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A comparison of the criteria used for notifying childhood tuberculosis at Coronation and Johannesburg General Hospital paediatric outpatient departments and those used by the World Health Organization for the diagnosis of tuberculosis

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A Comparison of the criteria used for notifying childhood tuberculosis at Coronation and Johannesburg General Hospital paediatric outpatient departments and those used by the World Health Organization for the diagnosis of tuberculosis

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University of the Witwatersrand, in partial fulfilment of the requirements for the degree of

Master of Science in Medicine

(Child Health Community Paediatrics)

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DECLARATION

I, Johanna Jedida Nalumango, declare that this research report is my own work. It is being submitted for the degree of Master of Science in Medicine (Child Health Community Paediatrics) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature:  Date: 08 /08 / 2014

DEDICATION

To my late father, Mashekwa Nalumango for the encouragement he gave me to register for this Masters degree.

To my mother, Pauline Nalumango who has tirelessly encouraged me to complete the course.

To my husband Felix Chembe and children, Lwipa and Peter for their patience love and support.

To God Almighty who has given me the strength and focus to complete this work.

I say Thank You to All.

ABSTRACT

Study Aim: To identify the criteria used to diagnose childhood tuberculosis (TB) at two paediatric outpatient departments in Johannesburg between 01 November 1997 and 30 June 1998 and to compare the criteria used to those used by the World Health Organization in the diagnosis of childhood TB.

Study Design: An observational descriptive, retrospective, hospital outpatient-based study.

Setting: Paediatric outpatient departments of Coronation Hospital (CH) and Johannesburg General Hospital (JGH).

Patients and Methods: Patients ranging from the ages of 3 months to 14 years who attended the two paediatric outpatient departments and were diagnosed and notified as having TB, comprised the study population. Criteria used to establish the diagnosis of TB for each patient were extracted from patient records. Clinical history and baseline clinical characteristics were analysed using standard statistical methods, and criteria used to make a diagnosis of tuberculosis were compared to those recommended by the World Health Organization.

Results: One hundred and one patients were diagnosed with TB at the two outpatient departments during the eight month study period. The combination of symptoms suggestive of active TB, which included persistent cough >1 month associated with fever, weight loss and loss of appetite, was more common in the JGH cohort (32 of 51 patients;

63%) compared to the CH cohort (10 of 50 patients; 20%); Odds Ratio (OR) 6.74 (95% Confidence Interval [CI], 2.54-18.41), P<0.001.

One third (32%) of the total group of children had a positive TB exposure history.

Tuberculin skin test (TST) reactions were positive in 86% of the total cohort, with a similar result being seen at both hospitals.

Submission of specimens for microbiological assessment was not a common practice in either outpatient department, with 95% (96 of 101 participants) not having any specimens collected.

Overall, 93% (94 of 101 participants) were classified as having 'Probable' TB.

Conclusion: Criteria being used to diagnose childhood TB in the two paediatric outpatient departments are comparable to the WHO criteria recommended for the diagnosis of childhood TB. The majority of children diagnosed were classified as 'Probable' TB. TST was the main diagnostic tool used in the two outpatient departments at the time of study conduct.

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NOMENCLATURE

AFB	Acid-alcohol fast bacilli
ARI	Annual risk of (TB) infection
BCG	Bacillus Calmette-Guérin
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CH	Coronation Hospital
EPTB	Extrapulmonary TB
HIV	Human immunodeficiency virus
IRIS	Immune reconstitution inflammatory syndrome
IUALTD	International Union Against TB and Lung Disease
JGH	Johannesburg General Hospital
LRTI	Lower respiratory tract infection
MTB	*Mycobacterium tuberculosis*
PPD	Purified protein derivative
PTB	Pulmonary TB
RMMCH	Raheema Moosa Mother & Child Hospital

TB	Tuberculosis
TST	Tuberculin skin test
WAZ	Weight-for-Age Z-score
WHO	World Health Organisation
WRHI	Wits Reproductive Health Institute

Chapter 1: Introduction

Chapter Summary

This study was conducted in the context of the ambulatory paediatric settings at two academic hospitals in Johannesburg between 01 November 1997 and 30 June 1998. The clinical approach to diagnosing tuberculosis (TB) in children in the ambulatory setting has not changed significantly over the intervening time period. This chapter discusses the burden and epidemiology of TB, the impact of human immunodeficiency virus (HIV) infection on TB disease, the diagnostic approach to childhood TB and the World Health Organization (WHO) classification of childhood TB.

1.1 INTRODUCTION

1.1.1 The Burden of TB Internationally and Locally

TB was declared to be a global emergency by the World Health Assembly in 1993 (1). Before then, it had been a relatively neglected disease in both industrialized and developing countries (2). It is estimated that a third of the global population is infected with *Mycobacterium tuberculosis* (MTB), which infects approximately 7-8 million individuals every year (3). It kills an estimated 3 million people each year (1), being the largest cause of death from a single infectious agent in the world (3). In South Africa, the burden of TB reflects that of the global community – it causes more deaths than any other infectious disease (4) and is the most common notifiable condition (5). Factors contributing to the TB epidemic in South Africa include the HIV epidemic,

accelerated urbanization, poverty, improperly managed treatment programmes, and poor compliance to anti-tuberculous therapy (6).

TB is attracting renewed interest locally and globally, with significant efforts being undertaken to revive control activities because of the increasing incidence of HIV-related TB disease (7), the threat of drug-resistant TB (8), the availability and proven effectiveness of short-course chemotherapy (9), and the realization that TB control is one of the most cost-effective health interventions in developing countries (2).

Although recent advances have been made in terms of the diagnosis of TB in the 21st Century, with heavier reliance on molecular-based techniques such as the GeneXpert diagnostic assay (10) most outpatient TB diagnosis in children still relies on the classical approach of history, clinical examination, and the use of routine diagnostic tests, e.g. Mantoux, and chest x-ray. These, routine approaches have changed little over the past decades.

1.1.2 HIV and TB

According to the World Health Organization (WHO), South Africa now ranks first in terms of TB burden, with a disease incidence of 1,003 per 100,000 population (11). HIV has been identified to be a major contributor towards fuelling the TB epidemic in the South African context, with more than 70% of TB patients also living with HIV (11). The dramatic spread of the HIV epidemic throughout sub-Saharan Africa in the past decades has been accompanied by an up to fourfold increase in the number of TB cases registered by National TB programmes in countries in the sub-Saharan African region (12).

The rising HIV epidemic has resulted in a marked increase in the incidence of adult TB (13) which may be either sputum smear-positive or -negative pulmonary TB (PTB). These adults are often parents of young children, and hence expose their children to increased risk of infection with MTB.

1.1.2.1 HIV and Child TB in South Africa

The annual risk of TB infection (ARI) amongst children living in high-burdened communities in South Africa is 4% (14), and this is largely driven by the HIV epidemic. As mentioned above, the HIV/TB epidemic has resulted in a high incidence of infectious TB occurring among young adults (20–40 years) (15); these are often parents of young children exposing their children to an increased risk of TB.

In South Africa, there is a high prevalence (around 50%) of HIV co-infection in children with culture-confirmed TB (16), thus it is recommended that an HIV test be performed on all children suspected of having TB (15,17).

HIV-infected children with their suppressed immune function, once infected with MTB have a markedly increased risk of developing TB disease. In HIV-infected children younger than 3 years, the risk of TB disease is four times greater in those with a low CD4 count (<15%), as compared to those with a higher CD4 count (≥15%) (18). Furthermore, the prevalence (2.7%) (19) of HIV amongst infants and young children compounds the burden of TB in this age group. The risk of developing culture-confirmed TB in HIV-infected infants in a TB endemic setting is over 20 times higher than in HIV-uninfected infants (15, 20). Response to TB treatment and clinical outcome has been shown to be poorer for HIV-infected children when compared to HIV-uninfected children (21). A substantial proportion

of deaths in children with HIV/TB co-infection occur in the first two months following commencement of TB treatment (15, 22). Compounding factors for poor treatment response and increased mortality include severe malnutrition, HIV related co-infections, chronic lung disease, severe immune-suppression and immune reconstitution inflammatory syndrome (IRIS) (15).

1.1.3 Programmatic Management of TB

TB control is, in theory, simple and highly cost-effective (23). Passive case-finding and the provision of short-course (six-month) chemotherapy will cure the majority of cases and, if coverage is high enough, will lead to a sustained reduction in the number of TB cases in high-burdened communities (16). This is the basic strategy advocated by WHO and the International Union Against TB and Lung Disease (IUATLD) (24).

The main focus of TB control has been on the detection of MTB in sputum smear-positive adults who spread the disease (i.e. infectious cases), but if early detection of children with TB can be achieved, this will prevent progression of the disease in these children, and also help with the tracing of (often undiagnosed) infectious adult source cases (25).

1.1.4 Childhood TB

Children become exposed to MTB when they come into contact with an infectious TB source case. The risk of becoming infected is determined by the degree of infectiousness of the source case, and the closeness and the duration of contact (15).

