

# COMPUTERISED TOMOGRAPHY FINDINGS OF LYMPHOBRONCHIAL TUBERCULOSIS IN CHILDREN: A COMPARISON BETWEEN INFANTS AND OLDER CHILDREN

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## Declaration

I, Heleen Catharien Hanekom, declare that this research report is my own work. It is being submitted for the degree of MMed (RadD) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

A handwritten signature in black ink, appearing to read 'H Hanekom'.

DR HELEEN CATHARIEN HANEKOM

On this 27<sup>th</sup> day of October 2015.

To Willie

## **Publications and presentations**

This work has never been published.

It was presented as an oral presentation at the University of the Witwatersrand Faculty of Health Sciences Research Day on 17 September 2014.

It was also presented as a poster exhibit at the 15<sup>th</sup> Asian Oceanian Congress of Radiology in Kobe, Japan on 26 September 2014.

## **Abstract**

**INTRODUCTION:** Pulmonary tuberculosis (TB) in children is characterised by mediastinal and hilar lymphadenopathy. Lymphobronchial TB (LBTB) describes the situation where tuberculous lymph nodes affect the airways by compression or erosion. Infants may be more susceptible to severe complications due to their specific airway anatomy and immature immune systems.

**AIM:** The purpose of this study was to compare the computerised tomography (CT) findings of infants and children older than 12 months with LBTB to determine whether infants are more severely affected in terms of bronchial compression secondary to mediastinal lymphadenopathy and the complications thereof.

**METHOD:** The CT scans of 98 children (< 13 years) with LBTB were reviewed retrospectively by a paediatric radiologist for a previous study and the results captured in a database. The relevant data was extracted from the existing database and the two age groups were compared with regard to lymphadenopathy, airway narrowing and parenchymal complications.

**RESULTS:** Of the 98 patients, 51% were infants. There was no statistically significant difference between infants and children older than 12 months with reference to the frequency and distribution of airway compressions, lymphadenopathy and parenchymal findings. However, there was a statistically significant difference ( $p < 0.05$ ) in the number of infants with complete compressions when compared to the older children. Infants also had a 1.9 times higher risk than older children, of having complete compressions.

**CONCLUSION:** As opposed to older children, infants' airways are more susceptible to complete airway compression as a result of LBTB. This is due to airway size and anatomic

development. We therefore recommend that when infants present with symptoms of airway compression secondary to LBTB, they should be imaged using CT scanning and managed urgently.

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## **1. Rationale**

Tuberculosis is a major problem in South Africa and has a high prevalence in children (1, 2). Lymphobronchial TB (LBTB) is a severe and potentially life-threatening complication of pulmonary TB mainly seen in children (3). Due to the smaller size and increased compliance of the airways in infants compared to older children (4, 5), the tuberculous lymph nodes can compress and then erode the airways. CT scanning has been proven to aid in the diagnosis and the detection of complications of pulmonary TB, and especially LBTB, in children (6). Data has been published with regard to the CT findings of LBTB in children; however the findings vary between infants and older children (7). This project will aim to compare the CT findings in infants, less than one year of age, and children, above the age of one year, with confirmed LBTB. The complications secondary to LBTB will also be compared between these two groups to ascertain whether the complications are more severe in infants. These findings could be used to determine if a more aggressive management approach should be employed in this age group.

## 2. Introduction

### 2.1. Epidemiology of TB

TB is a worldwide epidemic. According to the World Health Organisation (WHO) the highest incidence of TB is in Africa and Asia, with Africa harbouring a quarter of the world's cases of TB (1). Africa also has the highest rate of cases and deaths from TB per capita amounting to 280 incident cases per 100 000 per year, which is more than double the global average (1). TB has a high mortality if left untreated and is second only to HIV as the leading infectious cause of death in the world (1).

In 1993 the WHO classified TB as a global public health emergency and the WHO subsequently launched the Stop TB Strategy in accordance with the Millennium Development Goals to decrease the global burden of TB by 2015 (1). The targets of the Stop TB Strategy include a 50% reduction in the prevalence of TB and mortality due to TB compared with a baseline established in 1990 (1). It also aims to eliminate TB as a public health problem by 2050 (1). According to the 2014 WHO Global Tuberculosis Report there has been a marked global reduction of 45% in the TB mortality rate since 1990 and a steady decline in the global incidence of TB of 1.5% per year indicating that the Millennium Development Goals of curbing and reversing the incidence of TB have, in fact, been met and that the targets of the Stop TB strategy are within reach in most of the WHO regions (1). South Africa, however, has **not** followed the same trend, although there has been a decline in the incidence rate according to the WHO report, South Africa is not on track to reach these targets (1).

### **2.1.1. TB in South Africa**

South Africa has a TB incidence rate of 860 per 100 000 (1, 2). It is estimated that 80% of the South African population is infected with TB and 1% of the population progress to develop TB disease each year (2). Wood conducted a study in Cape Town and found that HIV-uninfected individuals have a 22% lifetime risk of contracting TB (8). Children, immunocompromised patients especially those living with human immunodeficiency virus (HIV), and malnourished patients are some of the groups identified to be at an increased risk of progression from TB infection to TB disease (2).

The devastating effects of TB are exacerbated by the impact of HIV. It is reported that infection with HIV increases the patient's chances of developing TB disease by 30 times (1). Roughly 62% of TB patients in South Africa are co-infected with HIV which is staggering compared to the global estimates of 13% (1, 2).

### **2.1.2. TB in children**

The 2014 WHO Report estimates 550 000 new cases of TB in children and 80 000 deaths from TB in HIV-uninfected children for the year 2012 (1). However, these statistics remain underestimated due to several factors, one of which is that TB is notoriously difficult to diagnose in children, which leads to under-diagnosing and thus under-reporting (9). Many TB control programmes also lack paediatric surveillance data which further complicates the process of accurately determining the global burden of TB in children (10).

In South Africa, recent data has reported that pneumonia is the leading cause of death in children under the age of five, (11) and it remains undetermined how many of these deaths can be attributed to TB.

A study based in Cape Town, where the data utilised in this study originates, found that there is a peak incidence of TB in children under the age of 4 years with young HIV-uninfected children in Cape Town having a 4% annual risk of contracting TB (8).

## **2.2. Pathophysiology of TB**

TB is caused by infection with *Mycobacterium tuberculosis*. Transmission occurs from the respiratory tract of an infected individual who releases airborne droplets containing the pathogen into the environment (12). These droplets are then inhaled by the uninfected individual (13). The organism is subsequently deposited in the respiratory tract where an initial inflammatory reaction ensues (14). An area of focal consolidation, the primary parenchymal focus, develops at the area of deposition (13, 14). From the primary focus the bacilli migrate via the lymphatics to the regional lymph nodes, mainly the ipsilateral para-tracheal and perihilar lymph nodes (14). The parenchymal focus, together with the regional lymphadenopathy, is termed the Ghon complex (13, 14). The infection up to this point has historically been termed primary TB (15). The majority of TB infection in children is thought to be as a result of primary or recent TB infection (15-17).

Primary TB is often subclinical and frequently the only sign on a chest radiograph is hilar adenopathy (14). An immunocompetent individual will usually remain asymptomatic and will develop specific immunity to limit the infection resulting in resolution of the Ghon complex within a few weeks (13, 18). Some of the bacilli may, however, remain latent for years to be reactivated at a later stage; this is referred to as latent TB infection (18, 19). Sometimes the only evidence of previous TB infection or latent TB is a positive tuberculin skin test or a radiologically evident calcification at the site of the primary lung infection or affected lymph node (13, 18). TB may, however, progress from either primary or latent



infection to active disease (13, 18). Disease progression can occur locally (at the site of the primary focus or regional lymph nodes), or at distant sites via lymphohaematogenous spread (9, 13, 14).

### **2.2.1. Local disease progression at the primary focus (primary progressive TB)**

Local disease progression occurs as a result of poor disease containment (14). The parenchyma undergoes progressive caseation and necrosis resulting in a parenchymal cavity (14). The cavities provide an ideal environment for further multiplication of the organism and promote further disease progression (14). The eruption of the caseated material into a bronchus leads to intra-bronchial spread of the organisms with resultant patchy areas of bronchopneumonic consolidation that could involve multiple lung segments (14).

### **2.2.2. Local disease progression involving the regional lymph nodes (LBTB)**

The regional lymph nodes become inflamed, oedematous and enlarged (14). They subsequently cause both intra- and extra-luminal airway complications (14).

The enlarged lymph nodes can result in extra-luminal compression of the airways (14). This complication is particularly evident in infants and younger children (14). The airway compression leads to segmental atelectasis and obstructive emphysema (20).

