EVALUATION OF THE UTILITY OF SPECIFIC CXR FEATURES FOR DIAGNOSIS OF PULMONARY TUBERCULOSIS IN YOUNG CHILDREN USING MULTIPLE READERS

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Declaration

I, Ruschka Ho-yee, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of Cape Town, Cape Town. It has not been submitted before for any degree or examination at this or any other University.

DR RUSCHKA HO-YEE

On this 13th day of August 2015

I would like to dedicate this work to Professor Savvas Andronikou, Professor Beningfield and my family for all their help, support, understanding, encouragement and patience.

Thank you.

Publications and Presentations

This work has never been published.

It has never been presented at a congress.

Abstract

INTRODUCTION:

The diagnosis of childhood pulmonary tuberculosis (TB) can be notoriously difficult. The chest X-ray (CXR) is a significant diagnostic resource in the detection of PTB in children. However, non-specific radiological features combined with variable inter-observer assessments contribute to diagnostic uncertainty. The CXR would be of most value when used specifically to evaluate those features of childhood TB that it shows best and where expert observers agree, namely those signs indicating lymphadenopathy.

AIM:

To identify simple and reliable CXR features of primary TB in children by determining signs and anatomical sites of best observer agreement.

METHOD:

This is a retrospective descriptive study within a clinical trial performed by the South African TB Vaccine Initiative (SATVI). Healthy BCG-vaccinated newborn infants in a high TB prevalence rural area in Worcester, near Cape Town, South Africa, were followed for a minimum of two years for possible incidental pulmonary TB. Three independent, blinded, expert paediatric radiologists reported the resultant CXR images using a standardised data collection tick sheet, on which the specific anatomical sites and signs of pathology consistent with pulmonary TB were recorded. The first 200 original data collection tick sheets were sampled and recorded in a pre-compiled data spreadsheet for our study. The sampled data were then analysed using kappa statistics.

RESULTS:

The overall combined agreement for airway compression (by presumed lymphadenopathy) was 0.5%. Five % of the CXR's had soft tissue densities reflecting lymphadenopathy on the frontal view and 5% on the lateral view. The most common site reflecting lymphadenopathy through airway narrowing or displacement was the left main bronchus. The hilar region (kappa 0.27) on the frontal CXR and behind bronchus intermedius (kappa 0.18) on the lateral were the most common sites of soft tissue densities reflecting lymphadenopathy. There were no positive findings for cavitation or pleural effusion. The overall decisions reflecting PTB (lymphadenopathy or miliary) by each individual reader were 27.6% by Reader 1, 8.5% by Reader 2 and 24.6% by Reader 3. Abnormal findings not specific for PTB were found in 3.5% by Reader 1, 10.5% by Reader 2 and 3.5% by Reader 3. 68.3% of the radiographs were reported as normal by Reader 1, 81.9% by Reader 2 and 66.8% by Reader 3. Only 5% of the radiographs were found to be unreadable by one reader.

The overall agreement of all three readers on PTB was 14.6% and for normal CXR 49.2%.

CONCLUSIONS:

The fair degree of agreement amongst expert readers suggests that the CXR alone is not a reliable tool for detecting pulmonary TB and should be utilised in conjunction with the clinical features and/or skin tests and blood results. Soft tissue masses rather than airway compression are a more reliable sign for lymphadenopathy, with the most agreed upon sites on the frontal projection for soft tissue mass detection being the right hilar region, followed by the left hilum.

Unfortunately this study could not confirm the usefulness of the CXR in subcategorising PTB into severe and non-severe groups due to the absence of any positive features for severe PTB in the selected sample. The use of prescribed tick-sheets with specified features for detecting lymphadenopathy did not have the expected impact of promoting interobserver consensus of CXR findings in children in terms of detection of TB. The absence of a credible reference standard for lymphadenopathy remains a significant limitation.

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1. Introduction

1.1. Introduction

Diagnosing childhood pulmonary tuberculosis (PTB) is known to be an incredibly difficult task. The chest X-ray (CXR) remains a significant diagnostic tool in the process of identifying PTB in the paediatric population although atypical radiological features combined with inconstant inter-observer assessment of CXR's contribute towards the diagnostic dilemma. The CXR would be of most value if used specifically for the features of childhood TB that it shows best and where expert observers agree best, namely features of the presence of lymphadenopathy.

1.2. Background

Tuberculosis remains a considerable health issue in South Africa (SA) and worldwide [1], with rates in SA over twice those of other developing countries, and nearly 60 times more than the rate observed in the USA or Western Europe. TB is one of the most frequent notifiable communicable diseases in South Africa, according to the MRC National Tuberculosis Center. [1]. In 2011 the World Health Organisation (WHO) figures concluded that worldwide there were an estimated 8.8 million new cases of tuberculosis, of which approximately 13% were observed in human immunodeficiency virus (HIV) patients. [1, 2] Global TB data from the WHO includes only age subsets with positive TB smears, and therefore reflects a small portion (8%) of the actual disease burden faced. An estimated figure of 884,019 cases (11% of the total) within the under 15-year age group represented the global

age-specific burden of TB in 2000. [2] Between 15 and 20% of all sub-Saharan Africa TB cases are children. [3]

Undiagnosed and untreated TB leads to dire consequences in the paediatric population. This is further compounded by progression to disseminated TB. [4] Tuberculosis remains one of the most significant lethal infectious diseases. [2, 5] WHO statistics estimated 1.1 million HIV-negative deaths from tuberculosis, plus 350,000 HIV-linked tuberculosis deaths in 2010. [2] High morbidity and mortality resulting from extra-pulmonary dissemination and severe TB are common findings in those under 3 years. [6]

Note is also made of an added 3.2 million women with tuberculosis, and 320 000 female fatalities in 2010. [1] In 2009, parental deaths due to TB resulted in approximately 10 million orphaned children. [1] The global increase of multi drug-resistance in tuberculosis, leading on to extensively and totally drug-resistant forms pose additional daunting challenges in the management of tuberculosis, particularly in sub–Saharan Africa, Asia and Eastern Europe. [1, 7] The WHO Tuberculosis Program projects 3.5 million new cases and a minimum of 90,000 deaths over ten years if TB is uncontrolled. [2]

Reinforcing the confirmation of tuberculosis relies on improved tests [8, 9, 10], ideally applied in poorer communities without access to other means of diagnosis. [10] Cheaper, more accessible and accurate tests will aid tuberculosis control provided that there is political support for effective national tuberculosis programs. [10] In the interim, better use of currently available diagnostic tests such as CXR's can raise detection rates and reduce tuberculosis transmission. [1]

1.3. Clinical Diagnosis

1.3.1. Classical Diagnosis - Clinical Symptoms Approach

A structured clinical approach making use of clearly defined symptoms contributes towards diagnostic accuracy of TB [11] and allows for patients to be categorised into suspected or probable TB. [12] The suspicion of paediatric PTB is raised when there is a history of chronic debility with coughing or pyrexia, weight loss or failing to thrive, poor or no recovery following measles or whooping cough, tiredness, wheezing [12], malnutrition, lymphadenopathy, clinical chest findings, large liver or spleen, meningeal signs or ascites. [12]

Additionally, a positive Tuberculin Skin Test (TST), a suspicious CXR, caseation, poor response to a fortnight of antibiotics or a favourable reaction to anti-TB therapy with improved weight and clearance of signs is considered most compatible with probable TB. [13, 14]

Paediatric TB usually presents with pulmonary parenchymal disease plus intrathoracic nodes in 60–80%.[12] Extra-pulmonary TB includes lymphadenopathy (67%), central nervous system (CNS) manifestations (13%), pleural disease (6%), disseminated or miliary TB (5%), and bone disease (4%). [12] Miliary TB and TB meningitis are more often seen in under 3 year-olds or HIV patients [15], accounting for the detection of up to half of cases of paediatric TB. [16]

Paediatric tuberculosis may be detected by using symptoms in suitable risk categories, as shown in 2006 by Marais et al. in symptomatic HIV-negative children, especially in the low-risk group. [17] Houwert et al. in 1998 found the

WHO criteria able to strongly predict TB using the triad of persistent cough for over 2 weeks; measurable weight loss (failing to thrive) over 3 months; and fatigue. [18] Marais et al. showed that well-defined symptoms measured by using a standard symptom-based questionnaire held diagnostic value in paediatric TB. [19] Sequential diagnostic algorithms can limit diagnostic uncertainty and help health care workers find children requiring TB treatment. [12] Non-standardised clinical scoring systems lack clinical validation. [20, 21] Despite their simple utility, these algorithms are not often used in countries with limited technology. [3] Several attempts to refine symptom definitions have fared poorly in groups at greatest hazard for severe disease, with resultant unsatisfactory outcomes. These include sub 3 year-old children, those with HIV and malnourishment. [3]