Children who get primary MTB infection may not develop active disease; most are asymptomatic and do not have any symptoms suggestive of TB. During primary infection with MTB, a cell-mediated immune response to the organism develops which is crucial in containing the infection in a phase of latency. This is referred to as latent TB infection. TB infection can be confirmed by a positive tuberculin skin test (TST), although these tests are less sensitive in malnourished or immune compromised children (15, 21).

MTB infection may progress to TB disease, which may result in considerable morbidity and mortality (26). Children who are at risk for progression to active TB disease include infants, children under 3 years, malnourished children, those who are immune compromised, children not vaccinated with BCG, and those who have recently (within the past two years) had their primary exposure to MTB (15). Infants who are HIV-infected have a 20-fold higher risk of developing symptomatic TB disease compared to HIV-uninfected infants (15, 20)

Children enter a period of relative protection from TB disease between the ages of five and ten years. After the age of 10 years, there is an increased risk of TB disease and the nature of the disease changes from childhood (primary TB) to adult-type TB (27). TB disease in adolescence becomes characteristically that of adult-type PTB (26) where pulmonary

cavitation is a common finding. This contributes to the destruction of lung tissue, as well as to the spread of infection in the community.

1.1.4.1 Diagnosis of Childhood TB

Undiagnosed childhood TB can give rise to considerable morbidity and mortality. Unfortunately, TB is difficult to diagnose in children as the signs and symptoms of active disease are non-specific, x-rays are often not diagnostic and isolation of the organism may not be possible (28).

Culture-confirmation of TB disease in children is achieved by using whatever specimens are available. Clinical samples for the diagnosis of suspected PTB in hospitalised children may include gastric aspirates and/or induced sputum, or expectorated sputum from older children. For the diagnosis of extrapulmonary TB (EPTB), the organ system involved should be targeted for investigation. For example, fine-needle aspiration of enlarged lymph nodes, pleural fluid aspiration, joint aspiration, lumbar puncture and biopsies of suspicious masses or swellings can be undertaken. Diagnostic yield is greater for culture than microscopy because of the paucibacillary nature of childhood PTB (15).

It is important to note that microbiological specimens are usually obtained from hospitalised patients, and are less frequently obtained in the ambulatory setting where clinical interaction of the clinician and patient is brief. If the opportunity to investigate an ambulatory paediatric TB suspect through the submission of representative clinical specimens arises, appropriate specimens (e.g. gastric aspirates, induced sputum, or fine needle aspirate of enlarged lymph nodes) from the suspected sites of involvement may be obtained for microscopy and mycobacterial culture (29, 30).

Gold standard TB diagnosis depends on culture-confirmation of the disease process, with less robust TB categorisation representing scenarios in which a greater degree of uncertainty regarding the diagnosis arises. Therefore, the diagnosis of TB in ambulatory children frequently depends on a poorer degree of evidence as specimens for mycobacterial culture are less likely to be submitted (29). Further, limited resources in the ambulatory setting are frequently encountered thereby procedures for mycobacterial culture are frequently hindered. Consequently, the clinical history including history of contact with an infectious adult source case, clinical examination and results of a few goal-directed investigations (chest x-ray and/or TST) often form the basis on which a diagnosis of TB is made in these children.

The decision to institute anti-TB therapy in a child is influenced by the degree of diagnostic certainty, potential drug-drug interactions and the possible consequences of failure to start treatment timeously (31). Child and adult TB mortality has been directly linked to failure or delay in diagnosing the disease, or to ineffective treatment (2). To tackle this problem, WHO criteria for diagnosing childhood TB have been recommended for both clinical and epidemiological purposes. A delayed diagnosis of TB can lead to widespread complicated TB disease, e.g. disseminated TB disease, chronic lung disease with recurrent co-infections, development of resistant MTB strains, or increased TB-related deaths, that are still so commonly found in paediatric wards in South Africa and other high-burdened countries.

Early identification of suspected child TB cases and being able to make a diagnosis early enough will go a long way in improving the TB-related morbidity and mortality in South African children.

1.1.4.2 The 1983 WHO Criteria for the Diagnosis of Childhood TB (Appendix 1)

Culture confirmation of a case of TB ('Confirmed' TB according to WHO criteria) is difficult in younger children as gastric aspirates and/or induced or expectorated sputum specimens need to be obtained for microbiological assessment. Collection of gastric aspirates and induced sputum specimens may cause distress to the child. The finding of acid-alcohol fast bacilli (AFB) on direct smear by this method has low sensitivity as most childhood PTB is paucibacillary in nature, and low specificity since false-positives may be produced by environmental mycobacteria or other acid-fast organisms (32). Positive results on direct microscopy should ideally be confirmed by culture. However, positive cultures are obtained in a minority of children, generally no more than 20-40% (21, 33).

Thus in children, the diagnosis of TB is made through the combination of a variety of criteria (Appendix 1 and Appendix 2, Box 1), which include:

a) Clinical signs and symptoms:
    i. Loss of appetite, and/or loss of weight;
    ii. Flat growth curve;
    iii. Weight-for-age below the -2.0 Z-score;
    iv. Failure to catch up growth after one month of nutritional support in a malnourished child;
    v. Cough, wheeze or stridor for more than 2-3 weeks;
    vi. Lassitude;
    vii. Intermittent fever.

Childhood PTB commonly presents with a progressive, unremitting cough not improving on broad-spectrum antibiotics. Duration of the cough is also important, with a minimum duration of two weeks. The characteristic cough is more common and specific for PTB in children over three years of age (34). PTB can present as acute pneumonia in children and so needs to be considered in pneumonia cases not responding to conventional forms of treatment (16, 35). The presence of other symptoms such as fever, night sweats, weight loss or failure to thrive and fatigue will also contribute towards making the diagnosis. Weight loss and/or failure to thrive is often associated with TB; a poor response to nutritional support of a malnourished child is a sensitive clinical marker of TB or HIV (15).

b) A history of contact with a source case who has smear- or culture-positive PTB.

A close TB contact is defined as an adult who has had PTB in the last 12 months, living in the same household as the child, or someone with whom the child has had frequent contact and who is or was sputum smear-positive for AFB (36). Source cases that are sputum smear-negative but culture-positive are also infectious, but to a lesser degree (15).

c) The degree of skin reactivity to tuberculin.

The TST is a useful tool in providing additional information when assessing a child with suspected PTB. It is not a marker of disease activity but, if positive, merely indicates infection with MTB (32). Limitations of the TST are seen in HIV-infected children who may be unable to mount an immune response to the tuberculin derivative, so variable sensitivity is seen (15). Other conditions that may give false negative TST results include severe malnutrition, severe TB disease (32), acute viral infection (e.g. measles), immunosuppressive therapies, and incorrect administration technique or interpretation of the test (36).

A commonly used TST method is the Mantoux test whereby two units of tuberculin purified protein derivative (PPD RT23) are injected intradermally into the volar aspect of the left forearm (mid-third). This is read 48-72 hours after administration and measured in millimetres (15).

During the conduct of this study, definitions of Mantoux positivity included:

- A transverse induration of ≥15 mm in a child vaccinated with BCG (37);
- Induration of ≥10mm in a BCG-unvaccinated child (37);

It is these parameters that will be utilised in the study analysis (see Methods section).

Currently and from mid-2000s, a positive TST is defined as:

- ≥ 10 mm diameter of induration irrespective of BCG immunisation status (36);
- ≥ 5 mm is considered positive if the child is HIV-infected or severely malnourished (36);
- A negative TST does not rule out infection with MTB.

d) Special investigations, including chest x-ray and collection of appropriate specimens for bacteriological confirmation (15).

There are no specific features on clinical examination that can confirm that the presenting illness is due to MTB. However, careful clinical examination is necessary to evaluate for other systemic focal clinical signs, e.g. asymmetrical lymphadenopathy indicating TB adenitis, distended abdomen and ascites indicating abdominal or peritoneal TB, decreased level of consciousness indicating TB meningitis, asymmetrical joint effusion indicating TB of the joint, or gibbus indicating spinal TB.

Since young children, especially those under the age of two years, are prone to develop disseminated disease after primary MTB infection (38), clinicians generally feel compelled to initiate anti-TB therapy upon what may seem to be rather scant evidence (39). A plea has been made for the use of a uniform set of diagnostic criteria for childhood TB (6,40).

WHO has suggested a graduated approach to improve the degree of certainty with which the diagnosis of childhood TB is made. Cases are classified as 'Suspect', 'Probable', or 'Confirmed' TB (7), in a manner similar to that recommended by the WHO in 1983 (41).

Suspect TB (7,41)

1. An ill child with a history of contact with a confirmed case of PTB; or

2. Any child:

- Not regaining normal health after measles or whooping cough; and/or
- With loss of weight, cough and wheeze not responding to antibiotic therapy for respiratory disease; and/or
- Painless swelling in a group of superficial nodes.

Probable TB (7,41)

A child with probable TB would be classified as such if any of the following factors are identified:

- Positive induration on Mantoux TST (41);
- Suggestive appearance on chest x-ray;
- Suggestive histologic appearance of biopsy material;
- Favourable response to specific anti-tuberculous therapy.

Confirmed TB (7,41)

- Detection by microscopy or culture of AFB from secretions or tissues; and/or
- The identification of the organism as MTB by culture characteristics.