The inflamed lymph nodes can adhere to the bronchi that are in close proximity (14, 21). They in turn cause oedema and ulceration of bronchial mucosa and may eventually lead to the formation of granulomatous tissue within the airway (14, 21). These changes can lead to obstruction of the affected bronchus. Intra-luminal polyps or caseous material within the airway can also lead to bronchial obstruction (14). Air and fluid are resorbed in

the lung segment distal to this obstruction with resultant atelectasis (14, 21). In some cases a ball-valve type of obstruction can occur leading to hyperinflation of the distal lung segment (14, 21-23). Obstruction and atelectasis most commonly occur in the anterior segments of the right upper lobe, the right middle lobe and the lingular lobe (21).

Infected lymph nodes can cause further complications by eroding into adjacent structures such as the oesophagus, the pericardial space, the thoracic duct and the bronchi (14, 24, 25).

The airway disease, as well as the above complications resulting from lymph node involvement due to TB, are collectively referred to as LBTB (14). This is a severe and potentially life-threatening complication of TB (3).

### **2.2.3. Haematogenous spread (miliary and extrapulmonary TB)**

Haematogenous spread of TB can be divided into two groups. The first group is termed occult spread and occurs commonly after primary infection (14). It rarely progresses to disseminated disease but can involve any organ. In very young patients (age less than two years) or immunocompromised patients occult spread can progress to disseminated disease (14). The second type occurs when an infected lymph node or focus erodes into a blood or lymph vessel. This rarely occurs but usually leads to disseminated disease regardless of age or immune status of the patient (14).

Haematogenous spread of TB could result in extrapulmonary TB or miliary TB. Miliary TB occurs in 2-10% of primary TB cases and usually occurs within six months of tuberculous infection (12, 16, 21). It is a life-threatening complication of TB. In children, 54% of cases of miliary TB occur in children under the age of one year (16).

## **2.3. TB susceptibility in children and infants**

Newton described the transmission of TB in children in 2008 (10). He reported that, in most situations, children contract TB after exposure to a household contact (10). Several factors such as the infectiousness of the source, the proximity of the source and the duration of contact influence the risk of infection (10). Often, the source is an adult with cavitary disease or an older adolescent that the child is exposed to (10). Once the child is infected the risk of progression from latent TB to active disease is largely dependent on the child's age, immune status, nutritional status and vaccination history (10).

### **2.3.1. Environmental factors**

Environmental factors play a large role in determining the risk of infection with TB. The association of overcrowding and poor socio-economic status with TB infection is well known (26). In South Africa there has been prominent increase in the HIV and TB infection rates in women of childbearing age (27). This in turn directly affects the exposure of infants to both HIV infection and TB (27). Infants are restricted to environments where they are closely monitored by their caretakers. They are also usually kept indoors with their caretaker. If the caretaker is infected with TB the duration of exposure to the organism, the proximity of the source and, if they remain indoors, a lack of good ventilation, all place infants at an increasingly high risk to contract TB (10).

### **2.3.2. Nutrition**

Nutrition plays an important role in the integrity of the immune system. Malnutrition, a common finding in South African children, significantly impairs cell-mediated immunity as well as macrophage activation (10, 28). These factors are critical in the host's defence

against TB. Cell-mediated immunity is directly linked to the risk of progression from TB infection to active disease (28). Malnutrition is therefore an important risk factor for TB infection to progress to active disease (10, 28).

### **2.3.3. Immune status**

The immature immune systems of children and infants predispose them to infection with TB. Immunosuppression due to a variety of causes has the same effect (12). The host's innate immune response to the TB organisms starts when the organisms reach the alveoli (12). The alveolar macrophages ingest the organisms; if the macrophages cannot destroy the organisms they proliferate within the macrophages and are released (12). The organisms rapidly multiply and spread through the host's body (12). The development of cell-mediated immunity curbs this initial infection (12). The specific immunity of an immunocompetent patient is usually sufficient to then arrest the infection (12). The Ghon complex then heals, undergoing fibrosis and calcification while the host remains asymptomatic (12).

Infants have an immature immune system with poor monocyte recruitment to the site of infection (10). The monocytes of children are also less effective in killing the organisms compared to those of adults; thus the first line of defence is impaired (10). The organisms have the opportunity to overwhelm the infant's innate immune system before the antigen-specific immune response is activated (10). The neonatal BCG vaccination is a means to assist the immature immune system and it has been shown to decrease the risk of disseminated disease in this age group (10). Children with HIV (another cause of immunodeficiency) have been shown to have an eight times higher risk for contracting TB than HIV-uninfected children (24). This, again, emphasises the role of cell-mediated

immunity in protecting the host against TB (10).

#### **2.3.4. Age**

Children usually develop TB disease within the first year of infection and it is therefore believed that disease in young children is mostly as a result of recent infection or primary TB (10).

Compared to adults, children have a much higher risk of disease progression from latent to active TB and children below the age of two years have the highest risk (10). The risk of complications and progression to disseminated TB is also higher in children especially in children under the age of two years (16). LBTB is one of the complications of TB that is particularly prevalent in children under the age of five years and associated with a high morbidity (14, 29).

#### **2.4. Airway anatomy in children and infants**

Infants are more susceptible to respiratory infections due to the size and compliance of their airways (30). Airway anatomy and development is of significant importance in the pathogenesis of TB and especially in LBTB.

Most of airway development takes place before birth (31). The branching pattern of the airways is completely developed by the sixteenth week of intrauterine life (30, 31). After 22 weeks gestational age the airway diameter increases linearly with age (31) and the airway diameter and length can increase up to threefold between birth and adulthood (30, 31).

Airway cartilage develops from proximal to distal. It can be demonstrated in the trachea by the 4<sup>th</sup> week of gestational age and the main bronchi by the 10<sup>th</sup> week. It continues to extend more peripherally to the second and third order bronchi up until two months of age (31). After that cartilage progressively increases in amount and mass throughout childhood (30, 31).

Tracheal cartilage consists of intermittent c-shaped rings, while bronchial cartilage consists of cartilage plates that encircle the airways (32). Distally these cartilage plates decrease in size and become more discontinuous towards the bronchioles (32). The amount of cartilage decreases from the proximal to the distal airways irrespective of age (30).

The airways of infants are thus smaller in calibre with less cartilage than those of older children and adults. This makes the airways more susceptible to compression by enlarging lymph nodes surrounding the tracheobronchial tree (7, 33). These anatomical differences of the airways of infants and younger children affect the way they present with TB. This is especially evident in children younger than five years of age (10, 20).

## **2.5. Manifestations and classification of TB in children**

The differences in the manifestation of TB in the different paediatric age groups can be attributed to a variety of factors including the changing anatomy and the developing immunity of the child at various ages. It has been well researched and reported that certain age groups are more prone to develop specific manifestations and complications of TB (10, 14, 16, 20, 21, 34). Older children and adolescents appear to be more likely to develop parenchymal abnormalities, cavitary disease and pleural effusions;

lymphadenopathy is a less prominent feature of TB in this age group (10, 20). In contrast, children below the age of five and especially infants demonstrate lymphadenopathy as the main, and often the only, radiological feature of TB (7, 20, 35). As a consequence of the anatomy of the airways in this latter age group, patients with TB are predisposed to the development of complications secondary to the infected lymph nodes i.e. LBTB (7, 20).

In a recent article a new classification of TB based on disease severity was proposed (3). In this article LBTB, which might previously have been considered equivalent to latent disease, is classified as severe disease, which implies that it has serious sequelae and should prompt aggressive intervention (3).

## **2.6. Diagnosis of TB in children and infants**

The diagnosis of TB in children is a complicated and imprecise process (1). This is due to the paucibacillary nature of TB in children and the inability of a child to expectorate sputum (1). The diagnostic yield of gastric aspirates is also poor and the tuberculin skin test is not very sensitive or specific (1). TB is known to culture slowly and it may take up to six weeks to obtain results (9). Gene Xpert testing has been very helpful in adults. In children however, it is difficult to obtain the sputum sample required to perform the Gene Xpert test (1). The testing of stool samples for TB is currently under investigation and may show promise to aid in diagnosis in the future (36).

Radiological investigations therefore continue to be used to confirm the presence of TB infection and are recommended by the WHO (1). The value of chest radiographs is widely reported and it is suggested that all children with suspected TB should receive a chest

radiograph as part of the investigations (22). However, in young children, where the main feature of TB is lymphadenopathy (33), a chest radiograph may be insufficient to make the diagnosis. A study by Swingler et al centred in Cape Town demonstrated poor diagnostic accuracy in detecting lymphadenopathy utilising either frontal or both frontal and lateral chest radiographs (37). A contrast-enhanced CT scan of the chest has been shown to be the investigation of choice to detect lymphadenopathy (9). In up to 60% of children with normal chest radiographs, CT has detected lymphadenopathy (9).

