive changes on the chest radiograph. Chest radiography has major limitations as well; 1) the subjective nature of radiograph interpretation, 2) the fact that minimal radiographic changes in isolation do not necessarily indicate disease, and 3) the fact that it cannot be included in both the case definition and the diagnostic approach evaluated.

In summary, accurate diagnosis is essential in order to improve service delivery to children with tuberculosis in resource-limited settings. Novel diagnostic approaches are required as none of the available diagnostic approaches are adequately validated and/or feasible in these settings. Adequate validation of a novel diagnostic approach requires a large, prospective study with; 1) community-based study entry to limit patient selection, and 2) accurate case

definitions that are both independent of the predictor variables tested and inclusive of the full disease spectrum in children.

### **Study objectives**

The main objective was to develop a novel symptom-based approach to diagnose childhood tuberculosis in a prospective, community-based study. However, we had to apply a stepwise approach with multiple specific aims to achieve this objective.

- 1) to clarify basic epidemiologic and clinical concepts by critically reviewing the pre-chemotherapy literature that documented the natural history of tuberculosis in children

These aims are addressed in chapter 2.

Two review articles describe the clinical epidemiology and the natural history of intra-thoracic tuberculosis in children.

- 2) to document the burden of childhood tuberculosis and to determine the accuracy of community-based surveillance data in an endemic area

These aims are addressed in chapter 3.

A retrospective descriptive study documented the diagnostic criteria used and the contribution of children to the overall tuberculosis disease burden in an endemic area. A prospective descriptive study then evaluated the accuracy of community-based surveillance data and calculated the actual disease burden in children.

- 3) to accurately classify the diverse manifestations of intra-thoracic tuberculosis in children and document the disease spectrum found in children from an endemic area

These aims are addressed in chapter 4.

A radiological classification of childhood intra-thoracic tuberculosis, based on a thorough review of the literature, is proposed and the pathologic mechanisms that underlie these diverse disease manifestations are described. A case-series described the occurrence of adult-type disease in children aged 10-14 years of age. A prospective descriptive study documented the complete spectrum of disease in children treated for tuberculosis in an

endemic area. A sub-analysis of this study demonstrated that bacteriologic confirmation may be achieved in the majority of children with intra-thoracic tuberculosis. A separate prospective descriptive study described the clinical presentation of tuberculous lymphadenitis, the most common extra-thoracic manifestation of tuberculosis in children.

- 4) to explore the value of symptom-based approaches; a) to screen household contacts for tuberculosis, and b) to diagnose pulmonary tuberculosis in children from an endemic area

These aims are addressed in chapter 5.

a) A prospective descriptive study evaluated the potential value of symptom-based screening to improve access to preventive chemotherapy in resource-limited settings. b) To achieve our main objective we performed 3 separate studies. A community-based survey documented the prevalence of symptoms traditionally associated with tuberculosis in a random selection of children. Then a small prospective cohort study evaluated the diagnostic value of well-defined symptoms. Finally, the diagnostic value of a novel symptom-based approach to diagnose pulmonary tuberculosis in children was validated in a large prospective, community-based study.

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## Chapter 2.

### The pre-chemotherapy literature

The pre-chemotherapy literature documents the natural history of tuberculosis in children. Unfortunately, modern clinicians and researchers have limited access to these important studies as they were all conducted before 1950 and are not included in modern electronic data banks. After the discovery of safe and effective anti-tuberculosis treatment, it became unethical to repeat studies on the natural history of disease, and therefore these historic disease descriptions remain invaluable. We attempted to make the most important findings from the pre-chemotherapy literature accessible for modern researchers and clinicians, and to interpret its relevance for the situation clinicians are faced with today.

- 1. Marais BJ, Gie RP, Schaaf HS, Hesselning AC, Obihara C, Nelson LJ, Enarson DA, Donald PR, Beyers N. The clinical epidemiology of childhood pulmonary tuberculosis – A critical review of the pre-chemotherapy literature. *Int J Tuberc L Dis.* 2004; 8: 278-285**

This review focused on the two major transitions in tuberculosis; 1) from exposure to infection, and 2) from infection to disease. Exposure occurred both inside the household and in the community. The risk of infection was highest (70-80%) following household exposure to a sputum smear-positive adult index case, but the risk remained appreciable, although greatly reduced (30-40%), if the adult index case was sputum-smear negative. The annual risk of infection (ARI) was not constant across age groups, but increased during times of widening social contact. Disease definition was problematic and not consistent across studies. Routine surveillance data indicated that very young children and adolescents were the groups at highest risk for disease and death.



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This review focused primarily on the transition from infection to disease, which was poorly quantified in the epidemiologic studies. It demonstrated the difficulty of distinguishing infection from disease, as elements of the primary complex became transiently visible on the chest radiograph, in the majority of children (50-60%) following primary infection. It illustrated the diverse spectrum of pathology in children with intra-thoracic tuberculosis and the prognostic relevance of accurate disease classification. It quantified the risk to progress to disease following primary infection with *M.tuberculosis* and emphasized the important concept of risk stratification. The most important determinants of risk were; 1) the age and/or immune-status of the child, 2) the time elapsed since primary infection occurred, and 3) the presence or absence of significant symptoms, defined as the breakpoint of clinical relevance.

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This letter addresses the important issue of how to define normality and disease. The relevance of any condition depends on the risk it poses to the individual and/or the community, which illustrates the importance of accurate risk analyses. Relevant disease defines the point where the risk posed by a particular condition, increases significantly beyond the baseline risk within a particular community. This definition challenges both the classic public health approach, which ranks relevance according to the proportional contribution made to the total disease burden; and the approach promoted by the pharmaceutical industry, which defines any statistically significant benefit as the “accepted standard of care”, irrespective of the baseline risk within a particular community.

# The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era

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## SUMMARY

The pre-chemotherapy literature represents an impressive body of evidence that clarifies important epidemiological concepts in childhood tuberculosis. Reports describe the major transitions in tuberculosis, from exposure to infection and from infection to disease (morbidity and mortality), without the influence of chemotherapy. Children with household exposure to a sputum smear-positive source case experienced the greatest risk of becoming infected and of developing subsequent disease. Household exposure to a sputum smear-negative source case or non-household exposure still posed an appreciable, although greatly reduced, risk. Infection in

children less than 2 years of age indicated a probable household source case. The majority of older children who were infected did not have a household source identified, and presumably became infected in the community. The annual risk of infection (ARI) was not constant across all ages, but seemed to increase during periods of widening social contact. Infants and adolescents were the groups at highest risk for disease development and death following primary infection.

**KEY WORDS:** review; pre-chemotherapy; epidemiology; childhood pulmonary tuberculosis

THE TWENTIETH CENTURY witnessed major advances in the understanding of the pathophysiology of childhood tuberculosis as well as its diagnosis and treatment. In particular, the period from 1920, when chest radiography became available for diagnosis, to 1950, when effective chemotherapy became available, represented an optimal window for the documentation of the natural history of tuberculosis.

During this period tuberculosis was still highly prevalent in Europe and America, where adequate infrastructure permitted the careful diagnosis and follow-up of tuberculosis patients. Detection of infection was possible with the tuberculin skin test (TST), while chest radiography allowed a more accurate diagnosis of pulmonary tuberculosis in children.

The aim of this review is to document the findings from the pre-chemotherapy literature concerning the clinical epidemiology of childhood pulmonary tuberculosis in a critical manner. The relevance of these historic findings is interpreted for the public health challenges faced today.

## METHODS AND MATERIALS

Original studies on childhood pulmonary tuberculosis, including the period 1920 to 1950 and published in the English literature, were identified from textbook references and extensive cross-referencing. Only studies reporting on more than 1000 children, with a study duration of at least 10 years, were included.<sup>1–8</sup> The database collected was compared to the International Union Against Tuberculosis and Lung Disease (IUATLD) archive in order to ensure that no major study was excluded. One exception was made with the inclusion of Gedde-Dahl's community-based article on tuberculin conversion. He followed patients for a maximum of 8 years, before the Second World War interrupted the study. However, his unique approach provided valuable insight by documenting tuberculin conversion and subsequent disease development in the community. Hospital-based studies introduced bias by preselection and therefore the inclusion of community-based studies was essential.

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Studies are reported in chronological order to illustrate the progression in knowledge. This review summarises the clinical epidemiological aspects of pulmonary tuberculosis in children. During this same period, basic science studies also improved the understanding of the epidemiology of tuberculosis by the accurate description of droplet airborne infection. These studies have been reviewed previously and are not included.<sup>9</sup>

A brief description of the individual studies and the study design employed in each is provided (Table 1). This is followed by a summary of the key findings and major limitations of each individual study (Table 2). The combined study results summarise the most important findings, with reference to the individual studies described in Tables 1 and 2.

The risk of developing disease (morbidity) or of dying from tuberculosis (mortality), following primary infection within a specific age group, was calculated from the original data reported by Bentley et al. (Table 3).<sup>5</sup> The percentage of children who developed primary infection within a specific age period was calculated by deducting the cumulative percentage of children with a positive TST recorded at entry from the cumulative percentage of children with a positive TST at exit from that age category. Multiplying this percentage with the average number of children who entered that age category annually provided an estimate of the number of children who developed primary infection within that age period. This number was used as denominator. The annual number of notifications for tuberculosis-related disease and death within that age group was used as numerator when calculating the disease and mortality percentages (Table 3).

## COMBINED STUDY RESULTS

### *Exposure to infection*

The Mantoux TST using 5 tuberculin units (TU) was the optimal test to identify tuberculosis infection.<sup>6,7</sup> The use of different tuberculin strengths complicated the interpretation of TST results and comparison between studies.<sup>7</sup> Reaction to high dose tuberculin (1 mg or 100 TU) probably represented exposure to environmental mycobacteria and not infection with *Mycobacterium tuberculosis*.<sup>7,8</sup> High-dose tuberculin was used following a negative reaction to standard-dose tuberculin in three of the studies.<sup>3,5,8</sup> Those with a positive reaction to high dose tuberculin were included amongst the infected group without further subanalysis, but they represented a small minority. The degree of induction induced by BCG vaccination was usually <10 mm, compared to natural infection, which was usually >10 mm.<sup>7</sup> BCG-induced hypersensitivity diminished with time and tuberculin responses frequently reverted after variable time periods depending on the BCG strain used. After natural infection, permanent rever-

sion occurred in less than 0.5% of children.<sup>4,6–8</sup> Temporary tuberculin inhibition did occur and was associated with wasting, viral illnesses or severe forms of tuberculosis.<sup>7</sup>

Following prolonged household contact with a sputum smear-positive source case, 60–80% of children became infected.<sup>3,6–8</sup> When the source case was smear-negative, 30–40% of children became infected.<sup>4,7,8</sup> The probability of infection in children depended on the infectivity of the source case together with the proximity and duration of contact with the source case. Local cultural practices may have contributed to different epidemiological patterns of disease spread,<sup>7</sup> e.g., extensive socialisation within rural African villages or the isolation of children and women in certain cultures. Brailey was the only author who related the time of TST conversion in the child contact to the time of symptom onset in the adult source case. More than 60% of the children who became infected did so within 3 months of symptom onset in the adult source case.<sup>3</sup> Infection was often delayed in household contacts under 2 years of age compared to older children, suggesting some protection from their reduced social contact within the family.<sup>3</sup> This delay was not evaluated separately in cases where the primary caregiver was the source case. Viral upper respiratory tract infections may have increased the likelihood of tuberculosis infection and contributed to the observed peak in infection during winter months.<sup>7</sup>

Most children (80%) who became infected before 2 years of age were infected by a household source case.<sup>3,5,7</sup> Additional caregivers outside the household were also important, especially grandparents or extended family members who took care of the children during the day, if both parents worked.<sup>7</sup> The majority of children who became infected after 2 years of age had no household contact identified, and were therefore likely to have been infected in the community.<sup>2,3,5,7,8</sup>

A separate issue raised by these studies was how the contribution of household exposure to primary infection varied according to the prevalence of tuberculosis in a specific community. In high prevalence areas, household exposure contributed to primary infection up until 15 years of age, by which time most children were already infected.<sup>5,8</sup> In low prevalence areas, household exposure remained an important contributor to primary infection until old age.<sup>5,8</sup> The risk of infection following household exposure was reduced under good socio-economic conditions.<sup>5,8</sup> There were no racial differences in the rate of infection following household exposure.<sup>3,8</sup>

The annual risk of infection (ARI) was not constant across all ages.<sup>5,7</sup> There were specific age periods when infection rates increased.<sup>5</sup> These age periods seemed to correlate with times of widening social contact. This occurred with increased mobility after 2 years of age, school entry at 5 to 7 years of age and school exit at 15 to 20 years of age (Table 3).<sup>5,7</sup> Primary

**Table 1** Description of the original studies and individual study designs documenting the clinical epidemiology of childhood pulmonary tuberculosis

Individual study reference	Time frame	Study type	Study population	Data collection methods
1 Opie E, McPhedran F M, Putnam P – 1935 Henry Phipps Institute, Philadelphia, PA, USA The fate of children in contact with tuberculosis: the exogenous infection of children and adults <sup>1</sup>	1907–1934 Follow-up period of 1–27 years	Retrospective descriptive, out-patient based	Children <15 years from 1000 families with an adult source case Mortality data for the city of Philadelphia	Adult source cases were self-selected Annual clinical follow-up of all source case contacts Annual CXR (if available)
2 Pope A S, Sartwell M D, Zacks D – 1939 State Department of Public Health (Chadwick Clinics), Boston, MA, USA Development of tuberculosis in infected children <sup>2</sup>	1924–1939 Follow-up period of 5–15 years	Prospective TST survey, school based	400 330 school children 6–16 years TB notification data for Boston	TST survey (Von Pirquet) CXR done if TST positive Annual CXR if the initial CXR was abnormal
3 Brailey M – 1940 Johns Hopkins (Harriet Lane Clinic), Baltimore, MD, USA A study of tuberculous infection and mortality in the children of tuberculous households <sup>3</sup>	1928–1937 Follow-up period of 1–10 years	Retrospective descriptive, out-patient based	1383 children <15 years from 285 families with an adult source case Mortality data for Baltimore	All children from tuberculous households screened Old tuberculin TST (0.1 or 1 mg) Annual CXR if TST positive
4 Gedde-Dahl T – 1951 Kinn district, Bergen, Norway Tuberculous infection in the light of tuberculin matriculation <sup>4</sup>	1937–1944 Follow-up period of 1–8 years	Prospective TST survey, community based	6739 people of all ages 3138 children <15 years	Annual community based TST survey (Von Pirquet) Documented TST conversion/matriculation Annual CXR once TST positive
5 Bentley F J, Grzybowski S, Benjamin B – 1954 High Wood Hospital for children, Brentwood, Essex, UK Tuberculosis in childhood and adolescence <sup>5</sup>	1901–1952 Notification data used	Audit of TB notifications Mathematical deductions	UK national TB notification data British MRC national TST survey	Reviewed TB notifications for the whole UK and specifically for London (1901–1952) Reviewed TST surveys D'Arcy Hart (1929), Prophit (1935–1944), British MRC (1949–1950)
6 Davies P D B – 1961 Brompton Hospital, London, UK The natural history of tuberculosis in children <sup>6</sup>	1930–1954 Follow-up period of 1–25 years	Retrospective descriptive, out-patient based	2377 children <15 years in household contact with an adult source case	Included all asymptomatic household contacts Different TSTs were compared Annual CXR
7 Miller F J W, Seal R M E, Taylor M D – 1963 Royal Victoria Infirmary, Newcastle upon Tyne Children's Sanatorium, Stannington, Northumberland, UK Tuberculosis in children <sup>7</sup>	1) 1947–1954 2) 1951–1961 Follow-up period of 1–10 years	Retrospective descriptive, out-patient based	1) Children <7 years from 1000 families with an adult source case 2) 1500 children <5 years in household contact with an adult source case	1) 1000 family study Household contacts <7 years Annual CXR + TST (until positive) 2) Household contact study Household contacts <5 years Annual CXR + TST (until positive)
8 Zeidberg L D, Gass R S, Dillon A, et al. – 1963 Tennessee Department of Public Health, USA The Williamson County tuberculosis study: a 24 year epidemiologic study <sup>8</sup>	1931–1955 Follow-up period of 1–24 years	Prospective community cohort study	1746 children <15 years from 828 families with an adult source case Tennessee mortality data	Voluntary inclusion of all household contacts Detailed questionnaire and physical examination Old tuberculin TST (0.1 or 1 mg) 6–12 monthly CXR

CXR = chest radiograph; TST = tuberculin skin test; MRC = Medical Research Council; UK = United Kingdom.

**Table 2** Summary of key findings and major limitations of the original studies, documenting the clinical epidemiology of childhood pulmonary tuberculosis

Citation	Features	Key findings	Major limitations
Opie et al. <sup>1</sup>	First to focus on families and children	Sputum positive exposure increased the frequency and severity of disease in childhood contacts The lifetime risk for the development of cavitating disease depended on the age at primary infection, increasing significantly after 10 years of age	TST not recorded Age groups poorly defined Limited CXR availability Sputum positivity not specified (smear or culture)
Pope et al. <sup>2</sup>	TST positivity School survey	Only 30% of infected school children had household contact with a known source case Cavitating pulmonary tuberculosis was seen in children >10 years of age only	TST conversion not recorded Selective follow-up (only those with initial CXR abnormalities were followed) Documented cavitating disease only
Brailey <sup>3</sup>	Focus on children <2 years of age Racial comparison	Infected children <2 years of age indicated an active household source case The majority of household contacts were infected within 3 months of symptom onset in the adult source case No racial difference in infection following exposure Definite racial difference in disease and mortality following infection	Public health entry point selected the poor Response to high dose (1 mg) tuberculin, used in a small minority of patients, is not specific for <i>M. tuberculosis</i> infection Sputum positivity not specified (smear or culture) Socio-economic differences were not evaluated
Gedde-Dahl <sup>4</sup>	TST conversion Community survey	The rate of TB infection and TB related mortality was increased in urban areas Radiological abnormalities were visible in 75% of children following primary TB infection	Preschool children were selectively represented (only contacts and symptomatic cases included) Results from this isolated community may be difficult to generalise
Bentley et al. <sup>5</sup>	Tuberculosis disease and mortality specified per age group Concept of relative contribution	The annual rate of infection (ARI) was not constant, but varied between different age groups The majority (90%) of TB-related radiological abnormalities were not detected in routine clinical practice The risk of disease and death following infection was the highest during infancy The relative contribution of TB to age-specific all-cause mortality was the lowest during infancy TB contributed significantly to all-cause mortality throughout childhood	Response to high dose (100 TU) tuberculin, used in 24% of subjects in the British MRC survey, is not specific for <i>M. tuberculosis</i> infection Relied exclusively on TB notification data for disease and mortality analysis
Davies <sup>6</sup>	Long-term follow-up Persistence of TST conversion	The Mantoux skin test outperformed other TSTs A positive tuberculin response persisted for >20 years Exposure to a sputum smear-positive vs. a smear-negative source case doubled the risk of infection Infection after exposure to a sputum smear-positive source case doubled the risk for disease and death	Majority of patients were already infected at study entry Selected only asymptomatic children at study entry, to ensure clinical uniformity
Miller et al. <sup>7</sup>	Comprehensive literature review	Clarified the confusion surrounding the interpretation of different TST techniques and doses Described the importance of cultural influences and the extended family Viral respiratory infections might have contributed to the seasonal variation in TB infection	Few deductions were made from own studies Validity of quoted studies was not evaluated Relied extensively on notification data
Zeidberg et al. <sup>8</sup>	Long term follow-up in the community	Identified critical periods of risk for disease development (infancy, puberty) Documented a drastic reduction in TB-related disease and mortality over the 24-year study period in black patients	Age at primary infection was not documented Entry criteria were adapted during the study A controversial finding, not supported by mortality data or results from other studies reviewed, was the delayed progression of disease reported in children infected between 1 and 15 years of age

TST = tuberculin skin test; CXR = chest radiograph; MRC = Medical Research Council; TU = tuberculin units.

**Table 3** The calculated risk of developing primary tuberculosis (TB) infection, compared to the calculated risk of being notified with TB-related disease or death following primary TB infection, within specific age groups

Age group, years	Calculated risk to develop primary TB infection* %	Calculated risk to be notified with TB-related disease, following primary TB infection† %	Calculated risk to be notified with TB-related death, following primary TB infection‡ %	Relative TB-related mortality§ %
<1	<1	11.9	6	0.6
1–4	10	5.6	1	12.1
5–9	20	3.8	0.3	9.1
10–14	10	6.4	0.5	9.1
15–24	30	10 (males) 13 (females)	1.5 (males) 2.6 (females)	16.7 (males) 39.4 (females)

\* Indicates the calculated percentage of children who develop primary infection (tuberculin conversion) within a specific age group.

† Indicates the number of children notified with TB, as a percentage of the total number expected to have developed primary TB infection, within a specific age group.

‡ Indicates the number of children notified with death due to TB, as a percentage of the total number expected to have developed primary TB infection within a specific age group.

§ Indicates the percentage of TB-related mortality compared to all-cause mortality within a specific age group.

Data on primary TB infection were collected from the British MRC tuberculin skin test survey for London (1949–1950).<sup>5</sup> This was converted into the number of children expected to develop primary infection within a specific age group, using national census data for London (1951). Data on TB-related disease and death were collected from TB notifications and death certificates for London (1945–1949).<sup>5</sup> Absolute notification numbers were converted into percentages, using the number expected to develop primary infection within a specific age group as denominator and accepting that all notifications result from recent primary infection. Relative TB-related mortality was calculated from death certificates for England and Wales (1950), comparing TB-related mortality with all-cause mortality.<sup>5</sup>

infection occurred at a younger age in high-density, low-income, urban areas.<sup>4–7</sup> The age-specific infection rate was the single most important public health indicator of the prevalence of disease in a given community.<sup>5,7,8</sup>

#### *Infection to disease (morbidity)*

To describe the progression from infection to disease accurately, a clear case definition of disease is required. Definitions of disease were not consistent across studies and disease was not well defined. Notification data were routinely used, reflecting passive case finding where any radiological abnormality attributed to tuberculosis was reported as tuberculous disease.

With constant community surveillance and active case finding it was found that a high percentage of children (50–70%) developed radiological abnormalities following primary infection. This was most common (60–80%) following primary infection before 2 years of age.<sup>3–5</sup> On comparison with notification data, it was clear that only 5–10% of children who developed radiological abnormalities during the natural course of the disease were notified as diseased (Table 3). This implied that more than 90% of radiological abnormalities passed undetected in routine clinical practice.<sup>5,7</sup>

The risk of radiological abnormality in children with household exposure to a sputum smear-positive source case and a positive TST was 30–50%.<sup>1,4,6–8</sup> This risk was reduced by 50% when the source case was sputum smear-negative or not a household member.<sup>1,4,6–8</sup> Duration since primary infection and age at primary infection determined the risk for disease development.<sup>4,5,7</sup> Most disease developed in the first year following primary infection.<sup>1,3,4,5,7</sup> Children with

primary infection before 2 years or after 10 years of age<sup>5,7</sup> and black children<sup>1,3,7,8</sup> were at increased risk for disease development. The increased susceptibility of black children declined drastically as socio-economic conditions improved during the Tennessee study.<sup>8</sup>

The risk of developing cavitating pulmonary tuberculosis depended on the age at primary infection. The highest risk for cavitating disease (10–20%) occurred in children who were first infected after 10 years of age, with perimenarchal girls being most vulnerable.<sup>1,2,5–8</sup>

#### *Mortality*

Tuberculosis-related mortality following infection from a sputum smear-positive household source case was twice as high as when infection occurred from an unknown source case.<sup>6–8</sup> All-cause mortality was similar in both these groups, indicating that the difference was not due to general increased mortality in the households of sputum smear-positive patients.<sup>1,3,7,8</sup>

The highest risk for TB-related mortality following primary infection (5–10%), occurred during infancy.<sup>1,3–5,7,8</sup> This risk declined to 1% between 1 and 4 years of age, with the lowest levels maintained at less than 0.5% from 5 to 14 years of age, before rising to more than 2% from 15 to 25 years of age (Table 3).<sup>5,7</sup> Most deaths from tuberculosis occurred within the first year following primary infection in children under 10 years of age,<sup>1,3,4,5,7</sup> but mortality lagged 5–10 years behind the onset of cavitating disease in older children.<sup>8</sup>

All-cause mortality exhibited an age-related pattern similar to that of tuberculosis-related mortality.<sup>5</sup> Therefore, the relative tuberculosis-related mortality best described the impact of tuberculosis on all-cause mortality within a specific age group.<sup>5</sup> Tuberculosis contributed significantly to all-cause mortality in all



age groups, except in infancy.<sup>3,5</sup> The low rate of infection and the high mortality from other causes during infancy explain this contradiction (Table 3).<sup>3,5,8</sup> Urbanised, densely populated areas suffered increased mortality from both tuberculosis and other causes.<sup>4,6</sup>

Black children suffered double the tuberculosis-related mortality and four times the all-cause mortality experienced by white children.<sup>3,7,8</sup> The tuberculosis-related mortality in black children declined by 80% during the Tennessee study.<sup>8</sup> A 10-fold decline in tuberculosis-related mortality occurred in Britain between 1900 and 1950, without a comparable decrease in tuberculosis infection.<sup>5,7</sup>

## DISCUSSION

The combined studies represent an impressive body of evidence and clarify some important epidemiological concepts in childhood tuberculosis. Household exposure to a sputum smear-positive source case posed the greatest risk to children. Household exposure to a sputum smear-negative source case or non-household exposure to a sputum smear-positive source case posed a reduced, but still appreciable risk.

It is a public health priority to identify and treat all sputum smear-positive source cases in the community. Therefore, prudent public health policy should encourage active case finding amongst household members of children infected before 2 years of age, as part of an expanded ('reverse') contact investigation. In low prevalence areas this active case finding may be extended to household members of all recently infected or diseased children, irrespective of age.

After 2 years of age, the majority of children from high prevalence areas became infected in the community. However, household exposure to a sputum smear-positive source case remained an important contributor to primary infection up to 5–10 years of age. Children with primary infection at 5–10 years of age had the lowest risk of disease development and death. In low-prevalence areas household exposure remains an important contributor to primary infection throughout life, and all household contacts, irrespective of age, require screening. These findings provided the scientific basis for classical contact investigation practices, which focus on children less than 5 years of age in most developing countries and all household contacts in most industrialised countries.

Another public health priority is the identification of children at risk of disease development and death. The calculated risk for disease development and death following primary infection within a specific age group represents a reinterpretation of original data, as outlined under methods (Table 3). Infants were at highest risk of disease development and death following primary infection. However, the use of accumulated tuberculin positivity as denominator in the original publication,<sup>5</sup> instead of tuberculin con-

verters within a specific age group, obscured the emergence of the second high-risk period around puberty. Children who were uninfected at 10 years of age were at considerable risk of developing adult-type cavitating disease following primary infection. This marked increase in risk may be obscured by analysis of notification data, due to the delay in disease notification that results from passive case finding in adult-type disease. Disease and mortality data for the age group 15–25 years probably contain a significant contribution from delayed disease notification following primary infection in the 10–14 year age group (Table 3).

Previously uninfected adolescents are a particularly vulnerable group, especially in high-prevalence communities where the risk of future infection is high. Mantoux skin testing at 7–9 years of age may aid in the identification of children who are still uninfected. Effective immunisation or active case finding may be warranted in this vulnerable group to reduce individual morbidity and disease transmission in the community. Children with a significant Mantoux reaction without prior anti-tuberculosis treatment may be offered treatment of latent infection to reduce the possible risk of future reactivation.

The relative tuberculosis-related mortality indicates that tuberculosis contributes significantly to all-cause mortality in high-burden areas throughout childhood. The relative contribution to all-cause mortality is lowest in infancy, but it does not detract from the important observation that infected infants represent the group at highest risk of death from tuberculosis.

It is difficult to separate racial and genetic factors from socio-economic and cultural influences. However, the dramatic decline in disease and mortality documented within a single generation, without a comparable decrease in infection,<sup>5,8</sup> emphasises the considerable influence of socio-economic improvement. This is contrary to the natural selection view proposed by Grigg in his influential article, 'The arcana of tuberculosis'.<sup>10</sup> The nature versus nurture issue is complex, and is far from resolved,<sup>11</sup> but improvement in the environment rather than genetic selection seems to be the main contributor to the dramatic reduction in tuberculosis witnessed in the developed world during the 20th century.

Important limitations of the individual studies were identified, and although the combined study results compensate for many of the individual study deficiencies, major limitations remain. Different methods of tuberculin administration were used, with the Mantoux intradermal technique established as the best method. Different strengths of tuberculin were used, with 5 TU providing the best sensitivity whilst retaining specificity. The sensitivity of the TST could not be measured due to lack of a gold standard, but it correlated well with exposure and radiographic proof of infection. The Mantoux skin test remains the accepted

method of documenting infection. Even with the advent of more sensitive and specific T-cell based assays (e.g., ELISPOT),<sup>12</sup> the skin test's sensitivity and specificity remain favourable and its simplicity unsurpassed.

The most important limitation to this analysis was the absence of a clear definition of disease. To gain a better understanding of the crucial transition from infection to disease, it is important to accurately define disease. Pulmonary tuberculosis represents a whole spectrum of pathology, and different disease entities need to be separated. Notification data often provide unreliable information due to under- or over-reporting of disease and inaccurate cause of death identification. Under-reporting of primary pulmonary tuberculosis in children was a particular problem.<sup>7</sup> In addition, the reported rate of infection varied considerably among studies, especially within the important younger age groups. The rate of primary infection accepted at a specific age influences the calculated risk of subsequent disease and mortality. Due to these limitations, risk calculations may vary widely. The optimal way to define risk and to describe exact disease entities is by prospectively following an unselected cohort of children with recent primary infection for subsequent disease development and death. Studies that documented the natural history of disease achieved this.

Despite the limitations of the articles reviewed, valuable epidemiological information is provided, which may assist with the formulation of evidence-based public health policies. The recent emergence of human immunodeficiency virus (HIV) infection in many high-prevalence areas, and its influence on morbidity and mortality, establish the need for new epidemiological data and the global epidemiological surveillance of tuberculosis in children.

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### RÉSUMÉ

La littérature pré-chimiothérapique représente un ensemble de faits impressionnants qui permettent de clarifier un important concept épidémiologique au sujet de la tuberculose de l'enfant. Elle décrit les transitions majeures dans la tuberculose : de l'exposition à l'infection et de l'infection à la maladie (morbidité et mortalité) en dehors de toute influence de la chimiothérapie. Les enfants exposés à leur domicile à un cas-source à bacillogoscopie positive des expectorations ont le risque le plus élevé de développer une infection et une maladie ultérieure. L'exposition à domicile à un cas-source à bacillogoscopie négative ou l'exposition en dehors du domicile comporte toujours un risque appréciable quoique forte-

ment réduit. Les enfants chez qui l'on découvre une infection avant l'âge de 2 ans suggèrent la probabilité d'un cas-source dans le ménage. Chez la majorité des enfants plus âgés qui ont été infectés, on n'a pas pu identifier une source au sein de ménage ; ils ont probablement été infectés dans la collectivité. Le risque annuel d'infection (RAI) n'est pas constant au fil des âges mais semble augmenter au cours des périodes d'élargissement des contacts sociaux. Les nourrissons et les adolescents ont été les groupes où le risque de développement de la maladie et celui de décès sont les plus élevés dans les suites de la primo-infection.



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**RESUMEN**

La literatura de la era prequimioterapia representa un conjunto impresionante de evidencias que clarifican importantes conceptos epidemiológicos de la tuberculosis infantil. Ella describe las transiciones más importantes de la tuberculosis, desde la exposición y desde la infección hasta la enfermedad (morbilidad y mortalidad), sin la influencia de la quimioterapia. Los niños expuestos en el domicilio a casos índices con baciloscopia positiva tenían el mayor riesgo de desarrollar la infección y la enfermedad subsecuente. La exposición en el domicilio a casos índices con baciloscopia negativa o la exposición fuera del domicilio tenía un riesgo apreci-

able, aunque considerablemente reducido. La constatación de una infección en un niño menor de 2 años indicaba la existencia probable de un caso índice en el domicilio. En la mayoría de los niños mayores de 2 años que estaban infectados no se identificaba un caso índice en el domicilio y presumiblemente habían sido infectados en la comunidad. El riesgo anual de infección (ARI) no era constante a través de las edades, sino que parecía aumentar durante los períodos en los que los contactos sociales se multiplicaban. Los lactantes y los adolescentes eran grupos de alto riesgo para el desarrollo de la enfermedad y muerte después de la infección primaria.

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## The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era

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### SUMMARY

The pre-chemotherapy literature documented the natural history of tuberculosis in childhood. These disease descriptions remain invaluable for guiding public health policy and research, as the introduction of effective chemotherapy radically changed the history of disease. Specific high-risk groups were identified. Primary infection before 2 years of age frequently progressed to serious disease within the first 12 months without significant prior symptoms. Primary infection between 2 and 10 years of age rarely progressed to serious disease, and such progression was associated with significant clinical symptoms. In children aged >3 years the presence of symptoms represented a window of opportunity in which to establish a clinical diagnosis before serious disease progression. Primary infection after 10 years of age frequently progressed to adult-type disease. Early effective inter-

vention in this group will reduce the burden of cavitating disease and associated disease transmission in the community. Although the pre-chemotherapy literature excluded the influence of human immune deficiency virus (HIV) infection, recent disease descriptions in HIV-infected children indicate that immune-compromised children behave in a similar fashion to immune immature children (less than 2 years of age). An important concept deduced from the natural history of tuberculosis in childhood is that of relevant disease. Deciding which children to treat may be extremely difficult in high-prevalence, low-resource settings. The concept of relevant disease provides guidance for more effective public health intervention.

**KEY WORDS:** review; pre-chemotherapy; natural history; child pulmonary tuberculosis

DURING THE TWENTIETH CENTURY, major advances occurred in the diagnosis and treatment of tuberculosis. Detection of infection became possible with the tuberculin skin test (TST), and diagnosis of disease was enhanced with the use of chest radiography. When chest radiography became available after the First World War, it increased the capacity to detect pulmonary tuberculosis and permitted the evaluation of the extent of lung disease, but it was not particularly specific in determining disease activity. The most important advance in the diagnosis of tuberculosis was the ability to detect the causative organism on direct microscopy of clinical specimens and to isolate *Mycobacterium tuberculosis* in cultures of these specimens. This advance, however, had minimal impact on improving the management of tuberculosis in children, as compared to adults, few children display the organism in clinical specimens.

The first anti-tuberculosis drugs were introduced

after the Second World War with more effective drugs following in the early 1950s. This enabled most cases of tuberculosis to be cured of their disease. The period from 1920 to 1950 represents the time when chest radiography was available for accurate disease diagnosis and description, without effective treatment to influence the natural history of disease. Excellent observational studies were conducted during this time, characterised by the meticulous long-term follow-up of patients. This invaluable source of information provided detailed descriptions of disease presentation and progression without the influence of chemotherapy or human immunodeficiency virus (HIV) infection.

A review of the pre-chemotherapy literature and the knowledge gained is important for the following reasons: 1) to assist with establishing an optimal case definition to be used as an outcome measure for research purposes when evaluating new drug treatments, new

diagnostic modalities or new vaccines; and 2) to assist in establishing a working case definition to guide public health intervention by determining which infected cases (drug-sensitive or drug-resistant) require treatment.

The aim of this review was to document the findings of the pre-chemotherapy literature in a critical manner and to describe the natural history of intra-thoracic tuberculosis in children. The relevance of these findings is interpreted for the public health challenges faced today.

## METHODS AND MATERIALS

Original studies on childhood pulmonary tuberculosis, conducted between 1920 and 1950 and published in the English literature, were identified from textbook references and extensive cross-referencing. Major studies reporting on more than 1000 children and with a study duration of at least 10 years were included.<sup>1-9</sup> The database collected was then compared to the International Union Against Tuberculosis and Lung Disease (IUATLD) archive to ensure that no major study had been excluded. Three exceptions were made: 1) Avrid Wallgren's findings were based on a lifetime of personal experience and careful observation. Although he only reported prospectively on 100 exposed children who became infected under observation, he described the very influential timetable of primary tuberculosis.<sup>1-3</sup> 2) Tobias Gedde-Dahl included 3138 children, but the study was interrupted after 8 years due to the Second World War. The study's contribution is important because it provides the only accurate description of active community surveillance. 3) Edith Lincoln reported on 964 children followed for up to 25 years and provided unique descriptions of the clinical signs and symptoms that develop during disease progression.<sup>8</sup> The combination of community and hospital-based studies ensures representation of the whole spectrum of disease. Studies are reported in chronological order to illustrate the progression in knowledge.

A brief description of the individual studies and the design used in each study is provided (Table 1). This is followed by a summary of the key findings and major limitations of each individual study (Table 2). The combined study results provide a summary of the major findings.

A uniform template of disease classification was developed and applied to all the studies included in this review to facilitate the comparison and combination of results. This template is based on disease descriptions and concepts of pathology derived from the pre-chemotherapy literature (Table 3). It is important to note that more than one disease entity may co-exist at the same time or develop during the course of disease.

Children were defined as age less than 15 years. Only Bentley et al. included 15 years in their definition of a child.<sup>6</sup> Adolescents were defined as children aged over

10 years. Primary infection was defined as first time tuberculosis infection as represented by TST conversion.

## COMBINED STUDY RESULTS

Wallgren summarised the sequence of pathology following primary infection in childhood in great detail.<sup>1</sup> His pathological summary correlated well with clinical observations, which he documented in the timetable of tuberculosis. This was later confirmed and expanded by other investigators.

### *Sequence of pathology after pulmonary infection in childhood*

Pulmonary infection occurs when a few tuberculosis bacilli successfully reach a terminal airway after inhalation. A localised pneumonic inflammatory process results, called the parenchymal focus. From this parenchymal (Ghon) focus, bacilli drain via local lymphatics to the regional lymph nodes. The Ghon focus, with associated local tuberculous lymphangitis and involvement of the regional lymph nodes, is called the primary complex. From the regional lymph nodes, bacilli enter the systemic circulation directly or via the lymphatic duct. This occult haematogenous spread occurs during the incubation period, before adequate immune responses contain the disease. After dissemination, bacilli may survive in target organs for prolonged periods.<sup>1</sup> The future course of the disease depends on the dynamic balance between host immunity and the pathogen.<sup>1,3,6,8,9</sup>

### *Timetable of clinical disease after pulmonary infection in childhood*

- Phase 1 occurred 3-8 weeks after primary infection.<sup>1,3</sup> The end of the initial asymptomatic incubation period was heralded clinically by hypersensitivity reactions such as initial fever, erythema nodosum, a positive tuberculin skin test response and formation of the primary complex visible on chest radiograph.<sup>1,3</sup>
- Phase 2 occurred 1-3 months after primary infection.<sup>3</sup> This period followed the occult haematogenous spread that occurred during incubation, and represented the period of highest risk for the development of tuberculous meningitis and miliary tuberculosis in young children.<sup>1,3</sup> However, tuberculous meningitis and miliary disease occurred after any time interval following disease progression with haematogenous dissemination.<sup>5,6,8,9</sup>
- Phase 3 occurred 3-7 months after primary infection.<sup>3</sup> This was the period of pleural effusions in children aged over 5 years,<sup>3</sup> and bronchial disease in children aged less than 5 years.<sup>5,6,8,9</sup>
- Phase 4 lasted until the primary complex was calcified, 1-3 years after primary infection.<sup>3</sup> This was the period of osteo-articular tuberculosis in chil-

**Table 1** Description of original studies and individual study designs documenting the natural history of childhood intra-thoracic tuberculosis

Individual study reference	Time frame	Study type	Study population	Data collection methods
1 Wallgren A—1935, 1938, 1948 Children's Hospital, Gothenburg and the Karolinska Medical Institute, Stockholm, Sweden Primary pulmonary tuberculosis in childhood <sup>1</sup> Relation of childhood infection to the disease in adults <sup>2</sup> The timetable of tuberculosis <sup>3</sup>	1930–1950 Follow-up period not specified	Prospective descriptive, hospital-based Personal experience	100 newly infected children All children with TB seen on referral	Children observed after household exposure Meticulous documentation of signs/symptoms following infection In addition, Wallgren drew from vast personal experience
2 Brailey M—1940 Johns Hopkins (Harriet Lane Clinic), Baltimore, Maryland, USA Prognosis in white and coloured tuberculous children according to initial chest X-ray findings <sup>4</sup>	1928–1937 Follow-up period of 1–10 years	Retrospective descriptive, out-patient-based	285 families with 1383 children <15 years 40% white 60% black	All children from tuberculous households TST (Old tuberculin at 0.1 or 1 mg) Annual CXR if TST-positive
3 Gedde-Dahl T—1951 Kinn District, Bergen, Norway Tuberculous infection in the light of tuberculin matriculation/conversion <sup>5</sup>	1937–1944 Follow-up period of 1–8 years	Prospective TST survey, community-based	6739 people 3138 children <15 years	Annual community-based TST survey (Von Pirquet) Documented TST conversion Annual CXR if TST-positive
4 Bentley F J, Grzbowski S, Benjamin B—1954 High Wood Hospital for children, Brentwood, Essex, UK Tuberculosis in childhood and adolescence <sup>6</sup>	1942–1952 Follow-up period of 5–10 years	Retrospective descriptive, hospital-based Literature review	1) Sanatorium patients 1049 children <16 years 2) Death investigation 100 consecutive TB deaths in children	Successive referrals admitted over a 10-year period Observation and CXR in hospital Review CXR 5–10 years after hospital discharge
5 Davies P D B—1961 Brompton Hospital, London, UK The natural history of tuberculosis in children <sup>7</sup>	1930–1954 Follow-up period of 2–25 years	Retrospective descriptive, out-patient-based	2377 children <15 years	All asymptomatic household contacts Different TSTs compared Annual CXR 70% follow-up achieved
6 Lincoln E M, Sewell E M—1963 Bellevue Hospital, New York City, New York, USA Tuberculosis in children <sup>8</sup>	1930–1960 Follow-up period of 10–25 years	Prospective descriptive, hospital-based	Sanatorium patients 954 <15 years 50% white 25% black 25% Puerto Rican	Children referred with evidence of recent (uncalcified) TB Observation and CXR in hospital Hospitalised for extended periods with careful documentation of disease progression Annual CXR after discharge 90% follow-up achieved
7 Miller F J W, Seal R M E, Taylor M D—1963 Royal Victoria Infirmary, Newcastle upon Tyne and Children's Sanatorium at Stannington, Northumberland, UK Tuberculosis in children <sup>9</sup>	1) 1941–1951 2) 1951–1961 Follow-up period of 1–10 years	Retrospective descriptive, out-patient-based Literature review	1) Children <7 years from 1000 families with an adult source case 2) 1500 children <5 years in household contact with an adult source case	1) 1000 family study Household contacts <7 years Annual CXR+TST (until positive) 99 TST converted 2) Household contact study Household contacts <5 years Annual CXR+TST (until positive) 72 TST converted

TST = tuberculin skin test; CXR = chest radiograph; TB = tuberculosis.

dren aged under 5 years,<sup>3,9</sup> and adult-type disease in adolescents.<sup>2–9</sup> As a general rule the risk of disease progression following primary infection had passed by the time calcification appeared.<sup>4–9</sup> However, adult-type disease with delayed clinical onset after primary infection did occur after calcification was present.<sup>7,9</sup>

- Phase 5 occurred after calcification was completed, more than 3 years after primary infection. This

represented the period in which the late manifestations of tuberculosis, including pulmonary reactivation disease, developed.<sup>6,9</sup>

The classic timetable, illustrated schematically as the timeline of tuberculosis (Figure 1), described common clinical patterns of disease and does not represent dogmatic rules regarding the course of tuberculosis in

**Table 2** Summary of key findings and major limitations of the original studies that documented the natural history of childhood intra-thoracic tuberculosis

Citation	Age groups	Unique feature	Key findings	Major limitations
Wallgren <sup>1-3</sup>	2 groups <3, 3–14 years	Meticulous observation Detailed description of symptoms and signs following primary infection	Age at primary infection and time since primary infection were major determinants of risk for disease development following infection. It also influenced the type of disease manifestation Host immunity was influenced by age and considered to be of crucial importance Documented the timetable of disease	Study methodology was not specified Observations were illustrated with case studies Guidelines provided were dogmatic
Brailley <sup>4</sup>	5 groups <1, 1–2, 2–4, 5–9, 10–14 years	Relevant age groups Racial differences	In all children <2 years and in black children <5 years segmental lung lesions were predominant Black children suffered increased morbidity and mortality	Public health entry point selected the poor Type of segmental lesion not specified Socio-economic differences not evaluated
Gedde-Dahl <sup>5</sup>	3 groups <5, 5–9, 10–14 years	TST conversion in the community	Enlarged nodes were visible on CXR in the vast majority of recently infected children All CXR changes apart from cavitation and calcification were seen within 1 year after infection	Pre-school children were poorly and selectively represented Isolated community
Bentley et al. <sup>6</sup>	4 groups <1, 1–4, 5–9, 10–15 years	First dedicated childhood TB study in UK	Described the slow rate at which adenopathy undergoes radiological regression Suggested to focus on high risk groups: (<2 years and >10 years of age)	Excessive preselection occurred due to the referral system and long waiting periods Disease progression was not well documented
Davies <sup>7</sup>	4 groups <1, 1–4, 5–9, 10–14 years	UK study with longest follow-up period	Progression of disease was documented even after calcification became visible Risk of cavitating disease was highly dependent on age at primary infection (>10 years)	Selected only asymptomatic children at study entry, to ensure clinical unity Majority of children were already infected at study entry
Lincoln et al. <sup>8</sup>	4 groups <1, 1–4, 5–9, 10–14 years	Detailed description of disease progression	Meticulously documented disease progression together with the signs, symptoms and outcome associated with each specific disease entity	Study inclusion was selective (symptomatic children with CXR evidence of recent infection) Limited racial sub-analysis
Miller et al. <sup>9</sup>	5 groups <1, 1–2, 2–4, 5–9, 10–14 years	Relevant age groups Comprehensive literature review	Informative illustrations of lymph drainage and TB lung pathology Re-emphasised high-risk groups following primary infection (<2 years and >10 years of age) Cavitating disease may follow primary infection, reinfection or reactivation	Cavitation with visible calcification was accepted as proof of reactivation Validity of studies quoted were not evaluated

TST = tuberculin skin test; CXR = chest radiograph; UK = United Kingdom; TB = tuberculosis.

children. The vast majority of disease manifestations occurred in the first 6–12 months following primary infection.<sup>5,7,9</sup>

### COMBINED STUDY RESULTS ACCORDING TO THE TEMPLATE USED FOR DISEASE CLASSIFICATION

The pathology-based disease classification outlined in Table 3 describes distinct disease entities. This was used as a template to compare and combine results. The combined results illustrate the clinical and radiological presentation, as well as the risk factors for and the prognosis of each distinct disease entity.