1.3.2. Diagnosis of pulmonary TB

The need for greater diagnostic certainty in the diagnosis of paediatric TB is well recognised [10], especially pulmonary TB as the most frequent and most confounding diagnosis. [10] Culture facilities are often inadequate or inaccessible in tuberculosis-endemic regions and therefore the diagnosis of TB is generally seldom microbiologically confirmed. [10] Further complicating the situation is the difficulty in acquisition of sputum via expectoration in younger children, as well as the lower diagnostic yield. Even combining smears and cultures has a less than 50% yield, due to the scanty bacilli. [10] Despite newer methods, diagnostic accuracy of childhood TB remains difficult [22] and ideally needs accurate, quick point-of-care (POC) diagnostic tests. [1]

The finding of PTB in small children thus currently relies on a mix of epidemiology, clinical presentation and CXR features. [10] The CXR continues to be valuable in

high-burden areas. [23] The diagnosis of pulmonary TB in children also remains an arduous and confounding process due to the difficulties in acquisition of expectorated sputum and unusual radiological features. [24]

1.3.3. Mycobacterial Detection and Isolation

Owing to difficulties in sputum collection in young children and poor smear microscopy results, microbiological proof of TB is seldom attempted, even in populations at risk. [24] Children with PTB do not generally expectorate at will due to their inability to produce sputum and the distress involved with the process. [12] Gastric aspirates are used as an alternative for identification and M. tuberculosis culture without sputum samples. [25] Three sequential early morning gastric lavages or gastric aspirates are the usual means of obtaining mycobacteria, but the technique is bedeviled by low yield, the need for infrastructure and the fact that the low gastric pH can kill tuberculous bacilli. [26] Considering the above, it is clear why under 20% of paediatric TB cases have positive sputum smears or gastric aspirates. [12] Recent less invasive options include induction of sputum by sequential inhaled bronchodilator, nebulised hypertonic saline (3–5%) and then either suction in the nasopharynx or coughing up of lower respiratory tract mucus. [24] Zar et al. compared salbutamol-induced sputum induction with gastric lavage in HIV positive and negative infants and young children. They found that sputum induction was more effective at producing M. tuberculosis, and better tolerated and of lower risk (including in infants). [25] The intent of these other means of sampling is ultimately to improve yield, as a positive culture is deemed the benchmark to confirm TB in a symptomatic child. [13]

A negative culture or yields of less than 50% of M.tuberculosis often leads to a diagnosis based on a reactive tuberculin skin test (TST), supportive clinical presentation, CXR features or adult TB contact. [12]

1.3.4. Smear Microscopy

Developments in smear microscopy include centrifugation to concentrate specimens, the modified carbol fuchsin staining (for Kinyoun or Ziehl-Neelsen stains) with fluorescent auramine-rhodamine dye to improve accuracy and speed up the process. [27] However, even allowing for all these changes, the global sensitivity of smear microscopy is still below 15%, with the exception of older children presenting with more adult-like TB. [24]

1.3.5. Tuberculin Skin Test (TST)

The tuberculin skin test (TST), or Mantoux TST, relies on identification of a delayed cutaneous hypersensitivity reaction to injected protein derivative, which is an imprecise purified antigen mix derived from M. tuberculosis, M. bovis Bacille Calmette-Guerin (BCG) and other non-tuberculous mycobacteria. [28] The response in millimeters of induration is measured after 48 to 72 hours. [16] The value of the TST merely indicates an infection with a mycobacterium, without the ability to either affirm or discount the presence of TB. A TST is positive in a non-BCG-vaccinated young child when skin induration is exceeds 10 mm in diameter, and over 15mm in a BCG-vaccinated child. A negative TST does not however eliminate TB as a cause. [16] Any induration (5–14mm) could also be deemed compatible with the disease if coupled with suspicious clinical findings and contact

history. [29] Procedural, administrative and interpretation errors in distinguishing genuine TB from the results of past BCG-inoculation and other non-TB mycobacteria can arise. [16, 28, 30, 31, 32]. The response is variable and unknown in children with incapacitating or immune compromising diseases, malnutrition and some viral (such as HIV) and bacterial infections. [16, 28]

1.3.6. Polymerase Chain Reaction (PCR)

PCR used for diagnostic testing amplifies in-vitro DNA by utilising particular DNA oligonucleotide sequences as 'fishhooks' for microorganism DNA/cDNA. PCR is assumed to have the ability to identify a single organism in a variety of fluids, including from the stomach, airways, pleura, cerebrospinal space, plasma and urine. Several PCR assays exceed 90% sensitivity and specificity for identifying pulmonary TB in adults. [16] This method of disease detection is also affordable and quick [33]. PCR is particularly useful in the following circumstances: (1) confirmation of the diagnosis in samples with negative microscopy and culture, or for scant samples; (2) differentiation between M. tuberculosis and atypical mycobacteria; (3) detection of possible genetic variants or mutations related to anti-mycobacterial drug resistance. [34]

PCR boasts superior sensitivity compared with culture in younger children, as shown in many studies. In 2001, Gomez-Pastrana et al. showed a higher sensitivity for PCR versus culture. [35] In a group of children with highly probable tuberculosis, Montenegro et al. utilised a hemi nested PCR assay and reported a specificity of 67%, this being considerably better than Lowenstein-Jensen culture (54%) or staining for acid–fast bacilli (42%) [33]. 100% of smear-positive samples

were PCR positive, while 76.7% of negative smears were PCR positive. In comparison with culture, PCR sensitivity was 90.4% with a positive predictive value 89%. The specificity and negative predictive values were 94% and 95% respectively. [33] Other studies have revealed sensitivities between 4 to 80% and 80 to 100% specificity. [34] Gomez-Pastrana et al. found 56.8% sensitivity for PCR of gastric or bronchoalveolar lavage in active disease and felt that nested PCR was both fast and sensitive for the prompt detection of paediatric TB. [35] Supplementary distinctive sequences of M. tuberculosis that are nonexistent in, M. microti, M. bovis, M. africanum and M. bovis BCG have been recommended as diagnostic examinations for TB. [36]

PCR is exceptionally beneficial in detection of paediatric TB as sputum smears are frequently inadequate. [16] Difficulties related to the utilisation of PCR however prevail in developing countries. These include incorrect procedure in certain laboratories, financial constraints, the high-level equipment required, limited specificity, numerous samples required to optimise yield and sample cross-contamination. [3]

1.3.7. In-House Nucleic Acid Amplification (NAA) Assays

NAA assays depend on the operator, the target sequence selection and the process of DNA removal. Analysis of paediatric results in clinically suspected TB is hampered by the absence of a standard reference. NAA sensitivity versus culture is 40–83% but it may be positive despite negative culture [24]

1.3.8. Adenosine Deaminase (ADA)

Adenosine deaminase (ADA) can be elevated in pleural TB and TB meningitis in adults. As both these type of TB are thought to have sparse bacillary loads, ADA testing is useful. A 63-study meta-analysis using ADA for diagnosing tuberculous pleuritis showed a 0.92 sensitivity (95% CI 0.90–0.93) with 0.90 specificity (95% CI 0.89–0.91). [37]. Although some serum ADA testing for paediatric pulmonary TB has revealed good results, it varies widely and is felt to be inferior to PCR.

1.3.9. Serology and Antigen Detection

Antigen identification of mycobacterial elements has largely been assessed in adults, with little evaluation in children [16]. Despite its speed and the fact that the sample need not be acquired from the site of infection, serology is not favoured in routine paediatric TB diagnosis. Various factors could influence the results and contribute to low sensitivity. These include age, other mycobacterial exposure and BCG vaccination. The sensitivity and specificity are antigen dependent, as well as hinging on the criteria used and the nature of the tuberculous infection. [34]

Some of these serological tests focus on the composition of the antigen (e.g. Ag 60, 38 kDa, and lipoarabinomannan / LAM), whether of recombinant or native origin and their chemistry (whether lipid or protein), as well as how much antigen purification has been undertaken and the type of immunoglobulin. Most are enzyme-linked immunosorbent assays (ELISA).