## **2.7. Imaging features of LBTB**

CT scanning is the gold-standard for detecting hilar and mediastinal lymphadenopathy and thus for evaluating children with LBTB (6). It is utilised in diagnosing LBTB, determining the severity and evaluating the complications thereof (7).

The most common sites for lymphadenopathy are the subcarinal, hilar and para-tracheal regions (6, 7, 17, 33, 35) but multiple sites are often affected (7, 35). Lymph nodes larger than one centimetre are considered to be pathological (6). Diseased nodes can exhibit 'ghost-like' enhancement (6) or a 'rim-enhancing' pattern (38). Nodal calcifications appear to be an uncommon finding (6).

Any nodal group draining the pulmonary parenchyma can potentially be affected, however literature reports a tendency towards right-sided lateralisation of detected lymphadenopathy and parenchymal complications (7, 20, 35, 39).

Airway compression by the infected, enlarged lymph nodes, also termed LBTB, is more easily detected on CT scan than with chest radiography (7, 9).



Parenchymal complications including consolidation, collapse, expansile pneumonia, necrosis and breakdown may complicate LBTB and other findings related to TB such as miliary nodules, intracavitary bodies, pleural disease and oval focal bodies can be demonstrated with cross-sectional imaging (7).

## **2.8. Management strategies of complicated LBTB**

Management strategies that will be considered in children with debilitating airway symptoms secondary to LBTB include bronchoscopy and surgical enucleation of the diseased lymph nodes (29, 40).

Bronchoscopy is preferred for evaluation of airway stenosis and removal of caseating material from herniated lymph nodes from the airways (29).

In the event of life-threatening airway stenosis or a child requiring assisted ventilation due to airway stenosis, thoracotomy and enucleation of the affected lymph node groups are indicated (29).

There are several other indications for surgical enucleation of the tuberculous lymph nodes (29, 40). These include respiratory failure secondary to perforation of a node into a major airway, complete stenosis of a major airway with parenchymal complications, permanent airway stenosis as a result of fibrosis and superior vena cava or oesophageal obstruction (29, 40).

It is thus important that the presence of LBTB, the severity of airway compression and the complications thereof be accurately identified on imaging for management to be instituted timeously and prior to the development or evolution into severe complications.

## **2.9. This project in context: Literature on the topic**

Early diagnosis and treatment of TB in children is vital to prevent the development of complications. Although lymphadenopathy is characteristic of TB in children, not all children with hilar or mediastinal lymphadenopathy develop LBTB (7).

The radiological features and complications of TB have been described in several studies reporting on the chest radiography and CT findings of TB in children (6, 7, 15, 17, 33, 35, 41, 42).

These studies include children ranging from three weeks to 17 years in age and the prevalence of lymphadenopathy varies from 63% (41) to 100% (7, 33). Despite demonstrating a high prevalence of lymphadenopathy in children with TB, the differences relating to the ages of the patients in the study populations are not statistically compared.

In the studies where the mean age of the children was younger, the prevalence of lymphadenopathy was reported to be higher, and in most studies it approaches 100% (7, 33).

There was also a higher incidence of lymphadenopathy in children and infants undergoing CT (6, 7, 15, 17, 33) compared to chest plain film, raising the question whether the differences are due to the method of detection.

The distribution of lymphadenopathy varied between the studies; however the subcarinal and para-tracheal regions appear to be most commonly involved (6, 7, 15, 33).

The prevalence of airway involvement ranges from 29% (6) to 100% (7). Lucas et al (7) reported 100% airway involvement, however it should be noted that Lucas et al evaluated a pre-selected patient group presenting with airway symptoms to a paediatric pulmonologist. Andronikou and colleagues, however, reported a 29% prevalence of airway compression by lymphadenopathy in a paediatric group with TB that was imaged.

The three studies most representative of TB imaging findings in infants are the 2006 study by Kim et al (33) (mean age of six months) and the studies by Lucas et al (7) (mean age of 27 months) and Khatami et al (42) (63% of study population aged younger than one year). Kim et al and Lucas et al found 65% (33) and 100% (7) airway involvement on CT respectively and also high parenchymal complication rates of 100% (33) and 95% (7) respectively. The subcarinal, right para-tracheal and hilar lymph nodes were reported to be most commonly affected in infants (7, 33, 42).

In the report by Khatami et al, chest radiographs were the imaging modality studied (42). This study found a 90% lymph node involvement with a lower incidence of parenchymal disease of 83% (42), which may reflect the method of detection. Airway involvement was not evaluated and the study included a small study sample of only 30 patients ranging from two to 163 months (42).

Lucas et al (7) investigated the same patient group as the current study but the study by Lucas et al (7) did not separate the study population into various age groups for comparison and thus evaluated the sample population in its entirety. CT was the method of detection in this study and 100% lymph node involvement and 95% parenchymal involvement was demonstrated overall (7). Airway compression secondary to lymphadenopathy was present in all the patients, most commonly affecting the bronchus

intermedius. The presence of airway compressions in all the patients reflects the clinical indication for imaging in this study which was the presence of airway symptoms.

In 2006 Kim et al (33) investigated the radiological findings of a group of infants with tuberculosis who had received both chest radiographs and chest CT scans. A higher incidence of lymphadenopathy (100% vs. 72%), airway involvement (65% vs. 16%) and parenchymal disease (100% vs. 80%) was detected with CT compared to chest radiography (33). These differences confirm that the method of detection influences the frequency of findings reported especially with regard to airway compression and lymphadenopathy, which are underestimated on chest radiographs.

The studies most representative of radiographic findings of TB in older children are those by Lamont et al (41), Leung et al (35), Andronikou et al (6), Mukund et al (15) and the 1997 study by Kim et al (17).

Lamont et al (41) and Leung et al (35) studied chest radiographs. These studies demonstrated a 63% (41) to 92% (35) lymph node involvement and a 70% (35) to 82% (41) parenchymal disease prevalence. These findings are lower than in the comparable studies, however it should be noted that the studies by Lamont and Leung were conducted more than 20 years ago and the method of detection and advancements in technology aiding detection should be taken into account.

Andronikou et al investigated patients with suspected TB and found 92% lymph node involvement and 29% airway involvement on CT (6).

Mukund et al found 97% lymph node involvement and 70% parenchymal disease on CT in patients with confirmed TB (15).

The 1997 study by Kim et al reported on children with a higher mean age than the other similar studies and demonstrated a comparatively lower incidence of lymphadenopathy (17). This supports the findings in the previously discussed literature (10, 20), that lymphadenopathy is a less prominent feature of TB in older children than in younger children.

The most common locations of airway compression reported in the studies by Andronikou et al (6) and Lucas et al (7) were the left main bronchus and the bronchus intermedius respectively. A major difference between these studies is that Andronikou's patient group did not have symptoms of airway compression whereas Lucas's patient group had symptoms of airway compression warranting specialist consultation (6, 7). This suggests that one requires moderate to severe compression to cause airway symptoms and this degree of obstruction most frequently occurs at the bronchus intermedius according to Lucas's (7) study.

The current study compared the CT findings of LBTB in infants to those in children older than one year of age to determine whether airway compression and complications secondary to LBTB are indeed more severe in infants. This information will affect future management strategies for the different age groups, which include detecting surgical candidates.

## **2.10. Study objectives**

This study aimed to compare the CT findings of infants with confirmed LBTB to those of older children with regard to:

- the location, frequency and degree of airway stenosis
- the location and size of tuberculous lymph nodes implicated in airway stenosis
- the frequency of parenchymal complications of LBTB
- the frequency of other findings related to TB including oval focal lesions, miliary nodules, pleural calcifications and intracavitary bodies

### **3. Materials and Methods**

#### **3.1. Research paradigm**

This study was a retrospective analysis of CT scan reports and patient records from an established database that was developed by the Department of Paediatrics and Child Health at the University of Stellenbosch for a larger clinical project. Ethics approval for this study was obtained on 7 July 2014: ethics clearance number M131163 (the ethics clearance certificate is attached as Appendix A).

#### **3.2. Database**

The database comprised of children below the age of 13 years with confirmed TB who had symptoms of major airway compression and presented to a paediatric pulmonologist between 1 March 2004 and 31 August 2010. In patients who had persistent symptoms of airway obstruction after a month of treatment with quadruple anti-TB medication and steroids, a diagnosis of LBTB was made. These patients underwent fiberoptic tracheobronchoscopy and a CT scan of the chest as part of their routine clinical investigations.