As a high degree of suspicion is necessary to diagnose TB in childhood, it is important to know how much reliance can be placed on criteria being used to diagnose and notify TB cases.

1.2 STUDY AIMS

AIM: To compare and contrast the criteria used to diagnose childhood TB at two paediatric outpatient departments in Johannesburg between 01 November 1997 and 30 June 1998 and to compare these criteria to those used by the World Health Organisation in the diagnosis of TB (41).

We tested the hypothesis that there is no difference between the criteria used to diagnose TB in children between the ages of three months and fourteen years at Coronation and Johannesburg General Hospital when compared to the criteria used by the WHO to diagnose TB.

1.2.1 The objectives of the study were to:

a) To compare and contrast criteria being used to diagnose and notify TB in two paediatric outpatient departments in Johannesburg between 01 November 1997 and 30 June 1998.

b) To determine whether the criteria being used in the two outpatient departments are comparable with the criteria used by the WHO to diagnose TB(41).

c) To identify whether any differences exist between the criteria being used between the two paediatric outpatient departments and those of the WHO in the diagnosis of TB.

Chapter 2: Methods

Chapter Summary

This chapter defines the study cohort, baseline characteristics and the clinical and non-clinical variables used to determine the diagnosis of TB disease in the patient cohort. A description of the statistical analysis is also included in this chapter.

2.1 METHODS

This was an observational, descriptive, retrospective, hospital outpatient-based study. The setting was in two academic hospital paediatric outpatient departments, namely Coronation Hospital (now known as the Raheema Moosa Mother and Child Hospital (RMMCH)) and Johannesburg General Hospital (now known as the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)) in Johannesburg, South Africa. All children ranging from the ages of 3 months to 14 years, who attended the paediatric outpatient departments in the two academic hospitals, between 01 November 1997 and 30 June 1998, and were diagnosed and notified as having TB in these outpatient settings, comprised the study population.

The study cohort was identified by review of notification booklets completed by paediatric outpatient staff members. This approach may have led to the unanticipated outcome of missing some children diagnosed with TB but who were not notified for their condition. Identification of subjects from notification booklets was conducted on a weekly basis from each paediatric outpatient department, throughout the eight-month research period. Hospital folders were reviewed by retrieval of the records from hospital archiving departments.

Criteria used to establish the diagnosis of TB for each patient were identified by data abstraction from case hospital records. Data were abstracted onto a standardised abstraction sheet (Appendix 3), and included: clinical history, focussing on symptoms suggestive of symptomatic TB disease (e.g. fever, cough and duration, loss of appetite, weight loss, night sweats, neck swellings); history of contact with an adult PTB case; clinical details including age, gender, weight (in kilograms) at the time of notification, results of TST (the intradermal Mantoux test), chest x-ray findings, and results of microscopy and culture of sputum, gastric aspirates or other specimens.

Interpretation of the Mantoux skin test at the time the study was conducted was different to how it is currently being interpreted, and we therefore used the TST grading system used by clinicians working at the outpatient department at CH and JGH in 1997/98 (listed below) as this interpretation guided their clinical decision making. The interpretation was defined as:

- Positive if the transverse induration was ≥15mm in a child vaccinated with BCG (37);
- Positive if the induration was ≥10mm in a BCG-unvaccinated child (37);
- Negative if the induration was 5-10mm which may have indicated infection with MTB, or be a result of recent BCG immunisation (within the last two years) (42), or infection with a non-tuberculous mycobacterium (42).
- Negative if the induration was <5 mm; this would either suggest that there was no TB, or that the child had a sub-optimal immune response to tuberculin in spite of active infection with the MTB (i.e., a false negative result) (42).

HIV tests were not sought as part of this study as the majority of participants did not routinely have an HIV test done in the late 1990s.

2.1.1 Study Sample Size

An estimate as to the number of children who would be diagnosed during the study time frame was made by interrogating the number of children notified as having TB at the paediatric outpatient department of CH between 01 January and 31 July 1997. During that seven-month time period, 42 children (i.e. six children per month) had an outpatient-based diagnosis of TB. It was therefore anticipated that approximately 50 children would be diagnosed with TB at each of the study hospital outpatient departments during the eight-month study period.

2.1.2 Statistical Methods

Data were captured manually and then entered into a personal computer using Excel software (Microsoft Corporation, Seattle, USA) and analysed in Excel and Stata version 12.0 (StataCorp, College Station, Texas, USA), with the assistance of a statistician (Mr Alfred Musekiwa) from the Wits Reproductive Health Institute (WRHI).

Dichotomous outcomes were analysed using frequencies and proportions (percentages), and were represented in bar charts and pie charts. Pearson's Chi-squared test (or Fisher's exact test where appropriate) were used to compare proportions of children evaluated

using different diagnostic methodologies at each of the paediatric outpatient settings, and P-values <0.05 were considered to be statistically significant; P-values were derived using Stata version 12.0 (StataCorp, College Station, Texas, USA).

Continuous variables with normal distributions were summarised using the mean and standard deviations, while those with skewed distributions were summarised using the median and interquartile ranges. Means were compared using the Student's t test and medians were compared using the two-sample Wilcoxon rank-sum test. Weight-for-age Z-scores (WAZ) were derived using WHO AnthroPlus software, version 1.0.4 (WHO, Geneva, Switzerland).

Microsoft Excel was used for the calculation of frequencies, percentages, means, SDs, medians, and ranges. Excel was also used for the construction of bar charts, histograms and pie charts.

Chapter 3: Results

Chapter Summary

This chapter describes results of the statistical analysis of all the indicators examined, with comparisons of results from the two hospitals with the criteria used by the WHO to diagnose TB. Clinical histories and baseline clinical characteristics of the study participants are described. Graphic representations of baseline characteristics are also demonstrated in this chapter.

3.1 RESULTS

3.1.1 Clinical characteristics of children diagnosed with TB at the two Outpatient Departments

One hundred and one children were diagnosed with TB in the outpatient departments at the two hospitals during the eight month study period. Folders for each of these children were retrievable from the hospital records departments. Features on clinical history that were enquired about as part of the clinicians' evaluation for TB at both outpatient departments are summarised below (Table 3.1 and Figure 3.1).

The combination of symptoms suggestive of active TB, which included persistent cough >1 month with fever, associated with loss of weight and loss of appetite, was more common in the JGH cohort (32 of 51 patients; 63%) compared to the CH cohort where only 10 of 50 patients (20%) had this combination of symptoms and signs; Odds Ratio (OR) 6.74 (95% Confidence Interval (CI), 2.54-18.41), P<0.001 (Figure 3.1).

Table 3.1: Clinical Characteristics of Children Diagnosed with TB at CH and JGH Paediatric Outpatient Departments

Clinical History	CH (N=50; %)	JGH (N=51; %)	CH + JGH (N=101; %)	Odds Ratio (95% CI)	P-value
Fever	1 (2)	0	1 (1)	-	0.243#
Weight Loss (WL) / Loss of appetite (LOA)	4 (8)	1 (2)	5 (5)	4.35 (0.41-218.28)	0.205#
Upper Respiratory Tract Infection (URTI)	10 (20)	4 (8)	14 (14)	2.88 (0.75-13.41)	0.084
URTI + WL + LOA + Fever	14 (28)	11 (22)	25 (25)	1.41 (0.52-3.92)	0.454
Cough > 1 month	7 (14)	1 (2)	8 (8)	8.14 (0.97-373.95)	0.031#
Cough > 1 month + WL + LOA + Fever	10 (20)	32 (63)	42 (42)	**0.15 (0.05-0.39)**	**<0.001**
Neck Swellings (NS)	2 (4)	1 (2)	3 (3)	2.08 (0.10-125.32)	0.618#
NS + WL + LOA + Fever	2 (4)	1 (2)	3 (3)	2.08 (0.10-125.32)	0.618#
Total	50 (100)	51 (100)	101 (100)	-	-

WL = Weight loss; LOA = Loss of Appetite; URTI = Upper Respiratory Tract Infection; NS = Neck Swellings.

Fisher's exact test.

Few patients presented with cough of greater than one month's duration alone: CH had seven such children in their cohort, and JGH had only one in their cohort.

Cervical tuberculous adenopathy was typically described as 'neck swellings' by clinicians in both outpatient departments: this presentation was uncommon in both cohorts with CH having two such patients and JGH having only one.