Hussey et al. in 1991 [38], sought serum antibodies to autoclaved M. tuberculosis suspension from 132 paediatric PTB cases. The test boasted a 62% sensitivity and specificity of 98%. Imaz et al. in 2001 [39] used recombinant 16-kDa M. tuberculosis antigen (re- Ag16) for the serological identification of TB in children, This they did by assessing IgA, IgG and IgM values, revealing enhanced antibody reAg16 reaction in exposed cases versus those with non-mycobacterial disease, with 95% specificity. Grouping of IgG and IgA assay results showed 43% positivity in actively infected children. [39]

1.3.10. In Vitro Interferon-γ (IFN-γ) Release Assays (IGRA's)

Immune-based assays using blood specimen analysis independent of sputum has been the focus of new developments [40]. IGRA's have been established as a more specific substitute for the tuberculin skin test in identification of latent TB [13, 30, 40]. These assays quantify interferon-gamma (IFN-γ) liberated by sensitised lymphocytes after contact with unique M. tuberculosis antigens. For example, the early secreted antigen target 6 (ESTAT-6), tb7.7 and culture filtrate protein-10 [13, 41] located on M. tuberculosis are not present on most non-TB mycobacteria including BCG. [41] Unfortunately latent and active disease cannot be separated [41]. The most up-to-date types of IFN-γ assays make use of highly specific M. tuberculosis antigens not found on BCG or other mycobacteria including M. avium. [40, 42] Tests such as enzyme-linked immunospot assay (ELISPOT) and Quantiferon TB-gold (QFT-G) have been used. [30] QFT-G and TST showed similar outcomes in a study done by Dogra et al. in 2007. [30] Lymphocytes releasing IFN-γ were seen in two-thirds of suspected paediatric TB cases in a study done by Nicol et al. in 2005. Positive findings were more commonly found

with culture-proven tuberculosis. [42] ELISPOT is thus a favorable instrument for diagnosing tuberculosis in children. [42] Detjen et al. also highlighted IGRA's ability to differentiate tuberculous and non-tuberculous mycobacterial disease. [31]

1.3.11. GeneXpert MTB/RIF System

GeneXpert is a simplified means of integrated DNA extraction and amplification, needing less sample handling and operator training. Real-time PCR (rt-PCR) also permits TB detection and identification of resistance to Rifampicin. The technique multiplies part of the M. tuberculosis rpoB gene. Mutations here lead to Rifampicin resistance in 95% of cases. The rpoB core region is adjacent to TB-specific DNA sequences, allowing concurrent assessment of both TB presence and insensitivity to rifampicin. [43] The ease, speed and accuracy of the Xpert system is very advantageous when compared with culture. [11]

Nicol et al. found that two Xpert tests doubled case-detection rates when judged alongside smear microscopy, leading to suggestions that this test may replace smear microscopy. [8]

1.3.12. Gas Sensor Array Electronic Nose (Electronic Nose)

An array of 14 sensors "smell" by using electrical changes induced by specific odours. The E-Nose identified 89% of patients with positive cultures with 91% specificity. [11] The usefulness of the method in diagnosing paediatric TB in the future requires continued evaluation. [11]

1.3.13. Other Developments in Progress

Distinct Lama glama antibodies to the 16kDa Heat Shock Protein of M. tuberculosis could serve as a rapid method of identifying active PTB infection by infrared spectroscopy of blood serum. This test has not yet been clinically used. [12]

The use of alternating magnetic field frequencies to accelerate culture growth up to seven-times has been developed by Noreiko et al. [12]

Gas sensor technology has also been used to measure exhaled unstable organic composites in the patient's breath to detect cancer, asthma, and TB. [12]

1.4. Imaging Diagnosis

1.4.1. Chest X-Ray (CXR)

The CXR remains a valuable diagnostic tool in the clinical evaluation of paediatric intrathoracic TB. [10] The prognostic values of the criteria for diagnosing TB are influenced by various factors. These include the clinical and CXR differences between adult and paediatric TB and the influence of high prevalence environments. [10]

A commonly used criterion for detecting pulmonary TB in the paediatric population is the manifestation of lymphadenopathy on CXR [44], especially when pulmonary TB is already clinically suspected. [44]

One radiological classification of TB uses the following CXR features:

- Lymph node TB
- Air-space parenchymal TB (consolidation)

- Tuberculoma
- Miliary TB
- Cavities
- Pleural TB
- Fibrosis and destruction [45]

A disadvantage of the CXR is the radiation dose to the patient, especially if repeated. Children are more vulnerable to radiation from medical investigations because of the immature developing organs, the closer proximity of sensitive areas (due to shorter bodies), and the longer life ahead in which to develop malignancies. [45] The lateral CXR is not only an additional view but imparts approximately twice the radiation dose of the AP CXR. [45]

High cost and limited accessibility also restrict the use of imaging in certain areas. In addition, the differences in imaging technique can affect accuracy of interpretation. [45]

Furthermore, interpretation is made more difficult by the mediastinal variation on CXR in those under 5 years. The prominent thymus in this age group can be as wide as the thoracic cavity, obscuring visualisation of areas normally assessed for lymphadenopathy. [45] The cardiac silhouette also occupies a larger proportion of the chest in a child than in an adult, often masking the hila and making it almost impossible to evaluate the hilar points for lymphadenopathy. [45]

Other issues confounding the imaging diagnosis of TB include the variable pattern of disease, the effects of co-morbid infections such as human immunodeficiency

virus (HIV) and AIDS, the inability to identify drug resistance, nonspecific radiographic signs, subjective interpretation with inter- and intra-observer variability of readers, the possibility of a normal radiograph despite having PTB, and the difficulty in distinguishing active from inactive disease. [45]

Moyo and colleagues classified the patients in their study as ‘definite’, ‘probable’, ‘possible’ or ‘not TB’ based on history, examination and results of investigations including CXR’s. [46] CXR’s were reviewed independently by a panel of three paediatric radiologists blinded to the clinical information, who then categorised findings as ‘TB present’ (CXR findings consistent with TB), and ‘TB not present’ (no CXR findings consistent with TB), ‘TB equivocal' (CXR findings possibly associated with TB but also associated with other disease) or 'CXR not readable'. [46] The specific signs indicating TB were noted as a compressed or displaced airway, soft-tissue opacities in the hilar, paratracheal and paracardiac areas, or miliary nodules. [46] Those diagnosed with active TB disease were started on curative anti-tuberculosis treatment, while those felt to have latent TB were started on preventive anti-tuberculosis treatment. [46] The authors suggested that case definitions of TB in young children should include history, clinical and radiological features, as there are likely to be few bacteriologically confirmed cases. [46]

In children – In a study of inter-reader variability for CXR interpretation of TB in children by Swingler and colleagues, only ‘‘fair agreement “between individuals was shown. The agreement was found to be even less for the lateral projection. [44] In addition to these findings, they also reported that the overall diagnostic accuracy of expert paediatricians compared with primary level practitioners varied considerably and was much lower in the latter group, particularly when identifying

lymphadenopathy on CXR (compared with the gold standard of CT). The supplementary lateral radiograph did not substantially improve diagnostic accuracy. [44] The low level of accurate detection of lymphadenopathy even among expert observers implicated inadequacies related to chest radiography. [44] They subsequently supported tentative use of radiographic lymphadenopathy to diagnose tuberculosis, particularly where the other findings were ambiguous. [44] They also concluded that improving radiological criteria for lymphadenopathy on chest radiographs might enhance diagnostic accuracy. [44] Their study evaluated patients with suspected TB according to the WHO criteria, without setting CXR reading parameters in advance. They felt that a population group likely to have confirmed TB and readers using pre-defined criteria might have yielded a different result.

In a study by Swaminathan and colleagues, children from 6 to 12 years who had clinical features supportive of tuberculosis were examined further. [23] They found that in confirmed tuberculosis (using positive gastric aspirate cultures), a noteworthy proportion of patients had normal CXR's. [23]

A study done in 2005 by Theart, Marais and Gie aimed to record the criteria used to diagnose childhood TB at primary health facilities in high-risk communities [47] They demonstrated that despite good agreement with current clinical guidelines, the diagnostic criteria were massively dependent on accurate interpretation of the CXR. [47] Difficult interpretation of CXR's and their limited availability in most high-burden settings contributed to making this scenario problematic. [47] The study however maintained the CXR as a cornerstone investigation to diagnose paediatric pulmonary TB. [47]

The 2002 study by Du Toit, Swingler and Iloni measured variations within and between observers in detecting large nodes on CXR in high-risk scenarios. They found the inter-observer agreement among paediatric pulmonologists was “fair”, while intra-observer agreement was “moderate”. [48]

An older study presented in 1966 by Weber, Bird and Janower focused on the CXR features of childhood pulmonary TB, with particular emphasis on the effects on the tracheobronchial tree due to lymphadenopathy, as well as additional pulmonary opacities. [49]

In adults – In a study performed on adults older than 15 years, Den Boon and colleagues in testing a Chest Radiograph Reading and Recording System (CRRS) found good inter-reader agreement and excellent intra-reader agreement for TB-related abnormalities. [50] They concluded that the CRRS may be of value in the setting of large-scale TB-prevalence reviews and projects involving community respiratory disease. [50] They also proposed that although chest radiography could be considered better as a TB screening instrument, further evaluation regarding the process of evaluation and interpretation was required. [50]

Van Cleeff and colleagues demonstrated a low specificity of the CXR for the diagnosis of TB. [51] They advocated that the use of a precise rating system, clinical consensus and radiographic quality control could enhance the quality of diagnostic interpretation. [51]

Zellweger and colleagues concluded that CXR screening for TB based on a simplified code of interpretation is reliable and reproducible, particularly if the

readers are experienced. [52] In their findings, there was high agreement between and within readers compared with other previous studies. They maintained that the large intra- and inter observer disagreements in previous studies were partially associated with lack of experience. [52]

Dawson and colleagues, using CXR, demonstrated that independent readers were able to document with a substantial level of agreement, the presence of pulmonary radiological abnormalities consistent with TB. [53] They concluded that this was further validation of the CXR as a reliable tool for recording pulmonary radiographic abnormalities in its primary intended role as a screening tool in radiographic surveys. [53]

However the studies above reflect imaging findings of TB in adults and cannot be translated directly to paediatric practice where the detection of lymphadenopathy for primary TB potentially poses an interpretational reader discrepancy.