All CT scans were performed on a Toshiba four-slice Aquilon Multidetector CT scan. The Tygerberg Hospital radiology department's paediatric CT protocol was followed using 120kVP tube voltage and 50mA tube current. Intravenous contrast at 2ml/kg was administered via hand injection. Scanning was done in 1mm slices and reconstructed in 5mm slices for review. Mediastinal windows, lung windows and high resolution reconstructions on the lung windows were created and reviewed by one paediatric radiologist, who recorded:

- The presence and distribution of airway stenosis as well as the airway calibre measurement at the level of maximum stenosis.
- The presence and distribution of lymphadenopathy as well as the size of lymph node conglomerate causing the airway stenosis.
- The presence of parenchymal complications e.g. air trapping, collapse, consolidation, necrosis and cavitation.
- The presence of findings related to TB including oval focal bodies, miliary nodules, pleural disease and intracavitary bodies.

The clinical data as well as the CT reporting data were captured onto an Excel spreadsheet and stored as part of the database for use in a larger study. The relevant data was subsequently extracted for use in the current analysis.

### **3.3. Study sample**

#### **3.3.1. Inclusion criteria**

The original database included children below the age of 13 years who presented with airway symptoms, had culture-confirmed tuberculosis, and underwent multidetector CT scans and fiberoptic tracheobronchoscopy as part of their evaluation under the care of a paediatric pulmonologist. The first 100 patients from the database were included in this study.



### **3.3.2. Exclusion criteria**

Children in whom the clinical data and/or CT scan reports were unavailable or incomplete were excluded from the study. Two cases were excluded due to insufficient data.

### **3.4. Data collection and analysis**

100 patients were included in this study of which two were excluded with a remainder of 98 patients. Of these patients, ten were intubated and ventilated at the time of the CT scan. The ventilated patients were analysed as a separate group. The data from the remaining 88 patients were divided into two groups: children aged from birth up to and including 12 months ('infants') and children from 13 months to 13 years ('older children').

Eight distinct anatomic locations within the tracheobronchial tree were evaluated. These areas were the trachea, carina, right main bronchus, bronchus intermedius, right lower lobe bronchus, left main bronchus, left upper lobe bronchus and left lower lobe bronchus. Airway compression was assessed at these sites and the frequency of compression at these sites was compared between the two age groups. Images demonstrating examples of airway compression are shown in Figure 3.1.

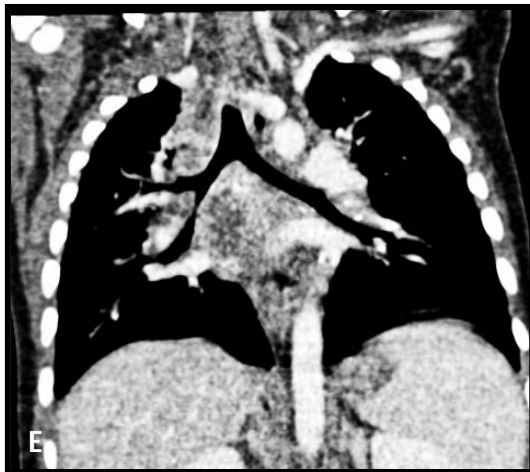
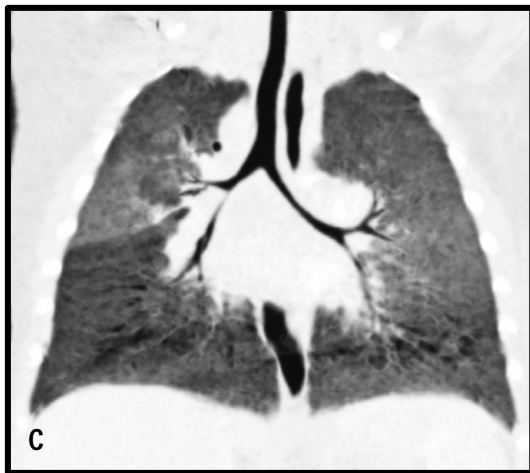
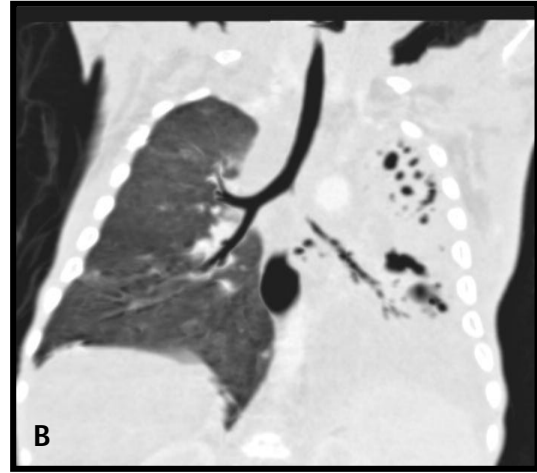
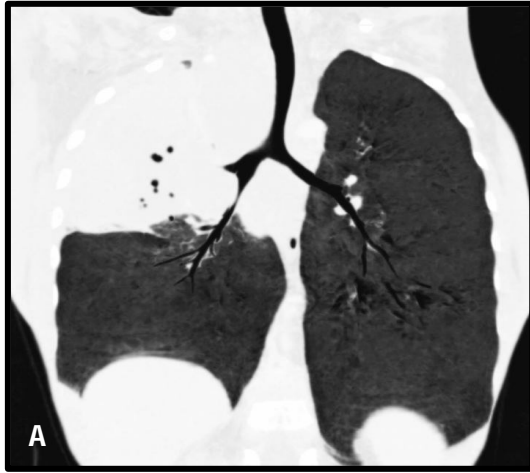
For determining the severity of airway compression, the airway diameter of the stenotic airway segment was expressed as a percentage of expected normal for age for that location. Normal reference values for airway diameter according to age was obtained from existing literature (7). The percentage airway compression of each airway in the respective age groups was classified according to severity. A severity classification was obtained from a previous publication that based on clinical severity: mild (1-50%), moderate (51-75%), severe (76-99%) and complete (100%) (43).

The severity of airway stenosis at each location was compared between the two age groups.

The size and location of the offending lymph node conglomerate mass resulting in airway compression was compared between the two age groups. Images demonstrating mediastinal lymphadenopathy are shown in figure 3.2.

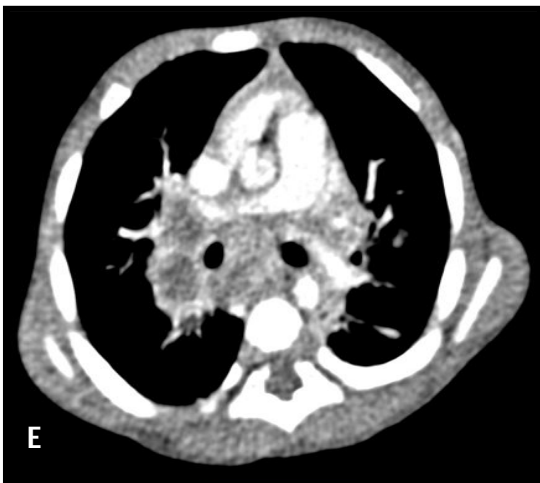
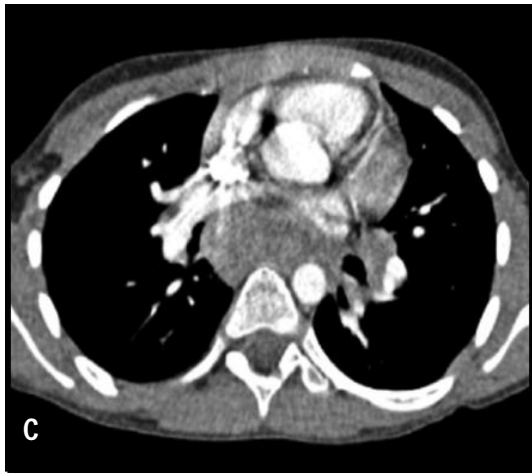
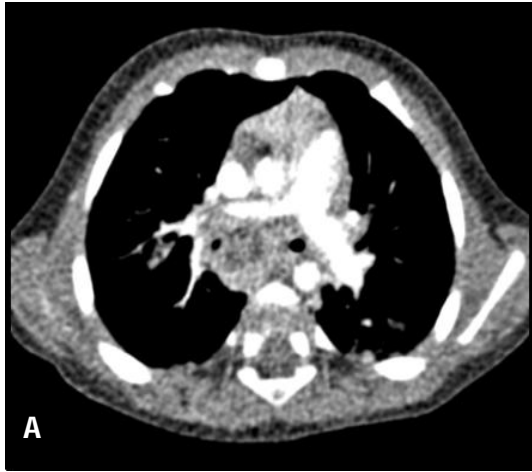
Any pulmonary parenchymal complications associated with tuberculosis were documented and their frequencies were compared between the two age groups. Images demonstrating parenchymal complications secondary to LBTB are found in Figure 3.3.