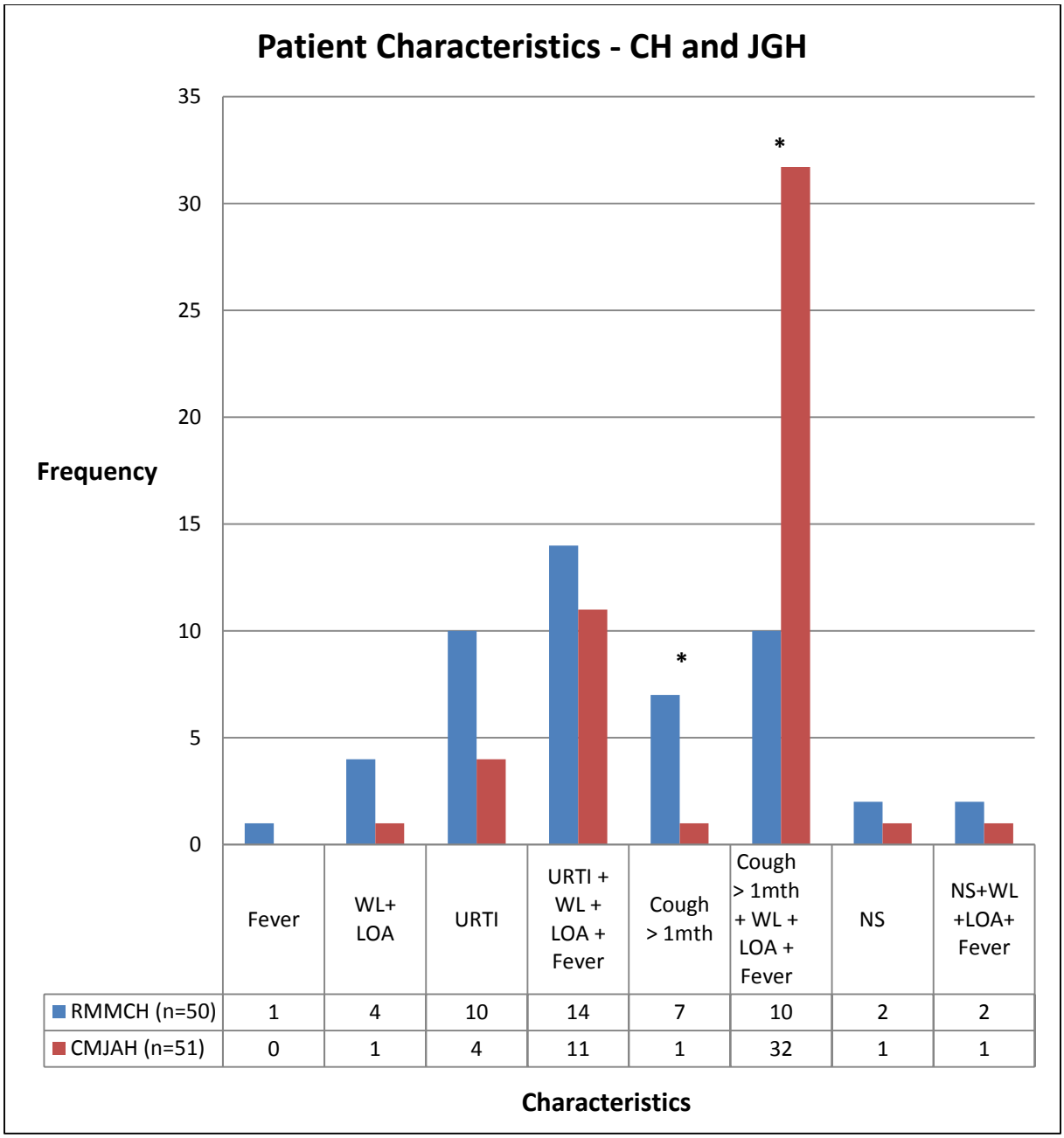


Figure 3.1: Comparison of Clinical Characteristics of patients at CH(RMMCH) **& JGH**(CMJAH)

WL = Weight loss; LOA = Loss of Appetite; URTI = Upper Respiratory Tract Infection; mth = Month; NS = Neck Swellings; RMMCH = CH; CMJAH = JGH

* P-value < 0.05

A presentation of fever alone was found in one patient from the CH outpatient clinic. No patients presented with fever alone in the JGH outpatient department.

3.1.2 Baseline Clinical Characteristics

Clinical parameters that were extracted from clinical notes and analysed included: age, gender, weight (in kilograms), history of TB contact, presenting symptoms, TST results, x-ray and microbiology (MTB smear and culture) results (Table 3.2).

3.1.2.1 Age Range of Children Diagnosed with TB in the Ambulatory Setting

The median age of the 101 TB-notified children was 24 months (Interquartile Range [IQR], 14-42 months), and did not differ significantly between hospitals, P=0.741 (Wilcoxon rank-sum test). Both cohorts presented a skewed age distribution with the majority (36%) of children lying in the <12 month age group at CH (Figure 3.2). At JGH, the majority (51%) of children were in the 13-24 month age group (Figure 3.3).

3.1.2.2 Gender Distribution

There was a slight male predominance in children diagnosed with TB on an outpatient basis, with 26 of 50 (52%) and 29 of 51 (57%) male children in the CH and JGH cohorts, respectively (Figures 3.4 and 3.5).

3.1.2.3 Weight at Time of TB Diagnosis

Weight-for-age data at time of TB diagnosis were available for 99 (98%) of the 101 children. The mean WAZ was -0.647 (Standard Deviation [SD] 1.25) amongst children managed through CH, and -0.273 (SD 0.970) amongst those managed at JGH, P=0.100.

Table 3.2: Demographic and Diagnostic Characteristics of Children Diagnosed with TB at CH and JGH Paediatric Outpatient Departments

Baseline Characteristic	CH (N=50)	JGH (N=51)	P-values	CH & JGH (N=101)
AGE (months), Median (IQR)	24 (10-52)	24 (16-36)	0.741^	24 (14-42)
SEX, N (%)				
Female	24 (48)	22 (43)	0.624*	46 (45.5)
Male	26 (52)	29 (57)		55 (54.5)
TB CONTACT, N(%)				
Positive TB contact	17 (34)	15 (29)	0.620*	32 (31.68)
No known TB contact	33 (66)	36 (71)		69 (68.32)
TST, N (%)				
Done/Positive	44 (88)	43 (84)	0.592*	87 (86.2)
Done/Negative	4 (8)	0 (0)		4 (3.9)
Not Done	2 (4)	8 (16)	0.092#	10 (9.9)
RADIOLOGY, N (%)				
Suggestive	33 (66)	19 (37)	**0.004***	52 (51.5)
Not Done	9 (18)	6 (12)		15 (14.8)
LRTI	6 (12)	0 (0)		6 (5.9)
Normal	2 (4)	26 (51)		28 (27.8)
MICROBIOLOGY, N (%)				
Done/Positive	2 (4)	1 (2)	0.205# (Comparison of proportion of cases that were investigated by means of submission of specimens at each hospital)	3 (3)
Done/Negative	2 (4)	0 (0)		2 (2)
Not Done	46 (92)	50 (98)		96 (95)

CH = Coronation Hospital; JGH = Johannesburg General Hospital; TB = Tuberculosis; TST = tuberculin skin test; LRTI = Lower respiratory tract infection; Microbiology = sputum/gastric aspirate cultures.

^ Wilcoxon rank-sum test.
* Chi-square test.
# Fisher's exact test.

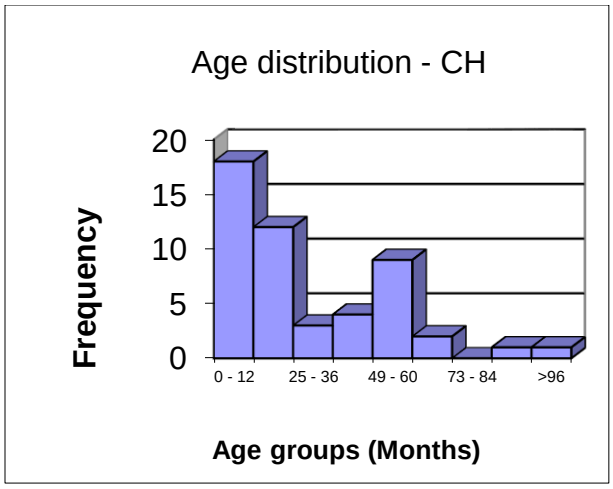


Figure 3.2: Age Distribution (CH)

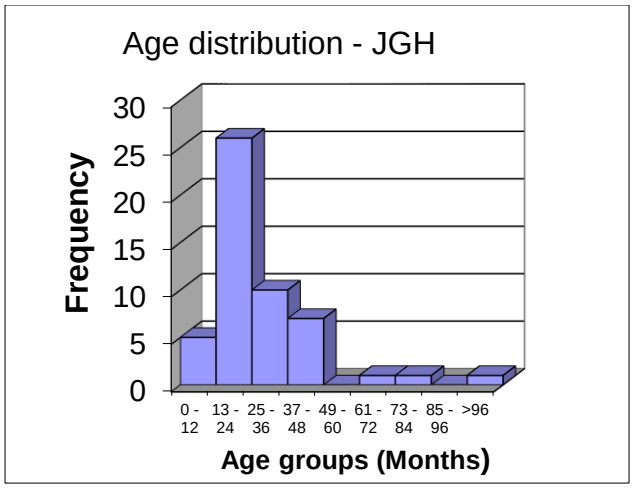


Figure 3.3: Age Distribution (JGH)