#### *Pulmonary infection*

Pulmonary infection was identified after active contact tracing or presentation of children by anxious parents.<sup>6,8,9</sup> Pulmonary infection was associated with

TST conversion and non-specific, self limiting, viral-like respiratory symptoms.<sup>1-3,6,9</sup> Enlarged regional lymph nodes on chest radiograph were the hallmark of pulmonary infection with or without a visible Ghon focus.<sup>5-9</sup> Following primary infection, 50–70% of children showed these radiological signs, irrespective of symptoms.<sup>5,7,9</sup> Good quality antero-posterior and lateral radiographic views were required for optimal visualisation of enlarged regional lymph nodes.<sup>6,8,9</sup> The Ghon focus had no predilection for any specific part of the lung:<sup>5,7,8</sup> a Ghon focus in the apex of the lung affected the ipsilateral paratracheal nodes;<sup>6,8</sup> a Ghon focus in other parts of the right lung caused right-sided hilar adenopathy; and a Ghon focus in the lower parts of the left lung caused bilateral hilar adenopathy.<sup>6,8</sup> Paratracheal nodes reflected a Ghon focus in the apex, spread from hilar glands, or haematogenous spread.<sup>6</sup> It occurred more frequently in children under 2 years of age and showed a consistent trend

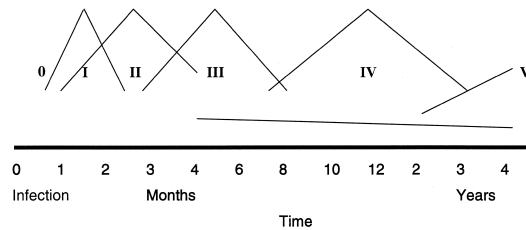
**Table 3** Disease classification of childhood pulmonary tuberculosis used as template

Pulmonary infection	Tuberculosis infection uncomplicated by clinical symptoms (other than self-limiting, viral-like illness) or radiological abnormalities (other than the primary complex). The primary complex includes the Ghon focus with associated tuberculous lymphangitis and affected regional lymph nodes. Pulmonary infection without progression to disease implies successful containment of the organism.
Pulmonary disease	Tuberculosis infection complicated by marked clinical symptoms or additional radiological abnormalities apart from the primary complex. Pulmonary disease includes a diverse spectrum of pathology, described as separate disease entities.
Separate disease entities	
Ghon focus with/without cavitation	Progressive parenchymal caseation surrounding the Ghon focus represents poor organism containment. The area of caseation may discharge into a bronchus, resulting in the formation of a cavity with possible endobronchial spread.
Lymph node disease	Regional lymph node enlargement forms part of the primary complex, but the presence of marked clinical symptoms differentiates lymph node disease from pulmonary infection.
Bronchial disease	With pulmonary infection, affected regional lymph nodes attach to the bronchus, but rarely progress to clinical or radiological disease. If disease progression follows this 'lympho-bronchial involvement', the affected bronchus may become partially or totally obstructed as a result of nodal compression, inflammatory oedema, polyps, granulomatous tissue or caseous material extruded from ulcerated lymph nodes. Distal parenchymal disease may result from aspiration of caseous material. Variation in the degree of airway obstruction, dose and virulence of the bacilli aspirated and the immune status of the host, determines the degree of pathology.
With airway obstruction	Airway obstruction occurs due to enlarged matted nodes encircling and compressing an airway, together with associated inflammation or additional processes described above.
With collapse/hyperinflation	Complete airway obstruction leads to resorption of distal air and collapse, while partial airway obstruction may cause a ball-valve effect with hyperinflation of the segment or lobe supplied.
With allergic consolidation	Nodal perforation into an airway with endobronchial aspiration of allergic products causes an acute hypersensitivity response (epituberculosis) with dense consolidation.
With bronchopneumonic consolidation	Nodal perforation into an airway with endobronchial aspiration of live bacilli causes local areas of caseation surrounding the airways, resulting in patchy consolidation.
With caseating consolidation	Nodal perforation into an airway with endobronchial aspiration of live bacilli causes extensive parenchymal caseation, resulting in dense expansile consolidation of the affected segment or lobe.
Pleural disease	Pleural involvement occurs after direct spread of caseous material from a sub-pleural parenchymal or lymph node focus, or from haematogenous spread. Variation in the dose and virulence of bacilli that enter the pleural space together with the immune status of the host determines the degree of pathology.
With effusion	The presence of caseous material in the pleural space triggers a hypersensitivity inflammatory response with the accumulation of serous straw-coloured fluid containing few tuberculosis bacilli.
With empyema	Active caseation in the pleural space causes thick loculated pus, containing many tuberculosis bacilli.
With adult-type disease	Excessive local containment may cause parenchymal destruction and resultant cavity formation. Tubercle bacilli flourish in these cavities from where they disseminate to other parts of the lung via endobronchial spread. Endobronchial spread occurs directly from these infected cavities and is not dependent on lymphobronchial breakthrough, as with bronchial disease.
Haematogenous spread	Tuberculosis bacilli may enter the blood stream via pulmonary lymphatic drainage, from affected regional lymph nodes or directly from the parenchymal focus. Haematogenous spread is a condition of infinite gradation, depending on the frequency, dose and virulence of the bacilli released as well as host immunity. During occult spread bacilli are seeded into susceptible organs, while the child remains asymptomatic.
With miliary disease	Following invasion of the blood stream, tuberculosis bacilli lodge in small capillaries, where they may progress to form tubercles, visible on chest radiograph as typical, even-sized miliary lesions (<2 mm) or atypical lesions of differing size.

towards increased haematogenous spread, even with correction for age.<sup>6</sup> During the first 3–4 months the lymph nodes were in a phase of 'full activity': vaguely defined, cloudy and homogeneous.<sup>6</sup> Over the following months the radiological signs of 'activity' regressed, the shadow became denser, better defined and more heterogeneous.<sup>6</sup> With serial radiographs, 40% of lesions cleared within 6 months, a further 30% within 1 year, and the remainder persisted for up to 4 years.<sup>6,9</sup> Calcification developed in 20–50% of children with visible lymph node involvement.<sup>6,7,9</sup> Calcification usually occurred between 12 and 24 months,

but was rarely delayed up to 4 years after primary infection.<sup>6,9</sup> Calcification in young children tended to be more extensive and developed earlier (within 6–12 months) than in older children.<sup>6,7</sup> In general, calcification was an indication of clinical quiescence, but not a guarantee thereof.<sup>7–9</sup> The disappearance of calcification was rare and was attributed to either resorption or bronchial escape of a pneumolyth.<sup>9</sup> The prognosis of pulmonary infection was favourable, with the associated risk mainly dependent on the age at the time of primary infection (Table 4).<sup>1–9</sup> Neither the presence of a visible parenchymal lesion nor the size of regional





**Figure 1** Schematic timeline of primary pulmonary tuberculosis. Phase of disease (adapted from the timetable of tuberculosis described by Wallgren<sup>3</sup>)

- 0 Incubation phase
- I Hypersensitivity phase
- II Phase of miliary tuberculosis and tuberculous meningitis
- III Phase of segmental lesions in children aged under 5 years and pleural effusion in those aged over 5 years
- IV Phase of osteo-articular tuberculosis in children aged under 5 years and adult-type disease in those aged over 10 years
- V Phase of late manifestations including pulmonary reactivation disease.

Not all these disease manifestations (phases) are equally common, and while hypersensitivity is a nearly universal phenomenon following primary infection, the late manifestations are extremely rare. Table 4 provides an indication of how common the most important of these disease manifestations are in specific age groups.

hilar lymph nodes influenced the prognosis, apart from an increase in segmental lesions.<sup>6</sup>

#### Pulmonary disease

Host immunity was considered to be the major determinant of risk for disease development following

**Table 4** Average age specific risk for disease development following primary infection

Age at primary infection	Immune-competent children (dominant disease entity indicated in brackets)	Risk of disease following primary infection %
<1 year	No disease	50
	Pulmonary disease (Ghon focus, lymph node, or bronchial)	30–40
	TBM or miliary disease	10–20
1–2 years	No disease	70–80
	Pulmonary disease (Ghon focus, lymph node, or bronchial)	10–10
	TBM or miliary disease	2–5
2–5 years	No disease	95
	Pulmonary disease (lymph node, or bronchial)	5
	TBM or miliary disease	0.5
5–10 years	No disease	98
	Pulmonary disease (lymph node, bronchial, effusion or adult-type)	2
	TBM or miliary disease	<0.5
>10 years	No disease	80–90
	Pulmonary disease (effusion or adult-type)	10–20
	TBM or miliary disease	<0.5

TBM = tuberculous meningitis.

infection.<sup>1</sup> Infants, with immature immune systems, were at highest risk,<sup>1–9</sup> with pulmonary disease developing in 30–40% and tuberculous meningitis (TBM) or miliary disease in a further 10–20%.<sup>4,6,8,9</sup> The risk decreased considerably in the second year of life, but remained significant, with 10–20% of infected children developing pulmonary disease and a further 2–5% TBM or miliary disease.<sup>8,9</sup> This risk decreased to less significant levels in the 2–5 year age group before reaching its lowest level at 5–10 years of age (Table 4).<sup>4,6,8,9</sup> Bronchial disease predominated in children aged under 5 years.<sup>6–9</sup> Pleural effusions increased in incidence from 5 years of age onward.<sup>6–9</sup> Disease rarely occurred in children aged 5–10 years, with pleural effusion the most common manifestation. Within this age group bronchial disease was more common in younger children and adult-type disease in older children.<sup>6–9</sup> Black children had an increased risk of developing bronchial disease across all age groups.<sup>4</sup> Primary infection during adolescence was associated with a high risk (10–20%) of developing adult-type disease.<sup>1–9</sup> The risk and the type of disease that followed primary infection is summarised for specific age groups (Table 4).

#### Ghon focus with/without cavitation

A Ghon focus with cavitation was rare. It occurred predominantly in black children aged under 2 years.<sup>4,6,8,9</sup> Clinical symptoms of Ghon focus cavitation included weight loss, fatigue, fever and chronic cough.<sup>8,9</sup> In those with cavitation, disease progressed to death within 1 year in the majority of cases.<sup>8,9</sup> Healing was rare, and even those that survived the initial illness ultimately died from tuberculosis or associated complications.<sup>8</sup> Cavitation following primary infection occurred frequently during adolescence,<sup>2,5–9</sup> but in this age group parenchymal breakdown probably reflected excessive rather than poor disease containment. This is discussed under the heading, adult-type disease.<sup>2,9</sup>

#### Lymph node disease

Enlarged regional lymph nodes on chest radiograph rarely caused symptoms except when they were associated with bronchial disease, or when excessive nodal caseation caused persistent fever and weight loss.<sup>9</sup> The subcarinal nodes were most commonly involved and rarely pericardial effusion developed following nodal erosion with caseous discharge into the pericardial space.<sup>9</sup>

#### Bronchial disease

Different degrees of airway obstruction and/or parenchymal involvement reflected a spectrum bronchial disease. Bronchial disease occurred predominantly in children aged under 5 years. It occurred more frequently in younger children, boys,<sup>6–9</sup> and black children.<sup>4</sup> The most frequently affected lobes were the right upper lobe (anterior segment), the right middle

lobe and the left upper lobe.<sup>6-9</sup> The lobes most frequently affected in combination were the right middle and lower lobes, indicating involvement of the bronchus intermedius.<sup>6-9</sup> Rebound enlargement of segmental lesions, attributed to immune reconstitution, were described after cessation of high-dose steroid treatment.<sup>9</sup> Bronchoscopy results reflected the pathological spectrum of bronchial involvement: no visible involvement, obstruction from external nodal compression, endobronchial nodal breakthrough with caseous drainage, granulation tissue with polyps and fistula formation.<sup>6,8</sup> A very rare sequel was the expectoration of a pneumolyth after perforation of a calcified lymph node into an airway.<sup>8,9</sup> The prognosis of bronchial disease and associated distal parenchymal involvement depended on the type and duration of involvement.<sup>6,8,9</sup>

### *Bronchial disease*

**WITH AIRWAY OBSTRUCTION.** Symptoms varied according to the degree of airway irritation and obstruction. Infants frequently developed a persistent cough, sometimes mimicking pertussis.<sup>8,9</sup> With disease progression the cough became more prominent, often brassy or bitonal, with associated large airway wheeze or stridor.<sup>1,8,9</sup> Imminent total airway obstruction was viewed as an indication for surgery.<sup>9</sup>

**WITH COLLAPSE/HYPERINFLATION.** Collapse and hyperinflation were mostly radiological diagnoses, with minimal clinical symptoms, unless large lung segments collapsed or hyperinflation caused symptoms related to pressure on surrounding structures.<sup>6,8</sup>

**WITH ALLERGIC CONSOLIDATION (EPITUBERCULOSIS).** The onset of symptoms could be dramatic, with a high fever, acute respiratory symptoms and signs of consolidation.<sup>8</sup> Chest radiography revealed a densely consolidated segment or lobe with minimal volume change.<sup>8,9</sup> Consolidation resolved completely within months, without permanent sequellae.<sup>8</sup>

**WITH BRONCHOPNEUMONIC CONSOLIDATION.** Bronchopneumonic caseating consolidation was rare. Symptoms were not well described, but depended on the extent of involvement. On chest radiograph patchy infiltration usually involved more than one lobe of a single lung.<sup>6</sup> Bilateral patchy infiltration was mostly due to protracted (atypical) miliary disease.<sup>6</sup>

**WITH CASEATING CONSOLIDATION.** Children with alveolar caseating consolidation were ill, with high undulating fever, chronic cough and even haemoptysis.<sup>8</sup> On chest radiograph expansile lobar involvement with or without areas of breakdown was visible, and mycobacterial cultures were positive in more than 80% of cases.<sup>6,8,9</sup> Secondary bacterial infection often complicated the picture.<sup>6,9</sup> Bronchoscopy showed total airway obstruction and surgical re-establishment of airway patency together with penicillin gave dramatic symptomatic relief.<sup>8,9</sup> Following resolution of the consolidation, non-parenchymal bullae appeared with extensive fibrotic scarring in the surrounding

lung tissue.<sup>6,8</sup> Without intervention the prognosis was poor, with frequent haematogenous spread terminating in tuberculous meningitis.<sup>6,8</sup>

The end result of bronchopneumonic or caseating consolidation was a contracted, fibrotic area.<sup>6-9</sup> Contracted segments were often impossible to visualise on follow-up chest radiographs.<sup>6,8</sup> Bronchial damage was a common sequel that resulted in bronchial stenosis and/or bronchiectasis, ranging from mild to severe saccular forms.<sup>6-9</sup> Most children with bronchiectasis remained asymptomatic on long-term follow-up.<sup>6-9</sup> Apical lesions hardly ever caused complications, but large basal lesions did predispose to future suppurative disease.<sup>6-9</sup> A few case reports of the middle lobe syndrome (recurrent bacterial pneumonia in adults with previous tuberculous damage of the right middle lobe) were quoted.<sup>9</sup> Surgery was only indicated when a bronchiectatic lobe caused symptomatic disease.<sup>6,8,9</sup> Very rarely, massive fibrosis and contraction of a whole lung (chronic fibroid lung) caused mediastinal shift and scoliosis.<sup>6,8</sup>

### *Pleural disease*

**WITH EFFUSION.** Localised pleurisy overlying a peripheral Ghon focus was common.<sup>8</sup> Limited adhesions developed between the visceral and parietal pleura, but this did not cause symptoms or lung function abnormality.<sup>8</sup> Effusions were rare in children under 5 years of age and were most common in adolescent boys.<sup>6,7,9</sup> A seasonal variation was observed, with the lowest incidence during late summer and autumn, accounted for by reduced tuberculous infection in the preceding summer months.<sup>6</sup> Pleural effusion had a characteristic clinical course, starting with an acute pleuritic pain in the chest, accompanied by a high fever in the absence of acute illness, an ill-defined loss of vigour and a dry cough.<sup>6,8,9</sup> The tuberculin skin test was highly reactive.<sup>6,8</sup> On chest radiograph, pleural effusions varied in size from small (obliterating only the costophrenic angle) to massive (causing opacification of a whole lung, with mediastinal shift to the opposite side).<sup>6,8</sup> In most cases only a third to a half of the lung was obliterated with a clear meniscus sign.<sup>6</sup> With fluid in the pleural space it is nearly impossible to exclude lesions in the underlying lung.<sup>6,8</sup> Localised interlobular effusions required radiological differentiation from segmental lesions.<sup>9</sup> A unilateral effusion, ipsilateral to the Ghon focus, indicated direct spread to the pleural space from a sub-pleural focus. Bilateral effusions indicated haematogenous spread or bilateral Ghon foci.<sup>6-9</sup> Pleural fluid was straw coloured and represented an exudate with high protein content and lymphocyte predominance,<sup>8,9</sup> although the amount of polymorphonuclear cells depended on the acuteness of onset.<sup>9</sup> Direct microscopy was negative, but culture yields were as high as 70% with immediate inoculation.<sup>8</sup>

In children the prognosis of pleural effusion was generally good. The high fever showed gradual effere-



vescence over 3–4 weeks,<sup>6,8</sup> while the fluid collection resolved slowly over 3–6 months.<sup>6,9</sup> Some obliteration of the costophrenic angle and slight pleural thickening remained permanently.<sup>6,8,9</sup> The main complication described was future adult-type disease, which was not a complication of the effusion per se, but reflected the risk associated with primary infection at an older age.<sup>6–9</sup> Rarely, extensive pleural fibrosis caused contraction of the affected hemithorax with scoliosis.<sup>4,6</sup> Bilateral effusions were associated with double the risk for haematogenous spread and future adult-type disease.<sup>6–9</sup>

**WITH EMPYEMA.** The presence of caseating empyema was indicated by a persistent high swinging fever and a loculated pleural collection on chest radiograph.<sup>9</sup> Aspiration was difficult due to thick pus with tubercle bacilli on microscopy.<sup>9</sup> Caseating empyema was rare and the prognosis was variable, with slow disease progression and death or slow resolution with pleural calcification and fibrosis.<sup>9</sup>

**WITH ADULT-TYPE DISEASE.** Adult-type disease resulted from primary infection, endogenous reactivation or exogenous reinfection.<sup>9</sup> Adult-type disease was most common after recent primary infection in children over 10 years of age.<sup>2,4–9</sup> The interval from primary infection to adult-type disease was widely variable (3 months to 20 years), mostly dependent on the age at primary infection.<sup>6–8</sup> The shortest time intervals and highest risk followed primary infection during adolescence, especially in girls of perimenarchal age.<sup>5–9</sup> Disease started off with minimal symptoms such as cough, loss of appetite and fatigue.<sup>8</sup> With disease progression, typical tuberculosis symptoms of chronic cough, chest pain, lethargy, anorexia and weight loss became evident.<sup>5,6,8,9</sup> Children with advanced disease became anaemic, developing an oscillating fever and haemoptysis.<sup>8</sup> A frequent complaint, even in the absence of fever, was night sweats.<sup>8</sup> On chest radiograph an initial rounded homogeneous shadow, 2–3 cm in diameter, situated in the vicinity of the clavicle was typical, followed by parenchymal breakdown and cavity formation.<sup>8,9</sup> Cavities did not contain a fluid level and were characteristically surrounded by inflammation.<sup>9</sup> Bilateral disease was common, mainly involving the apical segments of the upper lobes, with lower lobe involvement less frequent.<sup>9</sup> Previous radiographic appearances were non-predictive and highly variable, ranging from no visible abnormality to a densely calcified primary complex.<sup>6</sup> The prognosis of adult-type disease was poor, with 50–60% mortality within 5–10 years.<sup>5,6–9</sup> These children were sputum smear-positive and able to transmit infection.

#### *Haematogenous spread*

During incubation and occult spread, bacilli seed to susceptible organs, especially the spleen, bone, kidney and cerebral cortex, and possibly to the lung apices (Simon foci).<sup>1,8,9</sup> The age at the time of infec-

tion and the time since infection were the main determinants of risk for metastatic disease development. Infection under 2 years of age carried a significant risk of serious disease, even if the radiograph was considered normal.<sup>6,9</sup> TBM was present in over 30% of children who presented with tuberculosis before 2 years of age.<sup>6,9</sup> The risk of TBM after 3 years of age was extremely low and those who did develop TBM had significant preceding symptoms.<sup>8,9</sup>

**WITH MILIARY DISEASE.** Infants were most vulnerable to developing miliary disease.<sup>1,8,9</sup> The symptoms included prolonged pyrexia, lassitude, anorexia and weight loss.<sup>6,8,9</sup> Children appeared acutely ill, with minimal physical signs apart from possible tachypnoea and hepatosplenomegaly.<sup>6,8</sup> Radiological mottling followed 7–21 days after febrile onset, starting as barely visible nodules that slowly progressed to large, poorly defined patches.<sup>8</sup> The initial miliary lesions were often difficult to visualise, with 30–40% of autopsy proven miliary lesions missed on chest radiograph before death.<sup>6</sup> Bone marrow biopsy and ophthalmoscopy were useful diagnostic aids.<sup>6</sup> The reported presence of choroidal tubercles varied widely, from 10% to 70%.<sup>6,8,9</sup> The majority of children were TST positive, and in those children with an initial negative TST, skin test conversion occurred within 1–4 months when effective treatment became available.<sup>8</sup> The prognosis of miliary disease was poor. Clinical progression with persistent fever, increased irritability and weight loss frequently terminated in TBM.<sup>6,8,9</sup> The majority died within 6 months, but chronic forms were occasionally seen where children eventually died from toxæmia, malnutrition or amyloidosis.<sup>8</sup> Typical even-sized miliary mottling indicated an acute invasion of the blood stream. Protracted release of bacilli from a chronic focus, e.g., a matted lymph node mass or, rarely, a skeletal lesion, also occurred.<sup>8</sup> The symptoms of protracted seeding were similar to those of acute invasion, but were initially intermittent, presumably corresponding to periods of bacilli or toxic product release.<sup>8</sup> This repetitive seeding was sometimes manifested by successive crops of papulonecrotic tuberculides.<sup>8</sup> The chest radiograph revealed large hilar lymph node masses with mottling of variable size.<sup>8,9</sup> Eventual progression occurred with acute or chronic deterioration.<sup>8</sup>

## DISCUSSION

Pulmonary tuberculosis in childhood is often considered a benign condition, with little risk to the child and no contribution to the transmission of disease within the community. Although this is true for the majority of infected children, specific high-risk groups exist where disease poses a high risk of fatality for the individual and/or a high risk of transmission to the community.

Recent primary infection posed the greatest risk

for disease progression in children. The period under 2 years of age represents the first high-risk period, as infected children showed frequent progression to miliary disease or tuberculous meningitis without significant prior symptoms. Children infected between 2 and 10 years of age rarely developed serious disease. However, the majority of children from high-prevalence communities were infected during this period, and therefore relative low risk still translated into large numbers and a significant burden of disease. In these low-risk children, persistent, non-remitting symptoms preceded progression to serious disease. This creates a window of opportunity for clinical diagnosis. Adolescence represent the second high-risk period, because primary infection after 10 years of age showed frequent progression to adult-type disease. Early intervention in this group may reduce the burden of cavitating disease and associated disease transmission in the community.

An important concept deduced from the natural history of tuberculosis in childhood is that of relevant disease. Relevant disease reflects the level of risk posed

by the condition together with the calculated risk-benefit ratio of treatment vs. no treatment in a particular setting. Thus, in well-resourced settings with a low prevalence of tuberculosis, the minimal risk posed to the individual and the community following infection may be unacceptable and treatment indicated. However, in low-resource settings with a high prevalence of tuberculosis, a different definition of relevant disease is required, as the majority of the population may be infected during childhood. The vast majority of these children will successfully contain the disease without chemotherapy. Priority for scarce resources indicates a need to target those children who are most likely to develop serious disease progression or pose a threat to the community. In high-burden settings, resources should be prioritised according to the clinical natural history of infection or the specific disease entity. Consideration of the risk posed to the individual and the community utilises the same rationale used in adult tuberculosis, with the focus on sputum smear-positive cases.

Previous guidelines did not provide clear definitions of relevant disease in a particular setting. This led to a

**Table 5** Suggested definition of relevant childhood tuberculosis\* in high-burden countries, according to the specific age and immune category of the child

Age category (years)	Relevant disease	
	Immune-competent	Immune-compromised
<2 years Positive Mantoux important Household source case important Symptoms important Diagnostic need Sensitive/specific marker of infection (all infection is recent and primary)	Recently primary infection or symptomatic disease	
2–5 years Positive Mantoux less important Household source case less important Symptoms important Diagnostic need Validated symptoms-based algorithm Sensitive/specific marker of symptomatic disease	Symptomatic disease	All infection or symptomatic disease
5–10 years Positive Mantoux less important Household source case less important Symptoms important Diagnostic need Validated symptoms-based algorithm Sensitive/specific marker of symptomatic disease	Symptomatic disease	Positive Mantoux important Household source important Symptoms important Diagnostic need: Sensitive/ specific marker of all infection (primary or reinfection; recent or past)
>10 years Positive Mantoux less important Negative Mantoux important Mantoux conversion important Household source case less important Symptoms important Diagnostic need Validated symptoms-based algorithm Sensitive/specific marker of recent primary infection or symptomatic disease	Recent primary infection or symptomatic disease	

\*This reflects the level of risk for disease development accepted, following tuberculosis infection in a specific setting, together with the risk-benefit ratio to the individual and the community of treatment vs. no treatment in that particular setting.

confusing multitude of scoring systems with adaptations suggested for high-prevalence, low-resource settings. A recent critical analysis of these scoring systems demonstrated a lack of uniform symptom definitions and scientific validation.<sup>10</sup> The confusion surrounding tuberculosis in childhood is related to our inability to confidently diagnose disease.<sup>11</sup> This diagnostic dilemma, highlighted in numerous recent review articles,<sup>12–16</sup> hampers scientific research and, most importantly, service delivery in the areas where it is most needed. The natural history of disease indicates that disease in childhood cannot be viewed as a single entity. The clear age-related patterns described in Table 4 indicate that relevant disease requires separate definition in each age category (Table 5).

Unfortunately, most low-resource settings bear the double burden of HIV and TB,<sup>17</sup> and this must be taken into account when defining relevant disease in these settings. Unlike adults, the majority of children with TB, even from HIV-affected communities, are not HIV-infected.<sup>18,19</sup> The natural history disease descriptions provided do not include the influence of HIV. However, recent disease descriptions in HIV-infected children confirm that those with significant immune compromise illustrate poor disease containment, similar to that seen in children under 2 years of age who are immune immature.<sup>20–24</sup> The definition of relevant disease in immune-compromised children is therefore similar to that in children under 2 years of age and include any infection, recent or past, primary or reinfection (Table 5).

Two major challenges emerge regarding the diagnosis of tuberculosis in childhood. The first challenge is to identify any untreated infection (recent or past, primary or reinfection), with a high degree of sensitivity and specificity in immune-compromised children. In immune-competent children, a positive TST under 2 years of age or TST conversion after 10 years of age indicate a high risk for disease progression and a need for intervention. The second challenge is to identify symptomatic disease as early as possible, especially in immune-competent children over 3 years of age. In this group the onset of clinical symptoms allows the differentiation between self-contained infection and

relevant disease. This is defined as the breakpoint of clinical relevance (Figure 2). A validated clinical diagnostic algorithm will be of great value to identify this breakpoint.

Tuberculosis is a curable disease, and it is possible to prevent the morbidity and mortality caused by tuberculosis in childhood. However, access to accurate diagnosis and treatment is imperative.<sup>25</sup> The concept of relevant disease allows a rational and focused approach to childhood tuberculosis in high-burden settings. Its application will improve service delivery to those children who need it most.

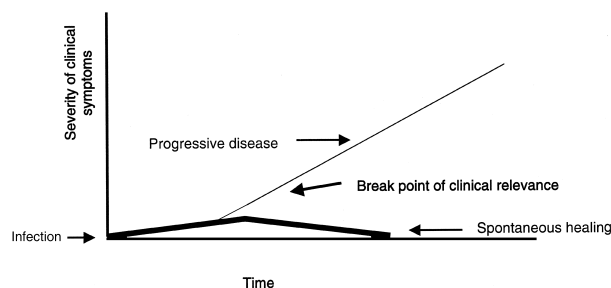
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**Figure 2** Defining the breakpoint of clinical relevance in childhood intra-thoracic tuberculosis for immune-competent children aged over 3 years.

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## RÉSUMÉ

La littérature avant l'introduction de la chimiothérapie spécifique permet de documenter l'histoire naturelle de la tuberculose dans l'enfance. Ces descriptions de la maladie restent d'une grande valeur pour guider la politique de santé publique et la recherche, puisque l'introduction d'une chimiothérapie effective a modifié radicalement l'histoire de la maladie. Des groupes spécifiques à risque élevé ont été identifiés. La primo-infection avant l'âge de 2 ans progresse fréquemment vers une maladie grave au cours des 12 premiers mois sans symptômes prémonitoires significatifs. La primo-infection entre les âges de 2 et de 10 ans ne progresse que rarement vers une maladie sévère, et cette progression est associée à des symptômes cliniques significatifs. Chez les enfants âgés de >3 ans la présence de symptômes a représenté une opportunité pour porter un diagnostic clinique avant la progression vers une maladie plus grave. L'infection primaire après l'âge de 10 ans progresse fréquemment vers une maladie

du type adulte. Une intervention efficace et précoce dans ce groupe réduira le fardeau des maladies cavitaires ainsi que la transmission de la maladie qui y est associée au sein de la collectivité. Bien que la littérature avant la chimiothérapie excluait l'influence de l'infection par le virus de l'immunodéficience humaine (VIH), des descriptions récentes de la maladie chez des enfants infectés par le VIH indiquent que les enfants en état de dépression immunitaire se comportent d'une manière similaire aux enfants négatifs pour le VIH âgés de moins de 2 ans dont l'immunité n'est pas arrivée à maturité. Un concept déduit de l'histoire naturelle de la tuberculose dans l'enfance est qu'il s'agit d'une maladie significative. Décider quels enfants doivent être traités peut être extrêmement difficile dans des contextes à haute prévalence et à faibles ressources. Le concept d'une maladie significative fournit des informations permettant de guider des interventions de santé publique plus efficaces.

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## RESUMEN

La literatura antes de la introducción de la quimioterapia específica informaba sobre la historia natural de esta afección de los niños. Estas descripciones de la enfermedad siguen siendo valiosas para orientar las políticas de salud pública y de investigación, a pesar de que la introducción de una quimioterapia eficaz ha cambiado radicalmente la historia de la enfermedad. Se habían identificado grupos específicos con alto riesgo. La infección primaria antes de los 2 años de edad con frecuencia progresaba a una enfermedad severa durante los 12 primeros meses sin síntomas premonitorios significativos. La infección primaria entre los 2 y 10 años de edad raramente progresaba hacia la enfermedad grave y la progresión se acompañaba de síntomas clínicos significativos. En niños más de 3 años de edad, la presencia de estos síntomas representaba una oportunidad para establecer un diagnóstico clínico antes de la presentación de una enfermedad grave. La infección primaria después de los 10 años frecuentemente progresaba hacia una

enfermedad de tipo adulto. La intervención eficaz y rápida en este grupo reducirá la frecuencia de la enfermedad cavitaria y la transmisión a la comunidad que le está asociada. Aunque la literatura de la era prequimioterapia no incluía la influencia de la infección por el virus de la inmunodeficiencia humana (VIH), las recientes descripciones de la enfermedad en niños infectados con el VIH indican que los niños inmunocomprometidos se comportan de manera similar que los niños inmuno inmaduros (menos de 2 años de edad). Un concepto importante que ha aportado el estudio de la historia natural de la tuberculosis infantil es su consideración como enfermedad significativa. La decisión con respecto a los niños que deben ser tratados puede ser extremadamente difícil en los contextos de alta prevalencia y escasos recursos. El concepto de enfermedad significativa puede servir de guía para realizar intervenciones más eficaces de salud pública.

## **On the definition of relevant disease**

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Historically the art of medicine was defined by the ability to develop a personal reference for normality. This internal reference allowed the subjective identification of abnormality by pure clinical acumen. In contrast, modern medicine provides an objective scientific definition of abnormality, based on accurate measurement and statistical analysis. However, the medical profession still struggles to find the optimal balance between the art (subjective) and the science (objective), in providing holistic health care.

Statistical differentiation into normal and abnormal serves us well when dealing with continuous physiological variables like blood pressure, cholesterol or weight. The differentiation becomes problematic when dealing with the complex biological balance that exists between infecting organisms and host responses. The initial simplistic differentiation into harmless colonizing organisms and dangerous invasive pathogens has been replaced by a more complete appreciation of the complex, dynamic relationship that exists between the host and the organism. The challenge facing modern medicine is to translate, improved scientific understanding into clear, pragmatic guidelines applicable in diverse settings.

Once abnormality is identified, whether subjectively or objectively, the crucial question that remains is: Does this abnormality constitute disease? Disease is defined by present reduced quality of life (morbidity) as well as the increased risk for future morbidity or mortality. Knowledge of a condition's natural history becomes invaluable when initial morbidity is minimal. Accurate description of the natural history of disease allows scientific risk:benefit analyses of a proposed intervention. The scientific quest does not end here; the true quest is to quantify the relative benefit of the suggested intervention within a particular setting.

The idea of relative benefit or risk, to an individual within a particular setting, differs from the classical public health approach. With this approach the relevance of disease is determined by the total burden placed on a specific society, completely ignoring the individual patient. Although it assists with focusing scarce resources, it undermines the moral basis of the medical profession, which promises sympathetic care to every individual who seeks help. In

contrast the concept of relative risk maintains the primary focus on the individual patient, but takes the baseline risk determined by his/her particular setting into account.

Relevant disease defines the point where the risk posed by a specific condition, increases significantly beyond the baseline risk within a particular community. This implies that contrary to the classic public health approach, any severe disease represents relevant disease, irrespective of its contribution to the total burden of disease. This definition also challenges the approach promoted by the pharmaceutical industry, which defines any statistically significant benefit measured against a minimal baseline risk as the accepted “standard of care”, irrespective of the baseline risk within particular setting.

Identifying the appropriate intervention once relevant disease is diagnosed requires careful analysis, weighing the relative risk posed to the individual and society against the possible benefit, risk and cost of available treatment. The challenge posed by the concept of relevant disease, is to identify the sub-population at highest risk in order to focus cost effective interventions appropriately.



## Chapter 3.

### The burden of disease

The contribution of children to the total tuberculosis caseload is poorly documented, especially in endemic areas where the emphasis is mainly on the diagnosis and treatment of sputum smear-positive disease. Observational studies in children are often hospital-based, and the considerable selection bias inherent to hospital-based studies prevents extrapolation of results to the community level. The reliability of epidemiological data on childhood tuberculosis is further limited by the difficulty of establishing an accurate diagnosis. We documented the routine criteria used to diagnose childhood tuberculosis in an endemic area, as well as the contribution of children to the overall disease burden recorded in the TB treatment register. We also evaluated the accuracy of community-based surveillance data and calculated the actual disease burden in children from an endemic area.

**1. Theart AC, Marais BJ, Gie RP, Hesselning AC, Beyers N. Criteria used for the diagnosis of childhood tuberculosis at primary health care level in a high-burden, urban setting. *Int J Tuberc Lung Dis* 2005; 9: 1210-1214**

This retrospective descriptive study describes the burden of childhood tuberculosis and the routine diagnostic criteria used in a high-burden setting, by retrospective analysis of TB treatment register data from two primary health care clinics. Children (<15 years) contributed 20.6% of all cases notified in the TB treatment register. The diagnosis of childhood tuberculosis demonstrated good agreement with current guidelines, but depended almost exclusively on the subjective interpretation of the chest radiograph. Chest radiography is rarely available in resource-limited settings.



**2. Marais BJ, Hesselning AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data in a high-burden setting. *Int J Tuberc Lung Dis* 2006; 10: 259-263**

Inadequate surveillance and diagnostic difficulties compromise the quality of epidemiologic data on childhood tuberculosis. This prospective study employed comprehensive, community-based surveillance to document the actual burden of childhood tuberculosis in an endemic area. The tuberculosis incidence calculated from the TB treatment register was 441/100 000/year for children, and 845/100 000/year for adults. Fifty-four (12.3%) children, treated for tuberculosis, were not recorded in the TB treatment register, including 21/28 (75%) children with tuberculous meningitis and/or disseminated (miliary) disease. Eighty-five (19.4%) children, included in the TB treatment register were judged not to have had tuberculosis. When this information was taken into account, the corrected tuberculosis incidence in children was calculated to be 407/100 000/year.

## Criteria used for the diagnosis of childhood tuberculosis at primary health care level in a high-burden, urban setting

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### SUMMARY

**BACKGROUND:** Children contribute a significant proportion of the total tuberculosis (TB) case load in high-burden settings and present a major diagnostic challenge.

**OBJECTIVE:** To document the criteria used at primary health care level to diagnose childhood TB in a high-burden, urban setting.

**METHODS:** This retrospective descriptive study was conducted at two primary health care clinics in Cape Town, South Africa. Information on all children (<15 years of age) entered into the TB register from January 2002 through December 2003 was retrieved for analysis.

**RESULTS:** During the study period, 1277 cases of TB were entered into the TB register, of which 268 (21.0%) were children. Information on 256 (95.5%) children

was available for analysis. The majority (206, 80.5%) had intrathoracic TB, of whom 107 (51.5%) had uncomplicated lymph node disease, 79 (38.3%) complicated lymph node disease, 8 (3.9%) a pleural effusion and 12 (5.8%) adult-type cavitating disease. According to modified WHO criteria, the diagnosis of TB was confirmed in 27 (10.5%), probable in 193 (75.4%) and suspect in 36 (14.1%).

**DISCUSSION:** The diagnostic criteria used at primary health care level demonstrated good agreement with current guidelines, but depended heavily on chest radiograph interpretation.

**KEY WORDS:** criteria; diagnosis; childhood; tuberculosis

THE DEVELOPING WORLD carries the brunt of the tuberculosis (TB) epidemic.<sup>1</sup> In these countries, children represent a significant proportion (up to 40%) of the total TB burden.<sup>2</sup> In South Africa, like most high-burden countries, the National Tuberculosis Programme (NTP) focuses on adults with sputum smear-positive disease, and childhood TB receives little public health emphasis. It is extremely difficult to assess the true impact of TB on child health, because although children with TB are recorded in the TB register, this information is not routinely reported to the NTP. The reliability of epidemiological data on childhood TB is further limited by the difficulty of accurate diagnosis.<sup>3,4</sup>

Childhood TB presents a major diagnostic challenge as, unlike adults, children usually have paucibacillary disease and bacteriological confirmation is rarely achieved.<sup>5-7</sup> Several guidelines exist for the clinical diagnosis of TB in childhood, but these are poorly validated.<sup>8</sup> Both the limited availability of reliable epidemiological data and the severe TB-related morbidity and mortality that children may suffer<sup>9</sup> provide compelling reasons to assess the burden of childhood TB and the criteria used for diagnosis at primary health level in a high-burden setting. A recent

post-mortem study from Zambia showed that TB rivals acute pneumonia as the most common respiratory cause of death in African children >6 months of age.<sup>10</sup> In addition to the risk posed to the individual child, adolescent children (>10 years of age) often develop adult-type cavitating disease,<sup>9,11</sup> which poses a significant risk of disease transmission to the community.<sup>12</sup>

There is limited data on the criteria used for the diagnosis of childhood TB at primary health care level, outside the academic or research setting. A recent audit from Malawi reported on diagnostic practices in referral hospitals,<sup>13</sup> but primary health care facilities were excluded. A previous study from South Africa evaluated the diagnostic practices in primary health care clinics,<sup>14</sup> but this was done in the pre-DOTS era and before the implementation of TB registers.

The aim of this study was to document the criteria used, at primary health care level, to diagnose childhood TB in a high-burden, urban South African setting.

### METHODS

This was a retrospective descriptive study where data were collected by folder review.

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### Study population

The study was conducted at two primary health care clinics in Cape Town, South Africa, that were not involved in TB-related research during the study period. All children (<15 years of age) entered into the clinic's TB register from January 2002 through December 2003 were eligible for inclusion.

### Data collection and analysis

According to the NTP, children under 5 years of age in household contact with an adult sputum smear-positive source case and all children with symptoms of TB should be evaluated with a tuberculin skin test (TST) and chest X-ray (CXR). If TB is diagnosed, the child's name is entered into the TB register and all relevant data such as possible contact with an adult source case, relevant symptoms, TST and CXR results, as well as treatment adherence, are recorded in the TB treatment folder. The TST used in the clinics is the transcutaneous, multipuncture Tine test, while referral hospitals use the intradermal Mantoux test. Children are only tested for human immunodeficiency virus (HIV) infection if there is clinical suspicion of HIV disease.

The TB register was used to identify all children diagnosed and/or treated for TB at the primary health care clinic. The TB treatment folders were retrieved and used as the data source for this study. Demographic information, clinical findings and treatment adherence were recorded. A Tine test result of  $\geq$  grade 2 and/or a Mantoux test result of  $\geq 10$  mm were regarded as positive (Tine  $\geq$  grade 1 or Mantoux  $\geq 5$  mm if the child was HIV-infected).<sup>15</sup> Suspicious symptoms were broadly defined as documented cough and/or weight loss, because relevant symptoms were not recorded in detail. Intrathoracic disease was classified using the interpretation of the CXR recorded in the TB treatment folders, according to a recently proposed radiological classification of intrathoracic TB in childhood.<sup>16</sup> Modified World Health Organization (WHO) guidelines were used to categorise children with TB.<sup>14,17</sup> All children who received anti-tuberculosis chemotherapy were regarded as suspects, those with radiological signs of TB were regarded as probable cases and those with bacteriological confirmation were regarded as confirmed cases.

Ethical approval was obtained from the University of Stellenbosch, the City of Cape Town Health Department and from the relevant local health authorities.

## RESULTS

During the study period, 1277 cases of TB were notified, of whom 268 (21.0%) were children. The folders of 256 (95.5%) children were available for evaluation. Their demographic features are summarised in Table 1. There was an equal sex distribution, but the majority of cases (170, 66.4%) were <5 years of age.

**Table 1** General demographics and characteristics of children notified with TB at the primary health care level

	<i>n</i> (%)
Total population*	30 940
All TB cases notified in a 2-year period	1 277
Calculated TB incidence	2 063/100 000/year
Children notified with TB (% of all notifications)	268 (20.6)
Children included in the study (% of child notifications)	256 (92.1)
Sex	
Male	127 (49.6)
Female	129 (50.4)
Age distribution, years	
<5	170 (66.4)
5–9	52 (20.3)
10–14	23 (9.0)
Age not recorded	11 (4.3)
HIV exposed, but not tested	6 (2.3)
HIV tested	26 (10.2)
HIV-positive	15 (5.9)

\* National census data, 2001.

TB = tuberculosis; HIV = human immunodeficiency virus.

Of the 26 (10.2%) children tested for HIV infection, 15 (5.9%) tested positive.

The specific disease manifestations documented are summarised in Table 2. The majority of the children (206, 80.5%) had intrathoracic disease, of whom 107 (51.5%) had uncomplicated lymph node disease, 79 (38.3%) had lymph node disease complicated by visible alveolar consolidation, airway compression and/or segmental/lobar collapse, 8 (3.9%) had a pleural effusion and 12 (5.8%) had adult-type disease. No cases of disseminated (miliary) disease were recorded. All documented pleural effusions occurred in children >5 years of age—two in the 5–9 year and six in the 10–14 year age group. The 12 children with adult-type cavitating disease were all >10 years of age, and eight (66.7%) were sputum smear-

**Table 2** Specific disease manifestation documented in children notified with TB

TB manifestation	<i>n</i> (%)
Intrathoracic TB	206 (80.5)
Specific radiological entities	
Uncomplicated lymph node disease	107 (51.9)
Complicated lymph node disease	79 (38.4)
Pleural effusion	8 (3.9)
Disseminated (miliary) disease	0 (0.0)
Adult-type disease	12 (5.8)
Cervical lymph node involvement	9 (3.5)
Tuberculous meningitis	2 (0.7)
Osteoarticular involvement	2 (0.7)
Hip involvement	1 (50.0)
Vertebral involvement	1 (50.0)
GA culture+, CXR normal	2 (0.7)
Insufficient information to classify	35 (13.7)
Total	256 (100)

TB = tuberculosis; GA = gastric aspirate; CXR = chest radiograph.

positive. Exclusive cervical lymph node involvement was noted in nine (3.5%) children. Tuberculous meningitis (TBM) was recorded in two (0.1%) children, both <2 years of age. Osteo-articular involvement included TB of the hip in one child and lumbar vertebral collapse with a gibbus in another. In 37 (14.4%) children, the information recorded was insufficient for accurate disease classification.

Table 3 reflects the main criteria used in the diagnosis of intrathoracic TB. Exposure to an adult sputum smear-positive source case was documented in more than 50% of children in all age groups. A TST result was recorded in 173 (83.4%) children, of whom 109 (63.0%) tested positive, indicating *Mycobacterium tuberculosis* infection. The Tine test was used in the majority (83.1%) of cases. Of the 15 children with known HIV infection, a TST result was recorded in 12 and only one (6.7%) had a positive reaction (Tine grade 2). A suggestive CXR was reported in all children with intrathoracic TB, apart from six of the eight sputum smear-positive children who did not receive a CXR. Sputum smear testing was the only confirmatory test performed at the primary clinic, and this was only done in children >10 years of age with productive cough. Gastric aspirates for culture are routinely performed at the referral hospitals, but it is uncertain how many children received these tests. Bacteriological confirmation was achieved in a total of 23 (11.2%) children.

The majority of the children (208, 81%) completed 6 months of directly observed chemotherapy. Treatment was stopped in three cases due to a revision of the diagnosis by the attending physician, 13 (5.1%) were transferred to another clinic and four (1.6%) died on treatment. Treatment was interrupted in 28 (10.9%) children. Three of the four children who died were <1 year of age; all four were HIV exposed. HIV infection was confirmed in three cases. The exact cause of death was known in only one child, who died from diarrhoeal disease.

The diagnosis of TB was made at the primary clinic level in 156 (60.9%) children, 86 (33.6%) were referred

**Table 4** Criteria used for the diagnosis of tuberculosis in children, categorised according to modified WHO guidelines<sup>14</sup>

	Tuberculosis category			
	Suspect n (%)	Probable n (%)	Confirmed n (%)	Unknown n (%)
Primary clinic	156 (100)	134 (85.9)	10 (6.4)	12 (7.7)
Secondary hospital	86 (100)	53 (61.6)	16 (18.6)	17 (19.8)
Tertiary hospital	14 (100)	8 (57.2)	1 (7.1)	5 (35.7)
Total	256 (100)	195 (76.2)	27 (10.5)	34 (13.3)

WHO = World Health Organization; suspect = all children who received anti-tuberculosis chemotherapy were regarded as suspect cases; probable = suggestive chest radiograph; confirmed = bacteriological confirmation, either smear- or culture-positive; unknown = insufficient information to be categorised.

to a secondary and 14 (5.5%) to a tertiary level hospital for diagnosis (Table 4). The majority of the children (222, 86.7%), irrespective of where the diagnosis was made, met modified WHO criteria for probable (193, 75.4%) or confirmed (27, 10.5%) TB. In 34 (13.3%) suspect cases, insufficient information prevented classification into either the probable or confirmed category.