Other findings related to TB were also documented and compared between the two age groups.



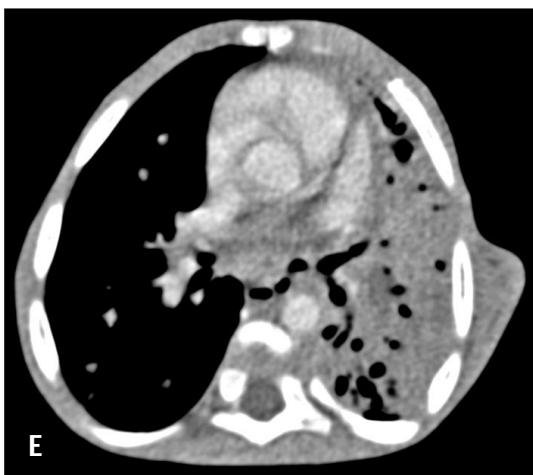
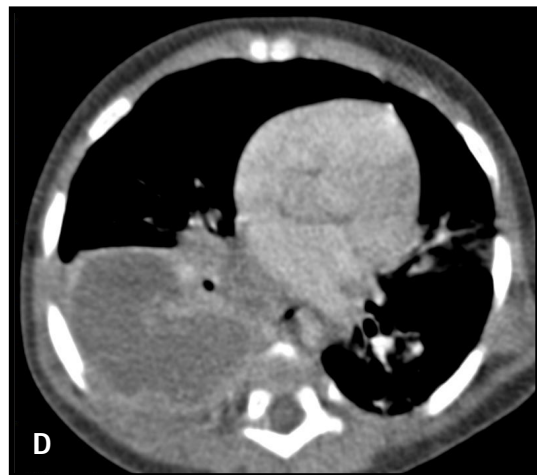
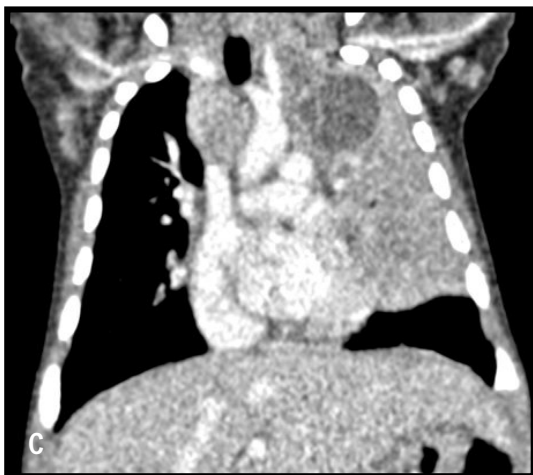
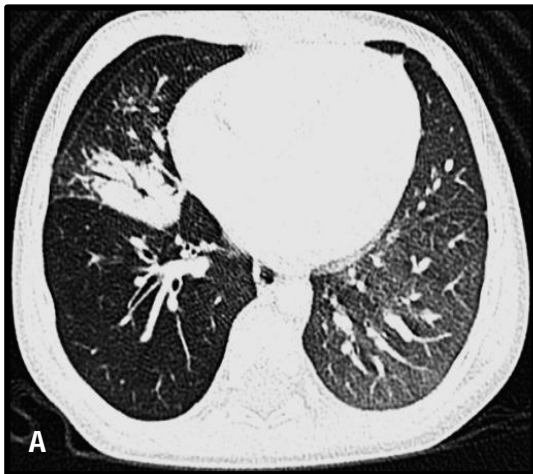
**A:** Complete obstruction of the right upper lobe bronchus with stenosis of the bronchus intermedius and consolidation of the right upper lobe  
**B:** Occlusion of the left main bronchus and left upper lobe bronchus with consolidation and cavitation of the left lung  
**C:** Stenosis of the bronchus intermedius  
**D:** Occlusion of the left main bronchus  
**E:** Stenosis of the bronchus intermedius

**Figure 3.1. Coronal reformatted CT images demonstrating airway stenosis secondary to compression by lymph nodes in children with LBTB**



**A:** Subcarinal lymphadenopathy with stenosis of the right and left main bronchi  
**B:** Superior mediastinal lymphadenopathy with ring enhancement  
**C and D:** Subcarinal lymphadenopathy  
**E:** Subcarinal and hilar lymphadenopathy

**Figure 3.2.** Axial and coronal post contrast CT images demonstrating lymphadenopathy in children with LBTB



**A:** Hyperinflation of right lung with an area of right middle lobe consolidation  
**B:** Stenosis of the left upper lobe bronchus with left upper lobe consolidation  
**C:** Left upper lobe consolidation and necrosis  
**D:** Right lower lobe consolidation and necrosis  
**E:** Consolidation and collapse of the left lung with bronchiectasis and cavitation

**Figure 3.3. Axial and coronal CT images demonstrating parenchymal complications in children with LBTB**

### **3.5. Permission and ethics approval**

Ethics approval for the larger study was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, Stellenbosch University (N10/08/282).

Permission to utilise the database was granted by the database gatekeeper and ethics approval from Tygerberg Hospital was obtained on 30 June 2014.

Ethics clearance from the University of Witwatersrand Human Research Ethics Committee was obtained; the clearance certificate (M131163) is attached as Appendix A.

### **3.6. Statistical analysis**

The data was analysed using the statistical analysis software, STATA.

The descriptive statistics of the data set were calculated for each of the specified age groups as well as for the overall data set. These descriptive values were compared between the age groups for each of the study objectives.

The Fischer's exact test was used to analyse and compare the location and severity of airway stenosis between the patient groups. It was also used to compare the lymph node location, parenchymal complications and related findings between the two patient groups.

The Wilcoxon rank-sum (Mann-Whitney) test was used to analyse and compare the lymph node sizes at the various locations.

Odds ratios were used to analyse and compare the severe and complete airway stenoses.

Regression analysis was also used to further evaluate the complete airway stenoses.

## 4. Results

### 4.1. Study population

This study was performed using data from 98 patients with confirmed LBTB. Ten of these patients were intubated at the time of the CT scan and were analysed as a separate group. The remaining 88 patients comprised of 42 infants (0-12 months) and 46 children (13 months to 12 years).

The ages ranged from two to 144 months. The mean age of the **non-intubated infant** group was 7.1 months and the median age was 7 months. The mean age of the non-intubated **older child** group was 47.4 months and the median age was 31 months.

The **intubated** group consisted of eight infants and two older children, ages ranging from two to 78 months. The mean age of the intubated patients was 14.9 months and the median age was 8 months.

## 4.2. Airway compressions in non-intubated patients: distribution and frequency

Eight locations within the tracheobronchial tree were examined for airway stenosis.

These areas included the trachea, carina, right main bronchus, bronchus intermedius, right lower lobe bronchus, left main bronchus, left upper lobe bronchus and left lower lobe bronchus.

The frequency of airway stenosis at each location within the tracheobronchial tree is summarised in Table 4.1. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.1. Distribution of airway compressions in non-intubated patients**

Site	Infants (n=42)	Children (n=46)
Trachea	29 (69%)	32 (69.6%)
Carina	23 (54.8%)	24 (52.2%)
RMB*	7 (16.7%)	10 (21.7%)
BI*	35 (83%)	32 (69.6%)
RLLB*	14 (33.3%)	10 (21.7%)
LMB*	31 (73.8%)	29 (63%)
LULB*	1 (2.4%)	2 (4.4%)
LLLB*	4 (9.5%)	6 (13%)

\* RMB: right main bronchus; BI: bronchus intermedius; RLLB: right lower lobe bronchus; LMB: left main bronchus; LULB: left upper lobe bronchus; LLLB: left lower lobe bronchus.



The sites most commonly affected were the bronchus intermedius (35/42 = 83%) in infants and the trachea (32/46 = 69.7%) and bronchus intermedius (32/46 = 69.7%) in older children.

The number of sites with airway compressions per patient is summarised in Table 4.2. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.2. Number of sites with airway compressions per patient in non-intubated patients**

Number of sites with compressions	Infants (n=42)	Children (n=46)
0	1 (2.4%)	1 (2.2%)
1	1 (2.4%)	6 (13%)
2	10 (23.8%)	10 (21.7%)
3	12 (28.6%)	10 (21.7%)
4	10 (23.8%)	12 (26.1%)
5	4 (9.5%)	4 (8.7%)
6	4 (9.5%)	3 (6.5%)
7	0	0
8	0	0
<b>Mean number of affected sites per patient</b>	3.4	3.1

In both patient groups the majority of patients had two or more sites involved. No patients had more than six of the eight sites involved. The mean number of locations affected was 3.4 in infants and 3.1 in children.