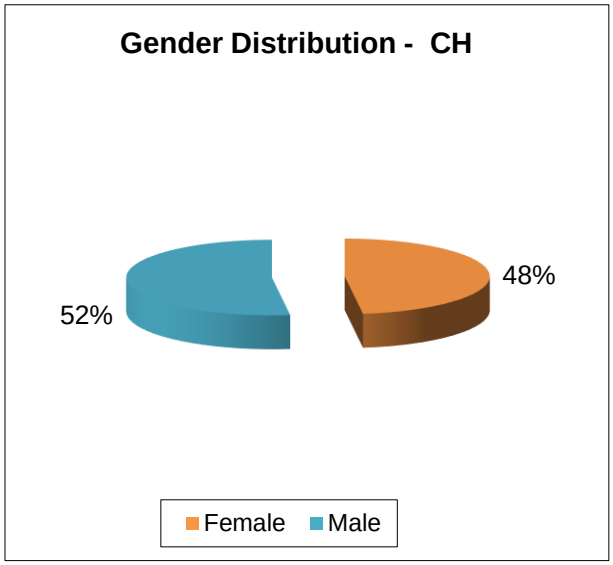


Figure 3.4: Gender Distribution (CH)

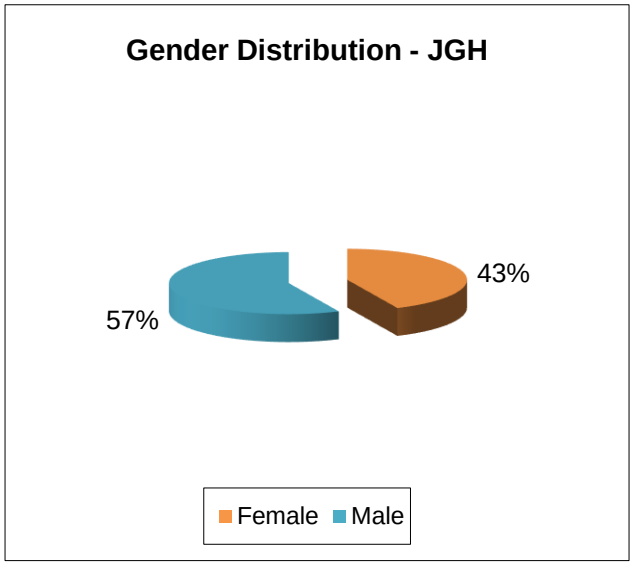


Figure 3.5: Gender Distribution (JGH)

The weight-for-age distribution (comparing WAZ distributions) in children with an outpatient TB diagnosis was similar at the two hospitals (Figure 3.6). CH had 53% (26/49) of the cohort lying between the -2 and 0 WAZ (Figure 3.7), and JGH had 54% (27/50) of the cohort lying between the -2 and 0 WAZ (Figure 3.8). Both hospitals also showed a similar distribution in their cohorts of patients lying above the 0 WAZ (median) line: CH, 33% (16/49); JGH, 38% (19/50), P=0.578.

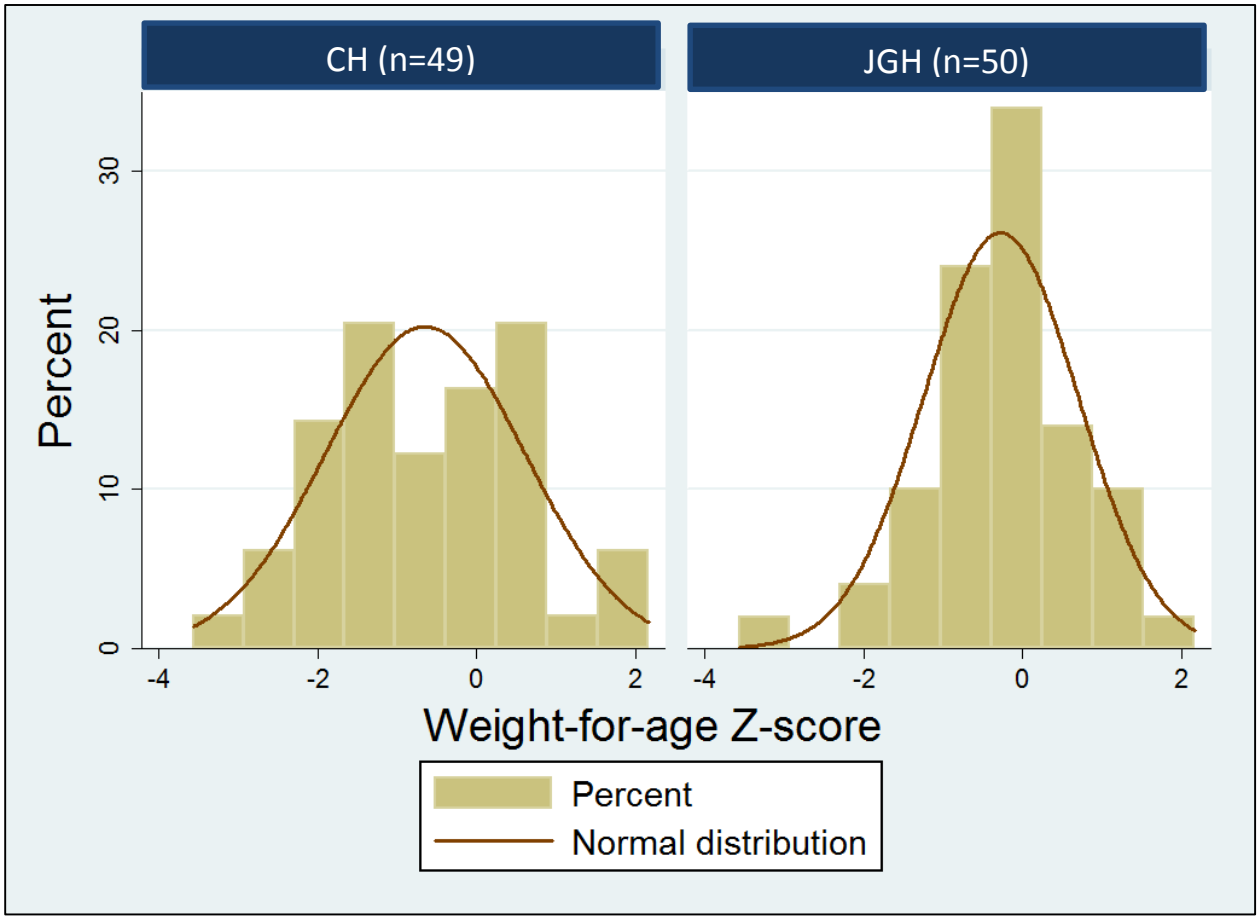


Figure 3.6: Weight-for-age Z-score distribution for CH and JGH

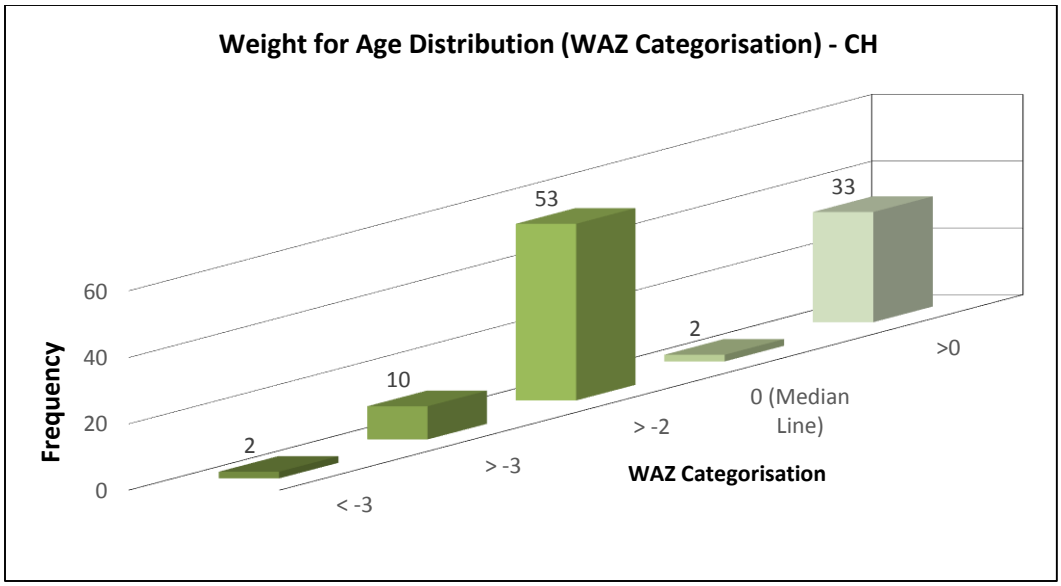


Figure 3.7: Weight-for-Age Distribution (CH)