## DISCUSSION

The criteria used for the diagnosis of TB, at all levels of health care, were in accordance with modified WHO guidelines. This finding is similar to that of a previous study from Cape Town, South Africa, conducted in the pre-DOTS era.<sup>14</sup> The diagnosis depended heavily on accurate CXR interpretation, but the reality is that CXR is often unavailable in high-burden settings. Although the interpretation of the chest radiograph may be difficult, its sensitivity and specificity increases when viewed in conjunction with relevant epidemiological and clinical information, and it remains the mainstay test to diagnose childhood TB.

As bacteriological confirmation was attempted in only 30–40% of children, the reported yield of 10.5% is probably a gross underestimation of the expected yield. No gastric aspirate or induced sputum samples were collected for culture at any of the primary health care clinics. Induced sputum, using

**Table 3** Criteria used for the diagnosis of children notified with intrathoracic TB within different age groups

Age group, years	Total n (%)	Exposed fraction n (%)	TST-positive fraction n (%)	Suspicious Sx fraction n (%)	Suggestive CXR fraction n (%)	Confirmed TB	
						ZN+ n	Cult+ n
<2	75 (36.4)	49/75 (65.3)	33/65 (50.8)	58/75 (77.3)	75/75 (100)	0	4
2–4	63 (30.6)	41/63 (65.1)	40/62 (64.5)	55/63 (87.3)	63/63 (100)	0	6
5–9	39 (18.9)	26/39 (66.4)	28/33 (84.8)	30/39 (76.9)	39/39 (100)	0	4
10–14	22 (10.7)	9/22 (40.9)	3/7 (42.9)	21/22 (95.5)	16/16 (100)	8	0
Unknown	7 (3.4)	3/7 (42.9)	5/5 (100)	4/7 (57.1)	7/7 (100)	0	1
Total	206 (100)	118/206 (57.3)	109/173 (63.0)	168/256 (65.6)	200/200 (100)	8	15

The results are expressed as the fraction of the children in whom the information was recorded. No denominator is provided for confirmed TB, because we were unable to establish in how many children bacteriological tests were done.

TB = tuberculosis; exposed = documented exposure to a sputum smear-positive source case; TST positive = tuberculin skin test (Tine test ≥ grade 2 or Mantoux test ≥ 10 mm); suspicious Sx = symptoms suspicious of TB (cough and/or weight loss); suggestive CXR = reported chest radiograph signs indicative of TB; confirmed TB = *Mycobacterium tuberculosis* isolated from sputum or gastric aspirates; ZN+ = sputum smear-positive for acid-fast bacilli by Ziehl-Neelsen stain; Cult+ = *M. tuberculosis* confirmed on culture.

hypertonic saline nebulisation, holds promise as a diagnostic tool,<sup>18</sup> but its safety and utility has not been validated in a primary health care setting, and its low yield remains a concern. Sputum samples were collected for routine microscopy in children >10 years of age with productive cough. It is notable that eight children, i.e., more than a third of the children with TB >10 years of age, were sputum smear-positive. It seems appropriate to encourage the routine collection of sputum for smear in all TB suspects >10 years of age. This can be done with relative ease at the primary health care level.

Childhood TB contributed to more than 20% of the total TB caseload. This is consistent with previous reports from this high-burden setting.<sup>19</sup> The proportion of TB contributed by children, especially those diagnosed with recent primary infection and uncomplicated lymph node disease, will be influenced by the diligence with which active contact tracing and screening is performed. The fact that no cases of disseminated (miliary) disease and only two cases of TBM were reported is not a true reflection of how commonly these disease entities occur, because these children are not routinely diagnosed or treated at the primary clinic. They are referred to hospital for diagnosis and usually complete their treatment under hospital supervision and not in the community, which probably explains why they were not recorded in the clinic's TB register. The fact that the percentage of children in the unknown category (Table 4) increased from primary through secondary to tertiary level also suggests that information from referral hospitals is not getting back to the records held by primary care clinics.

HIV testing was only done if the attending physician clinically suspected HIV disease, which explains why 57.7% of those tested were found to be infected. It is not possible to comment with confidence on the HIV prevalence amongst these children, because only a very select number were tested. Only one HIV-infected child had a positive TST, but the poor sensitivity of the TST to detect *M. tuberculosis* infection in this population is well documented.<sup>20,21</sup> In South Africa, primary clinics use the multi-puncture, transcutaneous Tine test because of concerns regarding the cost, need for refrigeration and operator dependence of the Mantoux intradermal test. Previous studies conducted in South Africa have shown good comparison between the two tests,<sup>22,23</sup> but the sensitivity of the Tine test has been seriously questioned even in immune-competent children.<sup>24</sup>

Despite limitations imposed by the study's retrospective design on the quality of the available data, this had the important advantage of providing a 'real-life' picture of what happens in a primary health care setting, without interference caused by ongoing research. Incomplete and inappropriate clinical information limited the value of the available data and it seems important to adapt the routine collection of

data in children with TB to ensure that all the relevant clinical information is captured. The study setting had an extremely high incidence of TB, and it is uncertain how well these results will translate to areas with a lower incidence.

In conclusion, children contribute significantly to the total TB caseload in high-burden communities. The criteria used for the diagnosis of childhood TB at primary health care level showed good agreement with current diagnostic guidelines, but were heavily dependent on chest radiography. The interpretation of CXRs is problematic, and its limited availability in most high-burden settings underscores the need for validated diagnostic guidelines that are applicable in these settings. Ultimately, improved service delivery to children with TB will depend on sufficient public health emphasis and political commitment.

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## R É S U M É

**CONTEXTE :** Dans les contextes à haute prévalence, les enfants contribuent une proportion significative de l'ensemble du fardeau des cas de tuberculose (TB) et représentent un défi diagnostique majeur.

**OBJECTIF :** Documenter les critères utilisés au niveau des soins de santé primaires pour diagnostiquer la TB infantile dans un contexte urbain à haute prévalence.

**MÉTHODES :** Cette étude descriptive rétrospective a été menée dans deux polycliniques de soins de santé primaires à Cape Town en Afrique du Sud. Les informations concernant tous les enfants (âge <15 ans) présents dans le registre de la TB de janvier 2002 à décembre 2003 ont été relevées pour analyse.

**RÉSULTATS :** Au cours de la période d'étude, 1.227 cas de TB ont été inscrits dans le registre de la TB ; 268 d'en-

tre eux (21,0%) étaient des enfants. Une information a été disponible pour l'analyse chez 256 (95,5%) enfants. Chez la majorité d'entre eux (206, 80,5%), la TB était intrathoracique ; parmi ceux-ci, 107 (51,5%) souffraient d'une maladie ganglionnaire non compliquée, 79 (38,3%) d'une atteinte ganglionnaire avec complication, 8 (3,9%) d'un épanchement pleural et 12 (5,8%) d'une maladie du type adulte avec excavation. Selon les critères modifiés de l'OMS pour le diagnostic de la TB, celle-ci est classée comme confirmée dans 27 cas (10,5%), probable dans 193 (75,4%) et soupçonnée dans 36 cas (14,1%). **DISCUSSION :** Les critères de diagnostic utilisés au niveau des soins de santé primaires s'avèrent en bonne concordance avec les directives actuelles, mais ils dépendent largement de l'interprétation des clichés thoraciques.

## R E S U M E N

**MARCO DE REFERENCIA :** Los niños representan una gran proporción de la carga de morbilidad global por tuberculosis (TB) en medios con alta incidencia y plantean una dificultad diagnóstica importante.

**OBJETIVO :** Verificar los criterios utilizados para el diagnóstico de la TB infantil al nivel primario de atención de salud en un medio urbano con alta carga de morbilidad por TB.

**MÉTODOS :** Fue este un estudio retrospectivo descriptivo llevado a cabo en dos consultorios de atención primaria en Ciudad del Cabo, Sudáfrica. Para el análisis se obtuvo información sobre todos los niños (<15 años) consignados en el registro de TB entre enero de 2002 y diciembre de 2003.

**RESULTADOS :** Durante el periodo del estudio, se

declararon 1277 casos al registro de TB, de los cuales 268 fueron niños (21,0%). Para el análisis se contó con información sobre 256 niños (95,5%). La mayoría (206 ; 80,5%), presentaron TB intratorácica y de ellos 107 (51,5%) tuvieron afectación ganglionar sin complicación, 79 (38,3%) afectación ganglionar complicada, 8 (3,9%) derrame pleural y 12 (5,8%) tuvieron enfermedad de tipo adulto, con cavernas. Según los criterios modificados de la OMS, TB fue confirmada en 27 pacientes (10,5%), probable en 193 (75,4%) y presunta en 36 (14,1%). **DISCUSIÓN :** Se observó que los criterios diagnósticos utilizados en el nivel primario de atención de salud están acordes con las recomendaciones vigentes, pero dependen en gran medida de la interpretación de la radiografía de tórax.

## The burden of childhood tuberculosis and the accuracy of community-based surveillance data

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### SUMMARY

**BACKGROUND:** Inadequate surveillance and diagnostic difficulties compromise the quality of epidemiological data on childhood tuberculosis (TB).

**OBJECTIVE:** To document the incidence of childhood TB and to evaluate the accuracy of community-based surveillance data in a high-burden setting.

**METHODS:** This prospective observational study was conducted from February 2003 to October 2004 at five primary health care clinics in Cape Town, South Africa. Comprehensive surveillance was done to ensure that all children <13 years of age treated for TB were included.

**RESULTS:** During the study period, 443 children (<13 years of age) received anti-tuberculosis treatment, of whom 389 (87.8%) were recorded in the TB treatment register. The TB incidence calculated from the TB treat-

ment register was 441/100 000/year amongst children and 845/100 000/year amongst adults. Fifty-four children treated for TB were not recorded in the TB treatment register, including 21/28 (75%) children with severe disease.

**DISCUSSION:** Children <13 years of age contributed 13.7% of the total TB burden, but experienced more than half (52.2%) the TB incidence recorded in adults. Community-based surveillance data excluded the majority of children with severe disease. The accuracy of surveillance data is an important consideration when describing the epidemiology of childhood TB or measuring the success of public health interventions.

**KEY WORDS:** childhood tuberculosis; burden; surveillance; epidemiology

THE CONTRIBUTION of children to the total tuberculosis (TB) caseload is poorly documented, especially in countries with a high burden of disease.<sup>1,2</sup> Official epidemiological data may not reflect the true burden of childhood TB in these countries, due to the inadequacy of existing surveillance systems and the difficulty of diagnosing TB in children. National Tuberculosis Programmes (NTPs) focus almost exclusively on the diagnosis and treatment of sputum smear-positive disease,<sup>1,3</sup> which excludes the vast majority of children with TB.<sup>4-6</sup> For these reasons, the International Union Against Tuberculosis and Lung Disease (IUATLD) stated in 1991 that reliable information on the incidence of childhood TB can only be obtained in industrialised countries.<sup>1,7</sup>

Observational studies in children with TB are often hospital-based, which results in considerable bias, preventing accurate extrapolation to the community level. The paucity of accurate epidemiological data,<sup>1,4</sup> together with the significant TB-related morbidity and mortality suffered by children in high-burden settings,<sup>8</sup> underline the need to obtain a more compre-

hensive picture of childhood TB at the community level in high-burden settings.

The aim of this study was to document the incidence of childhood TB and to evaluate the accuracy of community-based surveillance data in a high-burden setting.

### METHODS

This was a prospective observational study conducted from 1 February 2003 to 31 October 2004 in Cape Town, Western Cape Province, South Africa.

#### *Study population*

The study setting included five local clinics in Cape Town, served by Tygerberg Children's Hospital as the referral hospital. Local clinics provide primary health care services in the community, and coordinate the diagnosis and treatment of TB patients. All children <13 years of age started on anti-tuberculosis treatment during the 21-month study period were included. Paediatric services were accessible only to children <13

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years of age, and therefore children were defined as those <13 years instead of the customary 15 years of age. Two of the five local clinics were sites for ongoing epidemiological research, where a concurrent household contact study (with supervised tracing of household contacts <5 years of age) continued during the study period.

The study communities rarely utilise private medical services, and children diagnosed with TB are routinely referred to the local clinic, where they receive fully supervised treatment free of charge. The incidence of all TB in Cape Town was 678 per 100 000 population,<sup>9</sup> while the prevalence of human immunodeficiency virus (HIV) infection amongst women attending public antenatal clinics in the Western Cape Province was 13.1% (95% confidence interval [CI] 8.5–17.7%),<sup>10</sup> in 2003.

#### Data collection and analysis

According to the South African NTP guidelines,<sup>11</sup> all children with suspect symptoms, as well as those <5 years of age in household contact with a sputum smear-positive source case, should be routinely evaluated for TB with a tuberculin skin test (TST) and a chest radiograph (CXR). Once a diagnosis of TB is made and anti-tuberculosis treatment is commenced, the child's name is entered into the TB treatment register maintained at the clinic, which provides the only data source for community-based surveillance data.

For research purposes, a comprehensive prospective surveillance system was put in place to identify all children started on anti-tuberculosis treatment during the study period, irrespective of whether they were recorded in the clinic TB treatment register. The investigator visited each clinic on a weekly basis to evaluate children with suspect symptoms (as defined by the NTP)<sup>11</sup> and those newly diagnosed with TB. In addition, a study nurse documented all children started on anti-tuberculosis treatment at the referral hospital.

Two independent experts evaluated the CXRs of all children treated for TB to assess the accuracy of the diagnosis. Children were categorised as 'not TB' if they met all three of the following criteria: 1) both experts agreed that the chest radiograph CXR was not suggestive of TB; 2) no bacteriological confirmation was obtained; and 3) no extra-thoracic TB was documented. All children treated for TB who had radiological signs suggestive of TB, bacteriological confirmation or extra-thoracic manifestations of TB were categorised as 'probable TB'. Severe disease was defined as disseminated (miliary) disease<sup>12</sup> and/or central nervous system (CNS) involvement.

Unadjusted data from the 2001 national census were used for the calculation of TB incidence rates. One clinic was excluded from these calculations, as the population served by this clinic had increased considerably since 2001, due to new housing developments and informal settlements. The populations served

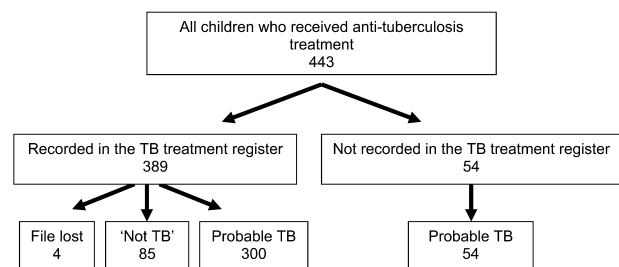
by the other four clinics are stable, as reflected by comparable 1996 and 2001 census data and the fact that these areas are completely built-up, with no recent housing developments or space for informal settlements. TB incidence was calculated by using the annualised number of entries (excluding those transferred in) recorded in the clinic TB treatment register during the 21-month study period as the numerator, and age-specific population figures for the area as the denominator. The corrected TB incidence in children was calculated by subtracting the number of children categorised as 'not TB' from the total number treated to determine the numerator, and using area- and age-specific population data as the denominator.

Ethics approval was obtained from the Institutional Review Board of Stellenbosch University, the City of Cape Town Health Department and local community health committees.

## RESULTS

During the study period, a total of 443 children were treated for TB, of whom 389 (87.8%) were recorded in the TB treatment register (Figure). The files of four patients were lost. Table 1 shows the demographics and clinical characteristics of all 439 children whose records were evaluated. The sex distribution was equal; 223 (52.6%) children were <3 years of age, and 283 (64.5%) were tested for HIV infection, of whom 25 (8.8%) were HIV-infected.

Eighty-five (19.4%) children were categorised as 'not TB'. Three had disease caused by non-tuberculous mycobacteria (NTM): one immune-competent child had a regional *Mycobacterium bovis* bacille Calmette-Guérin (BCG) abcess in the right axilla, and the other two were HIV-infected with *M. bovis* BCG and an unspecified NTM, respectively, cultured from their gastric aspirates. Fifty-five were asymptomatic household contacts of an adult index case, while 27 pre-



**Figure** Flow chart of all children <13 years of age treated for TB during the 21-month study period. 'Not TB' = both experts agreed that CXR was not suggestive of TB, no bacteriological confirmation was obtained and no extra-thoracic TB was documented. Probable TB = all children treated for TB who had radiological signs suggestive of TB, bacteriological confirmation or extra-thoracic manifestations of TB. TB treatment register = the clinic TB treatment register, which is the only data source used to compile community-based surveillance data. TB = tuberculosis; CXR = chest X-ray.



**Table 1** Demographics and clinical characteristics of all children <13 years of age treated for TB

Children treated for TB	<i>n</i> (%)
Total analysed (4 of 443 records lost)	439
Sex	
Male	217 (49.4)
Female	222 (50.6)
Age, years	
<3	231 (52.6)
3–5	96 (21.9)
5–9	76 (17.3)
10–13	36 (8.2)
Route	
Actively traced contact of an adult index case	140 (31.9)
Presented with suspect symptoms	299 (68.1)
HIV	
Tested	283 (64.5)
Infected	25/283 (8.8)
Proportion categorised as 'not TB'	85/439 (19.4)
Non-HIV-infected	26/253 (10.2)
HIV status unknown	49/161 (30.4)
HIV-infected	10/25 (40.0)

'Not TB' = both experts agreed that CXR was not suggestive of TB, no bacteriological confirmation was obtained, and no extra-thoracic TB was documented. TB = tuberculosis; HIV = human immunodeficiency virus; CXR = chest X-ray.

sented with suspect symptoms or possible contact outside the household. Ten of the 25 (40.0%) HIV-infected children were categorised as 'not TB', compared to 26/253 (10.2%) non-HIV-infected children (odds ratio [OR] 5.82, 95%CI 2.17–15.56,  $P < 0.001$ ).

Table 2 reflects the burden of childhood TB in the study area. During the 21-month study period 2830 people were treated for TB, of whom 389 (13.7%) were children <13 years of age. The proportion of

children <13 years of age was 18.0% (107/593) in the two clinics where active contact tracing was well-supervised, compared to 12.4% (278/2237) in the clinics where no supervised contact tracing took place (OR 1.55, 95%CI 1.21–1.99,  $P < 0.001$ ). The TB incidence amongst adults, using routine surveillance data, was 845/100 000/year, compared to 441/100 000/year in children <13 years of age. The corrected TB incidence in children was 407/100 000/year.

Table 3 reflects the TB manifestations documented in the 54 children who were treated for TB but not recorded in the clinic TB treatment register. In total, 21/28 (75.0%) children with severe disease were not recorded in the clinic TB treatment register, comprising 9/12 (75.0%) with disseminated (miliary) disease, 7/10 (70.0%) with CNS involvement and 5/6 (83.3%) with both disseminated disease and CNS involvement.

## DISCUSSION

In this high-burden setting, children <13 years of age contributed 13.7% of the total TB caseload, which compares remarkably well with the 15% contribution estimated for children <15 years of age in low-income countries.<sup>13</sup> This indicates that although results from this hyperendemic area may not be generalisable, it is reasonable to suspect a similar situation in other endemic areas. Efforts should be increased to measure the burden of childhood TB with greater accuracy in endemic areas.

A striking observation was the high incidence of childhood TB in the study community. Although children <13 years of age contributed 13.7% of the total

**Table 2** The burden of childhood TB in the study area using community-based surveillance data, and data corrected for both misdiagnosis and absence from the clinic TB treatment register\*

Community-based surveillance data	<i>n</i> (%)
Total number recorded in the TB treatment register	2830
Proportion of children <13 years of age	289/2830 (13.7)
Proportion of children recorded in the TB treatment register in clinics	
with supervised household contact tracing	107/593 (18.0)
without supervised household contact tracing	282/2237 (12.6)
Total population (unadjusted national census data from 2001) <sup>†</sup>	120 216
Proportion of children <13 years of age <sup>‡</sup>	30 607/120 216 (25.5)
All-TB incidence <sup>§</sup> in	
the total population <sup>†</sup>	742/100 000/year
adult population (≥13 years of age) <sup>†</sup>	845/100 000/year
children (<13 years of age) <sup>†</sup>	441/100 000/year
Corrected TB incidence <sup>§</sup> in children <13 years of age <sup>†</sup>	407/100 000/year

\* TB treatment register = this refers to the clinic TB treatment register, which is the only data source used to compile community-based surveillance data.

<sup>†</sup> Data from one local clinic where the unadjusted national census data from 2001 were considered to be unreliable were excluded from both the numerator and the denominator.

<sup>‡</sup> The all-TB incidence was calculated by 1) using the annualised number of entries (excluding transfers in) recorded in the TB treatment register during the 21-month study period as the numerator; 2) using area- and age-specific population figures as the denominator, and 3) expressing this ratio as the number of TB cases/100 000/year.

<sup>§</sup> The corrected TB incidence in children was calculated by subtracting the number of children categorised as 'not TB' from the total number treated to determine the numerator and using area- and age-specific population data as the denominator.

TB = tuberculosis.

**Table 3** The TB manifestations recorded in children with probable TB who were absent from the clinic TB treatment register

	<i>n</i> (%)
Total with probable TB (439–85 'not TB'*)	354
Proportion absent from the TB treatment register†	54/354 (15.3)
TB manifestations	
Intra-thoracic TB only	35/282 (12.4)
Ghon focus or primary complex	2/19 (10.5)
Lymph node disease	16/212 (7.5)
Pleurisy/pericarditis	5/25 (20.0)
Disseminated (miliary) disease	9/12 (75.0)
Adult-type disease	3/14 (21.4)
Extra-thoracic TB only	16/47 (29.6)
Peripheral lymph node involvement	3/22 (13.6)
CNS-TB	7/10 (70.0)
Abdominal TB	0/1
Osteo-articular TB	4/10 (40.0)
Skin manifestations	0/4
Both intra- and extra-thoracic TB	5/25 (23.5)
TBM and miliary TB	3/3 (100)
TBM and lymph node disease on CXR	2/3 (66.7)
Other combinations	0/19
Total with severe disease‡ absent from the TB treatment register	21/28 (75.0)

\* 'Not TB' = both experts agreed that CXR was not suggestive of TB, no bacteriological confirmation was obtained, and no extra-thoracic TB was documented.

† TB treatment register = this refers to the clinic TB treatment register, which is the only data source used to compile community-based surveillance data.

‡ Severe disease = CNS and/or disseminated (miliary) TB.

TB = tuberculosis. CNS = central nervous system; TBM = tuberculous meningitis; CXR = chest X-ray.

TB caseload, they experienced a TB incidence that was 52.2% (441 vs. 845/100 000/year) of the adult ( $\geq 13$  years of age) incidence, using data from the clinic TB treatment register. The incidence of childhood TB remained high (407/100 000/year) despite correcting for children with 'not TB', who received treatment inappropriately. The proportion of paediatric cases was influenced by the diligence with which active contact tracing was performed, as demonstrated by the significant difference in the proportion of child cases recorded in the clinics where active contact tracing was well-supervised, compared to those without supervised contact tracing.

The fact that significantly more HIV-infected children were categorised as 'not TB' reflects the tremendous diagnostic difficulties experienced in this group.<sup>14</sup> Preventive chemotherapy is advised in HIV-infected children infected with *M. tuberculosis* or exposed to an adult index case, once active TB has been excluded.<sup>15</sup> However, because adherence to unsupervised preventive chemotherapy is known to be poor<sup>16</sup> and radiological signs are difficult to interpret,<sup>14</sup> concerned clinicians often prefer to give fully supervised therapy to children whom they perceive to be at high risk of developing TB, such as HIV-infected children exposed to an adult index case.

The study is limited by the fact that contact tracing was not well-supervised in all five clinics; however, all children who presented with suspect symptoms were

screened. In addition, children with severe TB may have died without presenting to a health care facility, but access to local clinics and hospitals is good within the study area, which makes this unlikely. Despite these limitations, this study provides the best achievable estimate of the true burden of childhood TB in this high-burden setting.

The most important observation was the frequent omission of severe cases and the gross under-representation (7/28, 25%) of children at the severe end of the disease spectrum in the clinic TB treatment register, although the total number of children recorded was a slight over-representation of the true TB burden due to misdiagnosis (389 vs. 358, 108.7%). All 54 children who were not recorded in the clinic TB treatment register were diagnosed at the referral hospital, from where the majority were transferred to a TB hospital due to the severity of their disease or to social problems to complete their treatment under hospital supervision. Those discharged from the referral hospital on anti-tuberculosis treatment were not always captured in the clinic TB treatment register, although treatment was continued.

The current policy is that all children discharged from hospital on anti-tuberculosis treatment should be recorded in the clinic TB treatment register, but this policy needs to be re-emphasised to health care personnel. Children who complete their full duration of treatment in a TB hospital are currently entered into a hospital-held register, but these data are not relayed back to the local clinic. The most feasible solution in the study setting is that data from the hospital-held register should be transferred to the appropriate clinic register at the time of electronic data entry. The electronic register should then provide all-inclusive community-based data. However, current international TB surveillance categories preclude the identification of these more serious forms of TB, a limitation that we think needs to be addressed to determine the true burden of childhood TB.

In conclusion, children with severe forms of TB are inaccurately reflected in community-based surveillance data. The accuracy of surveillance data must be taken into consideration when reporting on the epidemiology of childhood TB or when determining the effectiveness of public health interventions.

#### Acknowledgements

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## R É S U M É

**CONTEXTE :** La qualité des données épidémiologiques concernant la tuberculose (TB) infantile est compromise par une surveillance inadéquate et par les difficultés de diagnostic.

**OBJECTIF :** Documenter l'incidence de la TB de l'enfant et évaluer la précision des données de surveillance basées sur la collectivité dans un contexte à haute prévalence.

**MÉTHODES :** Cette étude prospective d'observation a été menée entre février 2003 et octobre 2004 dans cinq polycliniques de soins de santé primaires à Cape Town, Afrique du Sud. Une surveillance complète a été menée pour s'assurer que tous les enfants âgés de moins de 13 ans et traités pour TB avaient bien été inclus.

**RÉSULTATS :** Au cours de la période d'étude, 443 enfants âgés de <13 ans ont reçu un traitement antituberculeux. Parmi ceux-ci, 389 (87,8%) avaient été inscrits

dans le registre de traitement de la TB. L'incidence de la TB, calculée à partir du registre de traitement de la TB, a été de 441/100.000 par an parmi les enfants et de 845/100.000 par an parmi les adultes. Cinquante-quatre enfants traités pour TB n'étaient pas inscrits dans le registre de traitement de la TB, et parmi ceux-ci se trouvaient 21 des 28 (75%) enfants atteints de TB grave.

**DISCUSSION :** Les enfants âgés de <13 ans ont représenté 13,7% du fardeau total de TB. L'incidence chez les enfants est supérieure à la moitié (52%) de celle enregistrée chez les adultes. Les données de surveillance basées sur la collectivité n'ont pas inclus la majorité des enfants atteints d'une maladie grave. La précision des données de surveillance est une considération importante lorsqu'il s'agit de décrire l'épidémiologie de la TB de l'enfant ou de mesurer les succès des interventions de santé publique.

## R E S U M E N

**MARCO DE REFERENCIA :** La calidad de los datos epidemiológicos sobre la tuberculosis (TB) infantil se deteriora debido a la vigilancia inadecuada y a las dificultades diagnósticas.

**OBJETIVO :** Verificar la incidencia de TB en la infancia y evaluar la precisión de los datos de vigilancia epidemiológica de base comunitaria, en un entorno con alta carga de morbilidad por TB.

**MÉTODOS :** Fue este un estudio observacional prospectivo realizado entre febrero de 2003 y octubre de 2004 en cinco consultorios de atención primaria de salud en Ciudad del Cabo, Sudáfrica. Se llevó a cabo una vigilancia exhaustiva para verificar la inclusión de todos los niños <13 años tratados por TB.

**RESULTADOS :** Durante el período del estudio 443 niños <13 años recibieron tratamiento antituberculoso, de los cuales 389 (87,8%) se declararon al registro de trata-

miento de la TB. La incidencia de TB calculada con base en el registro fue de 441/100 000 por año en los niños y de 845/100 000 por año en los adultos. Cincuenta y cuatro niños tratados por TB no fueron declarados al registro de tratamiento de la TB ; entre ellos 21 de los 28 niños con una enfermedad grave (75%).

**DISCUSIÓN :** La tuberculosis en niños <13 años representó el 13,7% de la carga total de morbilidad por TB. Sin embargo, los niños presentaron una incidencia de TB correspondiente al 52,2% de la incidencia de los adultos. Los datos de vigilancia de base comunitaria excluyeron la mayoría de niños con enfermedad grave. La precisión de los datos de vigilancia constituye una consideración importante cuando se describe la epidemiología de la TB infantil y cuando se evalúa el éxito de las intervenciones de salud pública.

## Chapter 4.

### The spectrum of disease

Childhood tuberculosis is often reported as a single disease entity, although it represents a diverse spectrum of pathology. Accurate classification of intra-thoracic disease in children is important, due to its prognostic significance. We propose a radiologic classification of intra-thoracic tuberculosis in children, and discuss the pathogenic differences that underlie the different disease manifestations. Thereafter, we documented the complete spectrum of disease in children treated for tuberculosis in an endemic area and demonstrated that bacteriologic confirmation may be achieved in the majority of children with intra-thoracic tuberculosis. We also described the clinical presentation and diagnosis of tuberculous cervical lymphadenitis, which is the most common extra-thoracic manifestation of tuberculosis in children.

1. **Marais BJ, Gie RP, Schaaf HS, Starke JR, Hesselning AC, Donald PR, Beyers N. A proposed radiologic classification of childhood intra-thoracic tuberculosis. *Pediatr Rad* 2004; 33: 886-894**

One of the obstacles in childhood tuberculosis is the lack of standard descriptive terminology to classify the diverse spectrum of disease. Accurate disease classification is important for optimal case definition and management, and to facilitate scientific communication. This review proposes a radiologic classification of intra-thoracic tuberculosis in children, based on the underlying disease pathology and the principles of pathological disease progression.

2. **Marais BJ, Donald PR, Gie RP, Schaaf HS, Beyers N. Diversity of disease manifestations in childhood pulmonary tuberculosis. *Ann Trop Paed* 2005; 25; 79-86**

Many factors can influence the dynamic host-pathogen balance, but host immunity is a crucial factor. This is illustrated by the vulnerability of immune-compromised individuals to develop tuberculosis and by the age-related spectrum of disease witnessed in immune-competent children. This review focuses on the age-related spectrum of disease in children with

tuberculosis and on the importance of understanding the ontogeny of the host immune response towards *M.tuberculosis*. It offers a hypothesis to explain the unique anatomical localization of adult-type tuberculosis and its sudden emergence around puberty.

**3. Marais BJ, Gie RP, Hesselning AC, Beyers N. Adult-type pulmonary tuberculosis in children aged 10-14 years. *Pediatr Inf Dis J* 2005; 24: 743-744**

This case series reported 8 children, 10-14 years of age, who were treated for tuberculosis at their local primary health care clinic in a 3-month period, after routine sputum testing was extended to all children older than 10 years of age with suspected tuberculosis. Of the 8, 7 had adult-type disease and were sputum smear-positive. Children with adult-type disease pose a significant transmission risk, especially in congregate settings such as schools. This case series emphasized the existence of adult-type disease in children and the fact that it can be diagnosed by sputum smear-microscopy.

**4. Marais BJ, Gie RP, Schaaf HS, Hesselning AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. *Int J Tuberc Lung Dis* 2006. In press**

Children contribute a significant proportion of the global tuberculosis caseload; particularly in endemic areas where little is known about their spectrum of disease. This prospective descriptive study documents the complete disease spectrum, and relevant age-related differences, in children treated for tuberculosis in a highly endemic area. Children suffered significant morbidity, with most severe disease recorded in very young and/or HIV-infected children. In HIV-uninfected children; disseminated (miliary) disease (9/11, 81.8%) and tuberculous meningitis (10/13, 76.9%) occurred predominantly in children less than 3 years of age. In HIV-infected children, disease manifestations that reflect poor organism containment such as complicated Ghon focus and disseminated (miliary) disease, were significantly more common (6/25, 24.0%) than in HIV-uninfected children (12/414, 2.9%) (OR 10.9, 95% CI 3.2-35.9).

**5. Marais BJ, Hesselning AC, Gie RP, Schaaf HS, Enarson DA, Beyers N.**

**Bacteriologic yield in children with intra-thoracic tuberculosis. Clin Infect Dis 2006. In press**

This report represents a sub-analysis of the disease spectrum study (referred to above) and documents the proportion of children treated for intra-thoracic tuberculosis, in whom bacteriologic confirmation was achieved. In total, bacteriologic confirmation was achieved in 122/196 (62.2%) children in whom specimens were collected. The lowest bacteriologic yield was recorded in children with uncomplicated lymph node disease (24/69, 34.8%).

Bacteriologic confirmation was achieved in an unexpected high proportion of children treated for intra-thoracic tuberculosis, which indicates a need to re-assess the value of bacteriology-based approaches to diagnose childhood tuberculosis, particularly in endemic areas where children often present with advanced disease.

**6. Marais BJ, Wright C, Gie RP, Hesselning AC, Schaaf HS, Enarson D, Beyers N.**

**Tuberculous lymphadenitis as a cause of persistent cervical lymphadenopathy in children from a tuberculosis endemic area. Ped Inf Dis J 2006; 25: 142-146**

Cervical lymphadenitis is the most common form of extra-pulmonary tuberculosis in children. This prospective descriptive study documented the clinical presentation of tuberculous lymphadenitis at the primary health care level, and its relative contribution as a cause of persistent cervical adenopathy in children from a tuberculosis endemic area. A total of 158 children were evaluated of whom 35 (22.2%) were diagnosed with tuberculous lymphadenitis. In children with a persistent cervical mass  $\geq 2 \times 2$  cm, without a visible local cause or response to antibiotics, tuberculous lymphadenitis was diagnosed in 31/33 (93.3%); sensitivity 88.6%, specificity 98.4%, positive predictive value 93.4%. The use of a simple clinical algorithm identified tuberculous lymphadenitis with a high degree of accuracy, while fine needle aspiration (FNA) provided a rapid and definitive diagnosis in the majority of children.



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## A proposed radiological classification of childhood intra-thoracic tuberculosis

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**Abstract** One of the obstacles in discussing childhood tuberculosis (TB) is the lack of standard descriptive terminology to classify the diverse spectrum of disease. Accurate disease classification is important, because the correct identification of the specific disease entity has definite prognostic significance. Accurate classification will also improve study outcome definitions and facilitate scientific communication. The aim of this paper is to provide practical guidelines for the accurate radiological classification of intra-thoracic TB in children less than 15 years of age. The proposed radiological classification is based on the underlying disease and the principles of pathological disease progression. The hope is that the proposed classification will clarify concepts and stimulate discussion that may lead to future consensus.

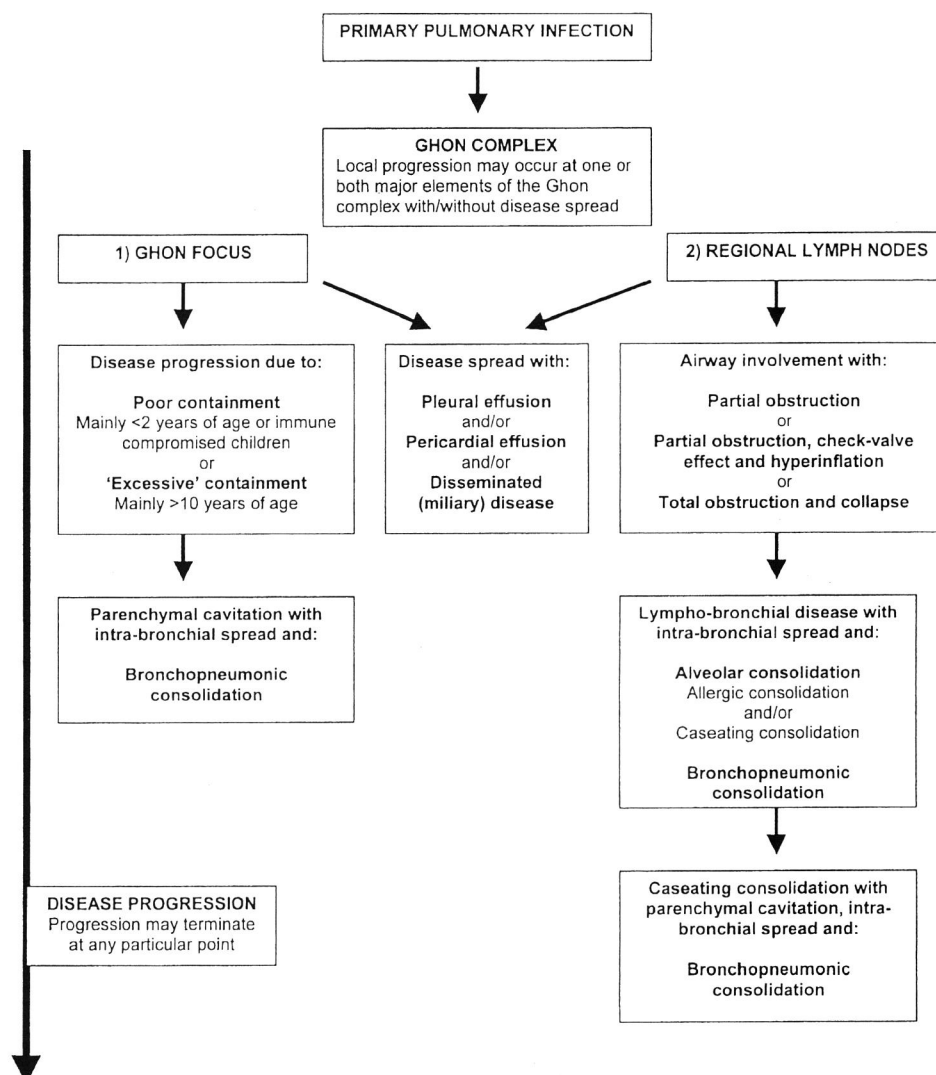
**Keywords** Tuberculosis · Lung · Mediastinum · Classification · Children

### Introduction

Inhalation is the predominant route of *Mycobacterium tuberculosis* (*M. tuberculosis*) infection [1, 2]. Infection is indicated by a significant tuberculin skin test (TST) [3]. A positive *M. tuberculosis*-specific lymphocyte stimulation test also indicates infection in an experimental setting [4]. Primary infection is followed by a sequence of events which in nearly every instance leads to the development of a Ghon complex and the dissemination

of bacilli throughout the body [2]. Identification of the radiological changes associated with primary tuberculosis (TB) infection may be difficult, and in the absence of information on clinical symptoms, the point at which these changes should be looked upon as a manifestation of disease is uncertain. In general, the pathological changes associated with TB in children are non-cavitary and pauci-bacillary. Therefore, the diagnosis of intra-thoracic TB in childhood depends largely on the interpretation of the chest radiograph [5].

Fig. 1 Progression of pathology in intra-thoracic TB following primary pulmonary infection in childhood



One of the obstacles in childhood TB is the lack of standard descriptive terminology to classify the spectrum of disease. Accurate disease classification is important, because the identification of specific disease entities has definite prognostic significance [5]. Accurate classification will improve study outcome definitions, facilitate study comparison and improve scientific communication. It will also improve understanding of the underlying disease and its implications for patient care. The aim is to provide practical guidelines for the accurate radiological classification of different intra-thoracic manifestations of TB in children less than 15 years of age.

## Materials and methods

The natural history of disease and associated pathologic descriptions from the pre-chemotherapy era provided the

scientific basis for the proposed radiological classification [1–3, 5–19]. A summary of the pathological progression of disease, deduced from the pre-chemotherapy literature, is provided to illustrate the principles that were applied (Fig. 1). More recent relevant reports, as well as the combined personal experience of the authors regarding the radiological manifestations of childhood TB, were included to provide a comprehensive picture. The proposed classification represents a compromise between descriptive accuracy and practical utility.

## Principles of the pathological progression of disease

A thorough understanding of disease pathology is essential, because the chest radiograph is merely a 2-D reflection of the underlying pathology.



Primary pulmonary infection occurs when an uninfected person inhales an infectious droplet, which successfully establishes infection in a terminal airway or alveolus [1–3, 5–7]. A localized pneumonic process, referred to as the primary parenchymal (Ghon) focus, results. From the Ghon focus, bacilli usually drain via local lymphatics to the regional lymph nodes. The upper lobes drain to the ipsilateral-paratracheal nodes, while the rest of the lung drains to the perihilar nodes, with dominant lymph flow from left to right [3]. The combination of the Ghon focus, local lymphangitis and regional lymph node involvement is called the Ghon complex [1–3, 5–7, 20, 21]. Some pleural reaction overlying a peripheral Ghon focus may form part of the Ghon complex [21]. The formation of the Ghon complex is often subclinical and a random chest radiograph following primary infection is often normal or reveals only a single component (usually hilar adenopathy) [2, 3, 21, 22].

Disease progression may occur at the site of organism deposition (Ghon focus), within the regional lymph nodes, or following disease spread [1–3, 5–7]. Disease spread may occur following lymphatic drainage with haematogenous dissemination or after local penetration across anatomical boundaries [1–3, 5–7]. Penetration may occur into an adjacent anatomical space or structure, into an airway with additional intra-bronchial spread or into a blood vessel with haematogenous dissemination.

The Ghon focus represents the first site of possible disease progression. Poor containment at the site of organism deposition may lead to progressive caseation. Discharge of the caseated material into a bronchus results in the formation of a parenchymal cavity [1–3, 5–7]. Infants [1–3, 5, 23, 24] and immunocompromised children [25–29] are most vulnerable to cavitation of the Ghon focus due to poor disease containment. A change in the immune response around puberty may result in 'excessive' organism containment, but this is a detrimental response leading to ultimate poor containment. Increased parenchymal damage results in cavities, where organisms multiply efficiently [7–10]. The exact pathological mechanism, as well as the relative contribution of recent primary infection, re-infection and re-activation is uncertain, but in older children (>10 years of age) adult-type cavitating disease is the dominant disease manifestation following recent primary infection [7–10, 30].

The second site of possible disease progression is within the regional lymph nodes, which enlarge due to central caseation and surrounding inflammatory oedema [1–3, 6, 7]. Lymph node disease is most common following primary infection before 5 years of age [1–3, 5]. This, in addition to the small airway size, makes young children the most vulnerable group to develop lympho-bronchial TB [1–3, 12, 31]. The term lympho-bronchial

TB refers to a whole spectrum of airway involvement and associated complications that may arise following lymph node disease [30]. Extra-luminal compression results from enlarged lymph nodes and associated inflammatory oedema [1–3, 5–7]. Intra-luminal obstruction results from polyps or granulomatous tissue that develop secondary to inflammatory changes in the bronchial wall, or from caseous material deposited on eruption of a caseated lymph node into the airway [1–3, 5–7]. Partial airway obstruction may cause a check-valve effect with distal hyperinflation [7, 13]. Total airway obstruction results in resorption of distal air with alveolar collapse [23]. The ultimate volume of the affected segment depends on the underlying alveolar pathology [1–3, 5–7, 15].

Intra-bronchial spread may occur from a parenchymal cavity with a high organism load [3, 7], or after eruption of a caseated lymph node with variable organism load, into a bronchus [3, 5–7, 31]. Patchy bronchopneumonic consolidation affecting multiple lung segments may result after intra-bronchial spread from a parenchymal cavity [3, 5–7]. Lymph node eruption into a bronchus with distal aspiration of caseous material usually results in dense alveolar consolidation of a single segment or lobe [1–3, 5–7], but patchy bronchopneumonic consolidation is also a possibility. Variation in the dose and virulence of the bacilli aspirated, the degree of airway obstruction and the immune competence of the host determine the resultant pathology [1, 7, 15]. The pathology may range from a pure hypersensitivity response, historically referred to as epituberculosis, to destructive caseating pneumonia [7, 15, 32]. Bulging fissures and cavitation indicates caseating pneumonia or possible secondary bacterial infection [1, 3, 33].

Disease spread may also occur after penetration into an adjacent anatomical space or structure [3, 6, 7]. A unilateral pleural effusion points to direct spread from a subpleural Ghon focus, while bilateral pleural effusions may indicate bilateral Ghon foci or haematogenous dissemination [3, 7, 17]. Pleural effusion develops mainly in children older than 5 years following recent primary infection [2, 3]. The accumulation of a lymphocyte-rich straw-coloured fluid containing few organisms represents a hypersensitivity response, but rarely tuberculous empyema may develop, depending on the dose and virulence of bacilli that enter the pleural space and the immune status of the host [1, 3, 7]. A pericardial effusion usually develops when a subcarinal lymph node erupts into the pericardial space, but it displays the same range of pathology as pleural effusions [3, 7]. Diseased lymph nodes may infiltrate other intra-thoracic structures with visible signs on the chest radiograph, e.g. the oesophagus, the phrenic nerve and the thoracic duct [3, 6, 7].

Two main types of haematogenous spread are differentiated, but dissemination represents a condition of

infinite gradation. Following dissemination, bacilli lodge in small capillaries where they may progress locally and give rise to further haematogenous spread [1–3, 7]. The first type (occult spread) occurs commonly after primary infection. It rarely progresses to disseminated disease, except in very young (<2 years of age) [1–3] and immunocompromised children [25, 26]. The second type occurs rarely and only after disease progression, when a caseous focus erodes into a blood or lymph vessel [1, 3, 7]. It frequently progresses to disseminated disease, irrespective of the child's age or immune status [1, 3].

### Proposed radiological classification of intra-thoracic tuberculosis

The diverse spectrum of disease is classified into separate principal disease entities, according to the underlying pathology (Fig. 1). Active radiographic surveillance following recent TST conversion indicates that elements of the Ghon complex are often visible following recent primary infection [19]. In isolation, elements of the Ghon complex can be viewed as radiographic proof of recent primary infection. The presence of clinical symptoms indicative of disease together with radiographic evidence of recent primary infection, or any other radiographic sign attributable to current disease, identifies intra-thoracic TB in childhood. The radiographic picture may be used to classify intra-thoracic TB according to the principal disease entities and the complications visible (Table 1).

### Principal disease entities

The principal disease entities are arranged according to anatomical location, following the rationale of disease progression outlined (Fig. 1). The Ghon focus involves the lung parenchyma, but is part of the Ghon complex and will be accompanied by lymph node disease in the majority of cases. Adult-type disease also affects the lung parenchyma, but does not form part of the Ghon complex and is usually seen in isolation.

### Lung parenchyma

#### *Ghon focus*

The Ghon focus forms part of the Ghon complex and is rarely seen in isolation. It is variable in size and may show an overlying pleural reaction (Figs. 2, 3) [21]. Complications include local progression with cavity formation and resultant intra-bronchial spread with bronchopneumonic consolidation [1, 23–25, 29].