### 4.3. Airway compression in non-intubated patients: severity

Airway stenosis at each evaluated location within the tracheobronchial tree was classified according to severity: mild (1-50%), moderate (51-75%), severe (76-99%) and complete (100%).

The number of patients with different grades of airway compression severity at the various sites in the tracheobronchial tree is summarised in Table 4.3. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.3. Frequency of airway compressions in non-intubated patients according to distribution and severity**

Severity of compression	Mild (1-50%)		Moderate (51-75%)		Severe (76-99%)		Complete (100%)	
	Infants (n=42)	Children (n=46)	Infants (n=42)	Children (n=46)	Infants (n=42)	Children (n=46)	Infants (n=42)	Children (n=46)
Site								
Trachea	27 (64.3%)	27 (58.7%)	0	2 (4.3%)	0	0	0	0
Carina	23 (54.8%)	21 (45.7%)	0	3 (6.5%)	0	0	0	0
RMB	7 (16.7%)	7 (15.2%)	0	2 (4.3%)	0	0	0	0
BI	24 (57.1%)	24 (52.2%)	2 (4.8%)	1 (2.2%)	0	0	9 (21.4%)	7 (15.2%)
RLLB	12 (28.6%)	9 (19.6%)	0	0	0	0	2 (4.8%)	1 (2.2%)
LMB	25 (59.5%)	24 (52.2%)	0	1 (2.2%)	0	0	5 (11.9%)	3 (6.5%)
LULB	0	3 (6.5%)	0	1 (2.2%)	0	0	1 (2.4%)	0
LLLB	3 (7.1%)	6 (13%)	0	0	0	0	1 (2.4%)	0
No. of compressions	121	121	2	10	0	0	18	11
No. of children with compressions	40 (95.2%)	44 (95.6%)	2 (4.8%)	8 (17.4%)	0	0	16 (38.1%)	10 (21.7%)

Mild compressions are most prevalent in both patient groups. Most of the mild compressions in infants involved the trachea (27/42 = 64.3%) and left main bronchus (25/42 = 59.5%). In older children most of the mild compressions involved the trachea (27/46 = 58.7%), bronchus intermedius (24/46 = 52.2%) and left main bronchus (24/46 = 52.2%).

There were more older children with moderate compressions than there were infants (8/46 vs. 2/42) ( $p=0.03$ ), however the patient numbers in this group were small which affects statistical reliability.

No patients (infants or older children) had severe compressions. There were no severe or complete compressions in either of the non-intubated patient groups at the trachea, carina and right main bronchus.

Infants consistently had more complete compressions than children at each site and in total. Most of the complete compressions in infants and older children were at the bronchus intermedius, (9/42 = 21.4% and 7/46 = 15.2% respectively). There were significantly more infants with complete compressions in total than children (16/42 vs. 10/46), ( $p=0.047$ ).

The risk of an infant having a complete airway stenosis at a given site, relative to that of an older child, is 1.89 fold increased.

#### 4.4. Lymphadenopathy in non-intubated patients: distribution

Six lymph node locations were evaluated, namely, subcarinal, right para-tracheal, right hilar, right azygo-oesophageal, right paracardiac and left hilar.

The number of patients with lymphadenopathy at each of the sites are summarised in Table 4.4. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.4. Distribution of lymphadenopathy in non-intubated patients**

Site	Infants (n=42)	Children (n=46)
Subcarinal	41 (97.6%)	44 (95.7%)
Right para-tracheal	41 (97.6%)	41 (89.1%)
Right hilar	36 (85.7%)	39 (84.8%)
Right azygo-oesophageal	35 (83.3%)	37 (80.4%)
Left hilar	28 (66.7%)	34 (73.9%)
Right paracardiac	4 (9.5%)	11 (23.9%)

The sites most commonly involved in both infants and older children were the subcarinal and right para-tracheal regions: infants, subcarinal (41/42 = 97.6%) and right para-tracheal (41/42 = 97.6%); older children, subcarinal (44/46 = 95.7%) and right para-tracheal (41/46 = 89.1%).

In almost all the non-intubated patients the subcarinal and right para-tracheal lymph node groups were enlarged (85 and 82 out of 88 patients respectively).

The number of lymph node groups enlarged per patient is summarised in Table 4.5. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.5. Number of sites with lymphadenopathy per patient in non-intubated patients**

<b>Number of lymph node sites involved</b>	<b>Infants (n=42)</b>	<b>Children (n=46)</b>
<b>0</b>	1 (2.4%)	0
<b>1</b>	0	1 (2.2%)
<b>2</b>	0	2 (4.4%)
<b>3</b>	2 (4.8%)	2 (4.4%)
<b>4</b>	19 (45.2%)	16 (34.8%)
<b>5</b>	17 (40.5%)	19 (41.3%)
<b>6</b>	3 (7.1%)	6 (13%)
<b>Mean number of sites per patient</b>	4.4	4.5

The majority of patients in both groups had more than three lymph node groups affected.

The mean number of sites affected in infants was 4.4 and in children 4.5.

#### 4.5. Lymphadenopathy in non-intubated patients: size of lymph nodes implicated in airway compression

At each location where airway stenosis was identified, the offending lymph node conglomerate implicated in the compression was measured. The approximate area of the lymph node was determined by calculating the product of the length and breadth of the lymph node.

The mean area (mm<sup>2</sup>) of the lymph nodes at each site of compression is summarised in Table 4.6.

**Table 4.6. Mean area (mm<sup>2</sup>) of lymph node conglomerate implicated in airway compression in non-intubated patients**

Site of compression	Infants (n=42)	Children (n=46)
Trachea	440	630
Carina	328	568
RMB*	243	591
BI*	369	575
RLLB*	394	445
LMB*	306	407
LULB*	135	234
LLLB*	234	290

\* RMB: right main bronchus; BI: bronchus intermedius; RLLB: right lower lobe bronchus; LMB: left main bronchus; LULB: left upper lobe bronchus; LLLB: left lower lobe bronchus.

The average sizes of the lymph nodes implicated in causing airway stenosis were consistently larger in older children than in infants. This difference in lymph node size could not be strongly correlated to age.

There is a statistically significant difference in the average lymph node areas between the two patient groups at the bronchus intermedius ( $p < 0.05$ ) with older children having larger lymph nodes.

The lymph node size was correlated with the degree of airway compression and no strong correlation could be found.

#### 4.6. Parenchymal complications in non-intubated patients

A number of parenchymal complications were identified in the patient groups, namely, consolidation, cavitation, air trapping, bronchiectasis, expansile pneumonia and collapse.

The frequency of the parenchymal complications is summarised in Table 4.7. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.7. Frequency of parenchymal complications in non-intubated patients**

Parenchymal complication	Infant (n=42)	Children (n=46)
Consolidation: right	32 (76.2%)	31 (67.4%)
Consolidation: left	18 (42.9%)	19 (41.3%)
Cavitation/breakdown: right	13 (31%)	14 (30.4%)
Cavitation/breakdown: left	6 (14.3%)	6 (13%)
Air trapping: right	13 (31%)	12 (26.1%)
Air trapping: left	5 (11.9%)	7 (15.2%)
Bronchiectasis: right	0	7 (15.2%)
Bronchiectasis: left	1 (2.4%)	4 (8.7%)
Expansile pneumonia: right	9 (21.4%)	10 (21.7%)
Expansile pneumonia: left	5 (11.9%)	4 (8.7%)
Collapse: right	5 (11.9%)	4 (8.7%)
Collapse: left	4 (9.5%)	4 (8.7%)
<b>Total no. of patients with right-sided findings</b>	<b>33 (78.6%)</b>	<b>36 (78.3%)</b>
<b>Total no. of patients with left-sided findings</b>	<b>21 (50%)</b>	<b>24 (52.2%)</b>



The most common parenchymal complication in both infants and older children is right-sided consolidation (32/42 = 76.2% and 31/46 = 67.4% respectively) and in both groups right-sided complications were more common than left-sided. No statistically significant difference was found between infants and children with regard to parenchymal complications.