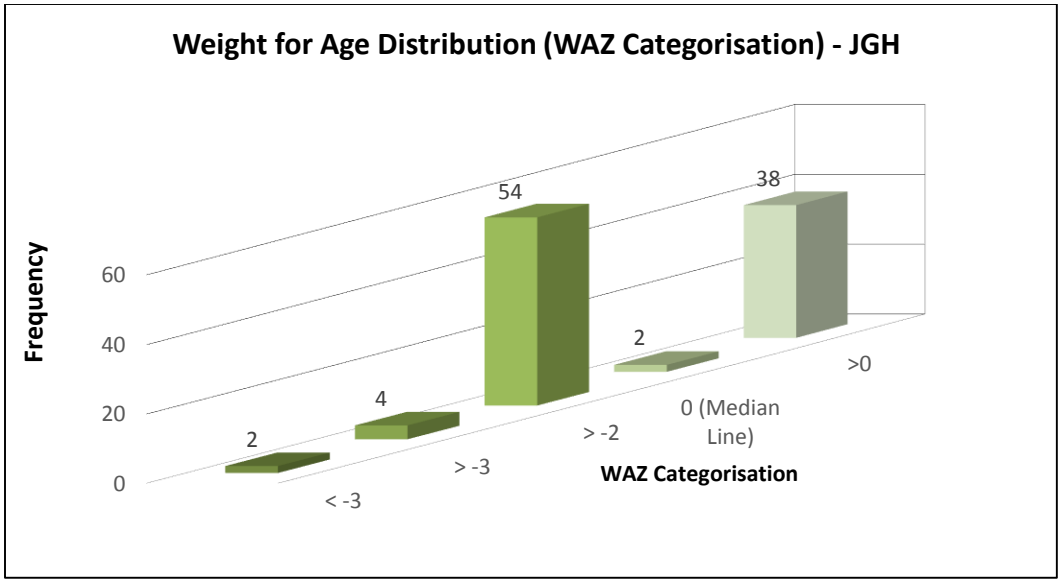


Figure 3.8: Weight-for-Age Distribution (JGH)

3.1.2.4 TB Exposure History

Almost one third (32/101; 32%) of the children had a positive TB exposure history, and this trend was seen at both hospitals, with 34% (17/50) having a positive TB contact at CH (Figure 3.9) and 29% (15/51) at JGH (Figure 3.10). Details as to who the TB contacts were, were not readily available from the hospital notes.

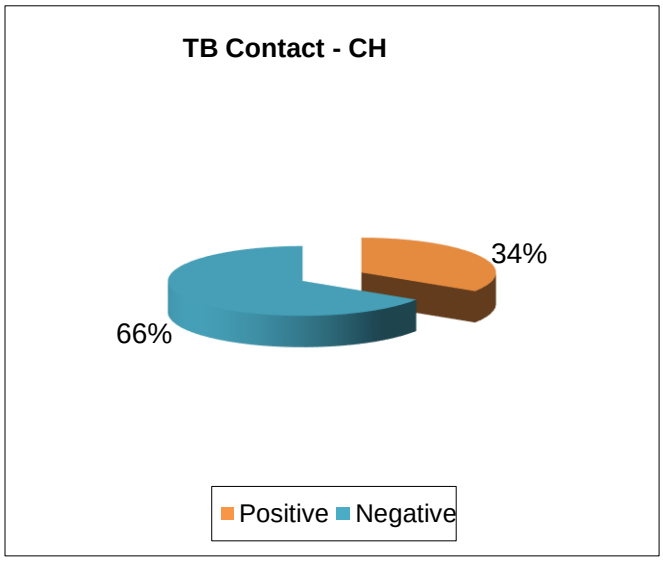


Figure 3.9: Proportion of Cases with History of TB Contact (CH)

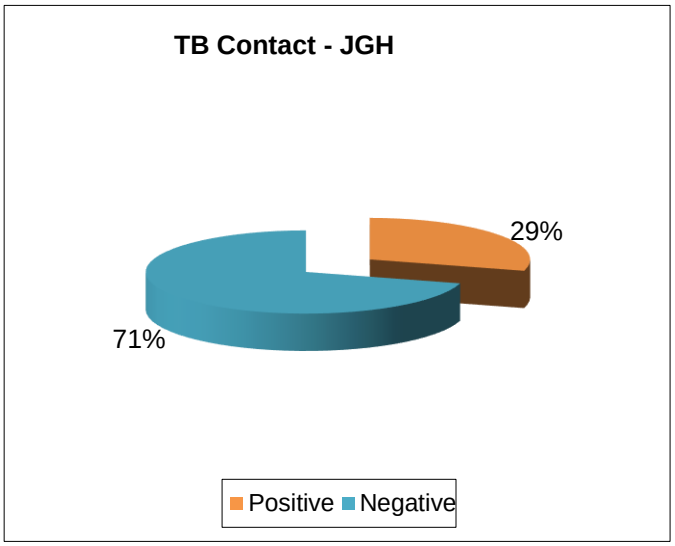


Figure 3.10: Proportion of Cases with History of TB Contact (JGH)

Although numbers were too small to derive statistical significance from the analyses, the majority (35%) of children with a positive TB contact were older than 60 months of age at CH whereas nearly half (47%) of those with a positive TB contact were in the 24 to 59 months age category at JGH (Table 3.3).

Combining the two cohorts, the majority (38%) of children with a positive TB contact were in the 24 to 59 month age group and three quarters of the children with a positive TB contact were under 60 months of age (Table 3.3).

Table 3.3: Comparison of Age Ranges with TB Contacts at CH and JGH

	CH (N = 50)		JGH (N = 51)		P-value	CH + JGH (N = 32)
AGE (Months)	**TB Contact – Positive N (%)**	**TB Contact – Negative N (%)**	**TB Contact – Positive N (%)**	**TB Contact – Negative N (%)**	**TB Contact – Positive**	**TB Contact – Positive N (%)**
0 - 11	4 (24)	13 (39)	3 (20)	1 (3)	0.088#	7 (22)
12 - 23	2 (12)	4 (12)	3 (20)	16 (44)	0.562#	5 (16)
24 - 59	5 (29)	12 (36)	7 (47)	18 (50)	1.000#	12 (38)
> 60	6 (35)	4 (12)	2 (13)	1 (3)	1.000#	8 (25)
Total (N)	17 (100)	33 (100)	15 (100)	36 (100)	-	32 (100)

Fisher's exact test

3.1.2.5 TST Reactivity amongst Children Diagnosed with TB as Outpatients

Using the Mantoux cut-off interpretation outlined by the 1983 WHO Child TB Diagnostic Guidelines (41,37) which would have been used by the staff at the outpatient departments at the time of conduct of this study, TST reactions were positive in 86% of the total cohort, with a similar result being seen at both hospitals; CH having 88% of participants with a positive TST (Figure 3.11) and JGH having 84% participants with a positive TST (Figure 3.12).

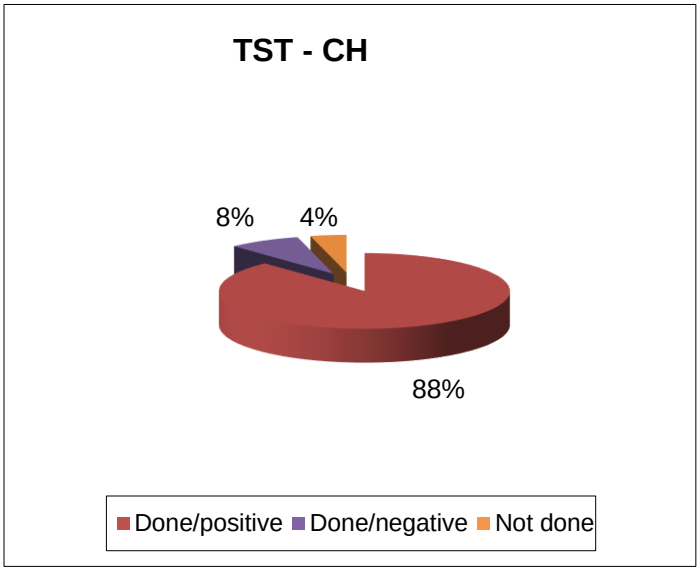


Figure 3.11: TST Results (CH)

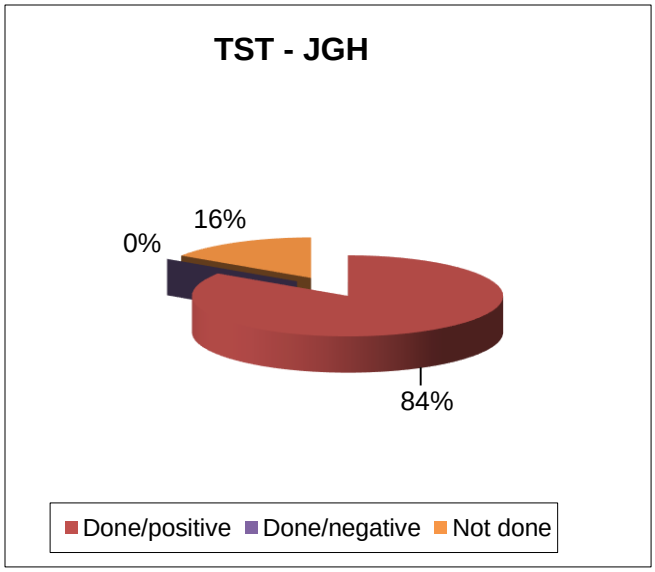


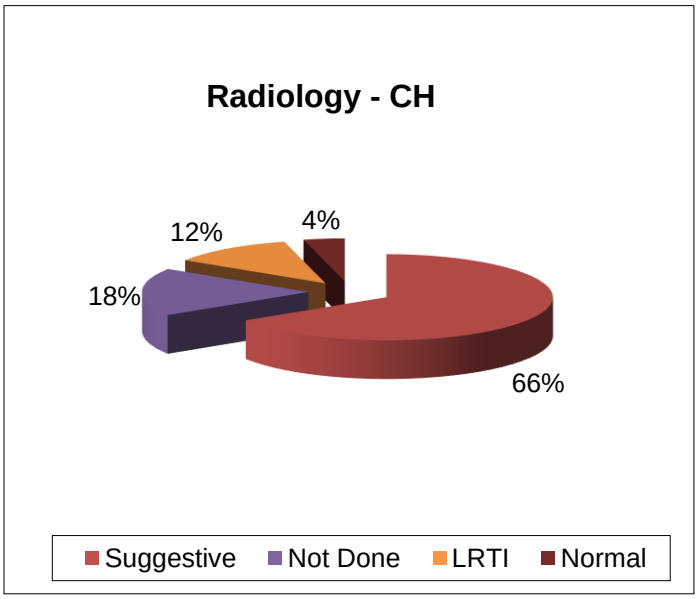
Figure 3.12: TST Results (JGH)