#### *Adult-type disease*

The initial presentation of adult-type disease may be with cloudy opacification in an apical lung segment, before coalescence and parenchymal breakdown (Fig. 4) [1, 21]. Usually the cavities already exist on presentation, surrounded by alveolar consolidation and fibrosis [3, 30, 34]. The apical and posterior segments of the upper lobe and the apical segment of the lower lobe are most

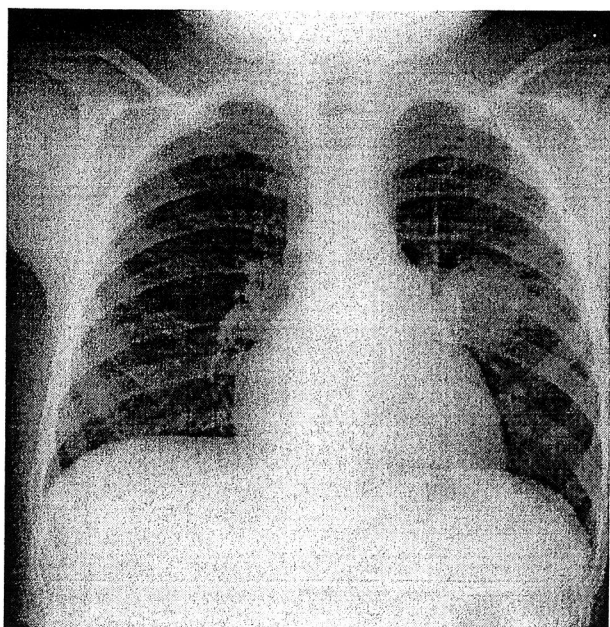
**Table 1** Proposed radiological classification of childhood intra-thoracic TB

Principal disease entity	Local complications	Complications following intra-bronchial spread
<b>Lung parenchyma</b>		
Ghon focus	With cavitation	And bronchopneumonic consolidation
Adult-type disease		
<b>Lymph node</b>		
Lymph node disease	<b>Obstruction</b> With bronchial and/or tracheal compression With hyperinflation or collapse <b>Infiltration</b> With tracheo- or broncho-oesophageal fistula With chylothorax With diaphragmatic palsy With tuberculous empyema With pneumothorax	With alveolar consolidation (-and cavitation/-and bronchopneumonic consolidation)  With bronchopneumonic consolidation
Pleural effusion		
Pericardial effusion		
Disseminated (miliary) disease		

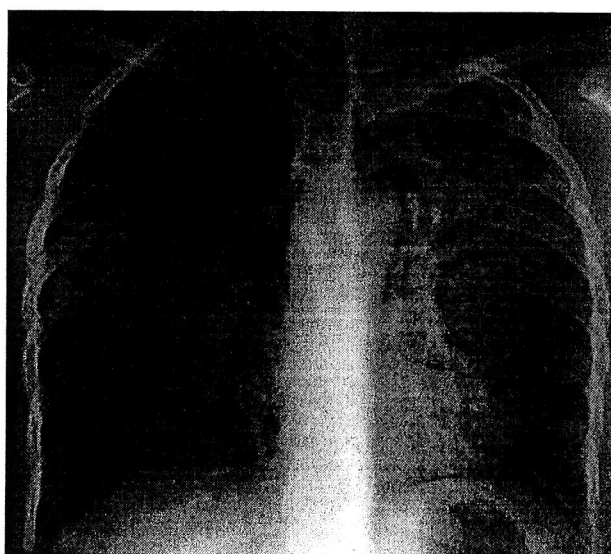
Identify the principal disease entity. Then specify the principal disease entity according to the visible radiographic complications. More than one principal disease entity may be present at the same

time or develop in succession. Some radiological manifestations may be difficult or impossible to classify accurately. Extremely rare entities (e.g. congenital TB) were not included in this classification

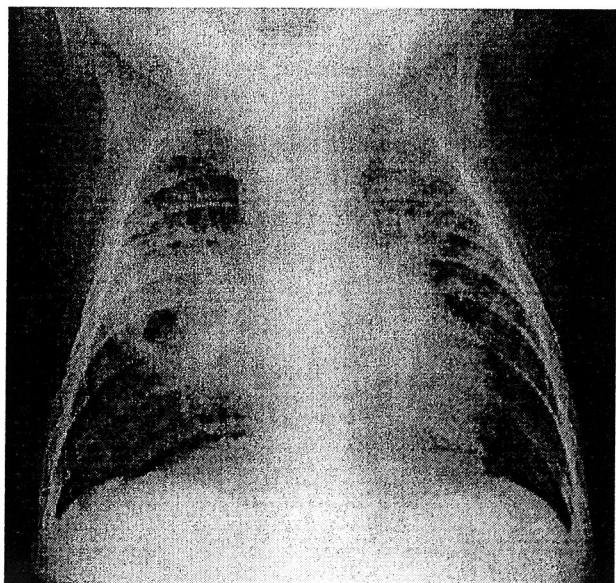




**Fig. 2** Radiological classification: Ghon focus. Pathological description: large uncomplicated Ghon focus in the left lower lobe



**Fig. 4** Radiological classification: adult-type disease with unilateral cavitation and unilateral bronchopneumonic consolidation. Pathological description: adult-type disease with alveolar consolidation and multiple cavities in the left upper lobe, leading to intra-bronchial spread with segmental bronchopneumonia in the right upper lobe. The calcified mediastinal glands on the left suggest previous primary infection



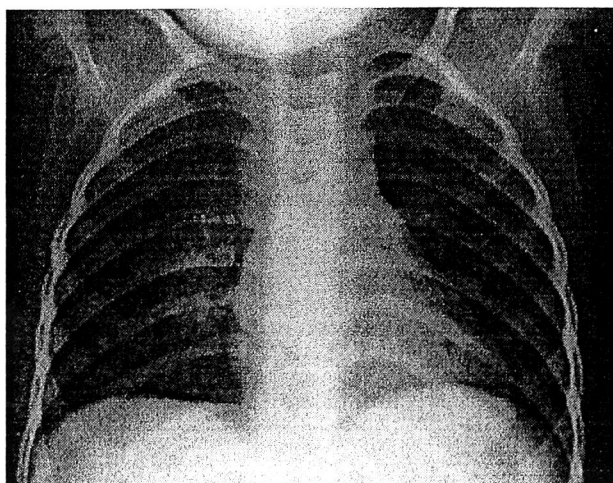
**Fig. 3** Radiological classification: Ghon focus with cavitation and bilateral bronchopneumonic consolidation. Pathological description: poorly contained Ghon focus with cavitation leading to bilateral bronchopneumonia

commonly affected. Complications include progressive cavity formation and intra-bronchial spread with bronchopneumonic consolidation [9, 17, 34].

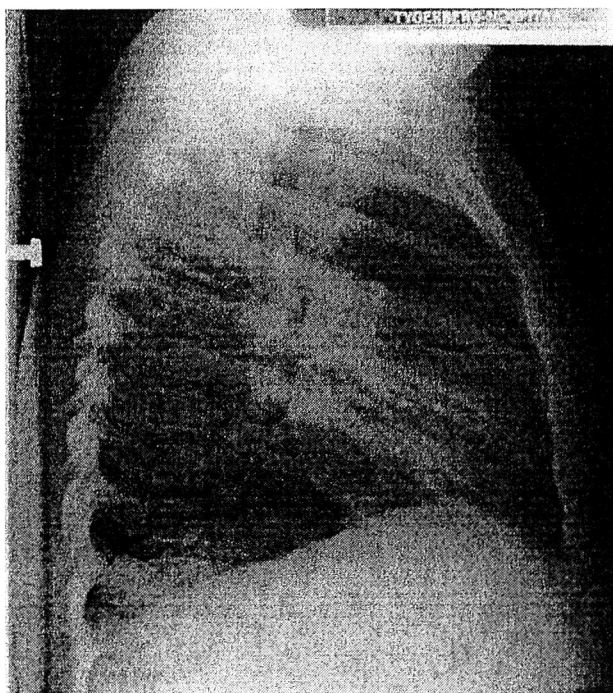
#### Lymph node disease

Regional lymphadenopathy (perihilar or paratracheal) is considered the radiological hallmark of primary infection in childhood (Figs. 5, 6, 7, 8) [17, 35, 36]. Initially, lymph nodes show poor delineation ('flaring') due to adjacent parenchymal involvement, but they become better circumscribed on resolution [17]. AP and lateral views are required for optimal lymph node visualization [22, 36], but it may remain difficult to visualize enlarged lymph nodes with certainty [37–39]. Complications include the full spectrum of lympho-bronchial disease. Airway compression may be better visualized with high-kilovolt exposure. A hyperlucent area with volume increase indicates hyperinflation (partial obstruction with check-valve effect), while segmental or lobar volume loss indicates alveolar collapse (total obstruction). With nodal eruption into an airway and associated alveolar consolidation, the relative contribution of hypersensitivity and caseating pneumonia can only be assessed in hindsight. A pure hypersensitivity response is rare and consolidation shows complete resolution without permanent sequelae [15]. Caseating pneumonia causes parenchymal destruction with cavitation and excessive fibrosis on resolution [15, 33]. Rare local complications visible on chest radiography include broncho- or tracheo-oesophageal fistula formation, diaphragmatic palsy and chylothorax.





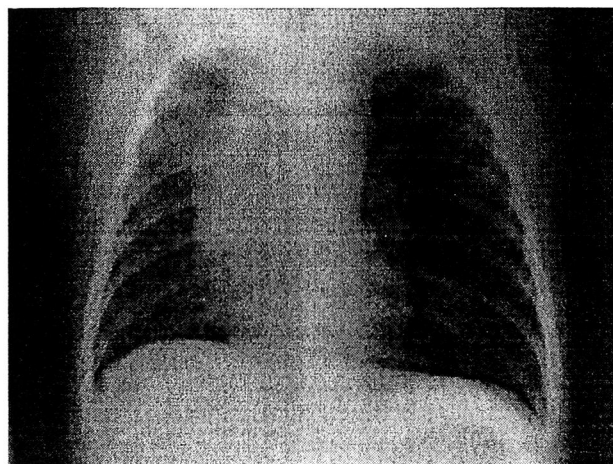
**Fig. 5** Radiological classification: lymph node disease (AP view). Pathological description: right hilar lymph node enlargement. Note the haziness ('flare') that surrounds the lymph node suggesting recent infection without signs of resolution



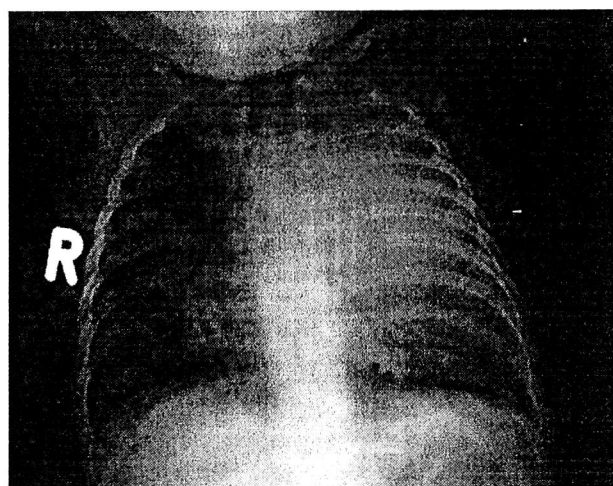
**Fig. 6** Radiological classification: lymph node disease (lateral view). Pathological description: the lateral chest radiograph confirms the enlarged hilar nodes, as indicated by the arrow

#### Pleural effusion

The amount of fluid is highly variable; it typically obliterates 30–60% of the affected hemithorax [17], but a massive fluid collection may occur causing mediastinal shift (Fig. 9) [3, 17]. Complications include a co-existent



**Fig. 7** Radiological classification: lymph node disease with bronchial compression and unilateral hyperinflation. Pathological description: lymph node enlargement with compression of the left main bronchus resulting in a check-valve effect with air trapping in the left lung. This causes unilateral hyperinflation, shifting the mediastinum to the right



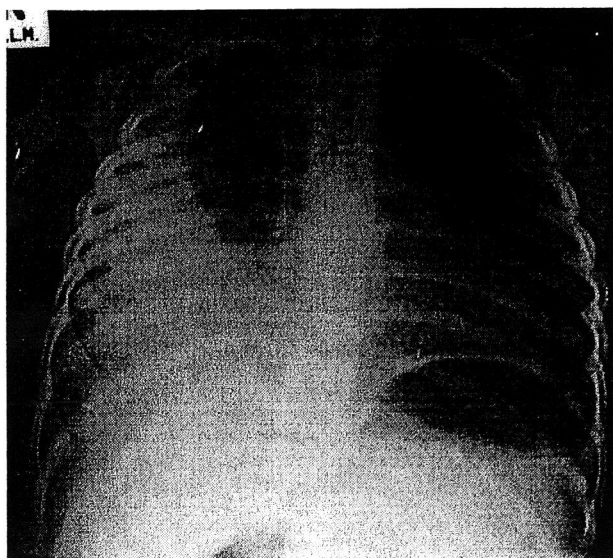
**Fig. 8** Radiological classification: lymph node disease with bronchial and tracheal compression, with lobar alveolar consolidation and cavitation. Pathological description: lymph node enlargement with compression of both the trachea and left main bronchus. Expansile alveolar consolidation of the left upper lobe and lingula due to caseating pneumonia, causes mediastinal shift to the right. A small cavity is visible in the left upper lobe

pneumothorax or a persistent loculated fluid collection, indicative of tuberculous empyema [3, 40].

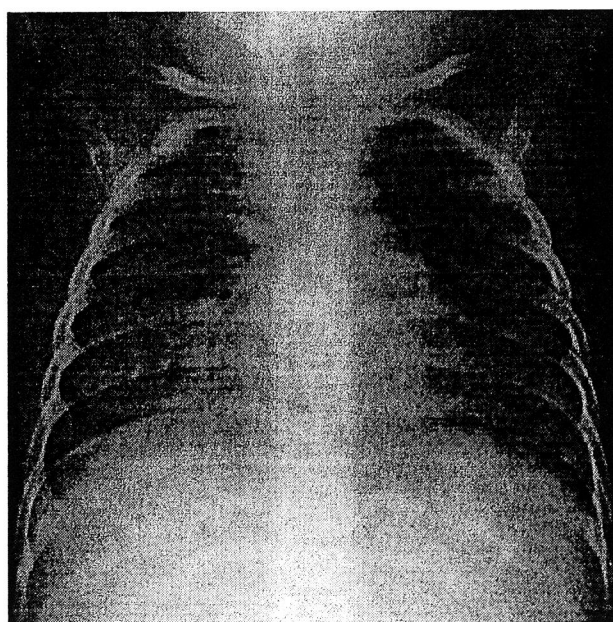
#### Pericardial effusion

The heart shadow may be enlarged with a suggestive globular appearance [3]. Cardiac ultrasound confirms the diagnosis.





**Fig. 9** Radiological classification: unilateral pleural effusion. Pathological description: large uncomplicated right-sided pleural effusion. No underlying pathology is visible



**Fig. 10** Radiological classification: lymph node disease plus disseminated disease. Pathological description: large right-sided paratracheal glands shifting the trachea to the left, with haematogenous disease dissemination

#### Disseminated (miliary) disease

Initial mottling may be invisible, only becoming visible after local progression (Fig. 10) [1, 17, 41–43]. Mottling

may vary in size depending on the degree of local progression [1], from typical even-sized miliary lesions (< 2 mm) to atypical poorly defined patches. The lesions are bilateral and evenly distributed into the periphery of the lung, although limited dissemination via a pulmonary artery may rarely occur [3, 44]. Disease dissemination may be a complication of another pre-existing disease entity, or it may occur in isolation.

#### How to use the disease classification

A summary of the proposed classification is provided to guide the radiological evaluation (Table 1). First identify the principal disease entities present. More than one entity may be present at the same time or develop in succession. Then specify each principal disease entity according to the radiographically visible complications. The extent of disease can be quantified using 'segmental', 'lobar', 'unilateral' or 'bilateral', where applicable. The correct use of the proposed classification has been illustrated with the examples provided (Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10).

Radiological distinction between the different types of cavitating disease may be difficult and is guided by the age of the child. Cavitation from a progressive Ghon focus is rare and occurs in very young (mainly < 2 years of age) or immunocompromised children. Cavitation from adult-type disease usually involves the apical segments of the lung and occurs in older children (mainly > 10 years of age). Cavitation due to caseating pneumonia occurs secondary to lympho-bronchial disease with segmental alveolar consolidation. It affects younger children (mainly < 5 years of age). With extensive bilateral involvement, distinction between advanced disseminated disease and bilateral bronchopneumonia may be problematic, but uniform bilateral involvement usually indicates haematogenous dissemination [17]. However, with HIV-associated immune compromise, lymphocytic interstitial pneumonitis (LIP), malignancies and opportunistic infections may cause additional diagnostic confusion [45, 46].

#### Consequences of previous pulmonary tuberculosis

##### Calcification

Areas of caseation (e.g. inside a Ghon focus or a diseased lymph node) frequently calcify. This may be the only sign of previous primary infection. Calcification may occur from 6 months to 4 years after infection, tending to occur earlier in young children [3, 9, 17]. In the absence of current disease, calcification points to a

previous well-contained infection. It indicates, but is not a guarantee of, clinical quiescence [1, 5, 17].

#### *Parenchymal destruction with fibrosis*

A check-valve effect causes distal volume increase and hyperinflation. Extensive parenchymal destruction causes a bullous appearance with volume loss due to associated fibrosis [1, 3, 47]. Fibrosis and contraction may influence the position of the hilum and lead to eventual collapse of the bullae [1, 17].

#### *Bronchiectasis*

Excessive airway and surrounding parenchymal damage, may cause permanent bronchiectatic dilatation [18, 19]. Recurrent bacterial infections may complicate bronchiectasis, especially if the lower lobes are affected [3, 5, 17].

#### *Consequences of immune reconstitution*

Immune reconstitution was historically described following nutritional rehabilitation or termination of high-dose steroid treatment [3]. Recent descriptions followed the introduction of highly active anti-retroviral therapy (HAART) in HIV-infected immune compromised patients [48, 49]. Immune reconstitution results in increased inflammation.

#### *Airway compression*

Airway compression may worsen due to increased inflammation surrounding diseased lymph nodes. Increased airway compression may be directly visible on the chest radiograph, or indicated indirectly by segmental hyperinflation or collapse.

#### *Alveolar consolidation*

In areas of previous uncontained parenchymal disease progression, excessive inflammation may result in dense alveolar consolidation and eventual parenchymal breakdown [49].

### **Conclusions**

The diversity of disease manifestations in childhood TB necessitates the use of standard descriptive terminology. Accurate classification of intra-thoracic TB is possible using a structured approach to interpret and record the findings on a standard chest radiograph. The hope is that the proposed radiological classification will stimulate discussion and lead to ultimate international consensus, to improve patient care and scientific communication.

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## Diversity of disease in childhood pulmonary tuberculosis

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**Abstract** Many factors can influence the dynamic balance that exists between the host and the pathogen (*M. tuberculosis*), but the host immune response seems to be the most important. This is illustrated by the vulnerability of immune-compromised individuals to develop tuberculosis and by the age-related spectrum of disease witnessed in immune-competent children. This age-related spectrum of disease reflects the ontogeny of the host immune response towards *M. tuberculosis*. Renewing our focus on the ontogeny of the immune response in children might provide valuable insights to direct future research regarding tuberculosis prevention, vaccine development and treatment.

### Background

Childhood covers the interval from birth to adolescence (defined as 0–15 years of age). It is a period of dynamic growth and maturation during which the natural response to infection undergoes profound change as the immune system develops. Few diseases illustrate this evolution of the immune response better than the diverse and changing spectrum of pathology seen in childhood tuberculosis.<sup>1</sup>

A recently proposed radiological classification of childhood intra-thoracic tuberculosis highlights this disease diversity and its relevance to prognosis and treatment.<sup>2</sup> Understanding the age-dependent differences in the immune response to *Mycobacterium tuberculosis* infection is crucial for

improved case management and for directing future research.

The aim of this paper is to explore the pathological mechanisms that underlie the diversity of disease manifestations observed in childhood intra-thoracic tuberculosis. General infectious disease principles are outlined and discussed for tuberculosis in general, before applying them to separate intra-thoracic disease manifestations in particular.<sup>2</sup>

### Principles of Disease

#### *Dynamic balance*

The clinical manifestation of an infectious disease depends on the balance between the organism's pathogenicity and the host's immune competence. In tuberculosis, an important dynamic dimension is added to this balance because initial organism containment rarely ensures organism eradication.<sup>3</sup> Persistence of dormant bacilli inside sequestered foci (latent infection) provides an 'ever-present' risk of reactivation whenever the balance shifts in favour of the

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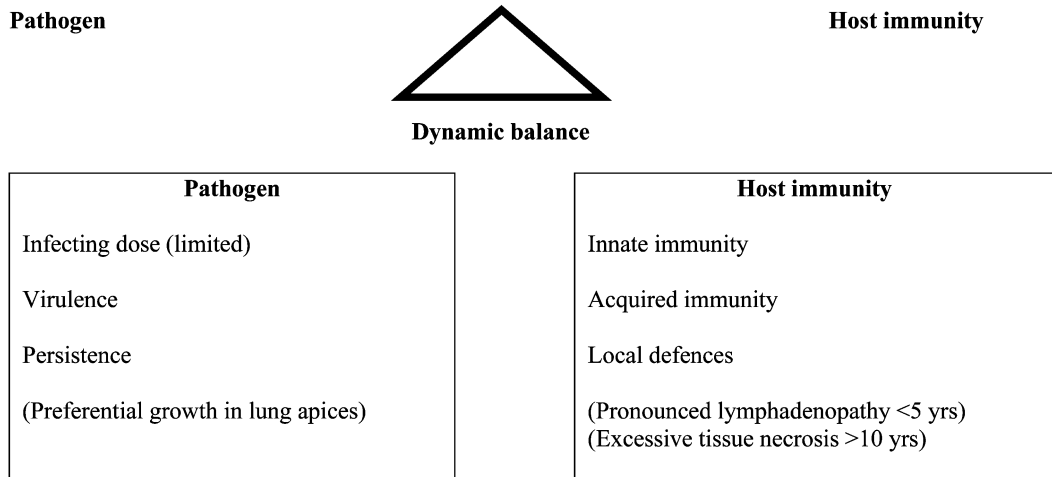


FIG. 1. Factors underlying different manifestations of pulmonary tuberculosis.

organism. In addition to the risk of reactivation following previous primary infection, high levels of transmission implies an additional risk of re-infection in high-burden settings.<sup>4,5</sup> The delicate and dynamic balance that is established between the pathogen and the host can be influenced by numerous variables (Fig. 1).

#### *The pathogen*

Variables related to the pathogen include the number of organisms inhaled (size of the infecting dose), the virulence of the organisms and their ability to resist eradication (persistence).

Variation in the infecting dose of *M. tuberculosis* seems negligible. Lung deposition studies indicate that only the tiniest aerosol droplets containing <5 bacilli are likely to reach the terminal airways and establish a pulmonary focus of infection.<sup>6-8</sup> Larger droplets are either not inhaled (since they are less likely to remain suspended in the air) or are deposited in the proximal airways where infection is effectively resisted.<sup>8-10</sup> Epidemiological evidence and experimental evidence from laboratory animals<sup>11,12</sup> suggests that the intensity of exposure influences the risk of both

infection and disease. It is well established that variables such as duration of exposure and number of infectious particles in the ambient air influence the risk of infection. However, natural infection in humans seems a fairly uniform event with little variation in the infecting dose which is generally thought to be a single aerosol droplet containing <5 bacilli. Other variables, including multiple infections or increased virulence of the infecting organisms, might explain the increased tendency to progress to disease following high-intensity exposure such as exposure in the home to a sputum smear-positive source case. Primary infection is usually visualised as a single parenchymal (Ghon) focus,<sup>1</sup> but exposure to multiple infective doses might increase the likelihood that a single infective dose is ultimately successful in establishing infection and/or disease. Variation in the virulence of the infecting organisms could be another explanation, as the phenotypic virulence might differ according to the sputum smear-status of the source case, while the proximity of the source case will determine the influence of environmental factors such as exposure to ultraviolet irradiation or drying.<sup>8,9</sup> Genetic variation in organism virulence is well documented<sup>13,14</sup> but it is unlikely that

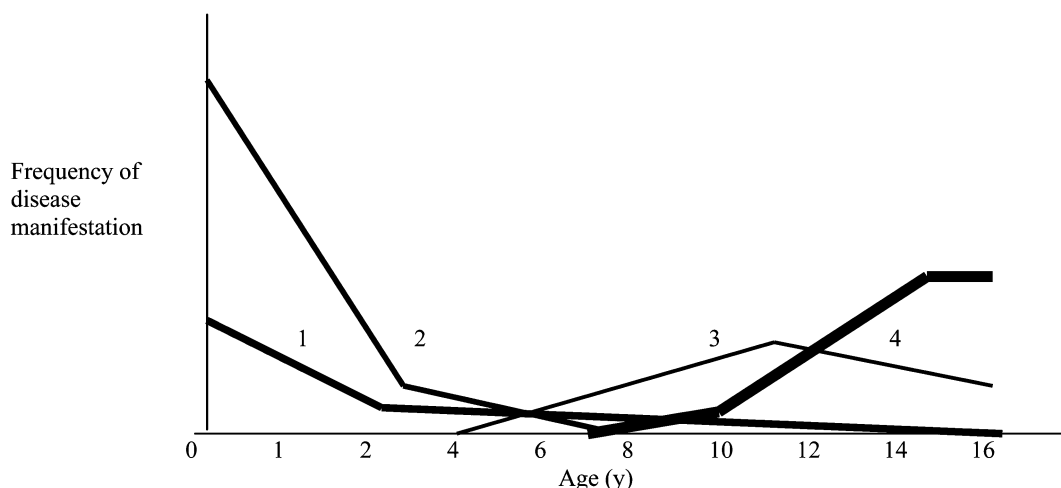


FIG. 2. Age-related manifestations of pulmonary tuberculosis in immune-competent children. 1. Complicated Ghon focus and/or disseminated disease. 2. Complicated lymph node disease. 3. Pleural effusion. 4. Adult-type disease.

strain differences can explain the consistent epidemiological finding that household contacts of sputum smear-positive source cases are more likely to progress to disease following infection.

Persistence describes the ability of the pathogen to evade eradication and to remain dormant for extended periods of time. Several mechanisms that might enable *M. tuberculosis* to persist both intracellularly (inside macrophages) and extracellularly (inside the caseous centres of granulomas) have been described.<sup>15,16</sup> The presence of dormant *M. tuberculosis* bacilli is not harmful to the host unless circumstances favour their reactivation, which explains why progressive immune compromise poses such a high risk of reactivation disease.

### Host immunity

Total host immunity includes a combination of innate and acquired immune responses together with local pulmonary defences, which seem more important than was previously appreciated. Compromised organism clearance, decreased mucosal immunity and a favourable micro-environment at the point of organism

deposition might all contribute to an increased risk of infection and disease. The importance of these local pulmonary influences is demonstrated by the co-morbidity that exists between pulmonary tuberculosis and silicosis<sup>17</sup> or tobacco smoking.<sup>18,19</sup>

The protection provided by the innate immune response seems limited because bacilli grow unrestrained within naive macrophages and occult haematological dissemination occurs frequently during the 1st 4–6 weeks after primary infection.<sup>20–23</sup> Acquired cellular immunity is of crucial importance to contain the organism and prevent uncontrolled disease progression.<sup>20–23</sup> In the absence of immune compromise, age is the dominant variable that determines the effectiveness of acquired cellular immunity to contain the organism. This is illustrated by the striking age-related risk of developing tuberculosis following primary infection and by the age-related differences seen between particular disease manifestations (Fig. 2).<sup>1</sup> Very young children (<2–3 yrs of age) with immature immune systems are at high risk of developing progressive disease while children aged 3–10 years are the least likely to progress to disease after primary infection.<sup>1,24,25</sup> After this 'golden period', there

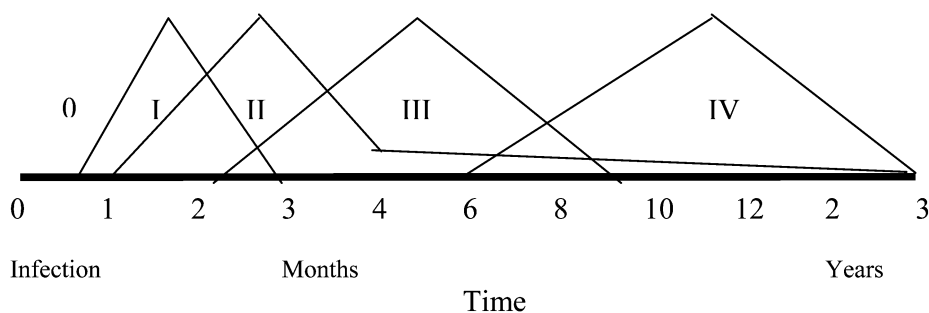


FIG. 3. Schematic timeline following primary pulmonary infection with *M. tuberculosis*. Adapted from the TB time-table first described by Wallgren.<sup>23</sup> O: Incubation; I: Tuberculin skin test conversion; II: Ghon focus and/or disseminated (miliary) disease; III: Lymph node disease (<5y)/pleural effusion (>5 y); IV: Adult-type disease (>10 y).

is a sudden increase in the risk of progressing to disease following recent primary infection during adolescence (>10 years of age).<sup>1,24–28</sup> The possible reasons for this sudden increase in risk around puberty are discussed in more detail under the heading *Adult-type disease*. In young children, disease is mainly related to regional lymphadenopathy and organism dissemination, while adolescent disease is differentiated by the tendency to develop adult-type pulmonary cavitation.<sup>1,28,29</sup> Apart from the age and immune status of the child at the time of infection, the time since infection is another important variable that influences the particular disease manifestation, as illustrated by the time-table of tuberculosis in children<sup>1,23</sup> (Fig. 3).

### Description of Specific Disease Entities

*Uncomplicated Ghon focus and/or lymph node disease<sup>2</sup> (risk group: children <5 years of age)*

With primary pulmonary infection, a localised pneumonic process develops at the site of organism deposition, referred to as the Ghon focus.<sup>1,24</sup> From the Ghon focus bacilli drain via local lymphatics to the regional lymph nodes and together these constitute the elements of the primary (Ghon) complex.<sup>1,24</sup> The formation of the primary complex is often subclinical<sup>25,27</sup> and detection usually follows active surveillance after

recent exposure.<sup>1</sup> In the absence of radiographic complications or clinical symptoms indicative of disease, the presence of the primary complex may be viewed as proof of recent primary infection but not necessarily disease.<sup>1,2,27</sup>

*Complicated Ghon focus and/or disseminated disease<sup>2</sup> (risk groups: children <2–3 years of age/all immune-compromised children)*

Very young (immune immature) and immune-compromised children often have sub-optimal cellular immune responses that result in poor disease containment.<sup>1,30–32</sup> Unrestrained multiplication of bacilli at the point of organism deposition can cause progressive parenchymal damage with eventual cavitation of the Ghon focus. Poor containment, particularly within the regional lymph nodes, can also lead to disseminated disease, the most dangerous of which is tuberculous meningitis. Disseminated disease rarely occurs in older immune-competent children and then usually as a result of advanced disease.<sup>1</sup>

*Complicated lymph node disease<sup>2</sup> (risk group: children <5 years of age)*

Lymph node disease can be complicated by a spectrum of airway complications appropriately referred to as lympho-bronchial

tuberculosis.<sup>33</sup> Children <5 years of age tend to show exuberant lymph node enlargement following primary infection which, in addition to the small size of their airways, predisposes them to lympho-bronchial disease. Extra-luminal compression results when an airway is compressed by enlarged lymph nodes and the associated inflammatory oedema.<sup>1</sup> Intra-luminal obstruction can result from polyps, granulomatous tissue or caseous material within the airway; partial airway obstruction can lead to a check-valve effect with distal hyperinflation whereas total obstruction results in distal atelectasis.<sup>1,2</sup> Intra-bronchial spread occurs when caseous material is aspirated from a diseased lymph node that has herniated into the airway. Depending on the dose and virulence of the aspirated bacilli, the degree of airway obstruction and the immune competence of the host, the resultant lung pathology can range from a pure hypersensitivity response (historically referred to as epituberculosis) to destructive, caseating pneumonia.<sup>1</sup> Diseased lymph nodes can also infiltrate other intra-thoracic structures such as the pericardium, the oesophagus, the phrenic nerve and the thoracic duct.<sup>1,24</sup>

*Pleural effusion<sup>2</sup> (risk group: children >5 years of age)*

A limited pleural reaction may overlie a peripheral Ghon focus and is viewed as part of the primary complex, but large effusions are less common. It occurs mainly in children >5 years of age and indicates recent primary infection.<sup>1</sup> Unilateral pleural effusions result when a few organisms spread from a sub-pleural focus into the pleural cavity; bilateral pleural effusions indicate either bilateral pulmonary foci or haematogenous dissemination.<sup>1,26</sup> A hypersensitivity response triggers accumulation of the typical straw-coloured fluid that contains very few bacilli<sup>1,25</sup> but, depending on the dose and virulence of bacilli that enter the pleural space as well as the immune

competence of the host, caseating tuberculous empyema can rarely develop.<sup>1,24</sup>

*Adult-type disease<sup>2</sup> (risk group: children >10 years of age)*

Adult-type disease is a phenomenon that suddenly appears around puberty and is distinguished by cavitation that occurs predominantly in the lung apices. Although the apices are especially vulnerable, the posterior segments of the upper lobes and the superior segments of the lower lobes are also frequently involved. The natural history of the disease indicates that this type might rapidly follow (within 6–12 months) primary infection (as documented by tuberculin skin test conversion),<sup>1,28</sup> and the majority of adolescents who develop adult-type disease do so within 2 years of primary infection.<sup>1,27</sup> This suggests that adult-type disease in adolescents most frequently follows inappropriate containment of a recent primary infection rather than reactivation of an old, well-contained infection, although reactivation remains an ever-present possibility following primary infection. Two hypotheses, summarised as preferential organism deposition and preferential organism growth, have been proposed to explain the typical anatomical distribution and the particular vulnerability of the lung apices.

*Preferential deposition*

On inhalation, airflow is directed towards the dependent lung zones, which should favour organism deposition in the lung bases.<sup>34</sup> However, it has been suggested that preferential deposition of tubercle bacilli in the apical lung segments might occur owing to air trapping during an episode of coughing<sup>1,24</sup> or preferential haematogenous spread (so-called 'Simon foci').<sup>1,3</sup> However, radiographically visible Ghon foci in children show no predilection for the upper lobes and, as expected, the dependent zones of the right lung (middle

and lower lobes) are the most frequently involved.<sup>1,27</sup> Thus the hypothesis of preferential deposition is not supported by clinical observation and, most importantly, it does not explain the distinct absence of adult-type disease before puberty.

#### *Preferential growth*

In isolation, the hypothesis of preferential organism growth also fails to explain the absence of adult-type disease until puberty but it might do so when viewed in conjunction with the changes that occur in the immune response around puberty. The importance of the host's immune response is clearly illustrated by the marked difference in disease manifestations seen in different animal hosts infected with the same strain of *M. tuberculosis*.<sup>35</sup> Although immune maturation occurs throughout childhood, major changes relating to the effective containment of primary *M. tuberculosis* infection seem to occur around 2 years of age and around puberty (>10 yrs of age) when hormonal changes might be an important factor in the altered pathogenesis. Some elements of the acquired cellular immune response seem to become a two-edged sword during adolescence,<sup>35,36</sup> while it is essential for disease containment, excessive tissue necrosis aids the development of parenchymal cavities.<sup>35</sup>

Although the exact immune mechanisms responsible for tissue necrosis in humans are not well described,<sup>37</sup> it seems reasonable to deduce from clinical observation that a change towards more destructive containment occurs around puberty. This destructive immune response might allow the organism to take full advantage of a favourable micro-environment. The growth of *M. tuberculosis* is enhanced in an oxygen-rich environment. Oxygen tension is highest in the lung apices owing to high ventilation/perfusion (V/Q) ratios,<sup>34</sup> which will encourage more vigorous growth and multiplication of *M. tuberculosis* in these areas. With progressive parenchymal damage the local

V/Q ratio and oxygen tension will rise higher, creating an even more favourable micro-environment to be exploited by viable bacilli. Apart from the relatively high oxygen tension, poor blood flow and decreased lymph formation may also contribute to the vulnerability of the lung apices.<sup>34</sup> Thus the combination of destructive attempts at organism containment together with increased organism survival and multiplication in the lung apices might initiate a positive feedback loop that results in a vicious circle of escalating parenchymal destruction. This hypothesis would explain the sudden emergence of adult-type tuberculosis around puberty as well as its anatomical localisation.

#### **Conclusion**

Although the exact immune mechanisms underlying the different intra-thoracic manifestations of tuberculosis in childhood remain incompletely understood, the evidence available allows a pragmatic understanding of disease pathology. The maturation of host immunity is an important variable that influences the ultimate disease manifestation in children. Variation in both the pheno- and genotypic pathogenicity of the organism might also influence the dynamic host-pathogen balance, but its clinical relevance is poorly documented. To improve our understanding of the mechanisms that underlie different disease manifestations in childhood tuberculosis, renewed focus on the ontogeny of the host immune response towards infection with *M. tuberculosis* is required.<sup>36</sup> The knowledge gained might be essential for directing future research into preventing and treating tuberculosis and developing a vaccine.

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groins and the neck. It appears predominantly in situations of peripheral insulin resistance, such as endocrine diseases, obesity and some malignant tumors.<sup>7</sup> It is used as a skin marker for insulin resistance, although this association has been called into question in recent endocrinologic studies.<sup>8</sup> The pathophysiologic mechanism of this skin alteration consists of direct or indirect activation of the insulin-like growth factor-1 receptor of fibroblasts and keratinocytes by elevated concentrations of circulating insulin, with subsequent proliferation of these epidermal cells. The skin alterations consist of hyperkeratotic and hyperpigmented plaques with velvet texture and brown coloration. The metabolic changes induced by antiretroviral therapy can lead to a state of insulin resistance,<sup>1,2</sup> which may result in acanthosis nigricans, as shown in the present case.

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### ADULT-TYPE PULMONARY TUBERCULOSIS IN CHILDREN 10-14 YEARS OF AGE

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**Abstract:** We report 8 children (10–14 years of age) who were diagnosed with tuberculosis at their local primary health care clinic from July to September 2004, after routine sputum testing was extended to all children older than 10 years of age with suspected tuberculosis. This case series emphasizes that older children develop adult-type cavitating disease, which can be diagnosed by sputum smear microscopy, in contrast to younger children for whom smear microscopy has very little diagnostic value.

**Key Words:** adolescent children, adult-type pulmonary tuberculosis

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Because of the rising burden of tuberculosis worldwide, the World Health Organization took the unprecedented step of declaring a global tuberculosis emergency in 1993. Children constitute a significant proportion of the tuberculosis caseload, up to 40% in high burden settings, and experience considerable tuberculosis-related morbidity and mortality.<sup>1,2</sup> Childhood tuberculosis is regarded as a paucibacillary disease that is difficult to diagnose and that poses little risk of *Mycobacterium tuberculosis* transmission. However, children older than 10 years of age develop a different spectrum of disease compared with younger children, with the majority developing adult-type cavitating disease that is sputum smear-positive.<sup>3,4</sup> This emphasizes the importance of correct disease classification in childhood tuberculosis, both for prognosis and estimation of the transmission risk.<sup>5</sup> We report 8 children (10–14 years of age) who were diagnosed with tuberculosis at their local primary health care clinic in Cape Town, South Africa during a period of 3 months (July–September 2004); after routine sputum testing was extended to all children older than 10 years of age with suspected tuberculosis.

### CASE SERIES

During the 3-month period, 92 cases of tuberculosis were recorded in total. Children (younger than 15 years of age) constituted 22.8% (21 of 92) of the total disease burden. All sputum smear-positive disease occurred in those 10 years of age or older. In total, 65 (70.6%) cases were sputum smear-positive, of whom 7 (10.8%) were children 10–14 years of age. One child in this age group, with a large pleural effusion and blistering tuberculin skin test, were sputum smear-negative. The male-female ratio was 2:6, and none of these children was infected with human immunodeficiency virus. The majority (6 of 8, 75.0%) reported known contact with a sputum smear-positive source case in the preceding 6–18 months (Table 1). All of the children were still at school.

Table 1 describes the clinical presentation and disease characteristics of the 8 cases. Two children reported erythema nodosum (probably indicative of primary *M. tuberculosis* infection) in the preceding year. Two children had a tuberculous pleural effusion, of whom 1 had additional parenchymal cavitation and was sputum smear-positive. Both presented with intense, localized pleuritic chest pain, accompanied by fever. Most children without pleural effusion (4 of 6, 66.7%) reported vague and poorly localized chest pain. The children with sputum smear-positive disease had high organism loads as reflected by their sputum smear grading. Complete symptom resolution occurred within 2 months of treatment in 7 (87.5%) cases, using the standard initial four-drug treatment of isoniazid, rifampin, pyrazinamide and ethambutol in a combined fixed dose tablet. Treatment adherence during the intensive phase was excellent (>90% of prescribed doses in all cases). Sputum smear conversion was documented in all 7 sputum smear-positive cases after 2 months of treatment. At this time, only 1 child reported incomplete symptom resolution, although she did show significant symptomatic and radiologic improvement. This was attributed to the extent of disease at diagnosis, and her treatment was continued with the standard short course (6 months) treatment regimen.

### DISCUSSION

Despite the methodologic limitations, this case series highlights a few clinical observations with important public health implications. It illustrates that tuberculosis in children 10–14 years of age frequently presents like adult tuberculosis,<sup>6</sup> and that the majority of these children can be diagnosed with routine sputum smear microscopy at the primary health care level. It is well-known that adolescent girls are at higher risk to develop tuberculosis after recent primary infection than are boys.<sup>3,4</sup> Erythema nodosum may represent a marker of recent primary *M. tuberculosis* infection, identifying those with a particularly high risk of progression to tuberculosis in the coming months.<sup>7</sup>



TABLE 1. Disease Characteristics in Children 10–14 Years of Age Diagnosed With Tuberculosis

Case	Age (yr)	Sex	TB Contact HH (Time Since)	Recent Erythema Nodosum	Symptoms at Presentation: Cough, Chest Pain, Fever, Night Sweats, Fatigue, Weight Loss [Uninterrupted Duration (wk)]	Sputum Smear*	Radiologic Disease Classification	Response to First 2/12 of Chemotherapy
1	14	F	HH: mother (12–18/12)	No	Cough (>12 wk), chest pain (1 wk), night sweats (8 wk), fatigue (8 wk), weight loss (8 wk)	++	Adult-type with cavitation	Asymptomatic, 2/12 sm <sup>-</sup>
2	13	F	HH: mother and father (6–12/12)	No	Cough (4 wk), night sweats (2 wk), fatigue (2 wk), weight loss (4 wk)	+++	Adult-type with cavitation	Asymptomatic, 2/12 sm <sup>-</sup>
3	10	F	Uncle (6–12/12)	Yes	Cough (4 wk), night sweats (3 wk), fatigue (3 wk)	++	Adult-type with cavitation	Asymptomatic, 2/12 sm <sup>-</sup>
4	11	M	HH: brother (6–12/12)	No	Cough (8 wk), chest pain (2 wk), fever (2 wk), night sweats (6 wk), fatigue (6 wk)	+++	Adult-type with cavitation	Asymptomatic, 2/12 sm <sup>-</sup>
5	12	F	Grandmother (6–12/12)	Yes	Cough (5 wk), chest pain (1 wk), fatigue (4 wk), weight loss (4 wk)	+++	Adult-type with cavitation	Asymptomatic, 2/12 sm <sup>-</sup>
6	13	F	HH: uncle (12–18/12)	No	Cough (8 wk), chest pain (1 wk), fever (1 wk), fatigue (4 wk), weight loss (4 wk)	+++	Adult-type with cavitation and pleural effusion	Marked improvement, 2/12 sm <sup>-</sup>
7	14	M	None	No	Cough (6 wk), night sweats (2 wk), fatigue (4 wk), weight loss (4 wk)	+++	Adult-type with cavitation	Asymptomatic
8	12	F	None	No	Cough (1 wk), chest pain (2 wk), fever (2 wk), fatigue (2 wk)	–	Pleural effusion	Asymptomatic

\*Sputum smear microscopy grading according to the number of AFB observed: – indicates no AFB in at least 100 fields; ++, 1–10 AFB/field in at least 50 fields; +++, >10 AFB/field in at least 20 fields.

TB contact indicates contact with a sputum smear-positive tuberculosis source case; HH, contact inside the household (time since), time since known contact with a sputum smear-positive source case in months; Recent erythema nodosum, probable primary *Mycobacterium tuberculosis* infection in the preceding 12 months; AFB, acid-fast bacilli; 2/12 sm<sup>-</sup>, sputum smear-negative after 2 months of treatment.

It is difficult to establish the exact time of *M. tuberculosis* infection, but it is striking that 75% of children had known contact with a sputum smear-positive source case in the preceding 6–18 months. This correlates with the natural history of disease, which indicates that adolescent children are at high risk to develop adult-type tuberculosis within 1–2 years after primary infection.<sup>3,7</sup> Therefore all contacts of sputum-smear positive source cases, especially adolescent girls, should be informed about their risk to develop tuberculosis, even if their initial screening tests are negative. Persistent, nonremitting symptoms should be reported without delay, and tuberculosis should be excluded. Delayed diagnosis poses a significant transmission risk to the community, especially fellow pupils<sup>8</sup> and household members.

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#### CONGENITAL CANDIDA GLABRATA INFECTION WITHOUT SPECIFIC NODULES ON THE PLACENTA AND UMBILICAL CORD

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**Abstract:** Two extremely premature infants died as a result of congenital *Candida glabrata* infection, and their placentas and umbilical cords were free of macroscopic *Candida* nodules. Because non-*Candida albicans* *Candida* infections are less likely to produce necrotic foci, we should not exclude *Candida* infections in the absence of macroscopic nodules on the placenta and umbilical cord.

**Key Words:** *Candida glabrata*, *Candida* nodules, placenta, pneumonia

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## **The spectrum of disease in children treated for tuberculosis in a highly endemic area**

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**Abstract****Background**

Children contribute a substantial proportion of the global tuberculosis caseload, particularly in endemic areas, where little is known about their spectrum of disease. The aims of this study were to document the complete disease spectrum, and relevant age-related differences, in children treated for tuberculosis in a highly endemic community.

**Methods**

A prospective descriptive study was conducted from February 2003 through October 2004 at five primary health care clinics in Cape Town, South Africa; including all children (<13 years of age) treated for tuberculosis.

**Results**

439 children received anti-tuberculosis treatment. The spectrum of disease included; 85 (19.4%) “not TB”, 307 (86.7%) intra-thoracic, and 72 (20.3%) extra-thoracic tuberculosis, of whom 25 (5.7%) had co-existing intra-thoracic disease. In HIV-uninfected children; disseminated (miliary) disease (9/11, 81.8%), and TBM (10/13, 76.9%), were predominantly documented in children <3 years of age. In HIV-infected children, complicated Ghon focus and disseminated (miliary) disease were significantly more common 6/25 (24.0%) than in HIV-uninfected children 12/414 (2.9%) (OR 10.9, 95% CI 3.2-35.9); without age-related differences.

**Conclusion**

This study describes the complete disease spectrum observed in children treated for tuberculosis, in a highly endemic area. Children suffered significant morbidity with most severe disease recorded in very young and/or HIV-infected children.