1.4.2. CT chest

The ability of CT to demonstrate parenchymal lesions and lymphadenopathy far more accurately than CXR makes CT a more valuable diagnostic tool in small children with TB. [54] The efficacy of CT is particularly significant when CXR's are equivocal, or where complications related to tuberculosis are concerned. [54] The sensitivity of CT allows for a far superior identification and description of vague localised or disseminated parenchymal disease and mediastinal lymphadenopathy. [55, 56, 57] When comparing CXR and chest CT, the following results highlight the efficacy of CT. Correctly diagnosed TB on CXR is found in

approximately 49% of all cases, with 34% for primary TB and 59% in reactivation TB. [58] On CT however, 91% of patients had TB correctly diagnosed, while it was accurately eliminated in 76%. [59] Furthermore CT accurately distinguished active disease in 80%, and inactive TB in 89%. [59]

The most frequently appreciated CT manifestations of PTB in small children include large mediastinal or hilar lymph nodes (often demonstrating necrosis in the centers) and mass-like air-space opacification with central break down or cavitation. [54] Diffuse pulmonary nodularity and airway involvement are also encountered. [54] High-resolution CT (HRCT) is valuable in identifying small cavities within areas of consolidation, dense nodularity or scarring. [55]

HRCT is especially useful in the identification and characterisation of active TB in adults, founded on the nature of parenchymal opacities, cavities and/or endobronchial spread as represented by classic centrilobular nodularity or a 'tree-in-bud' configuration. Lee et al. [59] accurately detected 80% of active TB and 89% of inactive disease on HRCT.

An additional advantage of CT is the ability to detect and further evaluate pleural disease and complications not always seen on CXR. These include TB effusions, empyema and bronchopleural fistulae. [60] Another advantage of CT is guiding the clinician toward the appropriate course of management, especially in cases of complicated or multi drug-resistant TB (MDR TB). [61] The presence of numerous cavities are often appreciated on CT in cases of MDR TB, which implies a large number of shedding bacilli with spread via the bronchi to unaffected areas of the ipsilateral and contralateral lung.

Poor penetration of drugs into the cavities harbouring many mycobacteria probably adds to drug resistance. Resection of these lesions is an option, although treatment mostly depends on pharmacotherapy. [61] If a surgical approach is warranted, CT provides an excellent surgical planning tool by showing the active disease and cavities. [61]

A noteworthy disadvantage of CT in the paediatric population is the significant radiation dose of CT compared with the relatively low dose of CXR (PA and/ or lateral). Traditional CT radiation dose is equivalent to that of approximately 100 CXR's. [45]

1.4.3. MRI chest

Peprah and colleagues used MRI on a limited group of older children with confirmed pulmonary TB. They distinguished between liquefactive necrosis, which has a high T2-weighted signal, and caseous necrosis, which has a low T2-weighted signal within regions of lung parenchymal air-space disease. [62]

Lymphadenopathy was found to have a characteristic T2-weighted low intensity on short Tau inversion recovery (STIR) sequences, likely related to paramagnetic free radicals associated with caseous necrosis. [45] TB lymphadenopathy was found to exhibit either solid nodular enhancement or rim enhancement (in the case of necrotic nodes) on MRI, similar to CT findings. [45]
Irrespective of the imaging modality used to detect lymphadenopathy, enlarged nodes are relevant for treatment. [44] The general rule is that those with abnormal

nodes usually receive full duration anti-TB therapy, while those without CXR abnormality and a positive skin test only would be treated for latent infection. [44]

1.5. Study Objectives

1.5.1. Aim

The aim is to identify simple and reliable CXR features of primary TB in children by determining the signs and anatomical sites of best observer agreement.

1.5.2. Objectives

The objectives are to:

- Determine agreement of three expert readers on the overall CXR diagnosis of PTB based on cumulative CXR features
- Determine the agreement of the three expert readers on lymphadenopathy causing airway compression overall and 'best agreement' at specific sites.
- Determine the agreement of the three expert readers on the presence of lymphadenopathy based on detecting soft tissue masses and best agreement at specific sites.
- Sub-categorise patients according to a majority decision into 'severe' and 'non-severe' according to a current proposed classification of Wiseman et al. [63] and determine inter-observer agreement for this.

2. Methods and Materials

This is a retrospective descriptive study nested in a clinical trial performed under the auspices of the South African TB Vaccine Initiative (SATVI). Healthy BCG-vaccinated newborn infants were monitored for at least two years for possible

incident pulmonary TB. A community surveillance system identified suspected paediatric TB on the strength of household adult TB contact or compatible symptoms (chronic cough, wheeze, weight loss, failing to thrive or unexplained pyrexia).

All children with suspected TB were admitted for standardised TB investigation, which included a CXR. All original CXR's were scanned using a high-quality radiography flatbed scanner and the images were stored in a database. Three independent blinded expert paediatric radiologists reported the CXR's using a standardised data collection form on which the specific anatomical sites and signs of pathology consistent with pulmonary TB were recorded.

These original data collection sheets were analysed in this study. The information of the first 200 patients was extracted from the records and analysed for the purpose of the current study.

Each individual tick sheet from all three readers was scrutinised and the information was added into a specifically compiled data sheet from which the necessary information could be statistically calculated and extrapolated. In retrospect, after the data sheet was compiled only 199 patient information sheets were complete and eligible for analysis. The inclusion and exclusion criteria of both the original study and subsequent data sheet are outlined in the following paragraphs.

2.1. Study Setting and sample size (original study)

A study was undertaken in a high TB risk rural geographic region in Worcester, near Cape Town, South Africa. All told, 4786 infants were included, of whom 800 children were investigated for TB, which included having CXR's.

2.2. Inclusion criteria

Healthy infants vaccinated with BCG (bacille Calmette-Guerin) were registered for the study within a fortnight of birth. These infants were randomly assigned to 3-monthly TB screening questionnaires at home visits, as well as the checking of TB registers, hospital admissions and health facility CXR lists for suspected and confirmed cases of PTB.

Overall 800 CXR's were performed and analysed by 3 independent expert readers (paediatric radiologists) from the City of Cape Town, South Africa. The findings were recorded on separate tick-sheets by the readers. The first 200 patients were selected for the nested study. In order to be eligible, all three readers' tick-sheets were required to be present, with each patient only being entered once.

2.3. Exclusion criteria

Infants that did not receive BCG at birth or who were generally unwell or whose parents did not consent to participation or whose parents did not plan to remain in the study area for duration of the trial were excluded.

Exclusion criteria for the nested study included incomplete, illegible, duplicated or incorrectly numbered tick-sheets.

2.4. Data collection

The data collection sheet included columns for the following: patient medical record number, case number, demographics (age at first admission in months, gender), lymphadenopathy (as identified by airway compression or soft tissue densities on frontal and lateral CXR projections by specific location), parenchymal/ airspace opacification (frontal and lateral projections by specific location), miliary TB, pleural effusions, cavitation and overall decision on the presence of PTB (see data collection tick sheet - Appendix A).

Findings were only considered ‘present’ when recorded as ‘definitely present’. All findings recorded as ‘maybe’ were considered with ‘negative’ as ‘not present’.

Data from the current tick sheets were collected for each reader under the following headings:

- Overall decision of TB
- Overall decision on presence of miliary nodules
- Overall decision on lymphadenopathy
- Overall decision on presence of airway compression
- Overall decision on presence of soft tissue densities
- Decision of presence of above by each specific location
- Recording the decision of three readers together (based on majority as ‘present’ i.e. 2 or 3 readers positive = present)
- Presence of parenchymal / air-space disease overall
- Presence of right-sided parenchymal / air-space disease
- Presence of left-sided parenchymal /air-space disease
- Declared ‘unreadable’ film

Patients were categorised as ‘severe’ and ‘non- severe’ based on the majority of the readers’ decisions, according to the published classification of Wiseman et al. below. [63]

Classification of Intrathoracic Disease:

'Non-severe' Disease:

A Ghon focus or non-expansile, non-bronchopneumonic single-lobe alveolar opacification seen on CXR, with or without uncomplicated intrathoracic lymph node disease, was classified as 'non-severe' disease. [63] Pleural fluid following presumed breakdown of subpleural foci or due haematogenous dissemination was classified as 'non-severe' if there was no evidence of severe underlying lung disease. [63] Classification followed after considering the presence and type of underlying lung disease and nature of the pleural fluid if a diagnostic tap has been completed. [63] In the case of an effusion obliterating radiographic visibility of the underlying lung, the disease could not be confidently classified. [63] It is noted that large effusions in young children (<5 years) are uncommon. [64, 65, 66, 67] More commonly small effusions overlying a peripheral Ghon focus are seen. [64, 65] In older children (>6 years), effusions may be large, obliterating visibility of the underlying lung. [65]

'Severe Disease'

Expansile alveolar opacification, tuberculous bronchopneumonia, multilobar alveolar opacification and cavitation all represent local complications and were classified as severe disease. [63] Complicated intrathoracic lymph node pathology, as in the presence of nodal compression of the large airways, was also classified as severe disease, regardless of whether disease was controlled or uncontrolled. [63] This includes the spectrum of endobronchial or lymphobronchial [68] disease such as bronchial compression, a currently caseating lesion, granulomas, a polypoidal lesion or lymph node mucosal erosion and ulceration. [63] Although

these lesions are only observed during bronchoscopy, [69, 70] features of large airway compression can often be suspected based on CXR findings. [69]
Empyaema (pus with or without TB mycobacteria in the pleural space) represents a disease complication, and was also classified as severe disease. [63]
Tuberculous pericarditis was classified as severe disease, as it is felt to arise by spread from adjacent paratracheal, peribronchial, or subcarinal nodes (i.e. complicated disease), or from haematogenous bacillary spread. [71] If unrecognised, it may have severe sequelae, including death, due to its mechanical effects.