The median age of children with a positive TST reaction was 24 months (IQR 14-48 months), and was not significantly different at each hospital, P=0.926. Children with a history of positive TB contact had larger TST reactions (median transverse induration 20mm, Range 10-28mm) compared to those who did not have a TB contact (median transverse induration 16mm, Range 0-30mm), P=0.0343.

3.1.2.6 Chest X-ray Findings in Children Diagnosed with TB as Outpatients

Two thirds of the children diagnosed with TB at CH had chest x-ray features suggestive of TB (Figure 3.13), whereas only 37% had x-ray features at JGH (Figure 3.14), P=0.004 (Table 3.2). Patient records did not specify if lateral films were taken. The CXR

interpretations were based on the clinician notes which did not draw the distinction between AP and lateral films. Both outpatient departments showed a similar percentage of x-rays not being done as part of their investigations in diagnosing TB (CH, 18%; JGH, 12%).



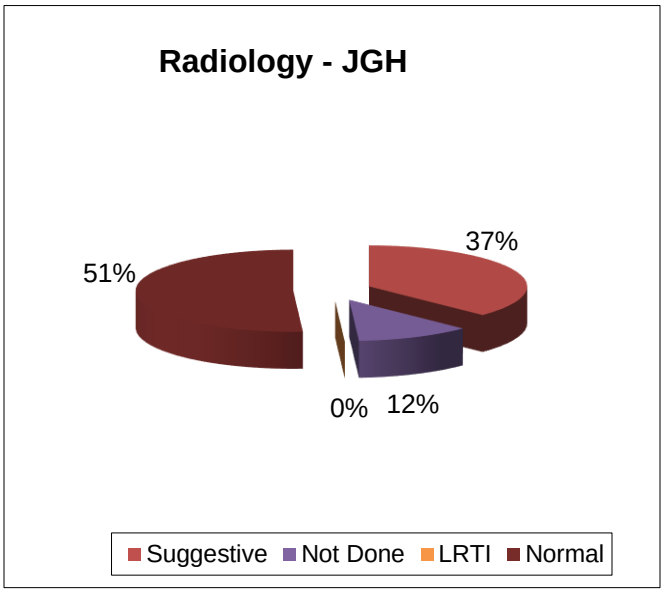


Figure 3.13: Radiology Results (CH)

Figure 3.14: Radiology Results (JGH)

LRTI = lower respiratory tract infection, a radiographic feature that was attributed in children notified for tuberculosis, but whose x-ray findings were not suggestive of PTB.

Suggestive = Persistent opacification with enlarged perihilar lymph nodes.

3.1.2.7 Microbiology Specimen Submission Practice at the Two Hospital Outpatient Departments

Submission of specimens for microbiological assessment was not a common practice in either outpatient department, with 95% (96/101) participants not having any specimens

collected. Ninety-two percent (46/50) of participants did not have any specimens collected at CH (Figure 3.15), as did ninety-eight percent (50/51) participants from JGH (Figure 3.16).

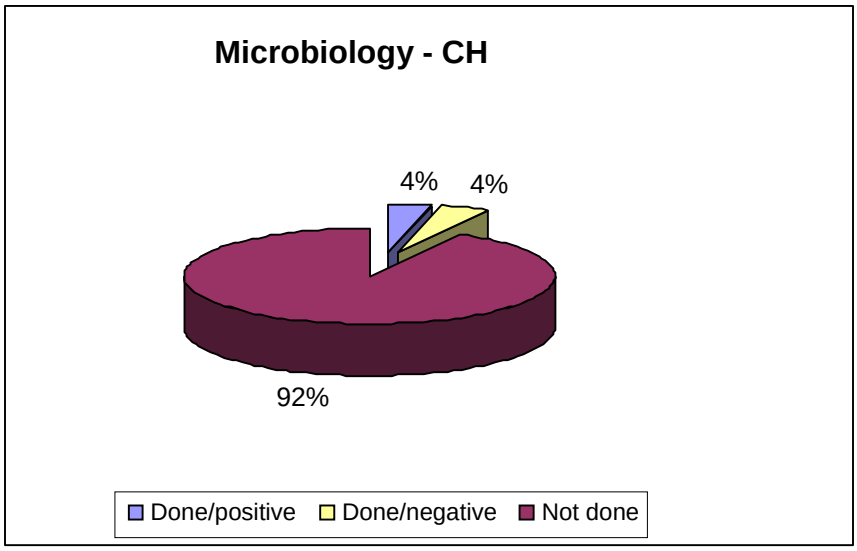


Figure 3.15: Microbiology Results (CH)

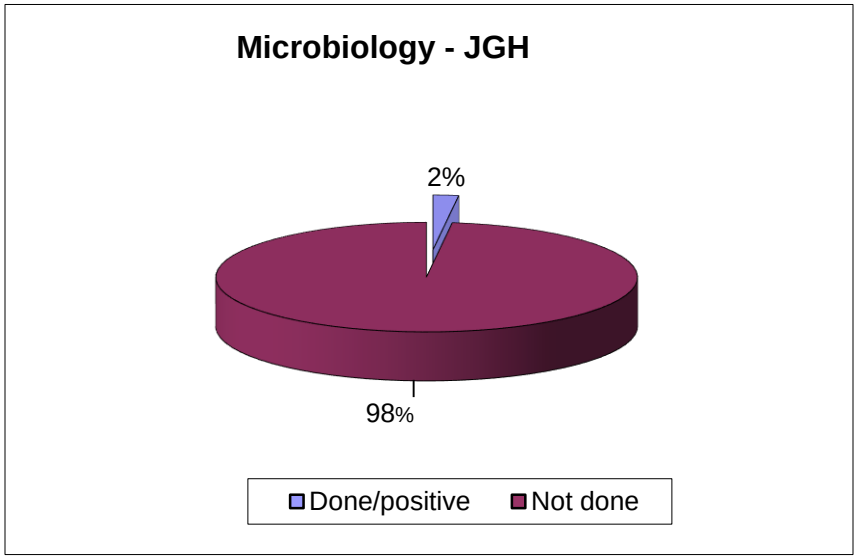


Figure 3.16: Microbiology Results (JGH)

3.1.3 WHO Classification of TB in the study cohort

Sixty five percent (33/51) of the children evaluated at JGH were notified for TB using five of the seven criteria (i.e., weight loss; chronic cough; neck swellings; TB contact history; TST; chest x-ray; submission of specimens for mycobacterial culture) recommended by the 1983 WHO Child TB Diagnosis algorithm, whereas 82% of the children notified for TB at CH had their diagnosis based on six or seven criteria, P<0.001 (Table 3.4).

Table 3.4: Number of Criteria Used to Make a Diagnosis of TB at CH and JGH Paediatric Outpatient Departments

Number of Criteria Used in the TB Work-up	CH N (%)	JGH N (%)	P-value
Five	9 (18)	33 (65)	<0.001
Six	39 (78)	18 (35)	<0.001
Seven	2 (4)	0	-
Total	50 (100)	51 (100)	

The majority of the children diagnosed with TB at both outpatient settings had a clinical presentation of 'Probable' TB. CH had 90% (45/50) of their TB patients classified as 'Probable' TB (Figure 3.17), and JGH 96% (49/51) (Table 3.5). 'Confirmed' TB contributed very low percentage of the cohort in both outpatient departments where microbiological specimen submission was not a common practice; CH only had two (4%) confirmed cases and JGH had 1 (2%) confirmed case (Table 3.5).

Table 3.5: WHO Classification of TB Outcomes for Children Diagnosed with TB at CH and JGH Paediatric Outpatient Departments

TB Category	CH (N=50; %)	JGH (N=51; %)	CH + JGH (N=101; %)	Odds Ratio (95% CI)	P-value
Suspect TB	3 (6)	1 (2)	4 (4)	3.19 (0.24-170.81)	0.362#
Probable TB	45 (90)	49 (96)	94 (93)	0.37 (0.03-2.40)	0.269#
Confirmed TB	2 (4)	1 (2)	3 (3)	2.08 (0.10-125.32)	0.618#

Fisher's exact test.