## Background

Children contribute a substantial proportion of the global tuberculosis caseload.<sup>1-3</sup> Reliable epidemiologic data is rarely available from endemic areas,<sup>2,3</sup> where children experience high tuberculosis-related morbidity and mortality.<sup>4</sup> Childhood tuberculosis is often reported as a single disease entity, although it represents a diverse spectrum of pathology with important prognostic significance, which warrants accurate classification.<sup>5</sup> Previous observational studies on childhood tuberculosis were mostly retrospective or hospital-based,<sup>6,7</sup> but due to the selection bias inherent to these study designs, the disease spectrum recorded is not representative of the disease spectrum at community level. To quantify the tuberculosis-related morbidity suffered by children in endemic areas, and to evaluate the relative contribution made by different disease entities, require a prospective study that documents the full spectrum of disease in children, at community level.

The natural history of disease, described in the pre-chemotherapy literature, documented the different disease entities observed in children with tuberculosis.<sup>8</sup> It identified clear age-related differences and specific high-risk groups, namely very young (<3 years of age) and/or immune compromised children.<sup>8,9</sup> Children less than 2 years of age were documented to be at high risk to progress to disease within the first 12 months following primary infection. This observation indicates that it is prudent to regard all children less than 3 years of age to be at high risk. However, it is unknown how relevant these historic observations are to assist our understanding of the current tuberculosis situation in highly endemic areas.

The aims of this study were to document the complete disease spectrum, and relevant age-related differences, in children treated for tuberculosis in a highly endemic community.

## Methods

A prospective descriptive study was conducted from 1 February 2003 through 31 October 2004 in Cape Town, Western Cape Province, South Africa.

**Study setting**

The incidence of all tuberculosis in Cape Town was 678/100 000,<sup>10</sup> and the prevalence of human immunodeficiency virus (HIV) infection in women attending public antenatal clinics in the Western Cape Province was 13.1% (95% CI 8.5-17.7%), in 2003.<sup>11</sup>

Five primary health care clinics, which utilize the same referral hospital (Tygerberg Children's Hospital) were selected. These clinics serve impoverished urban communities, providing both primary health care services and supervised anti-tuberculosis treatment. The study population rarely utilizes private medical services and children diagnosed with tuberculosis are routinely referred to the primary health care clinic, to report their tuberculosis and provide supervised anti-tuberculosis treatment. Paediatric services are only accessible to children less than 13 years of age.

According to South African National Tuberculosis Programme (NTP) guidelines,<sup>12</sup> all children with suspect symptoms and those less than 5 years of age in household contact with a sputum smear-positive source case, should be evaluated with a tuberculin skin test (TST) and chest radiograph (CXR). Children diagnosed with tuberculosis are entered into the tuberculosis treatment register and receive supervised anti-tuberculosis treatment free of charge.

**Study population**

All children (<13 years of age) who commenced anti-tuberculosis treatment during the study period were included. A prospective surveillance system ensured identification of all children treated for tuberculosis. The investigator visited each clinic on a weekly basis to evaluate children newly started on anti-tuberculosis treatment at the primary health care clinic, while a study nurse documented those started on anti-tuberculosis treatment at the referral hospital.

**Chest radiograph (CXR)**

Standard chest radiographs (antero-posterior and lateral views) were reviewed by 2 independent experts, blinded to all clinical information. Findings were documented on a

standard report form. Classification was done according to the most severe disease entity reported, using a recently proposed radiological classification of childhood intra-thoracic tuberculosis, which differentiates Ghon focus (uncomplicated or complicated), primary complex, lymph node disease (uncomplicated or complicated), pleurisy, pericarditis, disseminated (miliary) disease and adult-type disease.<sup>5</sup> A Ghon focus described the typical, localized pneumonic process that occurs at the site of primary infection within the lung.<sup>5</sup> A primary complex described the presence of both a Ghon focus and uncomplicated lymph node disease (regional hilar adenopathy).<sup>5</sup> Complicated lymph node disease described visible lymphadenopathy in conjunction with either airway compression (compression), or parenchymal consolidation other than a Ghon focus (consolidation).<sup>5</sup>

### ***HIV testing***

Screening for HIV infection was done by rapid testing (Determine Rapid HIV test, Abbott) or ELISA (Vironostika HIV Uniform II, Organon Teknika). Children diagnosed with possible HIV-infection were referred to the HIV family clinic at Tygerberg Children's Hospital for confirmatory tests (PCR in children <18 months and a second ELISA test in older children), and clinical management.

### ***Sample collection and culture***

An attempt was made to collect at least one culture specimen before treatment initiation; pulmonary specimens included gastric aspirates and/or induced/uninduced sputum; extra-pulmonary specimens included pleural or cerebro-spinal fluid, fine needle aspiration and/or biopsy specimens. Culture samples were inoculated into liquid medium using either the BACTEC or MGIT systems (Becton Dickinson, Sparks, MD, USA). Positive cultures were confirmed to be *Mycobacterium tuberculosis* by routine polymerase chain reaction (PCR) speciation.<sup>13</sup>

### ***Definitions***

"Not TB" was defined as meeting all 3 of the following criteria; 1) agreement by both independent experts that the chest radiograph indicated "certain not TB", and 2) no bacteriologic or histologic confirmation, and 3) no documented extra-thoracic tuberculosis.



Intra-thoracic tuberculosis was defined as any intra-thoracic manifestation of tuberculosis, identified by one or both of the experts. Extra-thoracic tuberculosis was defined as any extra-thoracic manifestation of tuberculosis; with/without concomitant CXR signs suggestive of intra-thoracic tuberculosis. Bacteriologic confirmation was defined as the presence of acid-fast bacilli in histologic or sputum specimens and/or culture confirmation of *M.tuberculosis*. Age groups were defined as; <3 years, 3-4 years, 5-9 years and >10 years, according to the most relevant age-related risk groups identified by the natural history of disease.<sup>8</sup>

Parents/legal guardians gave written informed consent for study participation. Separate consent was obtained for HIV testing, together with routine pre- and post-test counselling. Ethics approval was obtained from the Institutional Review Board of Stellenbosch University, the City of Cape Town Health Department and local health committees.

## Results

During the study period, 439 children (<13 years of age) were treated for tuberculosis. Demographics and HIV results are reflected in table 1; 283 (64.5%) children were tested for HIV of whom 25 (8.8%) were HIV-infected.

Table 2 reflects the complete disease spectrum in all 439 children who were treated for tuberculosis; 85 (19.4%) were categorized as “not TB”, 307 (69.9%) as intra-thoracic and 72 (16.4%) as extra-thoracic tuberculosis, of whom 25 (5.7%) had co-existing intra-thoracic disease. The 85 children categorized as “not TB”, were commenced on anti-tuberculosis treatment by the attending physician, due to known *M.tuberculosis* exposure together with a positive TST and/or a subjective opinion of possible hilar adenopathy on the chest radiograph. The study team did not interfere with the attending physician's decision to treat. In total, bacteriologic confirmation was achieved in 150/276 (54.3%) children in whom specimens were collected; in 0/36 with “not TB”, in 122/196 (62.2%) with intra-thoracic tuberculosis and in 33/49 (67.3%) with extra-thoracic tuberculosis. Bacteriologic confirmation was achieved in both respiratory and non-respiratory specimens in 5 children.

In children with intra-thoracic tuberculosis, uncomplicated lymph node disease was documented in 147(47.9%) children. Complicated lymph node disease occurred in 87 (28.3%), including; parenchymal consolidation in 62 (20.2%), of whom 9 had expansile tuberculous pneumonia, with cavities reported in 7, and airway compression in 25 (8.1%), of whom 10 had visible compression, 12 segmental or lobar collapse and 3 hyperinflation. Pleural effusions were documented in 24 (7.8%) children; 2 had massive fluid collections with mediastinal shift. Cardiac tamponade was documented in 1 child, while a second child had a small pericardial effusion against a background of disseminated (miliary) disease. Fifteen (4.9%) children had disseminated (miliary) disease; 4 with co-existing hilar adenopathy, 1 with pericardial effusion and 2 with tuberculous meningitis (TBM). The bacteriologic yield achieved in children with different intra-thoracic disease entities is described elsewhere (data not shown).

The most common disease entities identified in the 72 children with extra-thoracic tuberculosis were cervical lymphadenitis (35, 48.6%) and tuberculous meningitis (TBM) (14, 19.4%). Only 1 (1.4%) child had involvement of a lymph node outside the cervical area (unilateral involvement of an inguinal lymph node). CNS involvement occurred in 16 (22.2%) children, of whom 14 had TBM (6 with stage 1, 7 with stage 2 and 1 with stage 3 disease) and 2 had tuberculomas of the brain; 1 was an HIV-infected child in whom the tuberculoma represented a CNS relapse after completing 6 months of directly supervised TBM therapy in hospital. In children with extra-thoracic tuberculosis, bacteriologic confirmation (culture or microscopy) was achieved in 33/49 (67.3%), with the lowest yield in those diagnosed with TBM (1/10, 10.0%). Computed tomography (CT) or magnetic resonance imaging (MRI), provided supportive evidence in 18/21(85.7%) children with extra-thoracic tuberculosis, 11/14 with TBM, 2/2 with tuberculomas of the brain, 1/1 with abdominal tuberculosis and 4/4 with tuberculous spondilitis. Disseminated (miliary) disease and/or TBM was recorded in 26/439 (5.9%) children; 12 with miliary disease, 11 with TBM, and 3 with both miliary disease and TBM.

Osteo-articular tuberculosis was recorded in 11 (15.3%) children, involving mainly the vertebra and single weight bearing joints (4 vertebral, 3 hip, 2 knee), 1 had mastoiditis and another had osteitis of the cranium. No cases of urogenital tuberculosis were recorded. Skin manifestations included 2 children with papulonecrotic tuberculide (PNT), 5 with erythema nodosum and 1 with a superficial cold abscess on the back. Six children categorised as extra-thoracic tuberculosis had no bacteriologic or radiologic evidence of tuberculosis; 3 had a presumptive diagnosis of stage 1 TBM, based on cerebrospinal fluid (CSF) findings alone, and 3 had erythema nodosum in combination with a TST response >20mm. Co-existing intra-thoracic tuberculosis was documented in 25/72 (34.7%) children with extra-thoracic tuberculosis.

Table 3 reflects the disease entities documented in all high-risk children; HIV-uninfected children less than 3 years of age and HIV-infected children of all ages. In HIV-uninfected children; disseminated (miliary) disease (9/11, 81.8%), and TBM (10/13, 76.9%), especially TBM stage 2 and 3 (7/8, 87.5%), were predominantly documented in children less than 3 years of age. Complicated Ghon focus and/or disseminated (miliary) disease were significantly more common in HIV-infected children 6/25 (24.0%), compared to HIV-uninfected children 12/414 (2.9%) (OR 10.9, 95% CI 3.2-35.9). No age-related differences were noted in HIV-infected children.

Figure 1 reflects age-related differences in specific disease entities, documented in all children treated for tuberculosis, excluding those with HIV-infection. The figure illustrates differences between high-risk (<3 years) and low-risk children (≥3 years), with additional emphasis on the changes that occur after 10 years of age. Of all children with disseminated (miliary) disease and/or tuberculous meningitis stage 2 or 3, 16/19 (84.2%) were less than 3 years of age. Complicated Ghon focus with cavitation was reported in 1 infant. Intra-thoracic lymph node disease was most common in children less than 3 years of age, but it was documented with frequency until 5 years of age; 123/144 (85.4%) children with uncomplicated lymph node disease and 54/71 (76.0%) children with complicated lymph node disease were less than 5 years of age. Pleural effusions were most frequently documented in children 3-9

years of age (14/23, 60.9%). Adult-type disease was not reported in any child less than 8 years of age, the majority (10/14, 71.4%) being older than 10 years. Spondilitis occurred predominantly in children 3-5 years (3/4, 75%), while peripheral tuberculous lymphadenitis occurred with equal frequency in all age groups, except that no infants were affected.

## Discussion

This study provides a comprehensive overview of the disease spectrum seen in children treated for tuberculosis in a highly endemic area. A striking observation was the high morbidity suffered by children; 207/439 (47.1%) had disease manifestations other than uncomplicated lymph node disease, while 26/439 (5.9%) were diagnosed with disseminated (miliary) disease and/or TBM. The severity of disease suffered by children in this community may be largely attributable to high levels of transmission, which results in the infection of many children at a young and vulnerable age. Levels of transmission in this community, at least in the areas where it has been measured, is high.<sup>14</sup> Active tracing and prophylaxis of children exposed to an adult index case is often neglected due to resource constraints and the high burden of adult tuberculosis. Provision of effective preventative chemotherapy may have prevented disease in many children, but it is well documented that a substantial proportion of transmission in highly endemic areas, such as the study community, occurs outside the household.<sup>15</sup> Thus many children, especially those older than 2-3 years of age, become infected and develop disease following exposure in the community,<sup>16</sup> without known exposure inside the household.

Young (<3 years of age) children who are immunologically immature, and HIV-infected (immune compromised) children, were prone to develop disease manifestations indicative of poor organism containment, such as cavitation of the Ghon focus and disseminated (miliary) disease. This is consistent with recent observations that HIV-infected children,<sup>17-18</sup> and very young HIV-uninfected children,<sup>19-21</sup> are prone to develop cavitation and disseminated (miliary) disease. Overall, HIV infection had little impact on the disease spectrum observed in this community, as few children were HIV-infected; however, a bigger impact can be expected in settings where the prevalence of HIV infection in children is higher. The age-related disease

profiles documented show remarkable consistency, when compared to observations from the pre-chemotherapy literature.<sup>8,9</sup> Immune maturation seems less relevant in HIV-infected children, as no age-related differences were observed in these children.

Study limitations include the fact that we may have missed children with severe tuberculosis who died without presenting to a health care facility, but access to local clinics and hospitals is good within the study area, which makes this unlikely. The small number of HIV-infected children reduces our ability to comment on this sub-group and to show statistically significant differences. However, the fact that the majority of children, including all those with a clinical suspicion of HIV disease, were tested for HIV, is a major strength. Children not tested for HIV were mainly infants whose mothers tested HIV-negative during pregnancy, and older children (>8 years of age) who refused assent, but were otherwise healthy. Despite these limitations, we believe the spectrum and severity of disease recorded approximates the reality in highly endemic settings.

In conclusion, this study provides a comprehensive picture of the disease spectrum observed in children treated for tuberculosis in a highly endemic area. The age-related differences observed correlate well with disease descriptions from the pre-chemotherapy literature. Very young and HIV-infected children were at highest risk to develop severe disease, which emphasizes the need for preventative chemotherapy in these particular groups, while timely and accurate diagnosis of disease is important in all children.

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**Table 1**  
**Demographics and disease characteristics in all children treated for tuberculosis**  
**(n=439)**

	<b>Number (%)</b>
<b>Gender</b>	
Male	217 (49.5)
Female	222 (50.6)
<b>Age</b>	
< 3yrs	231(52.6)
3-5yrs	95 (21.6)
5-9yrs	77 (17.6)
10-13yrs	36 (8.2)
<b>HIV</b>	
Tested	283 (64.5)
Infected	25/283 (8.8)
Household contact reported	257 (58.5)
Diagnosed after active contact tracing	140 (31.9)

Table 2

The disease spectrum and bacteriologic confirmation achieved in all children treated for tuberculosis (n=439)

TB manifestation	Total (%) N=439	Bacteriologic Confirmation*
<b><u>Not TB</u></b>	85 (19.4)	0/36
<b><u>Intra- thoracic TB</u></b>	307 (69.9)	122/196 (62.2)
<b>Ghon focus</b>		
Uncomplicated	1/307 (0.3)	
Complicated	3/307 (1.0)	
<b>Primary complex</b>	15/307 (4.9)	
<b>Lymph node disease</b>		
Uncomplicated	147/307 (47.9)	
Complicated		
Compression	25/307 (8.1)	
Consolidation	62/307 (20.6)	
<b>Pleurisy</b>	24/307 (7.8)	
<b>Pericarditis</b>	1/307 (0.3)	
<b>Disseminated</b>	15/307 (4.9)	
<b>Adult-type</b>	14/307 (4.6)	
<b><u>Extra-thoracic TB</u></b>	72 (16.4)	33/49 (67.3)
<b>Peripheral lymphadenitis</b>		
Cervical	35/72 (48.6)	27/27(100)
Other	1/72 (1.4)	1/1 (100)
<b>Central nervous system TB</b>		
Meningitis	14/72 (19.4)	1/10 (10.0)
Tuberculoma	2/72 (2.8)	N/A
<b>Abdominal TB</b>	1/72 (1.4)	1/1 (100)
<b>Osteo-articular TB</b>		
Spondylitis	4/72 (5.6)	N/A
Other	7/72 (9.7)	2/7 (28.6)
<b>Skin</b>	8/72 (11.1)	2/3 (66.7)
<b>[Intra+Extra thoracic TB]</b>	25 (5.7)	17/21 (80.1)

TB – Tuberculosis

N/A – no bacteriologic confirmation attempted

Not TB - a chest radiograph that is not suggestive of tuberculosis (confirmed by two independent child TB experts), no bacteriologic or histologic proof and no extra-thoracic disease recorded

\*Bacteriologic confirmation – Culture confirmed *M.tuberculosis* or acid-fast bacilli seen on microscopy, as a proportion of those in whom specimens were collected

[Intra+extra thoracic TB] - Children with intra- and extra-thoracic TB were included in both groups

**Table 3**

**The disease spectrum documented in all high-risk children; HIV-uninfected less than 3 years of age and HIV-infected children**

<b>TB manifestation</b>	<b>All children Number (%) N=439</b>	<b>HIV-uninfected &lt;3 years of age N=231</b>	<b>HIV-infected N=25</b>
<b><u>Not TB</u></b>	85 (19.4)	59 (25.5)	8 (32.0)
<b><u>Intra- thoracic TB</u></b>	307 (69.9)	161 (69.7)	16 (64.0)
<b>Ghon focus</b>			
Uncomplicated	3/307 (1.0)	1 (0.4)	0
Complicated	1/307 (0.3)	1 (0.4)	2 (8.0)
<b>Primary complex</b>	15/307 (4.9)	11 (4.8)	0
<b>Lymph node disease</b>			
Uncomplicated	147/307 (47.9)	88 (38.1)	4 (16.0)
Complicated			
Compression	25/307 (8.1)	15 (6.5)	0
Consolidation	62/307 (20.6)	34 (14.7)	5 (20.0)
<b>Pleurisy</b>	24/307 (7.8)	2 (0.8)	1 (4.0)
<b>Pericarditis</b>	1/307 (0.3)	0	0
<b>Disseminated (miliary) disease</b>	15/307 (4.9)	9 (3.9)	4 (16.0)
<b>Adult-type disease</b>	14/307 (4.6)	0	0
<b><u>Extra-thoracic TB</u></b>	72 (16.4)	19 (8.2)	2 (8.0)
<b>Peripheral lymphadenitis</b>			
Cervical	35/72 (48.6)	6 (2.6)	0
Other	1/72 (1.4)	0	0
<b>Central nervous system TB</b>			
Meningitis	14/72 (19.4)	10 (4.3)	1 (4.0)
Tuberculoma	2/72 (2.8)	1 (0.4)	1 (4.0)
<b>Abdominal TB</b>	1/72 (1.4)	0	0
<b>Osteo-articular TB</b>			
Spondylitis	4/72 (5.6)	1 (0.4)	0
Other	7/72 (9.7)	0	0
<b>Skin</b>	8/72 (11.1)	1 (0.4)	0
<b>[Intra+Extra thoracic TB]</b>	25 (5.7)	9 (3.9)	1 (4.0)

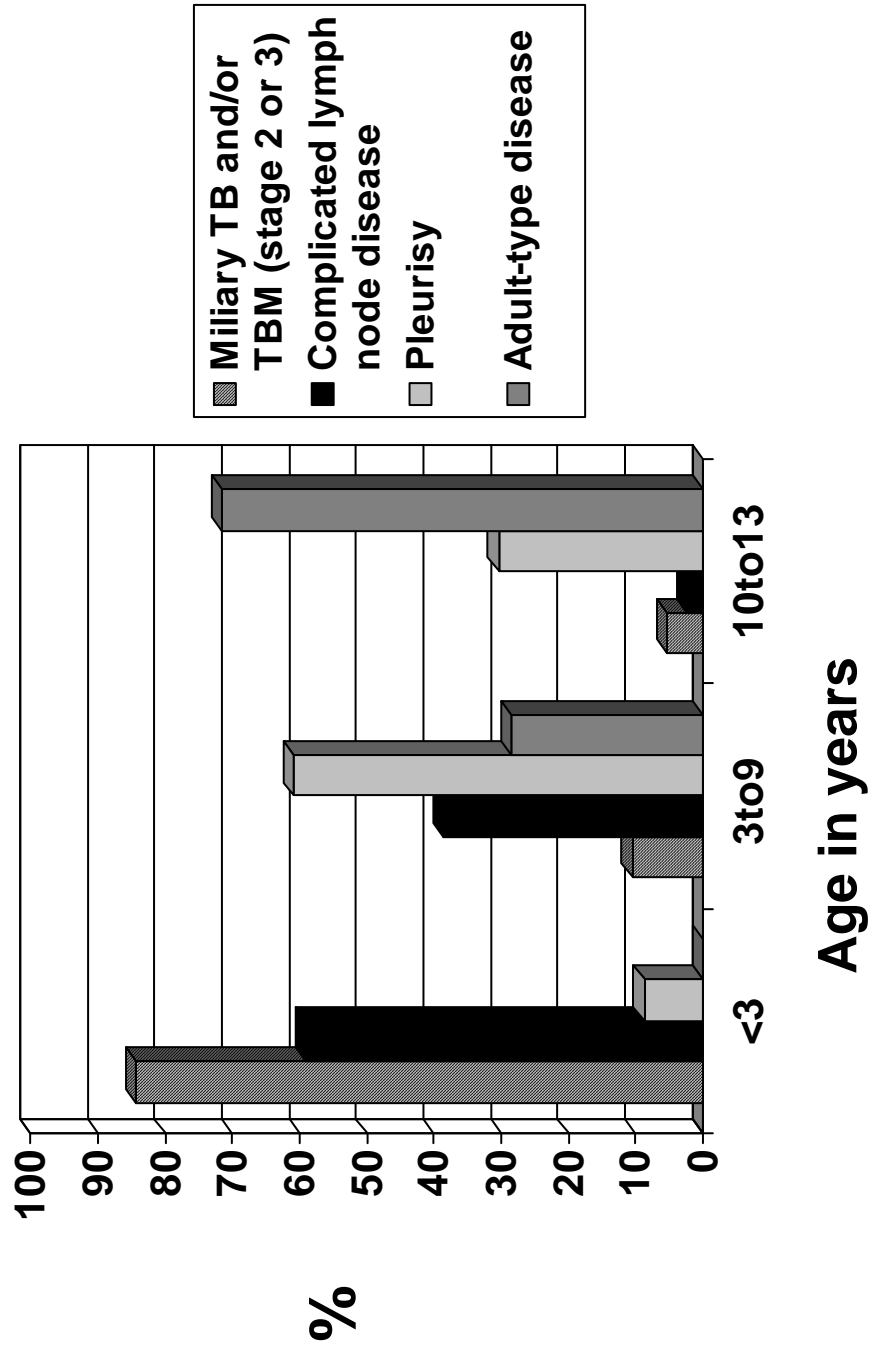
TB – Tuberculosis

HIV-uninfected – This includes all HIV-uninfected children and those not tested.

[Intra+extra thoracic TB] - Children with intra- and extra-thoracic TB were included in both groups.



**Figure 1**  
**Age distribution of specific disease entities recorded in HIV-uninfected children treated for tuberculosis**



## **Bacteriologic yield in children with intrathoracic tuberculosis**

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### **Abstract**

This report documents the bacteriologic yield in children who received treatment for intrathoracic tuberculosis in an area where it is highly endemic. All children (<13 years) treated for probable or confirmed intrathoracic tuberculosis at five primary health care clinics in Cape Town, South Africa were included. A total of 307 children were included in the study, and bacteriologic confirmation was achieved in 122/196 (62.2%) children from whom specimens were collected. The lowest bacteriologic yield was recorded in children with uncomplicated lymph node disease (24/69, 34.8%). In this highly endemic setting, bacteriologic confirmation was achieved in an unexpected high proportion of children treated for intra-thoracic tuberculosis, which indicates a need to re-assess the value of bacteriology-based diagnostic approaches in these settings.

## Background

The diagnosis of childhood tuberculosis is complicated by the absence of a practical gold standard, as the collection of bacteriologic specimens is difficult and culture yields are considered to be low.<sup>1</sup> It has reported that *Mycobacterium tuberculosis* is isolated from less than 30-40% of children with probable tuberculosis, while sputum smear microscopy is positive in less than 10-15%<sup>2,3</sup>

Bacteriologic confirmation is rarely attempted in children from highly endemic areas, due to resource limitations and the expected low yield. However, bacteriologic confirmation may have particular value in these settings, where epidemiologic indicators such as known exposure to and/or proven infection with *M. tuberculosis* contribute little diagnostic value. In addition to providing a definitive diagnosis, isolation of *M. tuberculosis* offers opportunities for drug susceptibility testing and molecular investigation. The aim of this study was to document the proportion of children given treatment for intra-thoracic tuberculosis in an area of high endemicity, in whom bacteriologic confirmation was achieved.

## Methods

A prospective community-based observational study was conducted from 1 February 2003 through 31 October 2004 in Cape Town, South Africa.

### **Study population**

Five primary health care clinics, all utilizing the same referral hospital (Tygerberg Children's Hospital), were selected. People living in the study area rarely access private medical services, and children diagnosed with tuberculosis are routinely referred to their local primary health care clinic for treatment. Paediatric services are only accessible to children less than 13 years of age.

All children (<13 years) from the study area, initiated on anti-tuberculosis treatment during the study period, were screened by the investigator. The investigator visited each clinic on a weekly basis to evaluate children newly started on anti-tuberculosis treatment at the primary

health care clinic, while a study nurse documented those started on anti-tuberculosis treatment in hospital. The chest radiographs of all children were reviewed and those with radiographic signs suggestive of intra-thoracic tuberculosis were included in the study.

### ***Chest radiograph (CXR)***

All children received standard anteroposterior and lateral chest radiographs. Chest radiographs were reviewed by the same 2 independent experts. Findings were documented on a standard report form. All children with radiographic signs suggestive of intra-thoracic tuberculosis (even if this was indicated by only 1 of the 2 independent experts) were included. Disease classification was done according to the most severe disease entity reported; using a recently proposed radiological classification of childhood intra-thoracic tuberculosis.<sup>4</sup> Those without any radiographic signs suggestive of intrathoracic tuberculosis were excluded.

### ***Sample collection and culture***

In all children, an attempt was made to collect at least one respiratory specimen for mycobacterial culture. However, in children diagnosed at the referral hospital, multiple specimens were collected as part of a separate hospital-based study that aimed to compare the bacteriologic yield achieved with different specimen collection methods. Specimens collected included; gastric aspirates and/or nasopharyngeal aspirates and/or induced/uninduced sputum, and/or pleural fluid aspiration. Samples were routinely inoculated into liquid broth using either the BACTEC or MGIT systems (Becton Dickinson, Sparks, MD, USA). *M.tuberculosis* was confirmed by polymerase chain reaction (PCR) speciation.

### ***Definitions***

Routine specimens were defined as the first 2 gastric aspirate and/or uninduced sputum specimens collected. Bacteriologic confirmation was defined as culture confirmation of *M. tuberculosis* and/or the presence of acid-fast bacilli on sputum microscopy.



Parents gave separate written informed consent for study participation and HIV testing. Ethics approval was obtained from the Institutional Review Board of Stellenbosch University, the City of Cape Town Health Department and local health committees.

## Results

During the study period, 439 children received anti-tuberculosis treatment (data on the complete cohort is described elsewhere),<sup>5</sup> of whom 307 had radiographic signs suggestive of intra-thoracic tuberculosis. The gender distribution was equal (152, 49.5% male). The age distribution was; 230 (74.9%) <5 years, 53 (17.3%) 5-9years, and 24 (7.8%) >10 years. The majority of children were tested for HIV (211, 68.7%), of whom 17 (8.1%) were HIV-infected.

Table 1 reflects the intra-thoracic disease manifestations documented and the proportion in whom bacteriologic confirmation was achieved. Uncomplicated lymph node disease was the most frequently documented intrathoracic disease manifestation (147, 47.9%). Adult-type disease was documented in 14 (4.6%) children and bacteriologic confirmation was achieved in all 14. This is the only group of children in whom sputum smear microscopy was performed; 7/10 (70%) children in whom sputum smears were performed were sputum smear-positive.

Overall, bacteriologic confirmation was achieved in 122/196 (62.2%) children, in whom specimens were collected; in 102/183 (55.7%) when only routine specimens were included in the analysis. The bacteriologic yield in children with intrathoracic disease manifestations other than uncomplicated lymph node disease was 98/127 (77.2%); significantly higher than the yield (22/69, 34.8%) in those with uncomplicated lymph node disease [odds ratio (OR) 6.3, 95% confidence interval (CI) 3.2-12.8]. The significance persisted when only routine specimens were included in the analysis [81/114 (71.0%) versus 21/69 (30.4%), OR 5.6, 95%CI 2.8-11.4].

## Discussion

Bacteriologic confirmation was achieved in the majority of children treated for intrathoracic tuberculosis in this highly endemic area. Possible reasons for this unexpected high yield are; 1) the selection criteria applied, as children without any radiographic sign suggestive of intra-thoracic tuberculosis were excluded; 2) the diligence with which specimens were collected and cultured, as the high yield persisted despite excluding non-routine specimens from the analysis; 3) the community-based approach, as hospital-based studies tend to accumulate more children with alternative diagnoses and radiographic signs that are difficult to interpret; 4) the fact that many children presented with advanced intra-thoracic disease, as the minority were classified as uncomplicated lymph node disease.

Although uncomplicated lymph node disease, often considered the typical manifestation of childhood tuberculosis, was the most common disease entity, it was documented in only 47.9% of children. The fact that the bacteriologic yield was the lowest in this group, may explain the low bacteriologic yields reported from non-endemic areas where active contact tracing programmes are usually well-established. Therefore, the majority of children are diagnosed at a very early stage with uncomplicated lymph node disease,<sup>6</sup> and few present with advanced disease.

To our knowledge, the bacteriologic yield achieved in children treated for intra-thoracic tuberculosis in an area of high endemicity has not been reported before. However, similar and even higher bacteriologic yields have been reported in select patient groups; such as children with lymph node disease complicated by expansile tuberculous pneumonia,<sup>7</sup> and infants who frequently develop rapidly progressive disease.<sup>8,9</sup> These studies support the observation that the bacteriologic yield is primarily influenced by the type of radiographic disease manifestation recorded. Radiographic disease manifestations show clear age-related patterns in children.<sup>10</sup> In this study the bacteriologic yield did differ according to age, but the age-related effect disappeared when the specific radiologic disease manifestation was taken into account, which illustrates the importance of accurate disease classification.<sup>4</sup>

The main study limitations were the fact that bacteriological confirmation was not attempted with equal vigor in all children. The multiple specimens collected at the referral hospital may have introduced sampling bias. We attempted to correct for possible sampling bias by restricting the analysis to routine samples only. However, more rigorous evaluation of the association between disease severity and bacteriologic yield, and the comparison between different specimen collection methods, will require accurate disease classification and standardized procedures for specimen collection.

In this highly endemic area, bacteriologic confirmation was achieved in an unexpected high proportion of children treated for intra-thoracic tuberculosis. This finding indicates a need to re-assess the value of bacteriology-based approaches to diagnose intra-thoracic tuberculosis in children, particularly in endemic areas where they frequently present with advanced disease.

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**Table 1**

**The documented radiologic disease manifestations in children treated for intrathoracic tuberculosis and the proportion with bacteriologic confirmation**

<b>Disease manifestation</b>	<b>Number (%)</b>	<b>Bacteriologic confirmation*</b>
<b>Ghon focus</b>	4 (1.3)	4/4 (100)
<b>Primary (Ghon) complex</b>	15 (3.6)	5/9 (55.6)
<b>Lymph node disease</b>		
Uncomplicated	147 (47.9)	24/69 (34.7)
Complicated		
Airway compression	25 (8.1)	10/18 (55.6)
Parenchymal consolidation	62 (20.6)	40/49 (81.6)
<b>Pleurisy</b>	24 (7.8)	10/17 (58.8)
<b>Pericarditis</b>	1 (0.3)	1/1 (100)
<b>Disseminated (miliary) disease</b>	15 (4.9)	14/15 (93.3)
<b>Adult-type disease</b>	14 (4.6)	14/14 (100) <sup>#</sup>
<b>TOTAL</b>	<b>307 (100)</b>	<b>122/196 (62.2)</b>

\*Bacteriologic confirmation – the numerator is the number of children in whom bacteriologic confirmation (positive *M. tuberculosis* culture and/or the presence of acid-fast bacilli on sputum) was achieved, and the denominator is the number of children in whom specimens were collected

<sup>#</sup>Three of these 14 children had positive results for sputum smears only, as no cultures were performed.

# Tuberculous Lymphadenitis as a Cause of Persistent Cervical Lymphadenopathy in Children From a Tuberculosis-Endemic Area

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**Background:** Cervical lymphadenitis is the most common form of extrapulmonary tuberculosis in children, although its relative contribution as a cause of persistent cervical adenopathy is not well-documented. The aim of this study was to determine the relative contribution of tuberculous lymphadenitis as a cause of persistent cervical adenopathy in a tuberculosis-endemic setting and to document its clinical presentation at the primary health care level.

**Methods:** A prospective descriptive study was conducted from February 2003 through October 2004 at 5 primary health care clinics in Cape Town, South Africa. The study included all children younger than 13 years presenting with persistent cervical adenopathy to the local primary health care clinic.

**Results:** A total of 158 children were evaluated of whom 35 (22.2%) were diagnosed with tuberculous lymphadenitis. Bacteriologic confirmation was achieved in 27 of 35 (77.1%) children; all 35 responded to standard antituberculosis treatment. The majority of those without tuberculous lymphadenitis (105 of 123, 85.4%) had a visible superficial lesion in the area drained by the affected nodes. In children with persistent lymphadenopathy  $\geq 2 \times 2$  cm, tuberculosis lymphadenitis was diagnosed in 31 of 33 (93.9%); specificity was 98.4%, sensitivity was 88.6% and the positive predictive value was 93.4%.

**Conclusion:** Children commonly present with persistent cervical adenopathy to the primary health care clinic. The use of a simple clinical algorithm provided an accurate diagnosis of tuberculous lymphadenitis in the study setting. Fine needle aspirations provided a rapid and definitive diagnosis in the majority of children and will have added diagnostic value in settings where alternative diagnoses are more likely.

**Key Words:** tuberculosis, lymphadenitis, children, persistent cervical adenopathy

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Peripheral tuberculous lymphadenitis predominantly involves the cervical lymph nodes<sup>1–5</sup> and is the most common form of extrapulmonary tuberculosis in children from tuberculosis-endemic areas.<sup>1,2</sup> However, its relative contribution as a cause of persistent cervical adenopathy in these communities is not well-documented.

Cervical lymphadenitis, caused by *Mycobacterium tuberculosis*, is generally considered to have its origin in the lymphatic spread of organisms from a primary pulmonary focus, but in a minority of cases it can originate from a primary focus in the mouth, tonsils, oropharynx or tissues of the head and neck.<sup>6</sup> Other mycobacteria can also cause cervical lymphadenitis; the relative contribution of different mycobacteria is influenced by the control of bovine tuberculosis,<sup>7</sup> the use of BCG vaccination,<sup>8</sup> the presence of environmental mycobacteria and the prevalence of tuberculosis within a particular setting.<sup>7</sup>

The diagnosis of tuberculosis in children is often difficult, given that symptoms and signs might be nonspecific, the collection of bacteriologic specimens problematic and bacteriologic yields low.<sup>9,10</sup> In children with peripheral tuberculous lymphadenitis, however, clinical signs are usually apparent, and fine needle aspiration (FNA) provides excellent bacteriologic yields.<sup>11–13</sup> Although the diagnostic value of FNA has been demonstrated in resource-limited settings,<sup>11–13</sup> to date it remains underutilized as a routine diagnostic modality in most endemic areas.

The aim of this study was to determine the relative contribution of tuberculous lymphadenitis as a cause of persistent cervical adenopathy in children from a tuberculosis-endemic area and to document its clinical presentation at the primary health care level.

## METHODS

A prospective descriptive study was performed from February 2003 through October 2004 in Cape Town, the Western Cape Province, South Africa.

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**Setting.** The study was conducted at 5 primary health care clinics served by one referral hospital. The incidence of all tuberculosis in Cape Town was 678/100,000,<sup>14</sup> and the prevalence of human immunodeficiency virus (HIV) infection among women attending public antenatal clinics in the Western Cape Province was 13.1% (95% confidence interval, 8.5–17.7%), in 2003.<sup>15</sup> Bovine tuberculosis is well-controlled within the study communities, and children receive routine neonatal Calmette-Guérin bacillus (BCG) vaccination. The study communities rarely use private medical services, and children diagnosed with tuberculosis are routinely referred to the local primary health care clinic, where supervised antituberculosis treatment is provided free of charge. Pediatric services are extended only to children younger than 13 years of age.

**Study Population.** All children (younger than 13 years of age) who presented with persistent cervical adenopathy; defined as lymph nodes  $\geq 1 \times 1$  cm, persisting for  $>4$  weeks despite a course of oral antibiotics (usually amoxicillin), were referred to the investigator for evaluation.

**Data Collection and Surveillance.** The principal investigator visited each clinic on a weekly basis to screen referred children, whereas a study nurse recorded children referred directly to hospital. The areas surrounding the affected cervical lymph nodes were inspected to exclude a visible superficial lesion within their drainage area (visible local cause), such as impetigo of the scalp, tinea capitis or traction folliculitis. Those with a visible local cause were given appropriate therapy and instructed to return if the lymph nodes persisted or increased in size. Surveillance was continued at all 5 clinics and the referral hospital throughout the study period, and for an additional 3 months after enrollment was stopped, to document any child who subsequently returned with symptom deterioration or a possible diagnosis of tuberculosis.

Children with no visible local cause of cervical lymphadenopathy received a Mantoux (2 tuberculin units of purified protein derivative RT23 intradermal) tuberculin skin test (TST) and a chest radiograph (anteroposterior and lateral). The Mantoux TST was interpreted as positive if induration was  $\geq 10$  mm. Two independent experts evaluated the chest radiographs for intrathoracic signs of tuberculosis. Symptoms and signs as well as possible tuberculosis contact were documented. Children diagnosed with tuberculous lymphadenitis were offered a rapid HIV test (Determine HIV 1/2; Abbott) after appropriate counseling. Standard 3-drug antituberculosis treatment was initiated,<sup>16</sup> and response to antituberculosis therapy was monitored after a period of 3 months. In the group not diagnosed with tuberculous lymphadenitis, symptom resolution in the absence of antituberculosis therapy was monitored.

**Case Definition.** Tuberculous lymphadenitis was defined as cervical lymphadenopathy  $\geq 1 \times 1$  cm persisting for  $>4$  weeks despite a course of oral antibiotics, in the presence of at least 1 of the following criteria: (1) bacteriologic confirmation: isolation of *M. tuberculosis* from a lymph node, or microscopically visible acid-fast or autofluorescent bacilli associated with amorphous necrosis on cytology; or (2) clinical diagnosis: significant therapeutic response (lymph node size decreased from  $\geq 2 \times 2$  cm to  $<1 \times 1$  cm after 3 months of standard antituberculosis treatment). All cultures positive

for *M. tuberculosis complex* were routinely speciated by polymerase chain reaction to differentiate *M. tuberculosis* from *Mycobacterium bovis* and *M. bovis* BCG.<sup>17</sup>

**FNA and/or Biopsy.** Of the children enrolled, only those with a positive TST ( $\geq 10$  mm) and/or a suggestive chest radiograph and/or a cervical mass  $\geq 2 \times 2$  cm were referred to the hospital for FNA. FNA was performed in the pediatric outpatient department with sedation and pain relief (chloral hydrate 20–50 mg/kg and paracetamol 10–20 mg/kg, administered orally 30–60 minutes before the procedure). The largest discrete node was identified by careful palpation of the cervical mass. Two needle passes were performed with a 23-gauge needle attached to a 10-mL syringe, applying 2 mL of suction. Aspirated material was placed on standard microscope slides, thinly smeared and air-dried or fixed with commercial spray fixative for Giemsa and Papanicolaou stains, before flushing the syringe and needle directly into a MGIT (Becton Dickinson, Cockeysville, MD) mycobacterial culture bottle. Microscopic evaluation included cytology, acid-fast staining and autofluorescence.<sup>18</sup> Excision biopsies were occasionally performed if children presented with persistent cervical adenopathy to the referral hospital without a letter from the investigator or if the FNA was inconclusive.

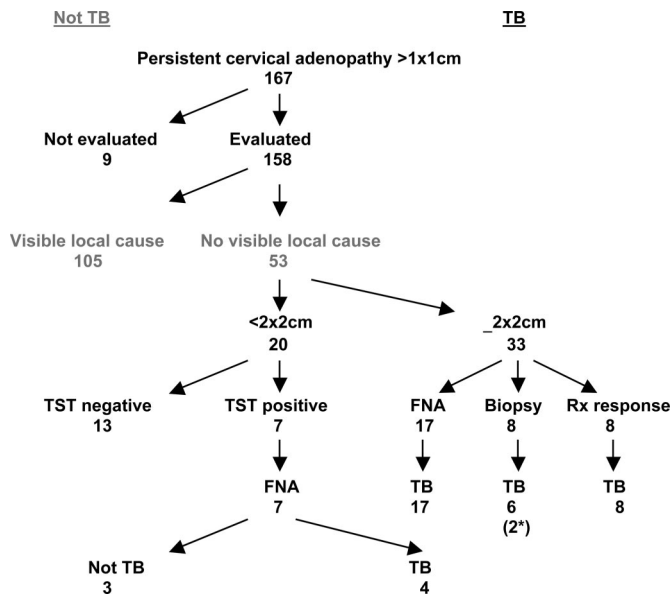
**Statistical Analysis.** Descriptive analysis was conducted with SPSS (version 11.5). The sensitivity and specificity of a simple clinical algorithm were calculated with the use of either bacteriologic confirmation and/or the clinical case definition (see case definition) as the “reference” test.

Parents gave written informed consent for study participation and ethics approval was obtained from the Institutional Review Board of Stellenbosch University, the City of Cape Town Health Department and local health committees.

## RESULTS

**Persistent Cervical Adenopathy.** Of the 167 children who were identified with persistent cervical adenopathy, 9 (5.4%) did not return to the clinic for evaluation by the investigator (Fig. 1). Of the 158 children evaluated, 53 had no visible cause of whom 40, with either a positive TST or a cervical mass  $\geq 2 \times 2$  cm, were referred to hospital to establish a histologic diagnosis. None of the 13 TST-negative children had radiographic or other clinical signs indicative of possible tuberculosis, and all children judged not to have tuberculosis on clinical grounds showed symptom resolution in the absence of antituberculosis treatment.

Table 1 summarizes the demographics and etiology of persistent cervical adenopathy in the 158 children who were evaluated. The majority of children (105, 66.5%) had lymph nodes  $<2 \times 2$  cm with a visible local cause; 28 returned for reevaluation within 1 month; the lymphadenopathy resolved in 18 and decreased to  $<1 \times 1$  cm in 9. Multiple discrete lymph nodes, 1–2 cm in diameter, remained in 1 child who was TST-negative and asymptomatic. The lymphadenopathy showed slow resolution, decreasing to  $<1 \times 1$  cm within 3 months. None of the children with a visible local cause returned to the clinic with symptom deterioration or with a possible tuberculosis diagnosis from any hospital, during the study period.



**FIGURE 1.** Flow diagram of children referred with persistent cervical adenopathy. Not TB indicates symptom resolution in the absence of antituberculosis chemotherapy. TB, bacteriologic confirmation: isolation of *M. tuberculosis* from a lymph node, or microscopically visible acid-fast or autofluorescent bacilli associated with caseating necrosis on cytology or clinical diagnosis; significant therapeutic response (lymph node size decreased from  $\geq 2 \times 2$  cm to  $< 1 \times 1$  cm after 3 months of standard antituberculosis treatment); Not evaluated, did not return to the clinic for evaluation by the investigator; Rx response, clinical diagnosis together with significant therapeutic response in the absence of FNA or biopsy-based diagnosis; \*classified as not TB: 1 chronic inflammatory process diagnosed after excision, 1 nonacute bacterial abscess diagnosed after incision and drainage.

**TABLE 1.** Demographics and Etiology of Persistent Cervical Adenopathy in Children (n = 158)

	No. of Instances
<b>Demographics</b>	
Gender	
Male	69 (43.7)*
Female	89 (56.3)
Age groups	
<5 yr	93 (58.9)
5–9 yr	51 (32.2)
≥10 yr	14 (8.9)
<b>Etiology</b>	
Visible local cause	105 (66.5)
Bacterial infection (crusted impetigo)	26 (16.5)
Tinea capitis (with secondary infection)	34 (21.5)
Traction folliculitis	44 (27.8)
Otitis externa	1 (0.6)
No visible local cause	53 (33.5)
Tuberculous lymphadenitis	35 (22.2)
Reactive nodes†	13 (8.2)
Nonspecific inflammation	4 (2.5)
Nonacute bacterial abscess	1 (0.6)
Malignancy	0

\*Numbers in parentheses, percent.

†Cervical mass  $< 2 \times 2$  cm, tuberculin skin test-negative and natural symptom resolution.

Of the 53 (33.5%) children without a visible local cause, tuberculous lymphadenitis was diagnosed in 35 (66.0%). Of those with a cervical mass  $\geq 2 \times 2$  cm, tuberculous lymphadenitis was diagnosed in 31 of 33 (93.9%). Of the 2 remaining children, 1 had an unidentified chronic inflammatory process diagnosed through excision biopsy, and the other developed a chronic bacterial abscess after repeat courses of oral antibiotics, requiring eventual incision and drainage. Two children presented with acute bacterial adenitis; both had a history of persistent lymph node enlargement that preceded the acute event. Both these children were TST-positive and were diagnosed with secondary bacterial infection, as *M. tuberculosis* was cultured after incision and drainage. One had signs suggestive of tuberculosis on the chest radiograph and reported a prolonged cough and night sweats, whereas the other had no additional suspect symptoms or signs apart from the cervical mass and a positive TST.

**Tuberculous Lymphadenitis.** Of the 35 children diagnosed with tuberculous lymphadenitis (Fig. 1), bacteriologic confirmation was achieved in 27 (77.1%) children. Of the 8 children without bacteriologic confirmation, 7 failed to attend the referral hospital, and 1 refused permission for FNA. All 8 had a TST response  $\geq 15$  mm and showed excellent response to standard antituberculosis treatment. In the 27 children with bacteriologic confirmation; FNA was performed in 21 children and formal biopsies in 6. No cases caused by *M. bovis*, *M. bovis* BCG, infection with environmental mycobacteria such as *Mycobacterium avium-intracellulare* complex or *Mycobacterium scrofulaceum* or malignancies were identified.