2.5. Statistical analysis

Readers were compared for features and sites of best agreement. Proportions and percentages of patients with severe and non-severe disease are presented. Subcategories of presence or absence of parenchymal/ air-space disease and readable or unreadable radiographs [as determined by majority] were created for comparison as confounding factors. Correlations were drawn between the categories and reader agreement.
Kappa statistics were calculated for determining best agreement and categorised as follows by kappa value:

Very good agreement 0.8 – 1

Good agreement 0.61 – 0.8

Moderate agreement 0.41 – 0.6

Fair agreement 0.21 – 0.4

Poor agreement < 0.2

The kappa statistic calculates the kappa measure of inter-rater agreement (in this case for multiple raters (m>2) and two ratings (k=2)). We are testing whether the value (of kappa) is significantly different to zero. A p-value of < 0.05 in our study reflects the cut-off below which a finding is deemed unlikely to be random and is statistically significant. A small p-value rounded off to 0 (< 0.00005) is considered extremely statistically significant, therefore inferring that the occurrences are less likely to be by chance. Therefore in our study kappa statistics reflect strength of agreement whereas low p-values indicate the likelihood of the variation of the reader findings occurring due to non-random cause(s).

2.6. Ethics approval

The current study is nested within a SATVI trial, with clearance from the University of Cape Town research ethics board [Number: 064/2005]. No new imaging studies were performed or patient information gathered and used for the nested study. Please refer to Appendix A.

3. Results

3.1. Demographics

A total of 200 patients were sampled from 800 reviewed patient chest radiographs. 1 patient was excluded from the data spreadsheet due to an administrative error, leaving 199 patients eligible for statistical analysis. Of this total, 92 (46.23%) were

female and 107 (53.77%) were male. Gender frequency and percentage are summarised in table 3.1.

Table 3.1. Frequency table for gender

Gender (M/F)	Frequency	Percentage
Female	92	46.23
Male	107	53.77
Total	199	100

Age data are summarised in table 3.2. The median admission age was 14.03 months. The minimum age was 2 months and the maximum age 36.6 months. No relationship or pattern between interpreted radiographic results and gender or age at admission was established i.e. the age and gender had no influence on the findings.

Table 3.2. Distribution of age at admission (months)

Variable	N	Min	Max	Mean	Std Dev.	Median	25th Percentile	75th Percentile
Age admission (months)	199	2	36.6	14.795	8.0230	14.03	7.66	21.36

3.2. Lymphadenopathy

Among the 199 eligible films reviewed by the three readers, the overall combined agreement for airway compression by presumed lymphadenopathy was 0.5%. A combined result of 5% of the radiographs were found to have a soft tissue mass likely reflecting lymphadenopathy on the frontal radiograph, as well as 5% on the lateral radiograph. Overall and individual reader interpretations of lymphadenopathy are summarised in Table 3.3.

Reader 1 found CXR airway compression in 5%, Reader 2 in 0% and Reader 3 in 0.5%. The most common site reflecting lymphadenopathy through airway compression was the left main bronchus.

Soft tissue densities on the frontal projection were found in 20.6% of patients by Reader 1, 4% by Reader 2 and 3 % by Reader 3. Reader 1 noted soft tissue density on the lateral projection in 19% of patients, Reader 2 in 2.5% and Reader 3 recorded 13%. Please refer Table 3.3. The majority of positive findings were in the right hilar region on the frontal projection and in the sub-carinal region on the lateral projection for all three readers.

The p-values for overall agreement on lymphadenopathy resulting from airway compression and soft tissue densities on the lateral projection are 0.036 and 0.001 respectively (more so for soft tissue densities). This infers high statistical significance, i.e. a high likelihood of non-random reader variability. The p-value of 0 for soft tissue densities on the frontal projection suggests an extremely high likelihood of a non-random inter-reader variability. These are shown in Tables 3.9, 3.10 and 3.11.

Table 3.3. Inter-reader interpretation of lymphadenopathy

Imaging Feature	Site	R 1	R 2	R 3	R1 OA	R2 OA	R3 OA	Combined
Lymphadenopathy								
Airway compression	**1. Right Para-Tracheal**	0 (0%)	0 (0%)	0 (0%)	10 (5%)	0 (0%)	1 (0.5%)	1 (0.5%)
	2. Right Main Bronchus	6 (3%)	0 (0%)	1 (0.5%)				
	3. Bronchus Intermedius	8 (4%)	0 (0%)	2 (1%)				
	4. Left Main Bronchus	14 (7%)	1 (0.5%)	2 (1%)				
Soft tissue Frontal	**1. Right Para-tracheal**	4 (2%)	2 (1%)	0 (0%)	41 (20.6%)	8 (4%)	6 (3%)	10 (5%)
	2. Right Hilar	42 (21%)	11 (5.5%)	11 (5.5%)				
	3. Right Paracardial	23 (11.6%)	1 (0.5%)	2 (1%)				
	4. Left Para-tracheal	2 (1%)	0 (0%)	0 (0%)				
	5. Left Hilar	31 (15.6%)	3 (0.5%)	7 (3.5%)				
Soft tissue Lateral	**1. Pre-carinal**	29 (14.6%)	0 (0%)	19 (9.6%)	38 (19%)	5 (2.5%)	27 (13%)	10 (5%)
	2. Sub-carinal	39 (19.6%)	5 (2.5%)	33 (16.6%)				

Imaging Feature		Site	R 1	R 2	R 3	R1 OA	R2 OA	R3 OA	Combined
		3. Behind Bronchus Intermedius	20 (10%)	6 (3%)	32 (18%)				

R1 = reader 1; R2 = reader 2; R3 = reader 3; OA = overall

3.3. Parenchyma

None of the readers indicated the presence of a miliary parenchymal pattern. The overall combined agreement for air-space opacification on the frontal projection was 4.5% and on the lateral projection, 3.5%. The individual results reflect positive findings of air-space opacification on the frontal projection in 10.6% by Reader 1, 6% by Reader 2 and 4% by Reader 3. 10% of radiographs were found to have air-space opacification on the lateral projection by Reader 1, 4.5% by Reader 2 and 2.5% by Reader 3.

The area most agreed upon for all three readers in terms of air-space opacification on the frontal projection was the right lower zone. On the lateral projection, the bulk of positive findings were in the lower zone for Reader 1. Readers 2 and 3 indicated their majority of positive findings in the right middle lobe. Overall and individual reader parenchymal findings are summarised in Table 3.4.

The p-values for overall agreement on opacification on both frontal and lateral projections are rounded to 0, inferring significantly high probability that the variability of reader findings did not occur by chance. Refer Tables 3.12 and 3.13.

Table 3.4. Inter-reader interpretation of parenchymal opacification

Imaging Feature	Location	R 1	R 2	R 3	R1 OA	R2 OA	R3 OA	Combined
Parenchymal								
Miliary		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Airspace Frontal	**1. Right Upper Zone**	3 (1.5%)	1 (0.5%)	0 (0%)	21 (10.6%)	12 (6%)	8 (4%)	9 (4.5%)
	2. Right Middle Zone	3 (1.5%)	5 (2.5%)	0 (0%)				
	3. Right Lower Zone	15 (7.5%)	15 (7.5%)	11 (5.5%)				
	4. Left Upper Zone	0 (0%)	0 (0%)	0 (0%)				
	5. Lingula	2 (1%)	2 (1%)	0 (0.5%)				
	6. Left Lower Zone	14 (7%)	3 (1.5%)	1 (0.5%)				
Airspace lateral	**1. Upper Zone**	0 (0%)	0 (0%)	0 (0%)	20 (10%)	9 (4.5%)	5 (2.5%)	7 (3.5%)
	2. Right Middle Lobe	5 (2.5%)	8 (4%)	4 (2%)				
	3. Lower Zone	21 (10.6%)	7 (3.5%)	2 (1%)				

R1 = reader 1; R2 = reader 2; R3 = reader 3; OA = overall

3.4. Cavitation and Pleural Effusion

None of the readers indicated positive findings for cavitation or pleural effusion.

Refer Table 3.5.

Table 3.5. Inter- reader interpretation of pleural effusions and cavitation

Imaging Feature	Location	R 1	R 2	R 3	R1 OA	R2 OA	R3 OA	Combined
Cavitation		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pleural effusion		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

R1 = reader 1; R2 = reader 2; R3 = reader 3; OA = overall

3.5. Overall Decision on PTB

The overall findings reflecting PTB (lymphadenopathy or miliary) by each individual reader of the total number of CXR's was 27.6% by Reader 1, 8.5% by Reader 2 and 24,6% by Reader 3. The overall final decision on PTB agreed upon by all three readers was 14.57%. Refer Tables 3.6 and 3.7.