The number of parenchymal complications per patient is summarised in Table 4.8. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.8. Number of parenchymal complications per patient in non-intubated patients**

Number of parenchymal complications	Infants (n=42)	Children (n=46)
0	3 (7.1%)	2 (4.4%)
1	6 (14.3%)	10 (21.7%)
2	9 (21.4%)	9 (19.6%)
3	17 (40.5%)	14 (30.4%)
4	3 (7.1%)	5 (10.9%)
5	1 (2.4%)	5 (10.9%)
6	2 (4.8%)	0
7	1 (2.4%)	1 (2.2%)
8-11	0	0
<b>Mean number of complications per patient</b>	2.6	2.7

Three infants and two children had no parenchymal findings. No patients had more than seven parenchymal findings. The mean number of parenchymal complications per infant was 2.6 and per older child was 2.7.

#### 4.7. Related findings in non-intubated patients

Findings associated with TB but not specific for LBTB were identified and recorded. These include intracavitary lesions, miliary nodules, oval focal lesions and pleural calcifications.

The frequency of these related findings is summarised in Table 4.9. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.9. Frequency of related findings in non-intubated patients**

Related finding	Infant (n=42)	Children (n=46)
Intracavitary lesions	3 (7.1%)	2 (4.4%)
Miliary pattern	9 (21.4%)	9 (19.6%)
Oval focal lesions	16 (38.1%)	15 (32.6%)
Pleural calcifications	3 (7.1%)	15 (32.6%)

The most common related complication in both patient groups was oval focal lesions.

The number of related complications per patient is summarised in Table 4.10. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.10. Number of related findings per patient in non-intubated patients**

<b>Number of related findings</b>	<b>Infants (n=42)</b>	<b>Children (n=46)</b>
<b>0</b>	18 (42.9%)	19 (41.3%)
<b>1</b>	17 (40.5%)	15 (32.6%)
<b>2</b>	7 (16.7%)	10 (21.7%)
<b>3</b>	0	2 (4.4%)
<b>4</b>	0	0
<b>Mean number of related findings per patient</b>	0.7	0.9

The mean number of related complication per infants is 0.7 and 0.9 per child.

#### 4.8. Airway compression in intubated patients: distribution, frequency and severity

Airway compressions were evaluated in the same manner as for non-intubated patients, however tracheal compressions could not be assessed radiographically as the patients were intubated at the time of imaging.

The distribution and severity of airway compressions in intubated patients are detailed in Table 4.11. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.11. Frequency and severity of airway compressions in intubated patients according to location**

Site	Infants (n=8)		Children (n=2)	
	Number	Severity	Number	Severity
<b>Carina</b>	7 (87.5%)	Mild: 5 <b>Moderate: 2</b>	0	
<b>RMB</b>	4 (50%)	Mild: 3 <b>Moderate: 1</b>	0	
<b>BI</b>	6 (75%)	Mild: 5 <b>Moderate: 1</b>	0	
<b>RLLB</b>	2 (25%)	Mild: 2	0	
<b>LMB</b>	6 (75%)	Mild: 5 <b>Complete: 1</b>	0	
<b>LULB</b>	0		0	
<b>LLLB</b>	0		0	

Compressions were detected in infants, however the majority of the compressions were mild. The largest number of compressions in infants was at the carina. No compressions were detected in the older children.

#### 4.9. Lymphadenopathy in intubated patients: distribution

Lymphadenopathy was evaluated at the same locations as for non-intubated patients.

Lymphadenopathy in intubated patients is detailed in Table 4.12. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.12. Distribution of lymphadenopathy in intubated patients**

Site	Infants (n=8)	Children (n=2)
Subcarinal	8 (100%)	2 (100%)
Right para-tracheal	8 (100%)	2 (100%)
Right hilar	7 (87.5%)	2 (100%)
Right azygo-oesophageal	4 (50%)	0
Left hilar	5 (62.5%)	1 (50%)
Right paracardiac	2 (25%)	0

The subcarinal and right para-tracheal regions were affected in all the intubated patients and were the most commonly affected regions in both age groups.

#### 4.10. Parenchymal complications in intubated patients

Parenchymal complications in intubated patients are detailed in Table 4.13. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.13. Frequency of parenchymal complications in intubated patients**

Parenchymal complication	Infant (n=8)	Children (n=2)
Consolidation: right	6 (75%)	2 (100%)
Consolidation: left	7 (87.5%)	2 (100%)
Cavitation/breakdown: right	0	1 (50%)
Cavitation/breakdown: left	1 (12.5%)	2 (100%)
Air trapping: right	3 (37.5%)	0
Air trapping: left	1 (12.5%)	0
Bronchiectasis: right	0	0
Bronchiectasis: left	0	0
Expansile pneumonia: right	0	0
Expansile pneumonia: left	0	1 (50%)
Collapse: right	1 (12.5%)	1 (50%)
Collapse: left	1 (12.5%)	0
<b>Total no. of patients with right-sided findings</b>	<b>7</b>	<b>2</b>
<b>Total no. of patients with left-sided findings</b>	<b>7</b>	<b>2</b>

The majority of the patients in both age groups had consolidation. All the intubated children had bilateral consolidation and left-sided cavitation.

#### 4.11. Related findings in intubated patients

The related findings in the intubated patients are detailed in Table 4.14. The number of affected patients expressed as a percentage of the total number of patients in the age group is included in brackets.

**Table 4.14. Frequency of related findings in intubated patients**

Related complication	Infant (n=8)	Children (n=2)
Intracavitary lesions	0	1 (50%)
Miliary pattern	3 (37.5%)	0
Oval focal lesions	1 (12.5%)	1 (50%)
Pleural calcifications	0	1 (50%)

Few patients had related complications and the majority of the related findings in infants were miliary nodules.

## 5. Discussion

### 5.1. Results in context

The TB epidemic in South Africa is a growing problem and children are increasingly exposed and affected. Differentiating between the features of LBTB in infants and children will enable targeting vulnerable age groups to prevent worsening and irreversible complications.

The infant age group appears to be most vulnerable to the effects of TB of the airways i.e. LBTB. Just over half of the randomly selected patients in our study were infants with the remainder of the total group ranging from 1 year up to 13 years of age. In addition the majority of the intubated patients were also infants.

In Table 5.1 the data from the non-intubated patients in the current study is compared to four similar studies where the CT findings of TB in children were evaluated. In 2006 Kim et al (33) investigated a study population with an age range similar to that of the infant group in the current study. The studies by Kim et al (17) in 1997, Andonikou et al (6) and Mukund et al (15) investigated study populations with age ranges spanning from infants to children, however the mean and median ages are older making them comparable to the older child group in the current study.



**Table 5.1. Comparison of similar studies on radiological findings of LBTB in children\***

Study	Kim (33)	Current study		Kim (17)	Andronikou (6)	Mukund (15)
Year	2006	2015		1997	2004	2011
Imaging	CT	CT		CT	CT	CT
TB	Confirmed	Confirmed. All patients with symptoms of airway compression		Confirmed	Suspected	Confirmed
No. of patients	17	<b>Infants</b>	<b>Children</b>	41	100	91
		42	46			
Age (months)	2 - 12	2 - 12	13 - 144	3 - 168	2 - 142	3 - 204
Age: mean (months)	5.9	7.1	47.4	72	Not specified	Not specified
Age: median (months)	Not specified	7	31	Not specified	21.5	132
Lymphadenopathy	100%	98%	100%	83%	92%	97% (<5yrs 100%)
Commonest sites of lymphadenopathy	Right para-tracheal & subcarinal	Right para-tracheal & subcarinal	Subcarinal	Right para-tracheal & right hilar	Subcarinal & hilar	Right para-tracheal & subcarinal
Airway stenosis	65%	98%	98%	17%	29%	35%
Commonest sites of airway stenosis	Not specified	Bronchus intermedius	Trachea and bronchus intermedius	Not specified	Left main bronchus	Not specified
Parenchymal disease	100%	93%	96%	76%	Not specified	70%

\* The current study is highlighted and divided into the 'infant' and 'older child' age groups. The study to the left of the 'current study' column is a study with a mean age group comparable to the infant group of the current study; the columns to the right of the 'current study' column are studies with older mean ages comparable to the 'older child' group of the current study.

Lymphadenopathy is the hallmark of TB and in our study 97.6% of infants had lymphadenopathy on CT. The one infant with no recorded lymphadenopathy at any of the specified sites, had mediastinal lymphadenopathy at other non-specified sites.

The lymph node regions most commonly affected in infants were subcarinal and right para-tracheal. These findings compare well with the 2006 study by Kim et al (33) with regards to the incidence and distribution of lymphadenopathy this age group.