Of the 21 children with tuberculous lymphadenitis in whom FNA was performed, 16 of 21 (76.2%) were acid-fast or autofluorescent smear-positive, which allowed rapid and definitive diagnosis. Culture confirmation was achieved in 19 of 21 (90.5%), of whom 2 had no microscopic features indicative of tuberculosis. One of the 2 children who were culture-negative had received antituberculosis treatment before FNA was performed. Either a positive culture or typical microscopic features were present in all 21 cases. One of the 2 children, who had no microscopic features indicative of tuberculosis on FNA, had an excision biopsy performed that established the diagnosis, before the FNA culture result became known. No immediate complications relating to the FNA procedure, apart from minimal bleeding, were noted. No long term complications, such as sinus formation, were recorded during the 3-month follow-up period.

Table 2 reflects the lymph node characteristics and associated findings in the 35 children diagnosed with tuberculous lymphadenitis. Using the clinical algorithm of a persistent cervical mass  $\geq 2 \times 2$  cm, without a visible local cause or response to antibiotics, accurately identified children with tuberculous lymphadenitis; sensitivity was 88.6%, specificity was 98.4% and the positive predictive value of this clinical algorithm was 93.4%.

Tuberculous lymphadenitis occurred in children of all ages, except in infants. In 18 (51.4%), lymph nodes occurred in the anterior triangle, with involvement of multiple regions in 5 (14.3%). Other regions involved were: posterior triangle, 8 (22.9%); submandibular, 2 (5.7%); and supraclavicular, 2 (5.7%). Lymph nodes occurred more regularly on the right

**TABLE 2.** Clinical Characteristics of Children With Tuberculous Lymphadenitis (n = 35)

	No. of Instances
Lymph node characteristics	
Persistence (present for >4 wk, no response to antibiotics)	35 (100)*
Size†	
<2 × 2 cm	4 (11.4)
(2–4) × (2–4) cm	25 (71.5)
>4 × 4 cm	6 (17.1)
Character	
Single	5 (14.3)
Multiple	
Discreet	14 (40.0)
Matted	16 (45.7)
Solid	28 (80.0)
Fluctuant	
Without secondary bacterial infection	5 (14.3)
With secondary bacterial infection (red and warm)	2 (5.7)
Associated findings	
Tuberculin skin test	
0 mm	2 (5.7)
1–9 mm	0
≥10 mm	33 (94.3)
≥15 mm	32 (91.4)
Mean response 19.1 mm (standard deviation 2.9 mm)	
Constitutional symptoms	
Any symptom	21 (60.0)
Fever	7 (20.0)
Cough	9 (25.7)
Night sweats	8 (22.8)
Fatigue‡	19 (54.3)
Failure to thrive§	10 (28.6)
Chest radiograph	
Suggestive of tuberculosis	13 (37.1)
Lymph node disease	
Uncomplicated	8 (22.8)
With airway compression	1 (2.9)
With parenchymal consolidation	4 (11.4)

\*Numbers in parentheses, percent.

†Transverse diameter of the largest cervical mass.

‡Less playful and active since the mass was first noted.

§Crossing at least 1 centile line in the preceding 3 months or having lost &gt;10% of body weight (minimum, 1 kg) over any time interval.

side: right, 19 (54.3%); left, 13 (37.1%); bilateral, 3 (8.6%). Most lymph nodes were multiple, either discreet or matted (30, 85.7%), either discreet or matted, and solid (28, 80.0%). All lymph nodes were nontender, either discreet or matted, except 2 with secondary bacterial infection. A sinus developed in 2 children, one before presentation and the other after surgical incision and drainage.

Associated findings in children with tuberculous lymphadenitis included a positive TST in 33 of 35 (94.3%). Two (5.7%) children had a nonreactive TST; 1 was HIV-infected, the other was severely ill with coexistent pulmonary tuberculosis. The TST in the latter patient measured 16 mm when repeated after 3 months of antituberculosis treatment. Twenty-nine (82.9%) children were tested for HIV, and 1 (3.5%) was HIV-infected. Contact with an adult index case was reported in 19 (54.3%), whereas in a further 2 cases, adults with suspicious symptoms were subsequently diagnosed with tuberculosis. Constitutional symptoms were present in 21 (60.0%) children, and the chest radiograph was suggestive of primary pulmonary tuberculosis in 13 (37.1%).

The response to standard antituberculosis therapy was good, and most children showed considerable improvement, with reduction in lymph node size to <1 × 1 cm after 3 months of standard antituberculosis treatment. Three (8.6%) children deteriorated initially; 1 developed upper airway obstruction that required surgical lymph node enucleation and the addition of corticosteroids. All 3 children showed good response after completing 6 months of standard antituberculosis therapy, although a cervical mass of >1 × 1 cm remained in 1 child.

## DISCUSSION

Children commonly presented with persistent cervical adenopathy to primary health care clinics in the study setting. The majority of these children had visible local lesions such as crusted impetigo, infected tinea capitis or traction folliculitis. The hair of most small girls in this community is tightly braided, which often leads to irritation and bacterial infection of the hair follicles. This also explains the overrepresentation of girls in the study population. It is understandable that none of these conditions responded to a short course of oral antibiotics, in the absence of etiology-specific systemic and/or local treatment.

A simple clinical algorithm that identified children with persistent (>4 weeks) cervical lymphadenopathy, no visible local cause or response to antibiotics and a cervical mass ≥2 × 2 cm showed excellent diagnostic accuracy within the study setting. The addition of a positive TST may be of value in settings where infection with *M. tuberculosis* is less common or where conditions other than tuberculosis, such as malignant lymph node involvement or other chronic infections, are more common and may present with a similar clinical picture. The fact that accurate clinical diagnosis is possible at the primary health care level might allow the initiation of antituberculosis treatment without hospital referral, which should improve access to care for children in extremely resource-limited settings. However, regular follow-up (at least monthly) is essential so that children who do not respond to standard antituberculosis treatment are referred as soon as possible to establish a definitive diagnosis. The value of this clinical approach requires further evaluation.

FNA proved to be a robust and simple technique, which provided an excellent bacteriologic yield. No significant side effects were noted. FNA provided a definitive bacteriologic diagnosis with the ability to speciate *M. tuberculosis* complex and to perform drug susceptibility testing. A definitive diagnosis is always desirable, but the diagnostic value of FNA will be even greater in settings where a clinical diagnosis is expected to be less accurate, such as areas where malignant lymph node involvement and/or other chronic infections are more common.<sup>11,12</sup>

The lymph node characteristics and constitutional symptoms recorded in this study correlate well with findings from Papua New Guinea and India.<sup>3,4,19</sup> The most distinctive features were the chronic persistent course, the lymph node size (≥2 × 2 cm) and the involvement of multiple, discrete or matted, lymph nodes. The study also emphasizes the value of



clinical follow-up and serial measurement of enlarged lymph nodes if the diagnosis is not apparent.<sup>20</sup>

Only 1 child with tuberculous lymphadenitis was HIV-infected. This reflects the low HIV prevalence among children in the study setting but might also illustrate a decreased tendency in HIV-infected children to develop peripheral tuberculous lymphadenitis, as suggested in a comparative study from Zambia.<sup>21</sup> FNA may have increased diagnostic value in HIV-infected children, because the relative contribution of tuberculous lymphadenitis to persistent cervical adenopathy in this group is expected to be smaller.

It is interesting that no environmental mycobacteria were isolated, although it is reported to be the most common cause of persistent cervical adenopathy in the developed world.<sup>22</sup> Paucity of disease caused by environmental mycobacteria has also been described in other tuberculosis-endemic countries, such as India.<sup>23,24</sup> This may result from the protective effect afforded by routine neonatal BCG vaccination,<sup>8</sup> whereas natural infection with *M. tuberculosis* might provide additional protection against disease caused by environmental mycobacteria.

An important study limitation is that bacteriologic confirmation was achieved in only 77.1% of the study patients, as it was not attempted in 8 children. However, we are confident that the diagnosis was accurate, given the fact that these 8 children all had a TST response  $\geq 15$  mm and showed excellent clinical response to standard antituberculosis treatment.

In conclusion, the use of a simple clinical algorithm identified tuberculous lymphadenitis with a high degree of accuracy in the study setting, whereas FNA provided a rapid and definitive diagnosis in the majority of children.

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## Chapter 5.

### Symptom-based screening and diagnosis

The pre-chemotherapy literature indicated the importance of symptoms to assist with the differentiation between infection and disease. This implies that symptom-based approaches may have value for screening and diagnostic purposes. We evaluated the potential value of simplified (symptom-based) screening to improve access to preventive chemotherapy for children exposed to tuberculosis in resource-limited settings. We then applied a step-wise approach to assess the potential value of symptoms to diagnose childhood tuberculosis. The first step was merely to document the prevalence of symptoms traditionally associated with tuberculosis, in a random selection of children from an endemic area. The second step was to develop optimal symptom definitions and to demonstrate that well-defined symptoms have improved diagnostic value compared to poorly defined symptoms. The final step was to validate the value of a novel symptom-based approach, using well-defined symptoms, to diagnose pulmonary tuberculosis in children from an endemic area.

#### 1. Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Enarson DA, Beyers N.

##### **Radiographic signs and symptoms in children treated for tuberculosis: possible implications for symptom-based screening in resource-limited settings. *Ped Infect Dis J* 2006; 25: 237-240**

The WHO advises active tracing of children less than 5 years of age who are in household contact with a sputum smear-positive index case. Current guidelines include tuberculin skin testing and chest radiography as prerequisite tests for adequate screening, but these tests are rarely available in endemic areas. As a result no preventive chemotherapy is offered to exposed children in these settings. This prospective descriptive study compared disease manifestations in two groups of children, those who presented with suspicious symptoms and those who were actively traced household contacts of an adult index case. Significantly more actively traced contacts were categorized as “not TB” (OR 7.4, 95%CI 3.8-14.3), or demonstrated elements of the primary complex only on chest radiograph (OR 26.2, 95%CI

8.6-89.2), compared to children who presented with suspicious symptoms. Only 20/230 (8.7%) children diagnosed with intra-thoracic tuberculosis reported no symptoms, all of whom demonstrated elements of the primary complex only. Simplified, symptom-based screening of child contacts may be justified to improve access to preventive chemotherapy in resource-limited settings

**2. Marais BJ, Obihara CC, Gie RP, Schaaf HS, Hesselning AC, Lombard C, Enarson D, Bateman E, Beyers N. The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high-burden community. Arch Dis Child 2005; 90: 1166-1170**

This community-based survey documented the prevalence of symptoms traditionally associated with tuberculosis in a random selection of children from a high-burden community. Of the 1397 children without tuberculosis, 253 (26.4%) reported a cough during the preceding 3 months and 66 (6.9%) reported a cough of more than 3 weeks duration. In addition, 50% of children with newly diagnosed tuberculosis reported no symptoms at all. These observations clearly limit the value of poorly defined symptoms to diagnose tuberculosis in children. The study emphasized the need for improved symptom and case definitions.

**3. Marais BJ, Gie RP, Obihara CC, Hesselning AC, Schaaf HS, Beyers N. Well-defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis. Arch Dis Child 2005; 90: 1162-1165**

We have demonstrated that poorly defined symptoms have little diagnostic value, but this may not be true for well-defined symptoms. According to the natural history of disease, childhood tuberculosis is associated with persistent, non-remitting symptoms. We conducted a small prospective cohort study to evaluate whether the use of well-defined symptoms improves diagnostic accuracy. Of 151 children referred with a cough of >2 weeks duration, only 17 (11.2%) reported a persistent, non-remitting cough. In this small study, a persistent, non-remitting cough was an almost universal feature in children with tuberculosis (15/16, 93.8%), while it was extremely rare in those without tuberculosis (2/135, 1.5%). The study demonstrated that accurate symptom definition might add significant diagnostic value.



However, formal validation of this novel approach requires a large, prospective community-based study.

### **Rationale applied to validate a novel symptom-based diagnostic approach**

There are multiple reasons for current scepticism about the utility of symptom-based approaches to diagnose childhood tuberculosis; 1) the poor validation and performance of existing clinical algorithms, 2) an appreciation that the symptoms traditionally associated with tuberculosis are not uncommon in endemic areas, even in children without tuberculosis, 3) literature reports that describe children with “asymptomatic tuberculosis”, 4) a perception that childhood tuberculosis may progress rapidly, implying that symptom-based diagnostic approaches may be dangerous, and 5) a belief that bacteriologic confirmation remains the only way to establish a definitive diagnosis of tuberculosis.

Despite these reservations, we felt confident that a novel symptom-based diagnostic approach may hold promise; based on evidence from the pre-chemotherapy literature, personal clinical experience and the results of our studies to date. There have been few recent advances in the diagnosis of childhood tuberculosis. The new T-cell based assays were greeted with great enthusiasm, but although these tests indicate *M. tuberculosis* infection with accuracy, they fail to differentiate latent infection from active disease. Accurate case definition and the distinction between infection and disease have caused a lot of confusion. The natural history of disease demonstrate that “asymptomatic tuberculosis” probably results from inappropriate disease classification, as elements of the primary complex became transiently visible on the chest radiograph in the majority of children following recent primary infection with *M. tuberculosis*. Radiological visibility of elements of the primary complex, in the absence of symptoms or radiologically visible complications, should be classified as recent primary infection and not disease.

Natural history disease descriptions also enabled accurate risk analysis and stratification according to a child’s risk to progress to disease following primary infection with *M. tuberculosis*. Appropriate risk stratification indicated that the risk of rapid disease

progression was restricted to high-risk (very young and/or immune compromised) children. In these high-risk children the identification and treatment of latent infection is important and the study protocol should ensure the provision of preventive chemotherapy. In low-risk children (immune competent and older than 3yrs of age), who represent the majority of children in the community, disease progression was associated with slowly progressive, persistent symptoms that provided a potential window of opportunity for symptom-based diagnosis.

Essential study design elements identified were; 1) prospective community-based recruitment to limit patient selection, 2) appropriate risk-stratification, 3) the use of accurate case definitions that are both independent of the predictor variables tested and inclusive of the full disease spectrum seen in children with pulmonary tuberculosis, and 4) the need for comprehensive disease surveillance to identify all children from the study community who received anti-tuberculosis treatment during the study period, irrespective of study entry. Comprehensive disease surveillance is an essential safety check to quantify the potential disadvantages of using a novel symptom-based diagnostic approach. Primary health care clinics were identified as the most practical, community-based point of entry into the study. In addition, clinic-based entry would be representative of the situation faced by healthcare workers in tuberculosis endemic areas.

The formulation of accurate case definitions provided a major challenge. Bacteriologic confirmation is the accepted gold standard. However, it is limited by a few major concerns; 1) the low bacteriologic yields achieved in children with tuberculosis, 2) the fact that culture positive children may represent a select group that does not reflect the full disease spectrum, and 3) the observation that positive cultures may be obtained in healthy children shortly after primary infection. Chest radiography is often used as a more practical alternative, but it has serious limitations as well; 1) radiologic visibility of elements of the primary complex may indicate recent primary infection and not necessarily disease, and 2) the subjectivity inherent to radiograph interpretation undermines its reliability as an objective endpoint. It is important to mention that the majority of children with tuberculosis have unequivocal radiologic signs. The poor inter and intra-personal correlation reported in the literature may be partly due to the

fact that expert readers were forced to make a diagnosis in every instance, without having the option of indicating uncertainty.

We concluded that the most accurate case definitions are provided by a combination of symptomatic presentation and either bacteriologic confirmation or radiographic certainty. This excludes asymptomatic children with either an unexpected positive culture and/or transiently visible elements of the primary complex on the chest radiograph. The following measures were identified to ensure that a radiographic diagnosis of tuberculosis do provide a reliable endpoint; 1) antero-posterior and lateral views should be taken, 2) all chest radiographs should be read by two independent blinded experts, who should first evaluate the quality of the radiograph and then document their findings on a standard report form, and 3) the expert readers must have the option to indicate uncertainty. Only when both independent experts agree on a certain diagnosis of tuberculosis, should it be accepted as an objective and reliable endpoint. Children without bacteriologic confirmation or radiologic certainty should be monitored for natural symptom resolution or response to anti-tuberculosis therapy, before assigning the most probable clinical diagnosis. These outcome criteria; 1) "bacteriologically confirmed TB", 2) "radiologically certain TB", and 3) "probable TB", in conjunction with symptomatic study entry, should provide accurate case definitions that are inclusive of the complete disease spectrum.

We proceeded to perform a prospective, community-based study to validate a novel symptom-based approach, based on the study rationale outlined.

**4. Marais BJ, Gie RP, Hesselning AC, Schaaf HS, Enarson D, Beyers N. A novel symptom-based approach to diagnose childhood pulmonary tuberculosis: a prospective, community-based study. Submitted to Pediatrics**

This final study determined the value of well-defined symptoms to diagnose pulmonary tuberculosis in children from a highly endemic area, and assessed its performance within relevant risk groups. Accurate diagnosis of pulmonary tuberculosis, using a simple symptom-based approach, was possible in most HIV-uninfected children, particularly those  $\geq 3$  years of age. Further confirmation is required, but this novel approach offers the exciting prospect of extending antituberculosis treatment to children in highly endemic areas with limited resources, where they currently have poor access to treatment.

# Radiographic Signs and Symptoms in Children Treated for Tuberculosis

## *Possible Implications for Symptom-Based Screening in Resource-Limited Settings*

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**Background:** The World Health Organization advises active tracing of children younger than 5 years old in household contact with a sputum smear-positive tuberculosis index case. This study compared radiographic disease manifestations in 2 groups of children treated for tuberculosis in an endemic setting: those who presented with suspicious symptoms; and those actively traced as household contacts of an adult index case.

**Methods:** We conducted a prospective descriptive study from February 2003 through October 2004 at 5 primary health care clinics in Cape Town South Africa, including all children (younger than 5 years old) treated for tuberculosis (TB).

**Results:** A total of 326 children (younger than 5 years old) received antituberculosis treatment; 190 (58.3%) presented with suspicious symptoms, and 136 (41.7%) were actively traced contacts. Children were categorized as; “not TB” 71 (22%), intrathoracic tuberculosis 230 (70%) and extrathoracic tuberculosis 25 (8%). Significantly more actively traced contacts were categorized as “not TB” (odds ratio, 7.4; 95% confidence interval, 3.8–14.3), or demonstrated elements of the primary complex only on the chest radiograph (odds ratio, 26.2; 95% confidence interval, 8.6–89.2), compared with children who presented with suspicious symptoms. Of all children diagnosed with intrathoracic tuberculosis, 20 of 230 (9%) reported no symptoms, all of whom demonstrated elements of the primary complex only.

**Conclusions:** The majority of actively traced contacts had minimal disease. Symptom-based screening would have identified all but 9% of children diagnosed with intrathoracic tuberculosis, all of whom

demonstrated elements of the primary complex only. Further investigation is required to establish whether symptom-based screening can be justified to improve access to preventive chemotherapy in resource-limited endemic settings.

**Key Words:** symptom-based screening, preventive chemotherapy, childhood tuberculosis

(*Pediatr Infect Dis J* 2006;25: 237–240)

Because childhood tuberculosis is often considered to be a mild disease with limited epidemiologic impact, the main reason for treating children is to eradicate the pool of latent infection from which future reactivation disease can result. However, children carry a heavy burden of disease in tuberculosis-endemic areas,<sup>1</sup> and tuberculosis is a major cause of respiratory tract-related disease and death,<sup>2</sup> which indicate the importance of preventive chemotherapy to reduce the tuberculosis disease burden in children.

The World Health Organization advises active tracing and screening of children younger than 5 years old in household contact with a sputum smear-positive tuberculosis index case.<sup>3</sup> Guidelines for screening include tuberculin skin testing and chest radiography. These tests are rarely available in endemic areas with limited resources; as a result, children exposed to *Mycobacterium tuberculosis* in these settings are not offered preventive chemotherapy.

The South African National Tuberculosis Program (NTP) guidelines state that all children younger than 5 years old in household contact with a sputum smear-positive index case should be assessed at the primary health care clinic.<sup>4</sup> Routine assessment includes documentation of suspicious symptoms, a tuberculin skin test (TST) and standard anteroposterior and lateral chest radiographs. Children diagnosed with tuberculosis receive standard multidrug treatment, whereas those in whom active tuberculosis has been excluded receive isoniazid preventive chemotherapy for 6 months.

This study compared radiographic disease manifestations in 2 groups of children treated for tuberculosis in an endemic setting: those who presented with suspicious symptoms; and those actively traced as household contacts of an adult index case. This comparison allowed us to evaluate the

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potential value of symptom-based screening in resource-limited settings, where chest radiography is unavailable.

## METHODS

**Study Setting.** We conducted a prospective descriptive study, from February 2003 through October 2004 in Cape Town, Western Cape Province, South Africa. The study area included 5 primary health care clinics served by Tygerberg Children's Hospital as the referral hospital. The population rarely use private medical services, and those diagnosed with tuberculosis are routinely referred to the local primary health care clinic where they receive supervised treatment free of charge. The incidence of all tuberculosis in Cape Town was 678 per 100,000 in 2003,<sup>5</sup> and the prevalence of human immunodeficiency virus (HIV) infection among women attending public antenatal clinics in the Western Cape Province was 13.1% (95% confidence interval (CI), 8.5–17.7%) in 2003.<sup>6</sup>

**Data Collection.** All children younger than 5 years of age who started antituberculosis treatment during the study period were identified by prospective surveillance. The investigator visited each clinic on a weekly basis to review children who had newly started antituberculosis treatment at the primary health care clinic. Children who started antituberculosis treatment in hospital were recorded by a study nurse and referred to the same investigator for review.

**TST.** A TST was performed on the volar aspect of the left forearm, using either the Mantoux test (intradermal injection of 2 tuberculin units of *M. tuberculosis* purified protein derivative RT 23; Statens Serum Institut, Copenhagen, Denmark) or the multipuncture tine test. A positive Mantoux test was defined as  $\geq 10$  mm ( $\geq 5$  mm if the child was HIV-infected). The tine test was regarded as positive if 2 or more of the papules showed confluence of induration.

**Chest Radiograph (CXR).** Chest radiographs were performed in all children and reviewed by the same 2 independent experts who were blinded to all clinical information. They used a standard report form and categorized their findings as "certain TB," "uncertain TB" and "certain not TB." Classification was done according to the most severe disease classification reported, with the use of a recently proposed radiologic classification of childhood intrathoracic tuberculosis.<sup>7</sup> Disease entities identified included Ghon focus, primary complex, lymph node disease (uncomplicated or complicated), pleurisy and disseminated (miliary) disease.

**Definitions.** Actively traced contacts were defined as children who did not present because of parental concern regarding suspicious symptoms but who were screened for tuberculosis because of known household contact with an adult index case. Suspicious symptoms were defined according NTP guidelines as cough or wheeze for  $>2$  weeks, and/or prolonged or recurrent unexplained fever and/or failure to thrive.<sup>4</sup>

"Not TB" was defined as meeting all 3 of the following criteria: (1) agreement by both independent experts that the chest radiograph indicated "certain not TB"; (2) no bacteriologic or histologic confirmation; and (3) no documented extrathoracic tuberculosis. Intrathoracic tuberculosis was defined as a child with signs suggestive of tuberculosis on the chest radiograph ("certain TB" or "uncertain TB") identified

by at least 1 independent expert. Extrathoracic tuberculosis was defined a child treated for an extrathoracic manifestation of tuberculosis, without CXR signs suggestive of intrathoracic tuberculosis.

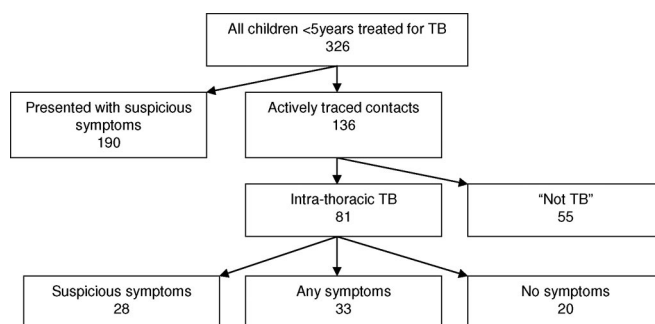
Patients were enrolled after the parents or legal guardians gave written informed consent for study inclusion. Separate consent was obtained for HIV testing, with pre- and posttest counseling. Ethics approval was obtained from the Institutional Review Board of Stellenbosch University, the City of Cape Town Health Department and local health committees.

## RESULTS

Antituberculosis treatment was given to 326 children (younger than 5 years of age), of whom 190 (58%) presented with suspicious symptoms and 136 (42%) were actively traced contacts. (Fig. 1).

Demographics and disease characteristics are presented in Table 1. Of the 194 children with a positive TST, Mantoux tests were done in 159 (82%). The 71 children categorized as "not TB" were given antituberculosis treatment by the attending physician because of known *M. tuberculosis* exposure together with suspicious symptoms and/or possible hilar adenopathy on the CXR. Significantly more actively traced contacts were categorized as "not TB" (55 of 136; 40.4%) than children who presented with suspicious symptoms (16 of 190; 8.4%) [odds ratio (OR), 7.4; 95% CI 3.8–14.3].

Table 2 reflects radiographic disease manifestations in children with intrathoracic tuberculosis. The majority of actively traced contacts (77 of 81, 95%) had elements of the primary complex only on CXR, compared with 63 of 149 (42%) children who presented with suspicious symptoms (OR 26.2; 95% CI 8.6–89.2). Four actively traced contacts had radiographic signs other than elements of the primary complex; 3 had complicated lymph node disease, and 1 had pleurisy. All 4 were symptomatic; 2 reported suspicious symptoms (as defined), 1 child reported a mild intermittent cough of recent onset and the child with pleurisy reported chest pain and fever of recent onset. None of these children presented to the health care facility because of concern regarding their symptoms. Only 20 of 230 (9%) children diagnosed with intrathoracic tuberculosis reported no symptoms, all of whom had elements of the primary complex only on CXR.



**FIGURE 1.** Flow diagram of all children younger than 5 years of age treated for tuberculosis.



**TABLE 1.** Demographics and Disease Characteristics Recorded in Children Younger Than 5 Years of Age Treated for Tuberculosis

Characteristics	Totals (N = 326)	Presented With Symptoms (N = 190)	Actively Traced Contacts (N = 136)	OR
Gender male	166 (51)*	100 (53)	66 (49)	0.9 (0.5–1.4) <sup>†</sup>
Age <3 yr	231 (71)	126 (66)	105 (77)	1.7 (1.0–2.9)
TST				0.5 (0.3–0.9)
Tested	307 (94)	184 (97)	123 (90)	
Positive	194 (60)	145 (76)	81/123 (66)	
HIV				1.0 (0.3–3.8)
Tested	183 (56)	148 (78)	35 (26)	
Positive	21 (6)	17 (9)	4 (3)	
Disease spectrum				
Not TB	71 (22)	16 (8)	55 (40)	7.4 (3.8–14.3)
Intra-thoracic TB	230 (70)	149 (79)	81 (60)	0.4 (0.2–0.7)
Extra-thoracic TB	25 (8)	25 (13)	0	

\*Numbers in parentheses, percent.

<sup>†</sup>Numbers in parentheses, 95% CI.**TABLE 2.** Intrathoracic Disease Manifestations Recorded in Children Younger Than 5 Years of Age Treated for Tuberculosis

Intrathoracic Disease Manifestation	Totals (N = 230)	Presented With Symptoms (N = 149)	Actively Traced Contacts (N = 81)	OR
Ghon focus	3 (1)*	3 (2)	0	
Primary complex	12 (5)	7 (5)	5 (6)	1.5 (0.4–5.7) <sup>†</sup>
Lymph node disease				
Uncomplicated	125 (5)	53 (36)	72 (89)	14.0 (6.2–32.8)
Complicated				
Airway compression	18 (8)	17 (11)	1 (1)	0.1 (0.0–0.7)
Parenchymal consolidation	48 (21)	46 (31)	2 (3)	0.1 (0.0–0.3)
Pleurisy	10 (4)	9 (6)	1 (1)	0.2 (0.0–1.5)
Disseminated (miliary) disease	14 (6)	14 (9)	0	

\*Numbers in parentheses, percent.

<sup>†</sup>Numbers in parentheses, 95% CI.

## DISCUSSION

We believe this study is the first to compare radiographic signs of tuberculosis in actively traced child contacts and children who presented with suspicious symptoms. Significant differences were noted. The majority of actively traced contacts had elements of the primary complex only on CXR. This observation might explain the discrepancy in disease severity reported from endemic and nonendemic areas, because most children in nonendemic areas are diagnosed after active contact tracing. The mild disease and low bacteriologic yield reported in such children are not unexpected.

More importantly, this study provided the opportunity to evaluate the potential value of symptom-based screening compared with CXR-based screening of children exposed to *M. tuberculosis*. TST results did not influence the decision to provide preventive chemotherapy as NTP guidelines stipulate that all household contacts younger than 5 years of age should receive preventive chemotherapy irrespective of the TST result. As in other endemic areas,<sup>8</sup> the diagnosis of childhood tuberculosis in the study area depended mainly on clinical criteria and subjective CXR interpretation.

The majority of children treated for tuberculosis presented with suspicious symptoms. Only 9% of children diagnosed with intrathoracic tuberculosis reported no symptoms, all of whom had elements of the primary complex only on CXR. The prechemotherapy literature that documented the natural history of tuberculosis in children demonstrated that elements of the primary complex become transiently visible in most children after recent primary infection.<sup>9</sup> The complete absence of symptoms indicated good containment of the organism, and the few children who did progress to disease developed symptoms.<sup>9</sup> Therefore, in the complete absence of symptoms or any other radiographic sign attributable to current disease, elements of the primary complex probably reflect recent primary infection only.<sup>7,9</sup>

It is important to provide preventive chemotherapy to children exposed to *M. tuberculosis*, particularly to those at high risk to progress to disease (children younger than 3 years and/or immune compromised children) after primary infection with *M. tuberculosis*.<sup>9</sup> Current guidelines, which regard TST and CXR as prerequisite tests for adequate screening, limit access to preventive chemotherapy in resource-limited

settings where these tests are unavailable. Our findings suggest that symptom-based screening could have considerable value in these settings given that <10% of children diagnosed with intrathoracic tuberculosis on CXR reported no symptoms, all of whom had visible elements of the primary complex only.

The main study limitation is the fact that it was not primarily designed to evaluate the value of symptom-based screening compared with CXR-based screening. We based our conclusion on an analysis of all children treated for tuberculosis, which provides an indication of whether children with tuberculosis would have been missed by symptom-based screening. In addition, very few children were HIV-infected, and not many of the actively traced contacts were tested for HIV infection.

Further investigation is required to determine whether symptom-based screening are justified in resource-limited, endemic settings to improve access to preventive chemotherapy. A symptom-based approach would provide preventive chemotherapy to all asymptomatic high risk contacts, while symptomatic children (cough, wheeze, fever or failure to thrive) would require further investigation to exclude tuberculosis. Whether 6–9 months of isoniazid monotherapy or shorter durations of multidrug therapy represent the optimal preventive regimen in these settings also require further investigation.

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## ORIGINAL ARTICLE

# The prevalence of symptoms associated with pulmonary tuberculosis in randomly selected children from a high burden community

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**Background:** Diagnosis of childhood tuberculosis is problematic and symptom based diagnostic approaches are often promoted in high burden settings. This study aimed (i) to document the prevalence of symptoms associated with tuberculosis among randomly selected children living in a high burden community, and (ii) to compare the prevalence of these symptoms in children without tuberculosis to those in children with newly diagnosed tuberculosis.

**Methods:** A cross sectional, community based survey was performed on a 15% random sample of residential addresses. A symptom based questionnaire and tuberculin skin test (TST) were completed in all children. Chest radiographs were performed according to South African National Tuberculosis Control Program guidelines.

**Results:** Results were available in 1415 children of whom 451 (31.9%) were TST positive. Tuberculosis was diagnosed in 18 (1.3%) children. Of the 1397 children without tuberculosis, 253 (26.4%) reported a cough during the preceding 3 months. Comparison of individual symptoms (cough, dyspnoea, chest pain, haemoptysis, anorexia, weight loss, fatigue, fever, night sweats) in children with and without tuberculosis revealed that only weight loss differed significantly (OR=4.5, 95% CI 1.5 to 12.3), while the combination of cough and weight loss was most significant (OR=5.4, 95% CI 1.7 to 16.9). Children with newly diagnosed tuberculosis reported no symptoms in 50% of cases.

**Conclusion:** Children from this high burden community frequently reported symptoms associated with tuberculosis. These symptoms had limited value to differentiate children diagnosed with tuberculosis from those without tuberculosis. Improved case definitions and symptom characterisation are required when evaluating the diagnostic value of symptoms.

In areas with a high prevalence of tuberculosis, children contribute a significant proportion of the disease burden and experience considerable morbidity and mortality related to tuberculosis.<sup>1–2</sup> This is demonstrated by the fact that pulmonary tuberculosis rivals bacterial pneumonia as a respiratory cause of death in African children older than 6 months of age.<sup>3</sup> The diagnosis of tuberculosis in children is difficult because bacteriological confirmation is rarely achieved and is often not even attempted.<sup>4–8</sup> Chest radiography is regarded as a valuable diagnostic tool, but it is often impossible to identify hilar adenopathy, considered to be the most consistent sign of primary pulmonary tuberculosis, with certainty.<sup>9</sup> In addition, the distinction between recent primary infection and active disease is highly problematic.<sup>10</sup> Most diagnostic algorithms are partly symptom based, but these algorithms are poorly validated and lack standard symptom definitions.<sup>11</sup>

To our knowledge, no previous study has documented the prevalence of symptoms associated with tuberculosis in randomly selected children living in a high burden community. In these communities a large number of individuals become infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) during childhood,<sup>12</sup> and symptom based diagnostic approaches are often promoted to screen children for active tuberculosis. The literature on tuberculosis related symptomatology in children is almost exclusively hospital based, which does not reflect the prevalence of symptoms in the general population.

A recent review of studies from the pre-chemotherapy era documented the natural history of tuberculosis in

childhood.<sup>10</sup> It confirmed that immune competent children, older than 2 years of age, are at low risk of disease progression following primary infection.<sup>10</sup> The presence of symptoms associated with tuberculosis had definite diagnostic value in these low risk children, in whom the principal diagnostic challenge was to distinguish self contained infection from progressive disease.<sup>10</sup>

The aims of this community based study were (i) to document the prevalence of symptoms associated with tuberculosis among randomly selected children living in a high burden community, and (ii) to compare the prevalence of these symptoms in children without tuberculosis to those in children with newly diagnosed tuberculosis.

## METHODS

A cross sectional community based survey was carried out between July and December 2002. A questionnaire was completed and a tuberculin skin test (TST) administered to each child (<15 years of age). Chest radiographs (CXR) were performed according to the South African National Tuberculosis Control Program (NTCP) guidelines.

## Study setting

The study area is an established epidemiological field site in Cape Town, South Africa, comprising two suburbs with a population of 38 656 (census 1996) and a high burden of

**Abbreviations:** CI, confidence interval; CXR, chest radiograph; HIV, human immunodeficiency virus; NTCP, National Tuberculosis Control Program; OR, odds ratio; TST, tuberculin skin test; TU, tuberculin units

**Table 1** Questionnaire

- 1) Did your child experience a daily cough in the preceding 3 months?  
What was the duration of daily cough?
- 2) Did your child experience any breathing difficulty in the preceding 3 months?  
What was the duration of difficult breathing?
- 3) Did your child experience any chest pain in the preceding 3 months?  
What was the duration of chest pain?
- 4) Did your child cough up any blood in the preceding 3 months?
- 5) Did your child experience any deterioration in appetite in the preceding 3 months?  
What was the duration of appetite loss?
- 6) Did your child lose any weight in the preceding 3 months?  
What was the duration of weight loss?
- 7) Did your child experience any abnormal lethargy/fatigue in the preceding 3 months?  
What was the duration of abnormal fatigue/lethargy?
- 8) Did your child experience daily or recurrent fever in the preceding 3 months?  
What was the duration of daily or recurrent fever?
- 9) Did your child experience night sweats in the preceding 3 months?  
What was the duration of night sweats?

Once a specific symptom was reported the duration was specified as: a) less than 1 week; b) 1–2 weeks; c) 2–3 weeks; or d) more than 3 weeks.

tuberculosis (average notification rate of new bacteriologically confirmed cases 320/100 000 per year).<sup>13</sup> Childhood tuberculosis constitutes a high percentage (39%) of the total caseload.<sup>14</sup> The proportion of the population infected with human immunodeficiency virus (HIV) is relatively low, less than the average of 8.8% (95% CI 4.9 to 12.7%) calculated for the Cape Town/Metropole region in 2001.<sup>15</sup>

### Sample selection

A 15% sample of residential addresses was randomly selected, based on a geographical information system of the area. Trained field workers enumerated the people at each of the 839 residential addresses selected. Written informed consent was obtained from the parent or legal guardian. The 218 addresses (26%) that refused consent were systematically replaced by neighbouring addresses. A CXR was performed in children less than 5 years of age who had been in household contact with a sputum smear positive source case or had a positive TST (induration  $\geq 15$  mm in diameter), and in all children with suspect symptoms according to World Health Organisation guidelines (loss of weight, cough  $> 3$  weeks, fever  $> 1$  week, or haemoptysis).<sup>16</sup>

### Questionnaire

A standard questionnaire recorded symptoms that are commonly associated with tuberculosis, experienced during the preceding 3 months (table 1). The duration of each symptom (other than haemoptysis) was categorised as less than 1 week, 1–2 weeks, 2–3 weeks, or more than 3 weeks. Questionnaires were completed by the parent under supervision of a trained field worker. Parents were requested (but put under no obligation) to confidentially report previous HIV tests and results.

### Tuberculin skin test

Trained field nurses performed TST by intra-dermal injection of 2 tuberculin units (TU) of *M tuberculosis* PPD RT 23 (Statens Serum Institut, Copenhagen, Denmark) 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 (AP) and lateral views were taken, using the same x ray machine in all children. A single expert screened all CXR. A second independent expert was used to

**Table 2** Demographics of all children enrolled (n = 1415)

	Total number (%)
Gender	
Male	709 (50.1)
Female	706 (49.9)
Age distribution in years	
<2	188 (13.2)
2–4	243 (17.2)
5–9	508 (35.9)
10–14	476 (33.7)
TST positive ( $\geq 15$ mm in diameter)	451 (31.9)
Age distribution of TST positive children in years	
<2	35 (2.5)
2–5	42 (3.0)
5–10	164 (11.6)
10–14	210 (14.8)
HH contact with an adult source case ever	201 (14.2)
Recent HH contact with an adult source case	53 (3.7)
CXR done	239 (16.9)
CXR suggestive of tuberculosis	18 (1.3)

The total number of children enumerated was 1593 of whom 1415 (88.8%) were enrolled. CXR, chest radiograph; HH, household; Recent HH contact, household contact with a sputum smear positive source case, currently on treatment; TST, tuberculin skin test.

confirm that the radiographical signs were suggestive of tuberculosis in all children identified with possible tuberculosis during the initial screening. Children with confirmed radiographical signs suggestive of tuberculosis had sputum or gastric aspirate samples taken for culture.

A probable tuberculosis case was defined as a child with a “diagnostic” CXR, confirmed by two independent observers (modified WHO guidelines).<sup>17</sup> A confirmed tuberculosis case was defined as a child with bacteriological proof of tuberculosis. All children with probable or confirmed tuberculosis were referred to a local clinic for treatment, in accordance with the NTCP guidelines. Children aged less than 5 years, in household contact with a sputum smear positive source case or with a positive TST, were referred for chemoprophylaxis or treatment of latent infection after active tuberculosis was excluded. The study was approved by the Ethics Review Board of Stellenbosch University and by the Department of Health, City of Cape Town.

### Statistical analysis

Data analyses were carried out with SPSS for Windows version 11.0. The frequencies of symptoms and specific symptom durations were compared between age groups, and TST positive and TST negative children, as well as between those with newly diagnosed tuberculosis and those without. Comparisons were performed by using the Mantel-Haenszel  $\chi^2$  test. The two sided Fisher's exact test was used to determine the p values.

**Table 3** Disease characteristics in the children with newly diagnosed TB (n = 18)

Characteristics	Number (%)
TST $\geq 15$ mm in diameter	17 (94.4)
Type of disease on CXR	
Elements of the Ghon complex only	15 (83.4)
Parenchymal consolidation (apart from the Ghon focus)	1 (5.5)
Parenchymal cavities	2 (11.1)
Bacteriological proof (culture positive)	2 (11.1)

TB, bacteriological confirmation or definite radiological signs with proof of *M tuberculosis* infection; TST, tuberculin skin test.



**Table 4** Demographics of children without TB (n = 1397) compared to children with newly diagnosed TB (n = 18)

Demographics	No TB (%)	TB (%)	OR (95% CI)	p value
Gender				
Male	701 (50.2)	9 (50.0)	1.00 (0.4 to 2.6)	0.998
Female	696 (49.8)	9 (50.0)	1.00 (0.4 to 2.6)	0.998
Age distribution in years				
<2	185 (13.2)	3 (16.7)		
2–4	232 (16.7)	11 (61.1)		
5–9	505 (36.1)	3 (16.7)		
10–14	475 (34.0)	1 (5.5)	$\chi^2 = 11.0$	0.001*
HH contact with adult source case ever	195 (14.0)	5 (27.8)	2.31 (0.3 to 20.0)	0.442
Recent HH contact with adult source case	50 (3.6)	3 (16.7)	5.39 (1.5 to 19.2)	0.004**
Positive TST ( $\geq 15$ mm in diameter)	434 (24.0)	17 (94.4)	37.7 (5.0 to 284.4)	0.000

\*p trend; \*\*p&lt;0.01.

CI, confidence interval; CXR, chest radiograph; HH, household; OR, odds ratio; Recent HH contact, household contact with a sputum smear positive source case, currently on treatment; TB, bacteriological confirmation or definite radiological signs with proof of *M tuberculosis* infection; TST, tuberculin skin test.

## RESULTS

In total, 1593 children were enumerated at the selected addresses. Questionnaire and TST results, available in 1415 (88.9%) children, were included in the analysis. Table 2 summarises the demographic characteristics of the whole group. A positive TST was recorded in 451 (31.9%) children. Seventy five children reported previous HIV testing, with only one reporting a positive test result. CXR were performed in 239 (16.9%) children, applying current NTCP guidelines. The main reasons for performing the CXR were as follows: (i) 177 (74.1%) <5 years of age with household contact ever, (ii) 33 (13.8%) <5 years of age and with TST  $\geq 15$  mm, and (iii) 29 (12.1%) with suspect symptoms. Eighteen (1.3%) children were newly diagnosed with probable or confirmed tuberculosis. Table 3 summarises the disease characteristics (type of disease) in these 18 children. Bacteriological confirmation (a positive *M tuberculosis* culture) was achieved in two cases (11.1%). None of the children with newly diagnosed tuberculosis had clinical signs suggestive of HIV disease.

Table 4 describes the demographics of the 1397 children without tuberculosis, compared to the 18 children with newly diagnosed tuberculosis. Most children with newly diagnosed tuberculosis (14; 77.8%) were less than 5 years of age. Household contact with a recent sputum smear positive source case was reported in three (16.7%) children with newly diagnosed tuberculosis, compared to 50 (3.6%) children without tuberculosis (OR = 5.4; 95% CI 1.5 to 19.2). The TST result was equal to or greater than 15 mm (median 17 mm; range 0–31 mm) in all but one child with newly diagnosed tuberculosis.

Table 5 compares the symptoms reported in children without tuberculosis to those in children with newly diagnosed tuberculosis. Of the 1397 children without tuberculosis, 253 (26.4%) reported a cough during the preceding 3 months. Prolonged symptoms were not uncommon, and 66 (6.9%) reported coughing of more than 3 weeks duration. No significant differences in symptom prevalence or symptom duration existed between age groups (<2 years, 2–4 years, 5–9 years, 10–14 years) or between those with and without TST proof of tuberculosis infection. Significantly more children with newly diagnosed tuberculosis reported weight loss in the preceding 3 months (OR = 4.5, 95% CI 1.5 to 12.3). None of the other symptoms showed statistically significant differences between the two groups, even when the reported duration of symptoms was taken into account. When children less than 5 years of age were analysed separately, to correct for possible selection bias in the older children, the results were similar.

The presence of more than one symptom increased the odds for tuberculosis, but this reached significance only with the inclusion of weight loss. The combination of cough and weight loss was most significant (OR = 5.4, 95% CI 1.7 to 16.9). Nine (50%) children with newly diagnosed tuberculosis reported no symptoms at all, compared to 910 (65.2%) of those without tuberculosis (OR = 1.9, 95% CI 0.7 to 4.7).

## DISCUSSION

This community based survey documents the prevalence of symptoms associated with pulmonary tuberculosis in the average child living in a high burden community. The results

**Table 5** Symptoms reported in children without TB (n = 1397) during the preceding 3 months compared to symptoms reported in those with newly diagnosed TB (n = 18)

	No TB (%)	TB (%)	OR (95% CI)	p value
Individual symptoms				
1) Cough	365 (26.1)	8 (44.4)	2.3 (0.9 to 5.8)	0.080
2) Difficult breathing	150 (10.7)	1 (5.6)	0.5 (0.1 to 3.7)	0.478
3) Chest pain	77 (5.5)	0 (0.0)	1 (0.9 to 1.1)	0.305
4) Haemoptysis	7 (0.6)	0 (0.0)	1 (0.9 to 1.1)	0.763
5) Anorexia	123 (8.8)	4 (22.2)	2.9 (0.9 to 9)	0.052
6) Weight loss**	110 (7.8)	5 (27.8)	4.5 (1.6 to 13)	0.002
7) Fatigue	110 (7.8)	3 (16.7)	2.3 (0.7 to 8.2)	0.172
8) Fever	162 (11.6)	4 (22.2)	2.2 (0.7 to 6.7)	0.164
9) Night sweats	153 (10.8)	3 (16.7)	1.6 (0.4 to 5.7)	0.443
Combined symptoms				
Cough and weight loss**	70 (5.0)	4 (22.2)	5.4 (1.7 to 16.9)	0.001
Cough, anorexia, and weight loss**	51 (3.7)	3 (16.7)	5.3 (1.5 to 18.8)	0.004
No symptoms	911 (65.2)	9 (50.0)	1.9 (0.7 to 4.7)	0.182

\*\*p&lt;0.01.

Symptoms 1) to 9): individual symptoms correlate with questions described in table 1. CI, confidence interval; OR, odds ratio; TB, bacteriological confirmation or definite radiological signs with proof of *M tuberculosis* infection.

demonstrate that within this setting, these symptoms are common in the general paediatric population. Only weight loss, alone or in combination with other symptoms, was significantly more common in children with newly diagnosed tuberculosis. Combinations of symptoms (symptom complexes) were more likely to be associated with tuberculosis than individual symptoms, but the small number of tuberculosis cases limited the analysis. This is an inevitable limitation of community based surveys that document relatively rare events.<sup>18</sup> The detection of 18 new tuberculosis cases during this survey demonstrate a high prevalence of undiagnosed childhood tuberculosis within this community (1272/100 000 of the child population).

The observation that nearly a third of children coughed in the preceding 3 months may be explained by the fact that both viral and bacterial infections are common in this community, especially during the winter months (May to September). It is also common practice for children to share a bed with their parents, which may increase parental awareness of night time symptoms such as cough, fever, or sweating. Similar to previous observations, some (exactly 50%) of the children with newly diagnosed tuberculosis reported no symptoms.<sup>19–21</sup> Although significant differences were found between the symptoms reported in children with tuberculosis and those without, these differences are of limited diagnostic value and only relevant from an epidemiological perspective. This is illustrated by the fact that the symptom complex with the highest significance, cough and weight loss, had a positive predictive value of only 5%.