Abnormal findings not specific for PTB were found in 3.5% of the CXR's by Reader 1, 10.5% by Reader 2 and 3.5% by Reader 3.

The overall cases reported as normal by all three readers were 98 out of the 199 cases reviewed. The overall agreed upon number of radiographs reported as normal was 49.2%; refer table 3.8. 68.3% of the radiographs were reported as normal by Reader 1, 81.9% by Reader 2 and 66.8% by Reader 3. Refer Table 3.7. Therefore the number of cases found to have an abnormality by one or more of the readers, including those deemed unreadable by one or more readers, was 101 out of the 199 cases reviewed, 50.7%

Table 3.6. Decision on PTB

Final decision on PTB			
Variable	**Response**	**Frequency**	**Percentage**
Final Result	0	170	85.43%
	1	29	14.57%

0 = absent; 1 = present

Table 3.7. Decision on PTB, abnormal and normal CXR

Decision on PTB	R1	R2	R3	Combined Average
PTB: lymphadenopathy or miliary	55 (27.6%)	17 (8.5%)	49 (24.6 %)	40.3 (20.1%)
Abnormal but not TB	7 (3.5 %)	20 (10.5%)	7 (3.5 %)	11.34 (5.7 %)
Normal	136 (68.3 %)	163 (81.9%)	133 (66.8%)	144 (72.33%)
Unreadable	0 (0%)	0 (0%)	10 (5 %)	3.34 (1.67%)

R1 = reader 1; R2 = reader 2; R3 = reader 3

The p-values for overall agreement on PTB and normal CXR's were rounded to 0 suggesting high likelihood of non-random cause for the variable reader findings, whereas the high p-values for abnormal CXR's (not PTB) and unreadable films suggest a higher likelihood that the variable findings were by chance. Please refer table 3.12.

Table 3.8. Decision on normal CXR

Final Decision on Normal CXR			
Variable	**Response**	**Frequency**	**Percentage**
Final Result	0	101	50.7%
	1	98	49.2%

3.6. Sub-categorising into severe and non-severe disease

According to the combined findings of all three readers, none of the patients who were thought to have radiographic features of PTB met the criteria for severe PTB. These patients did however meet the criteria for non-severe PTB.

3.7. Interobserver agreement

Interobserver agreement was determined for lymphadenopathy according to the presence of airway compression (table 3.9); lymphadenopathy according to soft tissue density on the frontal film (table 3.10); lymphadenopathy according to soft tissue density on the lateral film (table 3.11); final decision TB (table 3.12); parenchymal opacification on the frontal film (table 3.13) and parenchymal opacification on the lateral film (table 3.14).

Table 3.9. Kappa results for airway compression due to presumed lymphadenopathy

Lymphadenopathy: Airway compression		
Variable	**Kappa**	**P-value**
Rt Paratracheal	Not able to calculate (all zero values)	
Rt Main Bronchus	0.1327	0.0006
Bronchus Intermedius	-0.017	0.6614
Lt Main Bronchus	0.1523	0.0001
Overall Agreement	0.0738	0.0356

Table 3.10. Kappa results for soft tissue densities due to presumed lymphadenopathy (Frontal)

Lymphadenopathy: Soft tissue densities: frontal		
Variable	**Kappa**	**P-value**
Rt Paratracheal	-0.0102	0.598
Rt Hilar	0.265	0
Rt Paracardial	-0.0455	0.8671
Lt Paratracheal	-0.0034	0.5327
Lt Hilar	0.1881	0
Overall Agreement	0.219	0

Table 3.11. Kappa results for soft tissue densities due to presumed lymphadenopathy (Lateral)

Lymphadenopathy: Soft tissue densities: lateral		
Variable	**Kappa**	**P-value**
Pre-carinal	0.0258	0.2639
Sub-carinal	0.1352	0.0005
Behind Bronchus Intermedius	0.1788	0
Overall Agreement	0.1261	0.001

Table 3.12. Kappa results for decision on PTB

Final decision on PTB		
Variable	**Kappa**	**P-value**
PTB (miliary/lymphadenopathy)	0.2595	0
Abnormal but not PTB	0.0288	0.241
Normal	0.3383	0
Unreadable	-0.017	0.6614

Table 3.13. Kappa results for parenchymal/air-space opacification (Frontal)

Opacification: Frontal		
Variable	**Kappa**	**P-value**
Rt Upper Zone	-0.0067	0.5655
Rt Middle Zone	-0.0136	0.63
Rt Lower Zone	0.3715	0
Lt Upper Zone	Not able to calculate (all zero values)	
Lingula	-0.0067	0.5655
Lt Lower Zone	0.2553	0
Overall Agreement	0.3715	0

Table 3.14. Kappa Results for parenchymal/air-space opacification (Lateral)

Opacification: Lateral		
Variable	**Kappa**	**P-value**
Upper Zone	Not able to calculate (all zero values)	
Rt Middle Lobe	0.5762	0
Lower Zone	0.0875	0.0163
Overall Agreement	0.3139	0

Table 3.15. Comparison with other CXR studies

Title	**"Primary tuberculosis in childhood with particular emphasis on changes affecting the tracheo-bronchial tree"**	**"Criteria used for the diagnosis of childhood tuberculosis at primary health care level in a high-burden, urban setting"**	**"Observer variation in detecting lymphadenopathy on chest radiography"**	**"Evaluation of the utility of specific CXR features for diagnosis of pulmonary tuberculosis in young children using multiple readers"**
Authors	A. L. Weber, K. T. Bird, M. L. Janower	A. C. Theart, B. J. Marais, R. P. Gie, A. C. Hesseling, N. Beyers	G. Du Toit, G. Swingler, K. Iloni	R.F. Ho-Yee, S. Andronikou, S.J Beningfield, M. Hatherill
Year published	1968	2005	2002	Unpublished
Age of the patients	Ages not specified	Children under 15 years	Children 1 month to 11 years	Children 2 months to 36.6 months
Number of patients	85 children	256 children	100 children	199 children

Study description	Retrospective study conducted at Middlesex County Sanatorium Waltham Massachusetts. Data collected from 1960 to 1966	Descriptive retrospective study at two Cape Town primary health care facilities. Data collection from 2002 to 2003	Retrospective study at Red Cross Children's Hospital, Cape Town. Data collection from 1996 to 1998	Retrospective study conducted in a high TB rate rural area in Worcester, near Cape Town. Data collected through 2005
Aim	To review some of the important clinical and radiographic features of childhood tuberculosis	To evaluate diagnostic criteria used for childhood TB at a primary health care facility in a high risk urban environment	To assess inter- and intra-observer agreement in detection of large nodes by CXR in high risk children	To identify simple and reliable CXR features of primary TB in children by determining signs and anatomical sites of best observer agreement
Confirmatory tests	Positive tuberculin skin testkin test	Sputum smear testing	None	None
Conclusion	Pulmonary infiltrates with hilar and paratracheal nodes characterise primary TB Nodes frequently cause tracheobronchial narrowing with atelectasis and obstructive emphysema	Current diagnostic guidelines were well; followed, but depended heavily on the CXR The interpretation of CXR's is problematic, and its limited availability in most high-burden settings underscores the need for validated diagnostic guidelines that are applicable in these settings.	Concluded that lymphadenopathy in children is detected on chest radiography with fair inter- and moderate intra-observer agreement This suggests that the use of explicit criteria for lymphadenopathy could increase the repeatability of detection.	The fair agreement amongst expert readers suggests that the CXR alone is not reliable in detecting pulmonary TB and should be combined with the clinical features, skin tests and blood results. The high agreement on normality makes the CXR a reliable tool for excluding disease. Soft tissue masses rather than airway compression are a more consistent sign of lymphadenopathy with the most agreed upon sites for detection being the right hilum followed by the left hilum, both on the frontal projection. Parenchymal opacification is a relatively more reliable finding than lymphadenopathy according to overall agreement among readers.

				Unfortunately this study could not confirm the usefulness of CXR in subcategorising PTB into severe and non-severe due to the absence of any positive features for severe PTB in the selected sample

[49, 47, 48]

4. Discussion

This study addresses the inter-reader agreement of three expert readers on the presence of airway compression and soft tissue masses on CXR on the basis of presumed lymphadenopathy in children. The detection of lymphadenopathy on radiographs in an exposed population group of children is often used to diagnose PTB and has important consequences for anti-tuberculous medication. The study also addresses the agreement on the presence of air-space opacification not specific to tuberculosis, but rather as part of a constellation of features suggesting tuberculosis. An attempt was made to extrapolate the anatomical sites most reliable for the detection of lymphadenopathy according to the agreement of the three readers. Finally the study addresses the question as to whether PTB could be further sub-categorised into ‘severe’ and ‘non-severe’ on the basis of chest radiograph features alone.