100% of the older child group had lymphadenopathy with the most common sites affected also being subcarinal and right para-tracheal. When the findings of the older child group were compared to three other studies with similar age groups (6, 15, 17), the overall incidence of lymphadenopathy was higher than the 1997 study by Kim et al (17). This could possibly be attributed to the higher mean age of their study population where primary TB starts to give way to post primary TB without characteristic lymphadenopathy. The incidence of lymphadenopathy as well as the distribution of lymphadenopathy in our study compared well to the studies by Andronikou et al (6) and Mukund et al (15)

The findings in older children are similar to that of infants and no statistically significant difference could be demonstrated between the two patient groups with regards to the frequency and location of lymphadenopathy as well as average number of lymph node groups affected per patient.

The mean area of the enlarged lymph nodes implicated in each region with compressions were consistently larger in children compared to infants and the lymph nodes were significantly larger in children than in infants at the bronchus intermedius ( $p < 0.05$ ). There was no strong correlation between lymph node size and age and thus the difference in

lymph node size between the two age groups cannot be entirely attributed to age. There was also no strong correlation between the lymph node size and degree of airway compression. We have therefore **not** demonstrated any proof that larger nodes result in more severe airway compressions.

There was no statistically significant difference between infants and children with regard to the incidence of airway compression, however the overall incidence is much higher than the 17-65% incidence in similar studies (6, 15, 17, 33). This can be explained as our study evaluated a super-selected patient group presenting with symptoms of airway compression and does not reflect the true incidence of airway compression secondary to LBTB in the general TB-infected paediatric population.

There was no statistically significant difference in the mean number of sites with airway compressions per patient between children and infants (3.4 and 3.1 respectively).

The sites most commonly affected by airway compression were the bronchus intermedius (83%) in infants and the trachea (69.7%) and bronchus intermedius (69.7%) in older children. The only other comparative study that reported on the site of airway compression was by Andronikou et al (6). This study found that the left main bronchus was most commonly affected. This corresponds to the third commonest airway site involved in older children in the current study.

No other study has been dedicated to comparing the severity of airway compression secondary to LBTB between infants and children. In the current study, most of the detected compressions were mild (95.2% of the infant group and 95.6% of the older child group had a mild compression in at least one site in the tracheobronchial tree).

There was, however, no statistical difference between infants and children with regards to the incidence and distribution of mild airway compressions.

There was a higher number of older children with moderate compressions than infants (17.4% vs. 4.8%,  $p=0.03$ ), however the patient numbers were small which affects statistical reliability.

No severe compressions were detected in any of the patient groups. One of the possible explanations is that the airway measurements in infants and children are very small and there are technical limits to the smallest measurements possible.

Complete compressions were detected in 38.1% of infants and 21.7% of children and the difference between the two age groups was statistically significant ( $p<0.05$ ). The risk of an infant having a complete airway stenosis at a given site, relative to that of an older child, is increased 1.89 fold. The most frequent site of complete compressions in both infants and older children was the bronchus intermedius (21% and 15% respectively) but there was a consistently higher frequency of complete compressions in infants at each site in the tracheobronchial tree and overall.

The above findings show that the incidence, site and size of lymphadenopathy as well as the incidence and distribution of airway stenosis are not significantly different in infants compared to older children. However, infants are statistically more likely to have **complete** airway compressions than older children. This is probably because the airways of infants are both smaller in calibre and more compressible than those of older children based on developmental and maturational factors, which accounts for this vulnerability to LBTB.

There were parenchymal complications in 92.9% of infants, which is similar to the findings of Kim et al (33) in 2006 where 100% of patients were found to have parenchymal disease. 95.6% of older children had parenchymal complications. This is significantly higher than the 70% parenchymal involvement reported by Mukund et al (15) in 2011 and 76% reported by Kim et al (17) in 1997. A factor that could have contributed to this discrepancy are the higher mean and median ages of the patients in the studies by Kim et al (17) and Mukund et al (15). Another more significant factor that could explain the difference, is that the population in the current study comprised only patients that were seen by a pulmonologist due to airway symptoms and therefore presumably had more severe or more advanced disease.

The incidence of parenchymal complications was not statistically different between infants and older children in the current study. In both patient groups consolidation was the most common finding, and in both patient groups the findings were predominantly right-sided, which is similar to findings by Lucas et al (7) and Kim et al (17) in 1997.

There was also no statistically significant difference in the incidence of related findings and the mean number of related findings per patient.

The 10 intubated patients in the study group represent patients with clinically severe airway disease requiring ventilation. 80% of these patients were infants and only one of the intubated patients was older than 18 months. Surprisingly, the majority of compressions in this group were categorised as mild and were most commonly located at the carina. Two children in the intubated patient group had no detected compressions on CT. The only complete compression was at the left main bronchus.

Since all these patients were intubated at the time of the CT scan, a possible explanation for the discrepancy in findings could be that increased ventilatory pressures decreased the apparent airway compression severity.

Consolidation was the most common parenchymal finding in all the intubated patients, this could be a possible cause for the need for ventilatory support in these patients.

## **5.2. Current applications**

CT scan is a fast and non-invasive method of identifying patients with LBTB who are at risk to develop severe airway stenosis. However, in the paediatric population, there are concerns with regards to the radiation exposure and it is thus important to identify high-risk patient groups that should receive this advanced radiological imaging when they stand to benefit from interventional measures.

This study has demonstrated that there are no significant differences between infants and children with regards to the frequency and distribution of lymphadenopathy, airway compressions, parenchymal complications and related findings. This study has, however, demonstrated that infants have significantly more complete airway stenoses and a higher risk of developing complete airway stenosis than older children. This vulnerability to LBTB is due to the anatomical and developmental differences of the airways in infants and older children.

The patients in this study initially received medical management for one month and only if airway symptoms persisted after a month of medical treatment was cross-sectional imaging obtained. In light of the findings of this study, it can be recommended that

infants with TB presenting with symptoms of airway stenosis secondary to LBTB should be imaged using CT scanning and managed urgently to prevent further complications.

### **5.3. Limitations of the current study**

This study was a retrospective analysis of data collected for a larger study. The study population with available imaging data was limited and therefore when the population was divided into different age groups it resulted in small patient groups that made accurate statistical comparison challenging.

The CT scans in the database were interpreted by one paediatric radiologist for a larger study. The use of imaging interpretation retrospectively could lead to bias. In ideal circumstances and prospective studies more than one reader should review the images.

The tracheobronchial tree in infants has a small calibre. On analysis of the sizes of the compressed airway lumens it was noted that measurements of 1mm would have a significant impact on the severity category assigned to the airway compressions. It is also known that there are limitations to the smallest unit of measurement available during analysis of digital imaging. This created an area of potential technical limitations within the database.

Lymph node sizes were recorded in the database with two-dimensional measurements. It is, however, known that lymph nodes are three dimensional irregular structures and a two-dimensional calculation of the lymph node area could give an inaccurate representation of the true lymph node volume. It is also difficult to differentiate between a single node and a nodal mass in the setting where multiple nodes are enlarged. This decreased accuracy when comparing nodal sizes between infants and children.

#### **5.4. Future applications**

This study has demonstrated the importance of early imaging and intervention in children, and especially infants, with LBTB. Radiation exposure, however, remains a concern. Chest MRI may be a modality to pursue in an effort to reduce radiation to these children. At present, CT scans of the chest provide superior quality images of the airway and are faster and easier to obtain than MRI. Further refinement of MRI protocols may prevent the need for CT scanning in children in future.

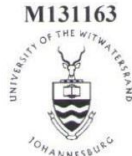


## 6. Conclusion

This study has demonstrated that there are no statistically significant differences between infants and older children with regards to the frequency and distribution of lymphadenopathy, airway compressions, parenchymal and related findings. Yet, as opposed to older children, infants with LBTB have been shown to have more complete compressions and have almost double the risk of complete airway obstruction. This is probably related to airway development and age related airway calibre.

We therefore recommend that when **infants** present with symptoms of airway compression, they should receive urgent cross-sectional imaging to guide further management including consideration for surgical lymph node enucleation.

# Appendix A: Ethics Clearance Certificate



## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL) CLEARANCE CERTIFICATE NO. M131163

**NAME:** Dr Heleen Catharien Hanekom et al  
**(Principal Investigator)**

**DEPARTMENT:** Diagnostic Radiology  
University of the Witwatersrand


**PROJECT TITLE:** Computerised Tomography Findings of Lymphobronchial  
Tuberculosis in Children: A Comparison between Infants and Older  
Children

**DATE CONSIDERED:** 29/11/2013

**DECISION:** Approved unconditionally

**CONDITIONS:**

**SUPERVISOR:** Dr S Lucas

**APPROVED BY:**   
\_\_\_\_\_  
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

**DATE OF APPROVAL:** 04/07/2014

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

### **DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

\_\_\_\_\_  
**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

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