The study had several limitations; of most importance is the fact that CXR were performed on a selective subgroup of children. Only children under 5 years of age were radiologically screened following household exposure or a positive TST and as a result older children with asymptomatic primary infection may not have been diagnosed. Although this could have biased the results, the statistical findings in children less than 5 years of age and in the group as a whole were similar when comparing symptoms in those with and without tuberculosis. This potential bias seems unavoidable as both the WHO and NTCP guidelines recommend that a CXR should only be performed in older children if they are symptomatic. It may even be argued that it is unethical to perform a CXR in an asymptomatic child older than 5 years of age, as the risk of developing disease following primary infection is less than 1%.<sup>10</sup> The group diagnosed with tuberculosis during this survey represents a true reflection of children who would have been diagnosed with tuberculosis in a “real life” setting, where resources permit active contact tracing and adequate investigation.

The majority of children diagnosed with tuberculosis had signs indicative of recent primary infection only (positive TST and elements of the Ghon complex on CXR). The natural history of tuberculosis in children illustrates that following primary pulmonary infection, transient visibility of the Ghon complex is common and does not necessarily indicate disease.<sup>10 22 23</sup> The fact that current, internationally accepted definitions of disease often reflect recent primary infection, especially in children who are diagnosed after active contact tracing, does hamper the interpretation. Therefore, it is important to point out that, although the study indicates that symptoms have limited diagnostic value, their value for differentiating active disease from recent primary infection requires further investigation.

Questionnaire driven surveys are inherently limited by recall bias and subjectivity. Bias was reduced by the use of standardised questionnaires and the fact that the diagnostic tests (TST and CXR) were performed after completion of the questionnaire. Reported weight loss reflected a subjective impression and objective weight measurements were not

### What is already known about this topic

- No previous community based report has described the prevalence of symptoms traditionally associated with tuberculosis in randomly selected children from a high burden community; hospital based reports are limited by selection bias.
- 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; current symptom based diagnostic algorithms are poorly validated.

### What this study adds

- This is the first report describing the prevalence of symptoms traditionally associated with tuberculosis in the average child from a high burden community.
- This study indicates that poorly defined symptoms, traditionally associated with tuberculosis, are too common in children from these communities to be of real diagnostic value.

taken into account, as these were not routinely done in all children. In addition, the questions used may have been too imprecise, as the pre-chemotherapy literature identifies important symptom characteristics, associated with progressive tuberculosis, that were not elucidated in the present study. These characteristics include persistent, non-remitting symptoms of recent onset.<sup>10</sup> Careful symptom characterisation may be essential to improve their diagnostic value.

Nearly a third (5, 27.8%) of children with newly diagnosed tuberculosis reported previous household contact with a sputum smear positive source case. This is in agreement with a study from the same community that employed restriction fragment length polymorphism (RFLP) analysis, providing proof that 34% of children acquired disease following infection from a source case within the household.<sup>24</sup> In high burden settings, most infection, particularly in children older than 2 years of age, is contracted outside the household within the community.<sup>9 13 24</sup>

In conclusion, this study illustrates the importance of community based research. It describes symptomatology within the general community and highlights the danger of extrapolating findings from hospital based studies to the community level. It is essential to know the prevalence of symptoms within the general community in order to evaluate the value of any particular symptom based diagnostic approach. Comparing the symptoms reported in children without tuberculosis to those in children with newly diagnosed tuberculosis demonstrates why current symptom based scoring systems perform poorly in clinical practice. Most importantly, the study emphasises the need for improved symptom characterisation and accurate outcome definitions which will adequately differentiate *M tuberculosis* infection from active disease.

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**ARCHIVIST****Paternal postnatal depression**

Much has been written about maternal postnatal depression: it affects the quality of infant care and may lead to problems with the child's later social, behavioural, cognitive, and physical development. By contrast, fathers have been relatively ignored. Data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in southwest England have been used to measure the effects on children of paternal depression in the postnatal period (Paul Ramchandani and colleagues. *Lancet* 2005;**365**:2201–5; see also Comment, *ibid*: 2158–9).

ALSPAC recruited 85–90% of all women in the Bristol area with an expected date of delivery between 1 April 1991 and 31 December 1992. Questionnaires were sent 8 weeks postnatally to 13351 mothers and 12 884 partners. Data on postnatal depressive symptoms were available for 11 833 mothers and 8431 fathers. Depression (a score of >12 on the Edinburgh postnatal depression scale (EPDS)) was diagnosed in 1203 mothers (10%) and 303 fathers (4%). Fathers were reassessed at 21 months and behavioural and emotional problems in the children were assessed at 3.5 years using maternal reports on the Rutter revised preschool scales.

There was a significant correlation between maternal and paternal EPDS scores. Maternal postnatal depression increased (by factors of two or three) the likelihood of high total Rutter scale scores and of high subscale scores for emotion, conduct, and hyperactivity, in the children. There was a smaller increase in prosocial subscale scores. Paternal depression increased (by factors of 1.5–2) total, emotional, conduct, and hyperactivity scores. On controlling for social class, education, and maternal depression, paternal depression was still associated with high total, conduct and hyperactivity, but not emotional, scores. After controlling for paternal depression at 21 months after the birth, there was still a significant association between paternal postnatal depression and high conduct and hyperactivity subscale scores in the children. While maternal postnatal depression was associated with increased Rutter scale scores in both sexes, paternal depression was associated with increased scores only in boys, particularly for conduct problems.

Postnatal depression in fathers seems to have an adverse effect on their sons at age 3½ years, in particular affecting their behaviour.

## ORIGINAL ARTICLE

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

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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.<sup>1–3</sup> Various symptom based diagnostic approaches have been developed, but these were mostly based on clinical experience and lack proper validation.<sup>4</sup>

Hospital based studies have reported widely varying results regarding the utility of a symptom based approach for the diagnosis of childhood pulmonary tuberculosis.<sup>5–7</sup> 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.<sup>8</sup> This community based survey found that these poorly defined symptoms were extremely common, even in children without tuberculosis.<sup>8</sup>

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.<sup>9</sup> 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).<sup>9</sup> In low risk children, progressive disease following primary infection with *Mycobacterium tuberculosis* was rare and was associated with persistent, non-remitting symptoms.<sup>9</sup> In high risk children, progressive disease occurred more frequently, but symptoms were also persistent and non-remitting, and sometimes had a more acute onset.<sup>9</sup> In the vast majority of children (>95%), disease progression occurred within 12 months of primary

infection.<sup>9–10</sup> 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.<sup>8</sup> These communities are similar as regards ethnic and socio-economic parameters,<sup>11</sup> high tuberculosis incidence (>300/100 000 new smear positive cases per year), and relatively low prevalence of HIV infection (<8%).<sup>12</sup>

## 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 amoxicillin), 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.<sup>8</sup> 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.

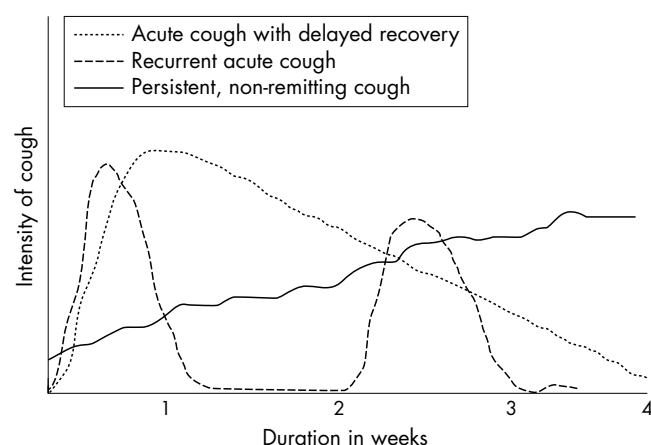


Figure 1 Differentiated cough patterns.

### *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  $\chi^2$  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.

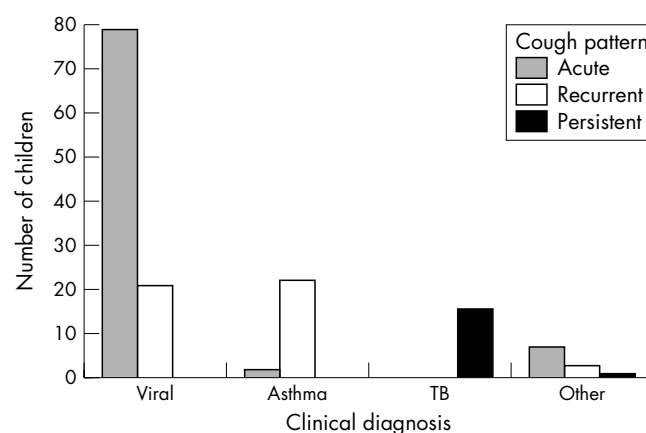
Viral infection was the most common diagnosis in all age groups, particularly in children less than 2 years of age (45/54, 83.3%). The frequency of asthma peaked in the 5–9 year age group (16/38, 42.1%), where it rivalled viral infection as the most common clinical diagnosis. Tuberculosis was diagnosed 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 (%)
<b>Demographics</b>	
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)
<b>Clinical diagnoses</b>	
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
<b>A. Symptoms reported in children without TB compared to children with TB</b>				
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>B. Persistent, non-remitting symptoms reported in children without TB compared to children with TB</b>				
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

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,<sup>9</sup> 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,<sup>13 14</sup> but is controversial, as patients with tuberculosis may show some symptomatic response, and anti-tuberculosis treatment of infectious patients may be delayed.<sup>14–16</sup> 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.

### ACKNOWLEDGEMENTS

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### 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

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**A novel symptom-based approach to diagnose pulmonary tuberculosis  
in children: a prospective, community-based study**

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**Abstract****Background**

The difficulty of diagnosing childhood tuberculosis contributes to the poor treatment access of children with tuberculosis. We determined the value of a novel symptom-based approach to diagnose childhood tuberculosis in a tuberculosis-endemic area.

**Methods**

A prospective, community-based study conducted in Cape Town, South Africa. All children <13 years of age reporting a persistent, non-remitting cough of >2 weeks duration were evaluated for tuberculosis. In addition, comprehensive disease surveillance was done to document the possible disadvantages of this symptom-based diagnostic approach.

**Results**

In total, 1024 children were referred for evaluation. A resolving cough was reported in 596 (58.2%); 428 (41.8%) with persistent, non-remitting symptoms at evaluation, were investigated for tuberculosis. Pulmonary tuberculosis was diagnosed in 197; 96 were categorized as “bacteriologically confirmed TB”, 75 as “radiologically certain TB”, and 26 as “probable TB”. Combining a persistent non-remitting cough of >2 weeks duration, documented failure to thrive, and fatigue, provided reasonable diagnostic performance (sensitivity 62.6%, specificity 89.8%, PPV 83.6%) in HIV-uninfected children, but performed poorly in HIV-infected children (sensitivity 56.2%, specificity 61.8%, PPV 61.9%). In the HIV-uninfected group, the diagnostic performance was better in children  $\geq 3$  years (sensitivity 82.3%, specificity 90.2%, PPV 82.3%) than in children <3 years (sensitivity 51.8%, specificity 92.5%, PPV 90.1%).

**Discussion**

Although its performance varied within relevant risk groups, this novel symptom-based approach would have enabled accurate diagnosis of pulmonary tuberculosis in the majority of children. It offers the exciting prospect of improving antituberculosis treatment access for children in tuberculosis-endemic areas with limited resources.

## Background

Tuberculosis control programs in endemic areas place an almost exclusive emphasis on adults with sputum smear-positive disease, as they are the most infectious and therefore mainly responsible for transmission, which maintains the epidemic. However, children contribute a significant proportion of the global tuberculosis caseload<sup>1,2</sup> and experience considerable tuberculosis-related morbidity and mortality.<sup>3</sup> Despite this huge disease burden, few children have access to antituberculosis treatment; particularly in endemic areas with limited resources.<sup>4</sup> The difficulty of diagnosing childhood tuberculosis is considered one of the major obstacles to the provision of antituberculosis treatment to children in these areas.<sup>5,6</sup>

The diagnosis of tuberculosis in children is complicated by the lack of a practical gold standard test. Bacteriologic confirmation, the gold standard test used in adults is not considered feasible in children, as bacteriologic specimens are difficult to collect and the reported bacteriologic yield is low.<sup>5,6</sup> Sputum smears, often the only test available in resource limited settings is positive in less than 10-15% of children diagnosed with tuberculosis; while confirmation by culture is achieved in only 30-40%.<sup>4,7</sup> In the absence of a gold standard test, the diagnosis of childhood tuberculosis in non-endemic areas is usually based on; 1) exposure to an adult index case, 2) a positive tuberculin skin test (TST), and 3) the presence of suggestive signs on the chest radiograph. This triad provides a fairly accurate diagnosis in non-endemic areas, but it has reduced value in endemic areas where exposure to *Mycobacterium tuberculosis* and/or a positive TST are both common occurrences. Consequently, the diagnosis of childhood tuberculosis in endemic areas rests predominantly on the subjective interpretation of the chest radiograph,<sup>8,9</sup> which has well known limitations.<sup>10</sup> In addition, chest radiography is rarely available in areas with limited resources.

Various clinical diagnostic approaches that incorporate symptoms suggestive of tuberculosis have been developed, but a review of these approaches emphasized the lack standard symptom definitions and inadequate validation.<sup>11</sup> Descriptive hospital-based studies report widely variable results regarding the potential value of symptoms to diagnose tuberculosis in children,<sup>12,13</sup> but the selection bias inherent to hospital-based

studies complicates interpretation and prevents extrapolation of these results to the community level. A recent community-based survey reported that poorly defined symptoms traditionally associated with tuberculosis, such as a cough of >3 weeks duration, occurred frequently in a random selection of healthy children, demonstrating the limited diagnostic value of poorly defined symptoms.<sup>14</sup> In general there is a sense of scepticism towards the potential value of symptom-based approaches to diagnose childhood tuberculosis with accuracy, and bacteriologic confirmation is considered the only way to establish a definitive diagnosis.

However, a critical review of the natural history of childhood tuberculosis confirmed the potential diagnostic value of symptom-based approaches, but it also emphasized the importance of appropriate risk stratification.<sup>15</sup> In low-risk children (immune competent and  $\geq 3$  years), progression to disease after primary infection with *M. tuberculosis* was rare and disease was associated with persistent, non-remitting symptoms, which provided a window of opportunity for symptom-based diagnosis.<sup>15</sup> In high-risk children (<2-3 years and/or immune compromised), progression to disease after primary *M. tuberculosis* infection occurred more frequently and was associated with more acute symptom onset,<sup>15</sup> reducing the opportunity and safety of establishing a symptom-based diagnosis.

In a limited prospective study, the use of well-defined symptoms that incorporate the symptom characteristics identified from the natural history of disease (persistent, non-remitting symptoms of recent onset) provided excellent diagnostic value.<sup>16</sup> The diagnostic value of these well-defined symptoms required further validation in a prospective community-based study. Community-based recruitment is necessary to limit selection bias, while comprehensive disease surveillance is essential to document the potential disadvantages of such a novel symptom-based diagnostic approach. The current study aimed to determine the potential value, within relevant risk groups, of using well-defined symptoms to diagnose pulmonary tuberculosis in children from a highly endemic area.

## **Methods**

### ***Study setting***

A prospective, community-based study was conducted from February 2003 through January 2005 in Cape Town, Western Cape Province, South Africa. The incidence of all tuberculosis in Cape Town was 678/100 000,<sup>17</sup> and the prevalence of human immunodeficiency virus (HIV) infection amongst women attending public antenatal clinics in the Western Cape Province was 13.1% [95% confidence interval (CI) 8.5–17.7%],<sup>18</sup> in 2003.

Five primary health care clinics, which utilize the same referral hospital (Tygerberg Children's Hospital) were selected. These clinics serve impoverished urban communities, providing both primary health care services and supervised antituberculosis treatment. The study population rarely access private medical services, and children diagnosed with tuberculosis are routinely referred to the primary health care clinic for antituberculosis treatment. Paediatric services are accessible to children <13 years of age.

### ***Study population***

Study entry criteria were defined as all children <13 years who reported a persistent, non-remitting cough of >2 weeks duration, without response to a course of oral antibiotics. The paediatric nurses within the selected clinics were trained regarding the study entry criteria and requested to refer all eligible children to the investigator. The investigator visited each clinic twice weekly to evaluate the children that were referred. The following measures were put in place to ensure that all children who met the entry criteria were evaluated by the investigator; 1) prominent notices in all the clinics, 2) clinic nurses received weekly feed-back and motivation from the investigator, 2) a study nurse was employed to screen all children admitted to the local referral hospital (Tygerberg Children's Hospital), as some children may have been sent to hospital without referral to the investigator. These hospitalised children were referred to the investigator by the study nurse and evaluated in the same fashion as those referred by the clinic nurses.

***Data collection***

A screening questionnaire that documented the presence and uninterrupted duration of symptoms was completed in all children. Children who were referred, but whose symptoms resolved or showed marked improvement before evaluation by the investigator, were not investigated for tuberculosis. However, they completed a screening questionnaire and were followed until symptom resolution. Children were only discharged after documented symptom resolution, and they were instructed to return at any time if symptoms recurred. Referral was not restricted to a single episode and children were evaluated in a similar fashion in the event of a second referral.

***Initial assessment and management***

All children with persistent, non-remitting symptoms were investigated for tuberculosis. Investigation included; completion of a comprehensive questionnaire, weight measurement and assessment of the Road-to-Health growth chart for poor weight gain during the preceding 3 months, performance of a TST and chest radiograph (CXR), and the attempted collection of at least one gastric aspirate and/or sputum specimen. HIV testing was offered together with standard pre- and post-test counseling.

Children diagnosed with tuberculosis were started on antituberculosis therapy. Children <2 years of age with known exposure or a positive TST, without active tuberculosis, received isoniazid preventative chemotherapy. All other children were treated according to the most likely alternative diagnosis and reviewed after 2-4 weeks. If symptoms persisted beyond an additional 4 weeks; full assessment, including TST (if previously negative), CXR and mycobacterial cultures, were repeated. At this time every effort was made to establish a final diagnosis, and antituberculosis treatment was initiated in all children in whom an alternative diagnosis could not be established. The duration of uninterrupted symptoms, until spontaneous symptom resolution or the onset of antituberculosis chemotherapy, was recorded. Children who received antituberculosis treatment were reviewed after 3 months to document response to therapy.

***Comprehensive disease surveillance***

All children who received antituberculosis treatment during the period of study enrollment, and for an additional period of 3 months after enrollment was stopped, were documented and reviewed by the investigator. The same two independent experts used in the study assessed all chest radiographs. Disease surveillance provided a comprehensive overview of all children affected by tuberculosis, irrespective of study inclusion, which allowed us to assess the possible disadvantages of applying this symptom-based diagnostic approach.

***Tuberculin skin test (TST)***

A tuberculin skin test, using intradermal 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 transverse diameter of induration was measured in millimeter after 48-72 hours. A positive TST was regarded as a measurement of  $\geq 10$ mm in HIV-uninfected children, and  $\geq 5$ mm in HIV-infected children.

***Chest radiograph (CXR)***

Standard antero-posterior (AP) and lateral views were done and read by two independent experts, blinded to all clinical information and to each other's interpretation. Findings were documented on a standard report form and categorized as "certain TB", "uncertain TB" or "certain not TB". Disease manifestations were classified according to a recently proposed radiologic classification of intra-thoracic tuberculosis.<sup>19</sup>

***HIV testing***

A rapid test was used to screen for HIV infection (Determine Rapid HIV test, Abbott). All children with a positive rapid test result were referred to the HIV family clinic at Tygerberg Children's Hospital for confirmatory tests (PCR in children <18 months and ELISA in older children) and clinical management.



***Specimen collection and mycobacterial culture***

We attempted to collect at least one culture specimen from each child, but multiple specimens were collected from children sent to the referral hospital. Samples were inoculated into liquid medium using either BACTEC or MGIT systems (Becton Dickinson, Sparks, MD, USA). Positive cultures were confirmed to be *M. tuberculosis* by routine polymerase chain reaction (PCR) speciation.<sup>20</sup>

***Definitions***

Children were categorized as; “bacteriologically confirmed TB”, “radiologically certain TB”, “probable TB”, or “not TB”. “Bacteriologically confirmed TB” was defined as the presence of acid-fast bacilli on sputum microscopy and/or *M. tuberculosis* cultured from a respiratory specimen or gastric aspirate. “Radiologically certain TB” was defined as agreement between both independent experts that the chest radiograph indicated “certain TB”; in the absence of bacteriologic confirmation. “Probable TB” was defined as the presence of suggestive radiologic signs and good clinical response to antituberculosis treatment; in the absence of bacteriologic confirmation and radiologic certainty. Good clinical response was defined as complete symptom resolution and weight gain of at least 10% of bodyweight at diagnosis, within 3 months of starting antituberculosis treatment. “Not TB” was defined as spontaneous symptom resolution or no response to antituberculosis therapy; in the absence of bacteriologic confirmation or radiologic signs suggestive of tuberculosis.

Pulmonary tuberculosis was defined as a symptomatic child with; 1) “bacteriologically confirmed TB” or 2) “radiologically confirmed TB”, or 3) “probable TB” (as defined), excluding isolated pleural effusion.

***Ethics***

Parents gave written informed consent for study participation and gave separate written consent for HIV testing after pre-test counselling. Ethics approval was obtained from the Institutional Review Board of Stellenbosch University, the City of Cape Town Health Department and from local community health advisory boards.

**Statistical analysis**

Data was dually entered into an Access relational database and validated. Descriptive analyses were done using SPSS (version 13, SSPS Inc., Chicago, IL). The sensitivity, specificity and positive predictive value (PPV) of individual variables were calculated.

Multivariate tree regression analysis was used to identify the individual variables that statistically contributed most diagnostic value. For analysis purposes, two high-risk groups were identified; 1) HIV-uninfected children <3 years of age and 2) HIV-infected children irrespective of age. HIV-uninfected children  $\geq 3$  years were regarded as low-risk. The sensitivity, specificity and PPV were calculated for each of these relevant risk groups, when cumulatively combining the 3 variables that statistically contributed the most diagnostic value on multivariate tree regression analysis. Results were reflected on a ROC-type curve, with sensitivity on the y-axis and 1-specificity on the x-axis.

**Results**

In total, 1024 children were referred with a cough of >2 weeks duration. In 596 (58.2%) children the cough resolved or showed marked improvement before evaluation by the investigator; 428 (41.8%) children were enrolled with a persistent, non-remitting cough at evaluation, of whom 197 were diagnosed with pulmonary tuberculosis. (Figure 1)

Of those diagnosed with pulmonary tuberculosis, 96 were categorized as “bacteriologically confirmed TB”, 75 as “radiologically certain TB”, and 26 as “probable TB”. There were no significant differences in age, sex or HIV-status between children with “bacteriologically confirmed TB” and those with “radiologically certain TB”, or “probable TB”. Alternative clinical diagnoses established in the 11 children, not treated for tuberculosis, in whom a non-remitting cough persisted beyond 4 weeks of follow-up were; known asthmatic with viral infection (1), bronchiolitis with cigarette smoke exposure (2), ex-premature baby with broncho-pulmonary dysplasia and bronchiectasis (1), cystic fibrosis (1), lymphocytic interstitial pneumonia (LIP)

with bronchiectasis (2), atypical pneumonia (2), and initial viral infection with secondary bacterial infection (2).

Table 1 reflects the demographics and clinical characteristics of all children referred for study participation. Demographic variables (gender and age group) were comparable between the hospital and clinic recruited cohorts. The only significant difference was the proportion of HIV-infected children; 19/87 (21.8%) in hospital, and 8/934 (0.9%) in the clinic (OR 21.1, 95% CI 8.5- 54.0). None of the other variables showed significant differences based on hospital or clinic recruitment.

Table 2 indicates the value of individual variables to diagnose pulmonary tuberculosis at presentation. A cough of >2 weeks duration was not included, as this was the entry criterion used. The diagnostic value of a positive TST differed significantly between relevant risk groups. The diagnostic value of a positive TST in HIV-uninfected children with pulmonary tuberculosis, comparing children <3 years to those  $\geq 3$  years, demonstrated similar sensitivity (81/93, 87.1% vs 75/86, 87.2%), but the specificity of a positive TST result was significantly better in children <3 years [44/67, 65.7% vs 65/135, 48.1%; odds ratio (OR) 2.1, 95% CI 1.1- 3.9]. Comparing the diagnostic value of a positive TST in HIV-uninfected and HIV-infected children demonstrated that the sensitivity of the TST was significantly better in HIV-uninfected children (156/179, 87.2% vs 3/17, 17.6%; OR 31.6, 95% CI 7.6-151.5). In HIV-infected children, a history of household contact with an adult tuberculosis index case seemed more sensitive (9/17, 52.9%) than a positive TST (3/17, 17.6%), but this did not reach statistical significance (OR 5.2, 95% CI 0.89-34.7). There were no significant differences between the symptoms recorded in children with "bacteriologically confirmed TB" versus those with "radiologically certain TB" or "probable TB".

Table 3 reflects data from the comprehensive disease surveillance, which included all 425 children treated for tuberculosis during the study period, irrespective of study inclusion. Of the 214 children diagnosed with pulmonary tuberculosis (as defined), 197 (92.1%) met the study entry criteria. Of the 17 children who did not meet the study entry criteria; 5/17 (29.4%)

had hilar adenopathy, all 5 were actively traced household contacts of an adult index case, 3 were completely asymptomatic and 2 reported a cough of <2 weeks duration; 3/17 (17.6%) had parenchymal consolidation and/or airway compression, all reported a cough of <2 weeks duration, 1 was HIV- infected, 2 were HIV-uninfected and <3 years of age; 9/17 (53.0%) had disseminated (miliary) disease, 3 reported a cough of <2 weeks duration and 6 reported no cough at all, 2 were HIV-infected, 6 were HIV-uninfected <3 years and 1 was HIV-uninfected  $\geq 3$  years of age.

None of the children with an uncertain diagnosis at the initial assessment progressed to severe disease such as disseminated (miliary) disease, tuberculous meningitis (TBM) or cavitation, during the period of observation. Fourteen children were referred twice, of whom 2 were diagnosed with pulmonary tuberculosis during the second episode. None of the children discharged without a tuberculosis diagnosis, were subsequently treated for tuberculosis during the period of surveillance, apart from the two who were referred a second time. One 3-month-old HIV-uninfected child presented with acute symptom onset and died in hospital from disseminated (miliary) disease.

Figure 2 illustrates the improved specificity achieved (moving closer to 0 on the x-axis), and the sensitivity sacrificed (moving away from 1 on the y-axis), by cumulatively combining the 3 variables that statistically contributed the most diagnostic value on multi-variate tree regression analysis. It reflects the symptoms documented at initial presentation in all HIV-uninfected children and in the 2 most relevant sub-groups; children <3 years and those  $\geq 3$  years of age. The sensitivity used as departure point (in the top right hand corner) considered all children diagnosed with pulmonary tuberculosis (as defined), as identified by the comprehensive disease survey.

Combining the 3 variables; 1) persistent, non-remitting cough of >2 weeks, which was the entry criterion, 2) documented failure to thrive during the preceding 3 months, and 3) fatigue, provided reasonable diagnostic performance in the HIV-uninfected group as a whole (sensitivity 62.6%, specificity 89.8%, PPV 83.6%), but it performed exceptionally well in the

sub-group  $\geq 3$  years (sensitivity 82.3%, specificity 90.2%, PPV 82.3%). In children  $< 3$  years, the use of a positive TST as the third cumulative variable provided better diagnostic accuracy (sensitivity 67.3%, specificity 93.8%, PPV 93.2%), than fatigue (sensitivity 51.8%, specificity 92.5%, PPV 90.1%). This was not the case in HIV-uninfected children  $\geq 3$  years where the use of a positive TST as the third cumulative variable, instead of fatigue, made little difference (sensitivity 69.6%, specificity 91.1%, PPV 81.8% with fatigue vs sensitivity 81.3%, specificity 90.2, PPV 82.3% with TST).

Figure 3 illustrates the diagnostic value of clinical follow-up, and the improved specificity achieved when using the presence of a persistent, non-remitting cough as an additional diagnostic criterion in HIV-uninfected children. Children diagnosed with tuberculosis during the initial assessment received antituberculosis treatment; for this analysis we accepted that their cough would have persisted in the absence of treatment, which explains why the sensitivity remained fixed during this analysis. In HIV-uninfected children  $\geq 3$  years, a non-remitting cough that persisted  $> 2$  weeks after initial evaluation, improved the specificity to 91.2% (sensitivity 98.9%, PPV 85.1%). In those  $< 3$  years, the specificity improved to 82.6% (sensitivity 92.2%, PPV 88.6%) after 2 weeks of follow-up, with further improvement 98.6% (sensitivity 92.2%, PPV 88.6%) if a non-remitting cough persisted  $> 4$  weeks of follow-up.

Figure 4 illustrates the sensitivity and specificity obtained in HIV-infected children, by cumulatively combining the same variables used in HIV-uninfected children; 1) persistent non-remitting cough of  $> 2$  weeks, 2) documented failure to thrive and 3) fatigue. The diagnostic performance was poor (sensitivity 56.2%, specificity 61.8%, PPV 61.9%), and the use of a persistent, non-remitting cough at follow-up provided little improvement in specificity; after 2 weeks, (sensitivity 56.2%, specificity 67.8%, PPV 65.9%), after 4 weeks (sensitivity 56.2%, specificity 75%, PPV 77.2%).

## Discussion

In this study, a simple symptom-based approach diagnosed childhood pulmonary tuberculosis with a high degree of accuracy, particularly in HIV-uninfected children  $\geq 3$  years. It is often

assumed that these children, who are at lowest risk to progress to disease following primary infection, contribute little to the tuberculosis disease burden. This is not true, as nearly 50% of pulmonary tuberculosis cases in this study were  $\geq 3$  years, which probably reflects the fact that the vast majority of children, even in highly endemic areas, become infected with *M.tuberculosis* after 2 years of age.

The observation that the diagnostic value of this symptom-based approach differed between relevant risk groups illustrates the importance of risk stratification. The concept of risk stratification is not novel; it provides the motivation behind current World Health Organization (WHO) guidelines to screen all children  $< 5$  years in household contact with an adult index case,<sup>21</sup> but it has not been widely incorporated into clinical diagnostic approaches. Exposure to, or primary infection with *M.tuberculosis* poses a high risk to very young and/or HIV-infected children, as demonstrated by the fact that 11/12 (91.7%) children with parenchymal consolidation and/or airway compression and/or disseminated (miliary) disease, who did not meet the entry criteria, were either  $< 3$  years or HIV-infected. An age of  $< 3$  years was used to define high-risk children, as the natural history of disease demonstrated a substantial risk of progression to disease within 12 months, following primary *M.tuberculosis* during the first 2 years of life.<sup>15,22</sup> Particular emphasis should be placed on the provision of preventive chemotherapy following exposure and/or documented infection in these high-risk children.

The combined presence of 3 well-defined symptoms; 1) a persistent, non-remitting cough of  $> 2$  weeks duration, 2) documented failure to thrive during the preceding 3 months, and 3) fatigue, provided good diagnostic accuracy in HIV-uninfected children  $\geq 3$  years. However, the sensitivity of 81.0% implies that nearly 20% of pulmonary tuberculosis cases would have been missed at presentation. The study demonstrates that clinical follow-up is a valuable diagnostic tool that may be used to identify those children missed at presentation, as symptom resolution occurred within 2 weeks of follow-up in  $> 90\%$  of HIV-uninfected children  $\geq 3$  years without tuberculosis. It has to be stated that the excellent diagnostic accuracy achieved in this highly endemic setting, using a combination of symptoms at presentation



and/or follow-up, may be much reduced in non-endemic areas where the pre-test probability of tuberculosis is lower.

The same symptom-based diagnostic approach performed less well in HIV-uninfected children <3 years. In this age group, fatigue added less diagnostic value, as it was difficult for parents/legal guardians to comment on its presence. However, the presence of a persistent, non-remitting cough together with documented failure to thrive provided a fairly accurate diagnosis on its own (sensitivity 68.3%, specificity 80.1%, PPV 82.1%). This illustrates the importance of regular weight monitoring, at least during the first 2-3 years of life. In our experience, documenting the response to simple measures such as food and/or iron supplementation and/or deworming, may improve the diagnostic value of weight monitoring considerably, as the majority of children referred with isolated weight loss responded well to one of these interventions. In contrast to the situation in older HIV-uninfected children, the use of a positive TST as the third cumulative variable, instead of fatigue, provided improved specificity in children <3 years. This is not unexpected in this highly endemic area, where the majority of older children would have been exposed to tuberculosis and may test TST positive.<sup>23</sup>

As in children  $\geq 3$  years, the use of clinical follow-up as an additional diagnostic tool seemed to offer good diagnostic value, apart from the fact that more children without tuberculosis reported symptom persistence beyond 2 weeks of follow-up. The majority of these children had a clinical diagnosis of viral bronchiolitis with household exposure to cigarette smoke. However, it is important to point out that in children who are at high risk to progress to disease following primary *M.tuberculosis* infection and in whom disease progression may occur rapidly, such as very young and/or HIV-infected children, prolonged follow-up is not advised.

In HIV-infected children, this symptom-based diagnostic approach was limited by poor sensitivity and specificity. Three of 20 (15%) HIV-infected children with pulmonary tuberculosis did not report symptoms of sufficient duration to warrant study inclusion, while 25% reported persistent, non-remitting symptoms even in the absence of tuberculosis. A

positive TST was insensitive, being positive in less than 30% of HIV-infected children diagnosed with pulmonary tuberculosis. The poor sensitivity of the TST in HIV-infected children with tuberculosis is well documented and has been shown to correlate with the degree of immune suppression.<sup>24</sup> Therefore, it is important to consider alternative tests that are more sensitive than TST to confirm infection with *M.tuberculosis* are required. New T-cell based assays, particularly the ELISPOT test, seem to offer improved sensitivity in HIV-infected children with tuberculosis.<sup>25</sup> In addition, it has been reported in HIV-infected adults that the performance of the ELISPOT test seems independent of the degree of immune suppression.<sup>26</sup> In this study, recent household contact with an adult index case seemed to provide more diagnostic value than a positive TST in HIV-infected children, although the sensitivity and specificity remained poor and numbers were small.

Study limitations include the small number of HIV-infected children enrolled, which limits our ability to comment on this particular group. However, we were able to demonstrate that a symptom-based approach, which does not include an accurate measure of *M.tuberculosis* infection, has little diagnostic value in HIV-infected children. On the positive side, the large number of HIV-uninfected children provided an excellent opportunity to describe both the diagnostic performance and potential disadvantages of this novel symptom-based approach in HIV-uninfected children. Despite the high risk of tuberculosis in HIV-infected children, the majority of children with tuberculosis remain HIV-uninfected, even in settings where most adults with tuberculosis are HIV-infected.<sup>3,27</sup> This indicates that a symptom-based diagnostic approach will retain its value in HIV-endemic areas, but it emphasizes the importance of ascertaining a child's HIV-status before symptom-based diagnosis is attempted.

In this study, children were recruited at both primary health care clinics and at the referral hospital. Hospital recruitment may have introduced some selection bias, however, the only significant difference between these two groups was the proportion of HIV-infected children. Pulmonary tuberculosis was diagnosed with different levels of certainty, but the fact that bacteriologic confirmation was achieved in nearly 50% of pulmonary tuberculosis cases, is a major strength of the study. In addition, there were no significant differences between the

symptoms recorded in children with “bacteriologically confirmed TB” versus those with “radiologically certain TB” or “probable TB”.

Isolated pleural effusion was excluded from the case definition as it represents a different pathologic mechanism and has a different prognosis. These children presented with a very typical clinical picture that allowed accurate clinical diagnosis. All 17 children with isolated pleural effusion presented with severe localized unilateral chest pain and intermittent fever. On examination the most distinctive features were an absence of acute illness or respiratory distress and the presence of extensive unilateral dullness on percussion

In conclusion; accurate diagnosis of pulmonary tuberculosis, using a simple symptom-based approach, could be achieved in the majority of HIV-uninfected children in this highly endemic setting. Although it is difficult to generalize these results without confirmation from other highly endemic areas, this novel diagnostic approach offers the exciting prospect of extending antituberculosis treatment to children in resource-limited settings, where current treatment access is poor due to a perceived inability to diagnose children with tuberculosis.

### Acknowledgements

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**Table 1****Demographics and clinical characteristics of all children referred with a cough of >2 weeks duration (n=1024)**

<b>Not investigated for TB Resolving cough at evaluation (n=596)</b>	<b>Number (%)</b>
Age group: <3 years ≥3 years	287 (48.2) 309 (51.8)
Gender: Male Female	297 (49.8) 299 (50.2)
HIV tested PTB	0 0
<b>Investigated for TB Persistent, non-remitting cough at evaluation (n=428)</b>	<b>Number (%)</b>
Age group: <3 years ≥3 years	185 (43.2) 243 (56.8)
Gender: Male Female	225 (52.6) 203 (47.4)
HIV: tested infected	297 (69.4) 37/297 (12.5)
TST: done ≥10mm (HIV-uninfected) ≥5mm (HIV-infected)	421 (98.4) 226/384 (58.8) 6/37 (16.2)
PTB	197 (46.0)
Relevant risk groups	
HIV-infected	17/197 (8.6)
<3 years (HIV-uninfected)	94/197 (47.7)
≥3 years (HIV-uninfected)	86/197 (43.6)

TB – tuberculosis

PTB – pulmonary tuberculosis defined as a symptomatic child with; 1) “bacteriologically confirmed TB” (from a respiratory or gastric aspirate specimen), or 2) “radiologically confirmed TB”, or 3) “probable TB” (as defined), excluding isolated pleural effusion.



**Table 2**

**The value of individual variables, documented at presentation, to diagnose pulmonary tuberculosis in children**

Individual variables at presentation*	Sensitivity	Specificity	PPV
Cough >3weeks	86.8%	61.5%	34.9%
Cough >4weeks	68.0%	89.8%	73.5%
Chest pain	5.6%	98.1%	40.7%
Haemoptysis	3.0%	98.7%	40.0%
Respiratory distress	9.1%	96.2%	37.5%
Fever	41.6%	89.6%	49.1%
Night sweats	47.7%	93.3%	63.5%
<b>Fatigue</b>	<b>81.7%</b>	<b>88.8%</b>	<b>64.7%</b>
Weight loss subjective	67.5	86.3%	54.0%
<b>Weight loss objective</b>	<b>80.0%</b>	<b>75.9%</b>	<b>74.5%</b>
<b>TST positive</b>	<b>79.9%</b>	<b>67.1%</b>	<b>67.9%</b>
Household contact	58.9%	65.5%	59.2%

PPV - positive predictive value

**\*Definition of individual variables**

Cough - persistent, non-remitting cough not responding to a course of oral anti-biotics

Chest pain – chest pain reported by the child

Haemoptysis – blood in the sputum (not haematemesis or a nose bleed)

Respiratory distress – difficult breathing at rest, reported by the parent /caregiver

Fever – fever reported by the parent /caregiver

Night sweats – regular sweating that requires a dry set of nightclothes

Fatigue - a perceived decrease in playfulness/activity since the onset of coughing, reported by the parent/caregiver.

Weight loss subjective - perceived weight loss during the preceding 3 months, reported by the parent/caregiver.

Weight loss objective - clear deviation from a previous growth trajectory and/or documented crossing of centile lines in the preceding 3 months, using accurate weight-for-age centiles,<sup>28</sup> in addition to the Road-to-Health growth chart

TST positive – Tuberculin skin test size  $\geq 10\text{mm}$  (or  $\geq 5\text{mm}$  if HIV-infected)

Household contact – Household exposure to an adult index case in the preceding 12 months

**Table 3**

**Comprehensive surveillance data, including all children treated for tuberculosis during the study period, irrespective of study inclusion**

<b>Treated for tuberculosis</b>	<b>Total Number (%)</b>	<b>PTB diagnosis*</b>	<b>Study inclusion</b>
<b>CXR signs absent</b>			
Exposure/infection	84 (19.8)	0	4 (1.7)
Extra-thoracic TB	45 (10.6)	0	0
<b>CXR signs present</b>			
Uncertain HA	69 (16.2)	3 (1.4)	27 (11.8)
Certain HA	76 (1.2)	76 (35.6)	71 (31.0)
Parenchymal consolidation and/or airway compression	107 (25.2)	107 (50.0)	104 (45.4)
Disseminated (miliary) disease	14 (3.0)	14 (6.5)	5 (2.2)
Adult-type disease	14 (3.3)	14 (6.5)	14 (6.1)
Pleural effusion only (excluded from PTB outcome definition)	17 (4.0)	0	4 (1.8)
<b>Total</b>	<b>425 (100)</b>	<b>214 (100)</b>	<b>229 (100)</b>

CXR – chest radiograph

TB – tuberculosis

CXR signs – signs suggestive of PTB on the chest radiograph

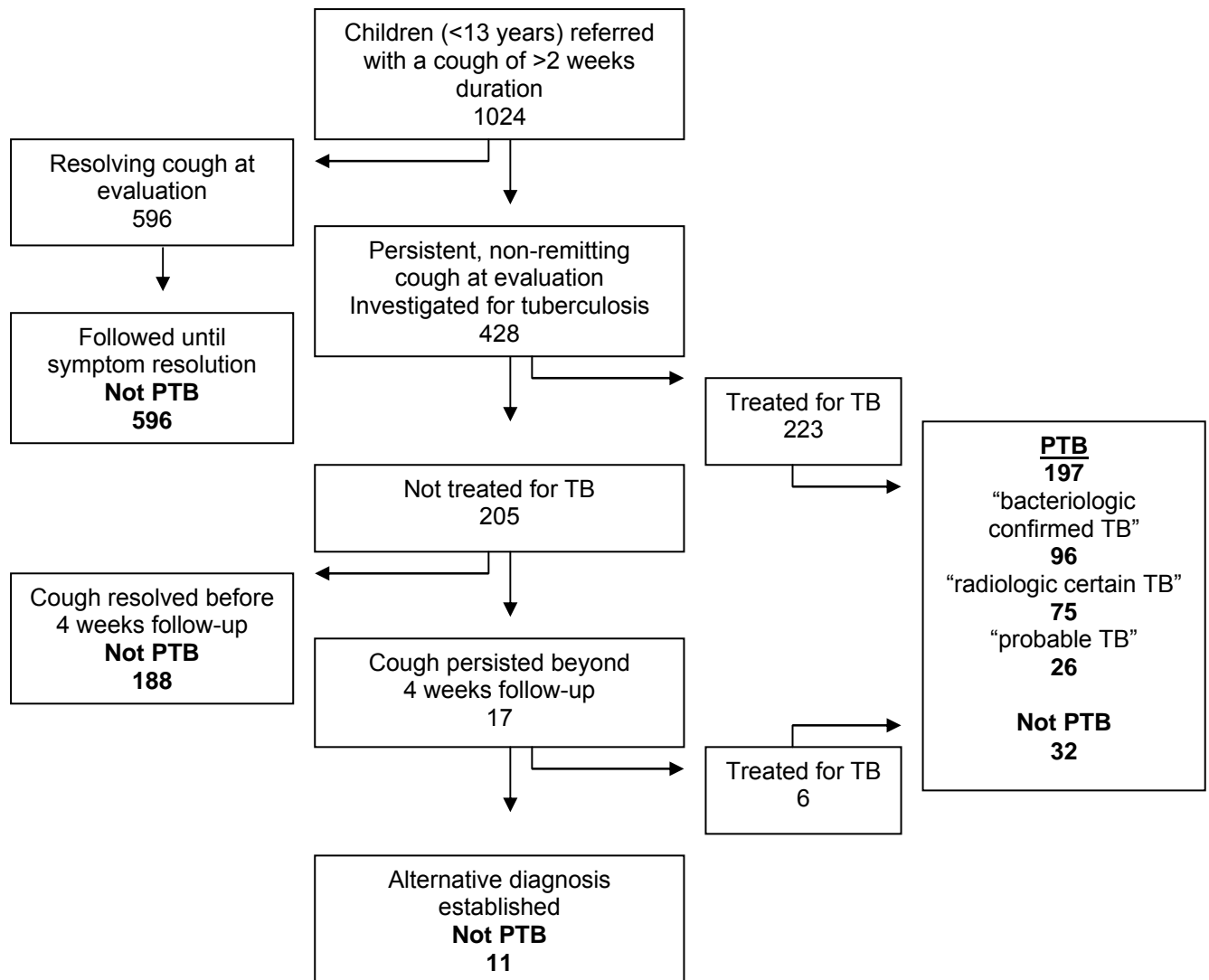
HA – Hilar adenopathy

\*PTB diagnosis – pulmonary tuberculosis defined as a symptomatic child with; 1)

“bacteriologically confirmed TB” (from a respiratory or gastric aspirate specimen), or

2) “radiologically confirmed TB”, or 3) “probable TB” (as defined), excluding isolated pleural effusion.

**Figure 1**  
**Flow diagram of all children evaluated**



TB – tuberculosis

PTB – pulmonary tuberculosis defined as a symptomatic child with; 1) “bacteriologically confirmed TB” (from a respiratory or gastric aspirate specimen), or 2) “radiologically confirmed TB”, or 3) “probable TB” (as defined), excluding isolated pleural effusion.

**Figure 2**

Title: Symptoms documented at presentation in HIV-uninfected children diagnosed with pulmonary tuberculosis

Subscript: This graph illustrates the improved specificity achieved (moving closer to 0 on the x-axis), and the sensitivity sacrificed (moving away from 1 on the y-axis), by cumulatively combining the 3 optimal variables identified by multi-variate tree regression analysis; 1) persistent non-remitting cough of >2 weeks, which was the entry criterion used, 2) documented failure to thrive during the preceding 3 months, and 3) reported fatigue, to diagnose pulmonary tuberculosis in HIV-uninfected children. The denominator used to calculate the sensitivity, included all children with pulmonary tuberculosis identified during comprehensive disease surveillance, irrespective of study inclusion.