The most reliable findings of lymphadenopathy on the CXR in our study were soft tissue densities reflecting presumed lymphadenopathy (kappa 0.219 -Table 3.10.), particularly at the right hilum (kappa 0.265 -Table 3.10.) and to a lesser extent the left hilum (kappa 0.19 -Table 3.10) on the frontal (AP) projection. Less reliable

findings include soft tissue densities on the lateral projection and airway compression due to presumed lymphadenopathy. According to the kappa statistics the overall concurrence on combined decision on the presence of PTB was fair (kappa 0.26 -Table 3.12.). This supports the findings of Swingler and colleagues who showed only ‘‘fair’’ agreement between readers, worse so for lateral projections. [44] Their patient group of children with suspected TB according to WHO criteria was similar to ours. Unlike our readers who had predefined tick-sheets specifying features to be recorded, they did not set CXR reading parameters in advance. They suggest that accuracy could be improved by clarifying stipulations for lymphadenopathy on CXR [44], but the use of tick-sheets in our study has not had the expected impact.

In our study the total number of cases found to have PTB as agreed upon by the readers was only 29 out of the 199 cases. However the number of normal radiographs agreed upon by all three readers was 98 of the 199 cases, almost half (49.2%); refer Table 3.8. These findings highlight the overall low prevalence of positive findings and the large number of normal findings in our study. Taking this into consideration, the calculated kappa statistics are somewhat unreliable. Illustrating this point is the relatively higher ratio of agreed upon positive PTB cases to abnormal chest radiographs, after excluding the agreed upon normal radiographs the sample (29 PTB cases of 101 abnormal cases, including those deemed unreadable by one of the readers). Therefore, as for Swingler and colleagues, we believe that in a population group which is more likely to have confirmed TB, the inter-reader agreement may be improved [44]. The fair number of agreed upon normal radiographs however, proves consensus on the exclusion

of any disease process. This is supported by the small p-value of normal CXR findings (Table 3.12) inferring high statistical significance.

Considering the emphasis placed on the presence of airway compression for diagnosing lymphadenopathy, there was surprisingly poor agreement on the overall presence of airway compression due to presumed lymphadenopathy, including low reader agreement at the right and left main bronchi, and poor agreement at bronchus intermedius (Refer Table 3.9.). Overall, airway compression was present in only 5% of the patients (Table 3.3).

According to the readers there were between 8.5% and 27.6 % of patients who had TB on X-ray (Refer table 3.7) with the percentage of these thought by those readers to have airway compression ranging from 0 – 5%. This is far lower than in previous reports of paediatric TB, with lymph node-induced airway narrowing from 35% [72] to 40% [73]. Either our sample is very different to those studies that may be reporting findings in very advanced cases of TB, or CXR is much less sensitive than CT for detecting this diagnostic feature and major complication.

When compared with the study of duToit, Swingler and Iloni on the inter-observer variation in detection of lymphadenopathy on CXR (Refer to table 3.15) and using identical kappa criteria, our study observed similar ‘fair’ inter-observer agreement with regards to overall detection of lymphadenopathy on CXR. [48] Interestingly, our study showed greater agreement on the absence of lymphadenopathy (kappa 0.34 - Table 3.12) as opposed to presence of lymphadenopathy (kappa 0.219 – Table 3.10) compared with the du Toit study where greater agreement was noted on the presence of lymphadenopathy. [48] This study also concluded that further

research is needed to find a reference standard to maximise validity and reproducibility in the detection of lymphadenopathy. This is similarly concluded in our study.

Comparison made with the study by Theart, Marais, Gie et al found that although the diagnosis is dependent on the accurate interpretation of the CXR, combined clinical correlation is essential [47]. This is similar to our own findings which suggests that the CXR alone is not a reliable diagnostic tool for a paediatric population at high risk for pulmonary TB and ought to be used in conjunction with clinical features, skin tests and blood results.

The remote study undertaken by Weber, Bird and Janower revealed that in addition to parenchymal disease, the paratracheal lymph nodes (particularly on the right) and bilateral hilar lymph nodes may be enlarged as seen by either bronchial compression or post obstructive atelectasis or emphysema. [49] Our study found that by using soft tissue densities, the right main bronchus (right hilum), followed by left main bronchus (left hilum) were the most agreed upon sites of detecting lymphadenopathy (refer table 3.10), similar to the Weber study [49]. In contrast to our low rate, a high incidence of right paratracheal lymphadenopathy (9 cases of the 23 cases positive for lymphadenopathy) [49] was found in the Weber study

With regards to parenchymal opacification, the agreement according to kappa statistic was relatively higher than lymphadenopathy on both frontal and lateral projections, despite both only falling into the 'fair' agreement category. The most agreed upon areas for detecting parenchymal opacities were the right lower zone on the frontal projection and lower zone and right middle lobe on the lateral

projection. From our study, it can therefore be deduced that the overall agreement on parenchymal opacification among the readers is relatively higher than for detecting lymphadenopathy and it can be inferred that the more reliable areas for appreciating parenchymal opacification are the right lower zone on the frontal view, and the right middle lobe and lower zone on the lateral.

In view of the absence of any findings of miliary TB, pleural effusions and cavitation, all of the patients who were found to have PTB fell into the non-severe category as per the documented criteria. These results were found to be inconclusive, neither illustrating nor disproving the point that PTB can be further sub-characterised into severe and non-severe on chest radiograph.

No relationship was established between the age and gender of the patients and the presence of active PTB. Considering that the median age was 14.03 months, with a minimum of 2 months and a maximum of 36.6 months at first admission, the findings of this study are not necessarily true for children older than this (Table 3.2.). The findings are therefore also not comparable to those of Swaminathan and colleagues who only reported on children from 6 to 12 years with clinical features of tuberculosis, and demonstrated that a significant proportion of children with positive cultures had normal chest X-rays. [23]

An important study limitation is the absence of a validated reference system for lymphadenopathy. Current practice norms were used in the assessment of detection of nodes in this study. The large number of negative findings (normal CXR’s) within the randomly selected sample of patients hampered the study. Of

the 200 patient CXR's selected from the sample of 800, 1 selected patient was excluded from the spreadsheet due to an administrative error.

5. Conclusion

The low agreement amongst expert readers suggests that the CXR alone is not a reliable tool in detecting paediatric pulmonary TB and should be used in conjunction with the clinical features and/or skin tests and blood results. The fair agreement on normal chest radiographs makes the CXR a fairly reliable tool for excluding disease.

Soft tissue masses rather than airway compression are a more reliable sign for lymphadenopathy and the most agreed upon sites for detection are the right hilum followed by the left hilum on the frontal projection.

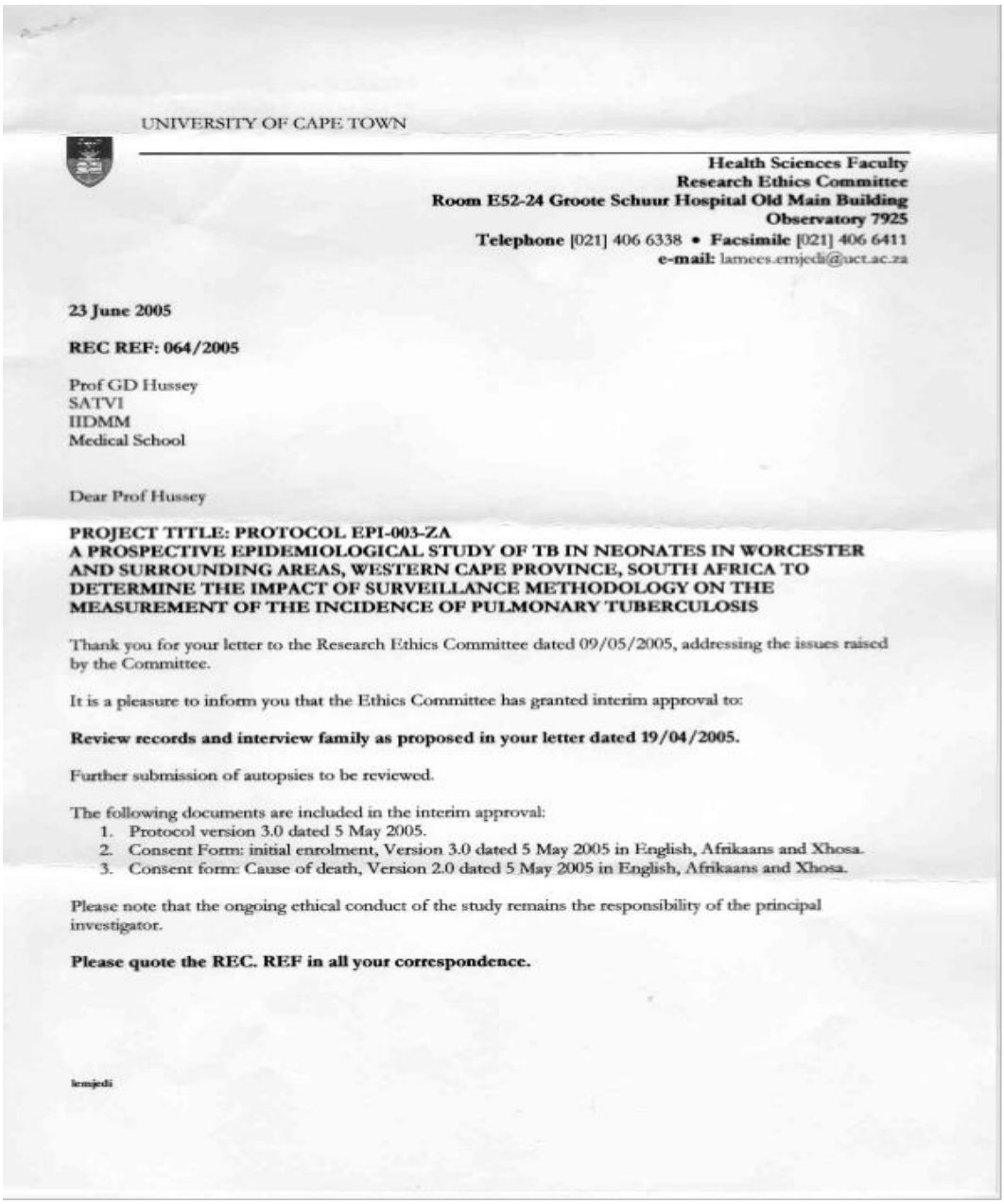
Parenchymal opacification is a relatively more reliable finding than lymphadenopathy according to better overall agreement among readers.