**Figure 3**

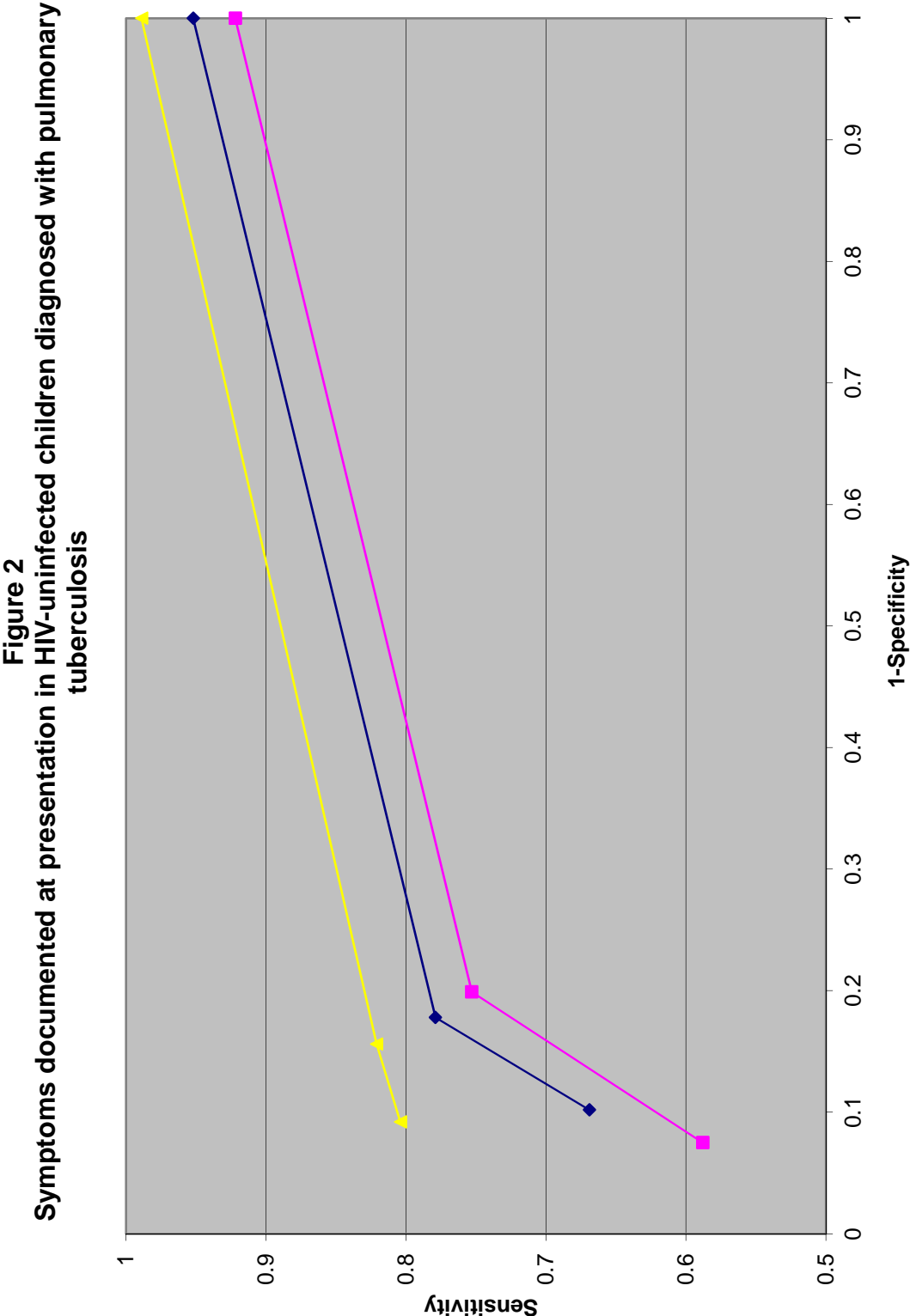
Title: The value of persistent, non-remittent coughing at follow-up to diagnose pulmonary tuberculosis in HIV-uninfected children

Subscript: This graph illustrates the improved specificity achieved (moving closer to 0 on the x-axis), by using the presence of a persistent, non-remitting cough at follow-up as an additional diagnostic criterion, to diagnose pulmonary tuberculosis in HIV-uninfected children. The denominator used to calculate the sensitivity, included all children with pulmonary tuberculosis identified during comprehensive disease surveillance, irrespective of study inclusion. For this analysis we accepted that coughing would have persisted in the absence of treatment in those children who were diagnosed with tuberculosis during the initial assessment, which explains why the sensitivity remained fixed.

**Figure 4**

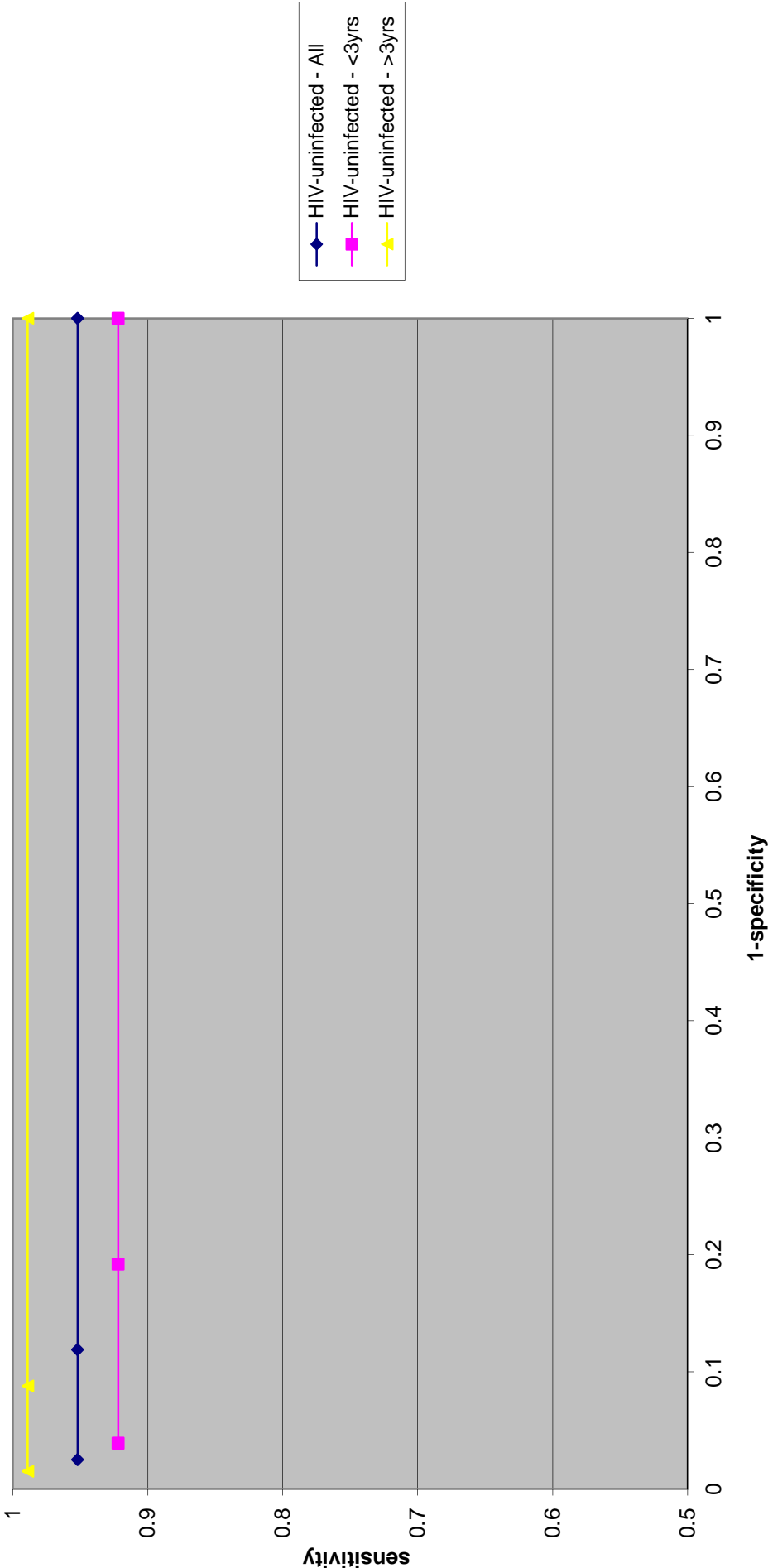
Title: Symptoms documented at presentation in HIV-infected children diagnosed with pulmonary tuberculosis, and the value of persistent, non-remittent coughing at follow-up.

Subscript: This graph illustrates the improved specificity achieved (moving closer to 0 on the x-axis), and the sensitivity sacrificed (moving away from 1 on the y-axis), by cumulatively combining 3 variables; 1) persistent non-remitting cough of >2 weeks, which was the entry criterion used, 2) documented failure to thrive during the preceding 3 months, and 3) reported fatigue, to diagnose pulmonary tuberculosis in HIV-infected children. The denominator used to calculate the sensitivity, included all children with pulmonary tuberculosis identified during comprehensive disease surveillance, irrespective of study inclusion. In addition, it illustrates the improvement in specificity achieved by using the presence of a persistent, non-remitting cough at follow-up, 1) after 2 weeks, and 2) after 4 weeks, as an additional diagnostic criterion.

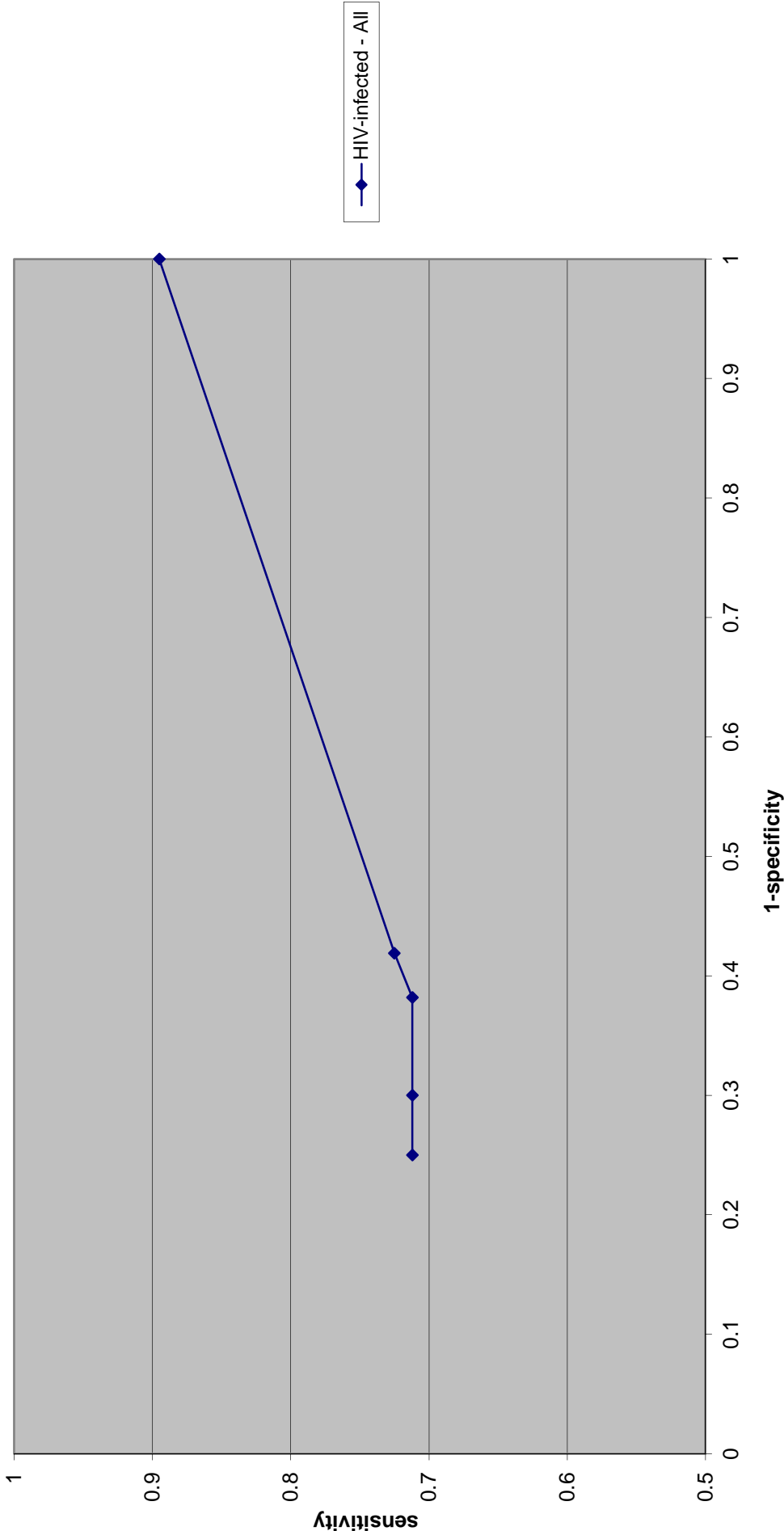




**Figure 3**  
**The value of persistent, non-remittent coughing at follow-up to diagnose pulmonary tuberculosis in HIV-uninfected children**



**Figure 4**  
**Symptoms documented at presentation in HIV-infected children diagnosed with pulmonary tuberculosis, and the value of persistent, non-remittent coughing at follow-up**



## Chapter 6.

### Conclusion

The aim of this dissertation was to address the dilemma of diagnosing childhood intra-thoracic tuberculosis, as the current diagnostic dilemma is one of the main reasons that limit the access of children from endemic areas to anti-tuberculosis treatment.

We first clarified basic disease concepts by critically reviewing the pre-chemotherapy literature that described the natural history of disease. Three central concepts were identified; 1) the need for accurate case definitions, 2) the importance of risk stratification, and 3) the diverse spectrum of disease, which necessitates accurate disease classification.

We then described the current situation regarding childhood tuberculosis in an endemic area. We documented the heavy burden of disease that children carry and the severe tuberculosis-related morbidity that they suffer. We demonstrated that the concepts identified from the pre-chemotherapy literature apply to endemic areas today and documented a similar spectrum of disease. In addition, we demonstrated that bacteriologic confirmation may be achieved in the majority of children with intra-thoracic tuberculosis, in highly endemic areas.

Current screening and diagnostic practices depend almost exclusively on the interpretation of the chest radiograph, but radiography is rarely available in resource-limited settings. We demonstrated that simplified symptom-based screening may be justified to improve access to preventive chemotherapy for children exposed to tuberculosis in resource-limited settings. In addition, we developed a novel symptom-based approach to diagnose pulmonary tuberculosis in children and validated its diagnostic value in a large prospective, community-based study. The use of this simple symptom-based diagnostic approach identified pulmonary tuberculosis with a remarkable degree of accuracy, particularly in HIV-uninfected children  $\geq 3$  years of age. In addition, we demonstrated that isolated pleural effusion, which was excluded from the pulmonary tuberculosis case definition used, had a typical clinical presentation, as

had tuberculous cervical lymphadenitis, which is the most common extra-thoracic manifestation of tuberculosis in children.

Using a symptom-based approach to diagnose tuberculosis in children offers the exciting prospect of extending antituberculosis treatment to children in endemic areas with limited resources, where current treatment access is poor. It is time to introduce a spirit of optimism to the field of childhood tuberculosis. Dedicated efforts are urgently needed to extend both preventive chemotherapy and antituberculosis treatment to children in endemic areas.

The main challenge that remains is the accurate diagnosis of tuberculosis in HIV-infected children. However, as in other high-risk groups, the emphasis in HIV-infected children should be on the provision of preventive chemotherapy. In this regard, the improved sensitivity provided by T-cell based assays to diagnose latent tuberculosis infection may be useful, while it may also provide important supportive evidence to establish a diagnosis of active tuberculosis in HIV-infected children.

## Chapter 7.

### The bigger picture

For the purpose of this dissertation I have restricted my focus to address the dilemma of diagnosing tuberculosis in children. Accurate diagnosis is important as the provision of effective antituberculosis treatment will drastically reduce the severe tuberculosis-related morbidity and mortality suffered by children in endemic areas. However, accurate diagnosis and effective treatment will not achieve a permanent reduction in the burden of childhood tuberculosis, as this is mainly determined by the level of epidemic control achieved within a particular community. We reviewed the main determinants of epidemic control and the burden of childhood tuberculosis. However, our vision should extend beyond the reduction of tuberculosis, to the promotion of child health in the broadest sense of the word. The final two letters reflect my personal view regarding our ultimate ethical obligation.

- 1. Marais BJ, Obihara CC, Wareen RM, Schaaf HS, Gie RP, Donald PR. The burden of childhood tuberculosis – a public health perspective. *Int J Tuberc Lung Dis* 2005; 9: 1305-1313**

This review describes the main determinants of the burden of childhood tuberculosis within a particular community. Basic infectious disease principles identify the community, and not the individual, as the central entity that sustains an epidemic. The prevalence of tuberculosis is determined by both the community's exposure to *M. tuberculosis* and their vulnerability to develop disease following exposure. Current efforts to control the tuberculosis epidemic are mainly directed towards reducing community exposure by treating sputum smear-positive adults, while little emphasis is placed on reducing the vulnerability of the community. Successful control of the tuberculosis epidemic is the most effective way to reduce the burden of childhood tuberculosis. This will require a holistic approach that acknowledges the importance of sustainable poverty alleviation.

**2. Marais BJ. Judged by our legacy. Arch Dis Child 2004; 89: 796**

As paediatricians we need to provide an articulate voice for all the children of our planet. This letter emphasizes the fact that while short-term goals are important, the true challenge facing our generation is to work towards improved health for all children, both for current and future generations.

**3. Marais BJ. Ethics: the third dimension. Arch Dis Child 2004, 89: 1077-1078**

Current ethical debate focuses on the delicate two-dimensional balance that should be maintained between the interests of the individual and that of the community. This letter introduces the novel concept that our ethical responsibility has a neglected third dimension, which we cannot afford to ignore any longer. It is not only the interests of the individual versus that of the community that requires a fair balance, but also the interests of future generations. The third millennium demands a broadened ethical perspective, where established ethical principles are applied within the framework of a global community and a vulnerable planet.



## The burden of childhood tuberculosis: a public health perspective

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### SUMMARY

The burden of childhood tuberculosis (TB) reflects recent transmission within a community and the level of TB control achieved within the adult (maintenance host) population. Children contribute little to the maintenance of the TB epidemic, but they may suffer severe TB-related morbidity and mortality. This review describes the main determinants of the burden of childhood TB within a particular community.

Basic infectious disease principles identify the community, and not the individual, as the central entity that sustains an epidemic. The prevalence of TB is determined by the community's exposure to *Mycobacterium tuberculosis*, and their vulnerability to developing disease following exposure. The main variables that influence both exposure and vulnerability are discussed. Multiple variables are linked to poverty, and it is their

cumulative effect, rather than the exact degree of poverty, that seems most important.

Diligent contact tracing and the use of preventive chemotherapy will reduce the TB-related suffering of children. The burden of childhood TB, however, is a reflection of our ability to control the epidemic; this remains the ultimate challenge. Current efforts to control the TB epidemic aim to reduce transmission by treating sputum smear-positive adults, while very little emphasis is placed on reducing the vulnerability of high-burden communities. Successful control of the epidemic is the most effective way to reduce the burden of childhood TB, but this will require a holistic approach that acknowledges the importance of sustainable poverty alleviation.

**KEY WORDS:** childhood tuberculosis; burden; prevalence; exposure; vulnerability

CHILDHOOD TUBERCULOSIS (TB) is difficult to diagnose accurately, has a low public health priority and its global epidemiology is consequently poorly documented.<sup>1,2</sup> The lack of public health priority results from the fact that the TB epidemic is maintained by adults with cavitating pulmonary disease, while children contribute little to disease transmission. However, cavitating disease becomes a prominent disease manifestation in children aged over 10 years,<sup>3–5</sup> and these children do pose a high transmission risk.<sup>6</sup> From an epidemiological perspective, children aged over 10 may be viewed as part of the adult, maintenance host population.

In essence, young children (<10 years of age) who tend to develop non-cavitating, paucibacillary disease, act as a 'spill-over' host for *Mycobacterium tuberculosis* and are an epidemiological dead-end for the organism.<sup>7</sup> However, children do contribute significantly to the TB caseload (up to 40%) in high-burden settings,<sup>8,9</sup> and may suffer severe morbidity and mortality.<sup>3,10</sup>

One of the most striking and intriguing epidemiological observations is the huge variation observed in the prevalence of TB between different communities.<sup>11</sup> Previous explanations and debate focused on the contribution of genetic vs. socio-economic factors,<sup>12–14</sup> while recent emphasis shifted to the profound influence of human immunodeficiency virus (HIV) infection.<sup>15–17</sup> The difficulty with such a multifactorial problem is that research tends to focus on a single aspect at a time, and while individual research reports contribute valuable knowledge, they may also confuse the priorities for public health intervention. Therefore, it is essential to evaluate the public health relevance of these findings within an objective scientific framework, based on basic infectious disease principles.

The aim of this review is to provide a systematic overview of current knowledge, within an objective scientific framework, trying to explain differences in the prevalence of TB, and by extrapolation, the burden of childhood TB between particular communi-

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ties. An improved understanding of the disease dynamics at the community level may guide future research and public health intervention.

#### Definition of terms

Maintenance host: the population that contributes to disease transmission and maintains the epidemic.

'Spill-over' host: the population that, although they may become ill, rarely contributes to disease transmission.

Community exposure: the combined exposure of all the individuals within a particular community.

Community vulnerability: the combined vulnerability of all the individuals within a particular community to develop disease following *M. tuberculosis* exposure.

### BURDEN OF DISEASE

In the absence of preventive chemotherapy, the burden of childhood TB is an accurate reflection of the level of TB control achieved within a particular community, because TB in children results from recent transmission. This is supported by several observations. The natural history of disease in children indicates that more than 95% of children who develop TB do so within 12 months after infection.<sup>3,18</sup> The incidence of childhood TB rises in tandem with adult incidence when control of the epidemic is lost and the geographical clustering of child and adult TB cases overlap.<sup>19–21</sup> In addition, the patterns of primary resistance to anti-tuberculosis drugs are similar in recently diagnosed adults and children, which indicates that disease in children reflects recent transmission within the community.<sup>22,23</sup> Children will continue to suffer from TB as long as adults do,<sup>7</sup> and the huge burden of childhood TB in developing countries alerts us to the fact that the pandemic remains out of control.

It is possible to considerably reduce the number of diseased children by diligent contact tracing and the use of preventive chemotherapy. The dramatic effect that may be achieved by the use of active case finding and treatment together with prophylaxis and treatment of latent infection was demonstrated in the Inuit populations of Canada and Alaska during the early 1960s.<sup>24</sup> The extreme isolation of these populations enabled this pro-active approach to 'stamp out' active disease and to eliminate all reservoirs of *M. tuberculosis* at the same time. The situation is unfortunately far more dynamic in today's high-burden settings where populations are highly mobile. Taking isoniazid (INH) for 6–9 months eliminates two thirds of the TB risk (with good adherence it may be as high as 90%)<sup>19</sup> in exposed children, while a 3-month course of INH and rifampicin (RMP) has also shown good efficacy.<sup>25</sup> However, poor adherence is a major concern, and it is not unusual for less than one third of participants to complete the full course of unsupervised preventive treatment.<sup>7</sup> Active contact tracing and screening

places an excessive burden on the health care system, and is a luxury that most high-burden countries simply cannot afford. In these settings, it seems appropriate to focus scarce resources only on those children who are at greatest risk of progression to disease following exposure.<sup>7</sup> This risk is highest in very young (<3 years of age) and immune-compromised children.<sup>3</sup> Fifty per cent of infants and 20–30% of 1–2 year olds progress to disease, usually within 12 months after primary infection. It is prudent therefore to give preventive chemotherapy to all infected or recently exposed children under 3 years of age once active disease has been excluded. Immune-compromised children share a similar high risk, irrespective of their age, and the same guideline should apply.<sup>3</sup> Immune-competent children older than 3 years of age are at a relatively low risk (less than 5% progress to disease following primary infection),<sup>3</sup> and their need for preventive chemotherapy may be reassessed, especially in settings where health care services are already overstretched.

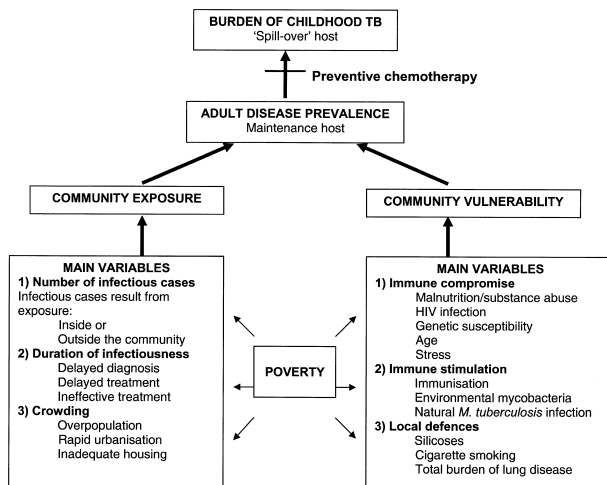
### BASIC PRINCIPLES

Conventional herd dynamics describe three factors that determine the ability of an organism to multiply and spread successfully within a community. These include the intensity of exposure to the organism, the virulence of the organism, and the vulnerability of the community to develop disease that will sustain organism transmission following exposure. In this respect, it is essential to view the community, and not the individual, as the central entity.

Genetic variability provides for continuous adaptation by the pathogen to the challenges posed by its environment. Different strains of *M. tuberculosis* have emerged and differences in virulence between strains are well documented.<sup>26,27</sup> Strain-specific virulence may be an important variable of disease prevalence in a particular community, but geographical isolation has been greatly reduced by the mobility of modern populations. This will encourage the most virulent strains, such as the modern lineage of the Beijing strain, to spread globally over time.<sup>28,29</sup> Because the geographic localisation of virulent strains is transient, differences in organism virulence are unlikely to explain persistent differences in disease prevalence between communities. This places the focus on the two remaining factors, namely community exposure and vulnerability (Figure).

#### Community exposure

Basic infectious disease principles indicate that the combined exposure of the community is determined by the number of individuals exposed and the intensity of their exposure. The intensity of individual exposure depends on the exposure duration and the number of infectious particles in the ambient air.<sup>30</sup> Using public health terminology, this implies that commu-



**Figure** The main variables that contribute to the prevalence of TB in adults and by extrapolation the burden of childhood TB. TB = tuberculosis; HIV = human immunodeficiency virus.

nity exposure is determined by the number of infectious cases, their degree and duration of infectiousness, their mobility within the community and the degree of crowding.

#### *Number of infectious cases*

It is self-evident that the level of disease transmission will depend on the number of infectious source cases that spread the disease within a community. New source cases may arise following exposure inside or outside the community. In most low-burden countries, the epidemic is sustained by the constant introduction of new source cases, following exposure outside the community. The introduction of new infectious cases may also fuel the epidemic in high-burden settings. The theoretical risk posed by those who are exposed outside the community can be illustrated using prisons as an example. The risk posed to the community by individuals who are incarcerated is determined by the intensity of their exposure inside the prison (the main variables of exposure remain constant: the number of infectious cases, their degree and duration of infectiousness, and the levels of crowding within the prison),<sup>31,32</sup> their vulnerability to developing infectious disease and the frequency of their release back into the community. Effective treatment before their release from prison will eliminate the risk they pose, but the concern is that most adult-type disease develops only 1–2 years (up to 5 years) after exposure, and disease may not be present at initial screening.<sup>3,33</sup> Short-term prisoners are most likely to develop disease only after release back into the community, and therefore prisoners who cycle in and out of prisons with a high prevalence of TB pose a considerable risk to the community. These same principles apply to immigrant populations, tourists and migrant workers who may introduce *M. tuberculosis* into their community.<sup>29,34–36</sup>

#### *Degree and duration of infectiousness*

Early diagnosis and treatment interrupt disease progression and drastically reduce organism transmission.<sup>37,38</sup> Early intervention is essential to limit the reproductive rate of the organism.<sup>39</sup> In the absence of early intervention, transmission represents a self-replicating cycle, and the reproductive rate of the organism will escalate according to the favourability of the circumstances.

#### DELAYED DIAGNOSIS

Diagnostic delay increases both the degree and duration of infectiousness. Due to the magnitude of the TB pandemic, current guidelines advocate passive case finding. The success of passive case finding depends on early symptomatic presentation, together with adequate diagnostic vigilance and access to sensitive diagnostic tools at the point of presentation.<sup>40</sup> Diagnostic delay is greatly exacerbated by factors that reduce health awareness and access to health care, such as poverty and discrimination.<sup>41–43</sup> There is also a need for more sensitive diagnostic tools to detect early disease, as sputum smear microscopy only identifies advanced cavitating disease.

Although most transmission in high-burden settings occurs outside the household,<sup>44,45</sup> household exposure to a sputum smear-positive source case represents an opportunity for active intervention.<sup>46–48</sup> Child contacts aged 2–3 years or less and immune-compromised individuals are particularly vulnerable to developing disease,<sup>3,49</sup> and should receive chemoprophylaxis once active TB has been excluded. Those aged over 10 years, with recent primary infection, are also at high risk of developing disease (10–20% progress to adult-type cavitating disease within 2 years after primary infection),<sup>3,46</sup> and it may be important to reconsider the use of preventive chemotherapy in such children.<sup>46,47</sup> The problem is that they are difficult to identify, especially in high-burden settings where many children are already tuberculin skin test (TST) positive by the age of 10 years. A major shortcoming of the TST is its inability to differentiate recent from previous primary infection.

#### DELAYED TREATMENT

Shortening the duration of infectiousness will reduce the exposure of the community and the reproductive rate of the organism. To achieve this requires not only limiting the diagnostic delay, but also ensuring that effective treatment is instituted as quickly as possible following diagnosis. Treatment may be ineffective due to inappropriate drug regimens, poor drug quality, poor adherence or drug resistance, but with proper implementation the current DOTS and DOTS expansion strategies adequately address most of these treatment-related issues.<sup>50</sup>

#### *Crowding*

The degree of crowding and the mobility of source cases within the community influence both the number of individuals exposed and the intensity of their exposure. The transmission of *M. tuberculosis* is strongly

associated with the degree of crowding.<sup>51,52</sup> Crowding is relevant in all congregate settings, including private homes, public transport systems, institutions such as prisons or health care facilities, and places of socialisation. The worst crowding occurs in urban and peri-urban slum areas, due to rapid urbanisation and overpopulation.<sup>53</sup> Paradoxically, crowding may be enhanced within formal housing structures that provide effective protection against the elements, encouraging dense congregation. Transmission is further facilitated by poor ventilation.<sup>54–55</sup> The seasonal variation observed in the frequency of childhood TB cases may illustrate increased transmission during periods of confinement in poorly ventilated, overcrowded conditions, enforced by harsh weather conditions.<sup>56,57</sup>

#### *Community vulnerability*

Herd immunity, the ability of a particular community to resist the spread of an infectious organism, forms a crucial element of infectious disease control and eradication. Although often restricted to acquired immunity within the immunisation context, this concept may be applied to any communicable disease. Community vulnerability is a more inclusive term, which reflects the combined resistance offered by the full spectrum of defence mechanisms that may limit disease spread within a particular community. In the immunisation model, effective disease containment is achieved by creating a high level of herd immunity within a naturally vulnerable population, using immune stimulation (vaccination). However, the level of natural resistance (without immune stimulation from vaccination or natural mycobacterial infection) offered by immune-competent individuals to *M. tuberculosis* is high, and the vast majority (>90%) of persons infected with the bacillus will never develop any clinical illness.<sup>58</sup> This high level of natural resistance against *M. tuberculosis* implies that a high degree of 'natural herd immunity' pre-exists in immune-competent communities. It is therefore reasonable to expect that the level of community vulnerability may be affected as much, or even more, by factors that compromise this high level of natural resistance as by those that aim to enhance it.

#### *Immune compromise*

The analogy of acquired herd immunity illustrates that a relatively small reduction in 'natural herd immunity' may cause a considerable increase in the vulnerability of a particular community to sustain the TB epidemic. On a public health scale, the biggest influence may be exerted by the cumulative effect of minor factors that affect large numbers of people within the community, even though their individual effect is small.

#### **NUTRITION**

Both macro- and micro-nutrient deficiency may reduce cellular immunity and the natural resistance against

TB.<sup>59–62</sup> The effect of malnutrition is best quantified for severe protein-calorie deficiency,<sup>62,63</sup> while evidence for moderate nutrient deficiencies often lacks scientific rigour. However, the large numbers of people who are affected by moderate degrees of malnutrition<sup>64</sup> probably contribute more to the overall vulnerability of a particular community than the few who suffer from severe malnutrition.<sup>62</sup> In this regard, the combined effects of malnutrition and alcohol (or other drug) abuse may be especially relevant in poverty stricken areas where large numbers of people are dually affected. Alcohol abuse does damage the immune system and seems to increase the vulnerability to develop TB,<sup>65</sup> but it is difficult to separate its independent effect due to the multiple comorbidities and increased exposure within the social context. People with drug and/or alcohol problems frequently congregate and their exposure is increased by prolonged diagnostic delay and poor compliance with therapy among their companions.<sup>66</sup>

#### **HIV**

HIV infection has a devastating effect on the immune system,<sup>67</sup> which explains the increased incidence of TB amongst HIV-infected individuals.<sup>15–17</sup> Rapid disease progression in severely immune-compromised individuals may reduce their duration of infectiousness and their contribution to transmission, as suggested by reports that TB incidence rates amongst non-HIV-infected adults remain stable in HIV-affected areas.<sup>68</sup> However, the widespread use of antiretroviral therapy in high-burden settings may increase the number of people in the community who are mildly immune-compromised, thereby increasing transmission and the incidence of TB at the community level.<sup>69</sup> Children from HIV-affected households may be particularly vulnerable, because TB cases tend to cluster within these households, and they may be immune-compromised themselves.

#### **HOST GENETICS**

The influence that infectious diseases exert on population genetics is well documented for many diseases, such as malaria and leprosy.<sup>70,71</sup> However, in TB it remains extremely difficult to differentiate between the impact of genetic and environmental influences. The fact that individual vulnerability is partly influenced by genetic variability is illustrated by adult adoptee studies,<sup>72–74</sup> and by the vulnerability of individuals with mutations or specific polymorphisms of the interferon-gamma (IFN- $\gamma$ ) receptor gene.<sup>75,76</sup> Host genetics certainly play an important role at the individual level, but the majority of genetic influences result from the complex interaction of multiple genes,<sup>72–74</sup> and their effect on vulnerability at the population level remains uncertain. The fact that TB incidence rates have plummeted wherever social upliftment succeeded argues strongly for the overriding influence of



the environment in the nurture vs. nature debate. This is best illustrated in the African-American population, where TB was nearly eliminated within a single generation (same gene pool) after their standard of living improved dramatically.<sup>77</sup> If genetic susceptibility is an important variable at the individual level, it implies that successful treatment will return these susceptible individuals to the community. This is of particular relevance in high-burden settings where the risk of future re-infection is high, and it is demonstrated by the fact that the rate of re-infection TB is higher in successfully treated individuals than the rate of new TB in individuals without previous TB.<sup>78</sup>

#### AGE

Both the innate and acquired immune response show prominent age-related variation. Young children under 2–3 years of age in whom the immune system is still immature are highly susceptible to developing disease following primary *M. tuberculosis* infection.<sup>3</sup> At the other end of the age spectrum, elderly people are often considered at high risk for reactivation disease, because they are over represented among cases in industrialised countries with a historic high prevalence of TB.<sup>79,80</sup> However, it is extremely difficult to demonstrate the contribution of old age, independent from the cohort effect, in such a setting. The ontogeny of the immune response is an important variable, as demonstrated by the fact that adult-type cavitating disease, which is responsible for continued disease transmission within the community, only emerges after 8–10 years of age.

#### STRESS

Stress has deleterious effects on the immune system, but the causal link between stress, immune function and TB requires further clarification.<sup>81</sup> The existence of a psychoneuro-immunological network is well described, and although it is still poorly understood, it represents a possible mechanism for increased community vulnerability.<sup>82</sup> The fact that TB incidence rates increase during times of war may be attributed to a combination of malnutrition, overcrowding, disruption of medical services and increased levels of stress.<sup>83</sup>

Many other factors may cause immune compromise, but these affect few individuals and will not influence the disease prevalence at a population level. These factors, which include rare immunodeficiency syndromes and iatrogenic immune deficiency caused by corticosteroid treatment or cancer chemotherapy, remain very important from an individual perspective.

#### Immune stimulation

Immune stimulation in the form of vaccination has practically eradicated some of the world's most devastating infectious diseases. However, compared to these highly virulent diseases, *M. tuberculosis* is a rather innocuous organism to which the vast majority

of immune-competent people exhibit a high level of natural resistance.

The effect of immune stimulation in the form of bacille Calmette-Guérin (BCG) vaccination has shown variable protection in different settings. This may be due to variations in strain-specific immunogenicity, timing or technique of vaccine administration, genetic factors and the presence or absence of environmental mycobacteria.<sup>84,85</sup> Neonatal BCG vaccination protects mainly against disseminated forms of TB during early childhood and confers no protection against adult-type TB.<sup>84,85</sup> BCG vaccination may offer improved protection against adult-type TB when administered to older children/adolescents who are TST-negative in locations with a low prevalence of environmental mycobacteria.<sup>86–88</sup> In the presence of exposure to environmental mycobacteria, the additional protection provided by BCG is negligible,<sup>89</sup> but without environmental mycobacterial exposure the protection provided by BCG vaccination seems to be of the same order (around 60%) as that afforded by previous natural infection that failed to progress to disease.<sup>90</sup> The possible deleterious effect of repeated exposure and multiple re-infections, as may occur in high-burden settings, requires further elucidation.<sup>91,92</sup> Novel vaccines are currently under development to try and improve the degree of protection provided by immune stimulation.<sup>93</sup> The provision of additional protection would be of particular value in high-burden settings, where exposure is nearly universal.

#### Local defences

Compromised local defences may contribute to the vulnerability of particular communities. Poor organism clearance, decreased mucosal immunity and a favourable micro-environment at the point of organism deposition may increase the risk of pulmonary infection and disease.<sup>94</sup> This is demonstrated by the comorbidity that exists between pulmonary silicosis and TB,<sup>95</sup> and by the increase in *M. tuberculosis* infection, subsequent disease and ultimate death from TB associated with cigarette smoking.<sup>96–98</sup> Passive smoking is also associated with a greatly increased risk (odds ratio 5.29, 95% confidence interval [CI] 2.33–12.82) in children to develop TB following recent infection.<sup>99</sup> The cumulative effect of smoking, environmental airborne pollutants, recurrent chest infections and previous TB all contribute to the total burden of lung disease within a community, which may be an important variable that contributes to the vulnerability of a particular community.

#### CONCLUSION

Although children rarely contribute to the maintenance of the TB epidemic, they do suffer severe morbidity and mortality. Their suffering can be greatly reduced by diligent contact tracing and pre-

ventive chemotherapy. In resource-limited settings, it may be necessary to target high-risk groups (children <3 years of age and immune-compromised individuals exposed to a sputum smear-positive household source case) for preventive chemotherapy. The accurate diagnosis of TB in children remains a major obstacle, and the development of new diagnostic tools is anxiously awaited. However, the burden of childhood TB results from recent transmission, and in the absence of preventive chemotherapy it represents a barometer of TB control within a particular community.

Basic infectious disease principles identify the exposure and the vulnerability of the community as the main determinants of TB prevalence. Multiple factors affecting both community exposure and vulnerability are linked to poverty, which explains why, on a global scale, TB reflects the plight of poverty stricken populations. It is the cumulative effect of these factors, rather than the exact degree of poverty, that seems most important. Exposure is increased by the large number of infectious cases and their prolonged duration of infectiousness due to poor health education, inaccessible health care, co-morbidity and the all-absorbing daily struggle for survival. Exposure is further enhanced within overcrowded, poorly ventilated living conditions that children share with adults. Poverty also increases the vulnerability of a community, due to the cumulative effect of factors such as malnutrition, substance abuse, stress and the total burden of lung disease, while the triangular shape of the population pyramid reflects the large number of very young and vulnerable children. Like TB, poverty represents a self-replicating cycle that requires active intervention. As stated by J Kevany, 'the world's biggest killer and the greatest cause of ill health and suffering across the globe is listed almost at the end of the International Classification of Diseases. It is given the code Z59.5—Extreme poverty.'<sup>100</sup>

The current DOTS and DOTS expansion programmes are aimed at reducing community exposure to *M. tuberculosis*, but it seems as important to reduce the vulnerability of communities if we aim to control the TB pandemic. Basic infectious disease principles emphasise the need to break the cycle of poverty in high-burden settings and to achieve sustainable social upliftment. The fight against TB serves as a prime example of the interdependence of the millennium development goals and the need for global political commitment to achieve these goals.

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## R É S U M É

Le fardeau de la tuberculose (TB) infantile est le reflet d'une transmission récente au sein d'une collectivité et du niveau de contrôle de la TB obtenu au sein de la population adulte (hôtes de persistance). Les enfants contribuent peu à la persistance de l'épidémie de TB mais peuvent souffrir d'une morbidité et d'une mortalité sévères liées à la TB. Cette revue générale décrit les déterminants principaux du fardeau de la TB infantile au sein d'une collectivité particulière.

Les principes de base en matière de maladies infectieuses identifient la collectivité et non l'individu comme étant l'entité centrale de persistance d'une épidémie. La prévalence de la TB est déterminée par l'exposition à *Mycobacterium tuberculosis* dans la collectivité et par la sensibilité de cette dernière au développement d'une maladie à la suite de cette exposition. Les variables principales influençant à la fois l'exposition et la vulnérabi-

lité ont été discutées. De multiples variables sont liées à la pauvreté, et c'est leur effet cumulatif plutôt que le degré exact de pauvreté qui semble le plus important.

Un dépistage attentif des contacts et l'utilisation de la chimiothérapie préventive permettront de réduire les atteintes d'enfants liées à la TB. Le fardeau de la TB infantile est toutefois un reflet de notre capacité de contrôler l'épidémie ; celle-ci reste le défi final. Les efforts actuels pour lutter contre l'épidémie de TB visent à réduire la transmission en traitant les adultes à bacilloscopie positive alors que l'on attribue peu d'importance à la diminution de la vulnérabilité des collectivités à haute prévalence. Un contrôle couronné de succès de l'épidémie est la manière la plus efficace de réduire le fardeau de la TB infantile, mais ceci exigera une approche holistique prenant en compte l'importance d'une réduction persistante de la pauvreté.

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RESUMEN

La carga de morbilidad por tuberculosis (TB) infantil refleja la transmisión reciente dentro de una comunidad y también el grado de control de la TB alcanzado dentro de la población adulta (huéspedes de mantenimiento de la epidemia). Los niños contribuyen en poca medida al mantenimiento de la epidemia de TB, pero pueden padecer en forma considerable la mortalidad y morbilidad causadas por la TB. En el presente análisis se describen los principales determinantes de la carga de morbilidad por TB infantil dentro de una comunidad particular.

Los principios fundamentales de las enfermedades infecciosas designan la comunidad, y no el individuo, como la entidad central que sostiene la epidemia. La prevalencia de TB está determinada por la exposición de la comunidad a *Mycobacterium tuberculosis* y la vulnerabilidad de la misma a la aparición de enfermedad tras la exposición. Se analizan aquí los principales factores que influyen en la exposición y la vulnerabilidad. Entre ellos,

los factores relacionados con la pobreza son múltiples y parecen más importantes sus efectos acumulados que el grado exacto de la pobreza.

El seguimiento cuidadoso de los contactos y el uso de la quimioprofilaxis reducirá el padecimiento de los niños por causa de la TB. Sin embargo, la carga de morbilidad por TB infantil refleja la capacidad del sistema para luchar contra la epidemia de TB, y esta sigue siendo la esencia del desafío. Las iniciativas actuales para controlar la TB tienen como objetivo reducir la transmisión mediante el tratamiento de los adultos con baciloscopia positiva, y hacen poco hincapié en la reducción de la vulnerabilidad de las comunidades con alta carga de morbilidad. El control exitoso de la epidemia constituye el medio más eficaz para reducir la carga de morbilidad por TB infantil, pero exigirá un enfoque integral que reconozca la importancia de un alivio sostenible de la pobreza.

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## **Judged by our legacy**

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Current global health strategies focus on important issues in child health, such as the eradication of polio by 2005 and the drastic reduction of child mortality by the year 2010. These short-term goals are essential to provide the necessary political focus and public health impetus. However, the ultimate success of our current health initiatives will be measured by its ability to provide sustained health to present and future generations.

At the beginning of the third millennium we celebrated the tremendous strides that health care has taken in the past century, while rightfully reflecting on current global inequities in access to health care. Reflection also emphasizes the unequaled human impact exerted on our planet in the 20<sup>th</sup> century and the environmental responsibility that faces health care providers in the 21<sup>st</sup> century.

As paediatricians we need to provide an articulate voice for all the children of our planet, both for current and future generations. Current initiatives stir more emotion and elicit more political commitment, but protecting the health of future generations is as much our ethical responsibility, as the reduction of present mortality. Short-term goals are important, but we have to redefine what is meant by the attainment of child health for all, within the framework of sustainability. The real challenge facing our generation is to improve child health for all, now and in the future.

## **Ethics – the third dimension**

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In essence, ethics provide the guidelines for civilized human interaction. It is an evolving concept, but through the ages some accepted ethical principles crystallized. The first crude definition focused on the individual's responsibility towards his community, prioritizing the interests of the community. However, the events preceding the French revolution and the brutality of the two world wars emphasized the need to protect individuals and minority groups against abuses of power. The ethical focus shifted from individual responsibility towards the protection of individual human rights. With the swing of the pendulum, individual rights were often protected to the detriment of the larger community.

In medicine the same shift in emphasis forced the current ethical debate on the delicate balance between the interests of the individual and that of the community, especially in resource limited settings. The reality of the third millennium is that all the world's inhabitants are essentially part of the same global community. The two-dimensional balance between the individual and the community need to reflect this global ethical responsibility.

The third millennium also confronts us with the neglected third dimension of our ethical responsibility. It is not only the interests of the individual versus that of the community that require a fair balance, but also the interests of future generations. No previous generation has been confronted with the importance of this third ethical dimension, as we have. Although current decisions may impact dramatically on the health of future generations, this has not entered into popular medical conscience or current ethical debate. As medical doctors the health of future generations is as much our ethical responsibility as the health of our individual patients or our immediate community.

Environmental issues are rarely viewed as medically relevant, but can the medical profession accept this status quo, when the health of future generations is at stake? The third millennium demands a broadened ethical perspective, where established ethical principles are applied, but within the setting of a global community and a vulnerable planet.

## Other tuberculosis-related manuscripts completed during the study period

1. Hesselning AC, Marais BJ, Gie RP, Schaaf HS, Fine PEM, Godfrey-Faussett P, Beyers N. Risk of disseminated Bacille Calmette-Guerin (BCG) disease in HIV-infected children. AIDS. Submitted January 2006.
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### List of abbreviations

ARI	annual risk of infection
BCG	bacillus Calmette-Guerin
CDC	Centres for Disease Control and Prevention
CI	confidence interval
CNS	central nervous system
CXR	chest radiograph
DOTS	directly observed therapy, short course
ELISA	Enzyme-linked immunosorbent assay
HAART	highly active anti-retroviral therapy
HIV	Human Immunodeficiency virus
INH	Isoniazid
IUATLD	International Union Against Tuberculosis and Lung Disease
MRC	Medical Research Council of South Africa
<i>M. tuberculosis</i>	<i>Mycobacterium tuberculosis</i> (organism causing TB)
NCHS	National Center for Health Statistics
NTM	non-tuberculous mycobacteria
NTP	National Tuberculosis Programme
NTCP	National Tuberculosis Control Programme
OR	odds ratio
PCR	polymerase chain reaction
TB	tuberculosis (diseased state caused by <i>M. tuberculosis</i> )
PTB	pulmonary tuberculosis
PZA	pyrazinamide
SA	South Africa
TBM	tuberculous meningitis
TST	tuberculin skin test
USA	United States of America
USAID	The United States Agency for Aid and International Development
WHO	World Health Organization