Unfortunately this study could not confirm the usefulness of CXR in subcategorising of PTB into severe and non-severe due to the absence of positive features for severe PTB in the selected sample. The use of prescribed tick-sheets with specified features for detecting lymphadenopathy did not have the expected impact of promoting agreement between observers in the interpretation of CXR's in children with suspected TB. The absence of a credible reference standard for lymphadenopathy remains a significant limitation.

Further research comparison with an imaging gold standard can pave the way for setting more accurate X-ray criteria both for improving sensitivity and specificity with improved inter-reader agreement in the diagnosis of paediatric TB. The CXR

may be more useful in children with more severe clinical presentations where CXR findings may be more obvious or occur more frequently.

Appendix A: Ethics Clearance Certificate



UNIVERSITY OF CAPE TOWN

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23 June 2005

REC REF: 064/2005

Prof GD Hussey
SATVI
IIDMM
Medical School

Dear Prof Hussey

PROJECT TITLE: PROTOCOL EPI-003-ZA
A PROSPECTIVE EPIDEMIOLOGICAL STUDY OF TB IN NEONATES IN WORCESTER AND SURROUNDING AREAS, WESTERN CAPE PROVINCE, SOUTH AFRICA TO DETERMINE THE IMPACT OF SURVEILLANCE METHODOLOGY ON THE MEASUREMENT OF THE INCIDENCE OF PULMONARY TUBERCULOSIS

Thank you for your letter to the Research Ethics Committee dated 09/05/2005, addressing the issues raised by the Committee.

It is a pleasure to inform you that the Ethics Committee has granted interim approval to:

Review records and interview family as proposed in your letter dated 19/04/2005.

Further submission of autopsies to be reviewed.

The following documents are included in the interim approval:

1. Protocol version 3.0 dated 5 May 2005.
2. Consent Form: initial enrolment, Version 3.0 dated 5 May 2005 in English, Afrikaans and Xhosa.
3. Consent form: Cause of death, Version 2.0 dated 5 May 2005 in English, Afrikaans and Xhosa.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

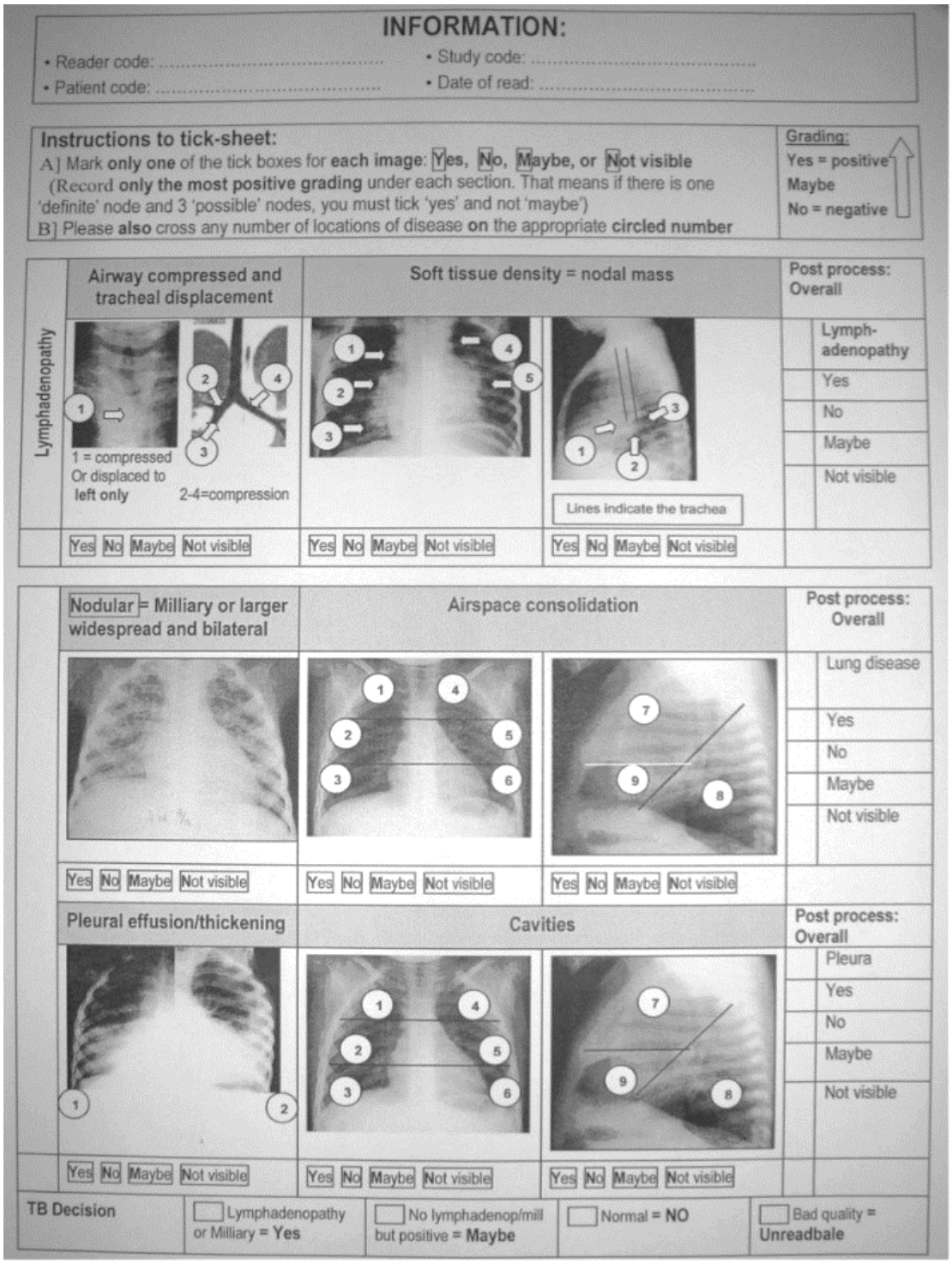
Please quote the REC. REF in all your correspondence.

lemjedi

Yours sincerely

PROFESSOR T. ZABOW
CHAIRPERSON, HSF HUMAN ETHICS

Appendix B: Data collection Tick Sheet



INFORMATION:

• Reader code: ..... • Study code: .....

• Patient code: ..... • Date of read: .....

Instructions to tick-sheet:

A] Mark **only one** of the tick boxes for **each image**: Yes, No, Maybe, or Not visible

(Record **only the most positive grading** under each section. That means if there is one 'definite' node and 3 'possible' nodes, you must tick 'yes' and not 'maybe')

B] Please **also** cross any number of locations of disease **on** the appropriate **circled number**

Grading:
Yes = positive
Maybe
No = negative

Lymphadenopathy

Airway compressed and tracheal displacement

1 = compressed Or displaced to **left only**

2-4=compression

Yes No Maybe Not visible

Soft tissue density = nodal mass

Yes No Maybe Not visible

Lines indicate the trachea

Yes No Maybe Not visible

Post process: Overall

Lymph-adenopathy
Yes
No
Maybe
Not visible

Nodular = Milliary or larger widespread and bilateral

Yes No Maybe Not visible

Airspace consolidation

Yes No Maybe Not visible

Yes No Maybe Not visible

Post process: Overall

Lung disease
Yes
No
Maybe
Not visible

Pleural effusion/thickening

Yes No Maybe Not visible

Cavities

Yes No Maybe Not visible

Yes No Maybe Not visible

Post process: Overall

Pleura
Yes
No
Maybe
Not visible

TB Decision

☐ Lymphadenopathy or Milliary = **Yes**

☐ No lymphadenop/mill but positive = **Maybe**

☐ Normal = **NO**

☐ Bad quality = **Unreadbale**

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