Chapter 4: Discussion and Conclusion

This was a retrospective, hospital outpatient-based observational study, conducted in two ambulatory paediatric settings in Johannesburg. Patients ranging from the ages of three months to 14 years, who attended the paediatric outpatient departments in the two academic hospitals between 01 November 1997 and 30 June 1998, and were diagnosed and notified as having TB in these outpatient settings, comprised the study population. A total of 101 patients were included in the research study; 50 patients from CH and 51 patients from JGH.

4.1 Baseline Clinical Characteristics

4.1.1 Age at TB Diagnosis

The results demonstrate that most (50%) children who presented to the two outpatient departments and were diagnosed and notified as having TB were in the under 24 month age group. This is comparable with the demographics of a prospective community based study conducted in two suburbs of Cape Town, where 35.8% of children were <2 years (43). The annual risk of TB infection (ARI) is not constant across all ages (44); there are specific age periods when TB infection rates increase (45), and these age periods seem to correlate with times of widening social contact (44). Most children who become infected with MTB before two years of age are infected by a household source case (44). Additional caregivers outside the household are also important, especially domestic workers, grandparents or extended family members who take care of the children during the day, if both parents are working. Primary infection occurs at a younger age in high-density, low income urban areas (44) as is the case with the feeder communities for CH and JGH.

Children who are infected with MTB before the age of two years frequently progress to active TB disease within the first twelve months without significant prior symptoms (46).

4.1.2 Gender Distribution among TB Cases

Gender distribution was similar in both hospitals with both CH and JGH showing a slight male predominance – CH, 52% (Figure 3.4); JGH, 57% (Figure 3.5). The male-to-female ratio for both hospitals is 1.2:1, similar to that observed in a retrospective study carried out in Parrow, Cape Town in 1987, which looked at the criteria used for the notification of childhood TB; boys were more affected than girls with the male-to-female ratio of the children being 1:0.3 (39); 46% percent of the children were < 2 years of age (39) which also compares well with this study where 51% of the children in the JGH cohort were in the 13–24 month age group (Figure 3.3).

Globally, the prevalence of infection with MTB is similar in males and females in children until adolescence, after which it is higher in males (47).

4.1.3 Nutritional Status of TB Cases

The weight-for-age distribution (comparing their WAZ distributions) in children with an outpatient TB diagnosis was similar at the two hospitals: 53% and 54% of the cohort plotted between the -2 and the 0 weight-for-age Z-score, at CH and JGH, respectively (Figures 3.7 and 3.8). Both hospitals also showed a similar distribution in their cohorts of patients lying above the 0 Z-score (median) line: CH, 33%; JGH, 38%. The nutritional status of the two cohorts is a reflection of a community that is able to provide sufficient nutritional requirements for their children. It would be expected to have a relatively better nourished cohort in children diagnosed with TB in the outpatient setting.

Childhood TB is usually associated with weight loss and/or failure to thrive (15); malnutrition may predispose to TB, and TB can in turn cause malnutrition (48). Regular documentation of weight becomes an invaluable tool in children suspected of having TB, as a child with TB will generally not thrive (15). A poor response to nutritional support of a malnourished child is a clinical marker of TB or HIV (15).

The degree of malnutrition has also been found to have an impact on the morbidity and mortality of patients diagnosed with TB (48). Poor nutrition has been found to increase the risk of early primary TB infection, disseminated TB disease and repeated infection with MTB (49). In a study conducted in a rural district in Malawi between 1999 and 2001, Zachariah et al were able to conclude that higher rates of early death occurred in patients with moderate to severe malnutrition, compared to those whose nutritional status was normal or mildly impaired; these differences were found regardless of age or HIV serostatus (48).

4.1.4 TB Exposure History

The majority of children evaluated in this study were in the under 24 month age group, and the median age of those with a positive TST was also 24 months; this strongly suggests that these children had a close family contact with TB. Furthermore, three quarters of the children with a positive TB contact history were under 5 years of age (Table 3.3), and those with a positive TB contact were more likely to have a strongly positive TST response. Although all children included in this study had TB exposure history recorded in their clinical notes, a positive exposure was surprisingly low in both cohorts: 68% of the total cohort gave a negative history of TB contact. This may reflect a large proportion of undiagnosed TB contacts in the adult population where these children have come from.

Unknown TB contacts contribute to the diagnostic uncertainty and difficulty in diagnosing TB in children where the signs and symptoms of active disease are non-specific. Early identification and diagnosis of adult source cases is crucial in preventing childhood TB infection and early identification of suspected child TB cases would be expected to improve the TB-related morbidity and mortality in children (6).

TB often carries a negative stigma in areas of high prevalence and a direct enquiry into a family history of TB may often be denied as was the case in a study carried out in a rural hospital in Kenya between 1981 to 1983, in which 144 children were studied and only 34 (24%) had a positive history of a TB contact in the family (49).

Healthcare workers have also been found to contribute to delay in diagnosis of childhood TB by failing to enquire about the presence of TB amongst close household adult contacts (6).

It must be noted that MTB infection may occur without known exposure and the absence of a potential source case does not exclude TB (50). Young children usually become infected after exposure to a sputum smear–positive household contact. Sputum smear–negative contacts generally are less infectious but may still infect children (50), for example in a low burdened TB setting in the Netherlands, adults with smear-negative, culture positive TB were responsible for 13% of TB transmission (51).

WHO and the IUATLD have recommended that contact tracing is a valuable means of identifying new TB cases (36), and this would be expected to impact substantially on TB infection control. Contact tracing has been advocated by the South African National Department of Health in 2009 as part of the National TB Management Guidelines (52). Emphasis is placed on contact tracing and case detection, increasing awareness amongst

communities on TB infection control, and integrating this programme into the District Primary Health Care system so as to ensure early TB case detection.

Contact tracing is a process whereby individuals in contact with a case of confirmed or suspected PTB are screened for the presence of TB infection or disease, with the aim of offering either INH preventive therapy or anti-TB chemotherapy to those who qualify for such management (50). In the event of a child being diagnosed with TB disease, reverse contact tracing should be adopted, and potential source cases from the home environment are sought by symptom screening and/or chest radiography (50).

Unfortunately, the widespread implementation of contact tracing activities in over-burdened TB Control Programs is often hampered because activities are focussed on treating the current TB case load (36). The adequacy of contact tracing activities within the context of the South African TB Program would be expected to be compromised due to the current patient load (296,996 new TB cases, 38,578 [13%] of whom were children under 15 years of age, were treated by the South African TB Programme in 2012) (11).

4.1.5 Mantoux Responses

The TST used in both outpatient departments was the Mantoux test. The Mantoux test remains the skin test of choice for diagnosing TB infection (53). CH paediatric outpatient department had a better record of the procedure being done, with 96% of their cohort receiving a Mantoux test. JGH only did the test on 84% of their cohort, all having a positive result (Table 3.2).

The young age at TB diagnosis (based on the finding of five criteria out of the seven (See Section 3.1.3)) in this cohort (median age of 24 months was found in the children with a

positive TST reaction), may suggest that the majority of these TB cases had a close family contact with TB.

In the revised recommendations of the WHO, a positive (or 'reactive') Mantoux skin test is defined as a transverse induration of ≥10 mm when read 48–72 hours after administration, irrespective of BCG immunisation status, or ≥5 mm if the child is HIV-infected or severely malnourished (36).

Prior to the early 2000s, at the time in which this study was conducted, interpretation of the Mantoux skin test was different (please refer to Sections 1.1.4.2 and 2.1 of this dissertation for details of the previous interpretation system)(37). We used the latter Mantoux classification system in attributing Mantoux positivity in the study cohort, as this was what was used by clinicians diagnosing childhood TB in the outpatient departments described in this study.

Changes in interpretation of the Mantoux skin test, using a positive cut-off of 10mm regardless of BCG vaccination status and 5mm in HIV-infected children, came about because of the changes in epidemiology of TB and its influence on skin testing; appropriate cut-off points for a positive reaction among different groups were re–classified(53). The impact of HIV infection on TST responses played a major role in dictating the revision in interpretation of Mantoux induration, and it remains important to interpret the TST in the context of the underlying nutritional status of the patient(54).

TST is more likely to be negative in children with severe malnutrition and/or with advanced immune suppression as they are unable to mount an immune response against tuberculin (15). We presume that, due to the high prevalence of positive Mantoux

responses in this cohort of children being diagnosed with TB infection in the study outpatient settings in the late 1990s, the majority of these cases were most likely HIV-uninfected and of a relatively good nutritional status. HIV-infected children who are long term survivors or 'slow progressors' may not become symptomatic until beyond two years of age, and may have accounted for a sub-set of the children with positive Mantoux responses in our cohort. TST is less sensitive in HIV-infected children than in HIV-uninfected (15) and variable sensitivity remains a major limitation of TST in the diagnosis of TB in HIV-infected children (15). It would have been helpful to have obtained HIV results in all of the children to test this conjecture.

4.1.5.1 Lack of HIV Test Results in the Study Cohort

HIV testing was not done routinely in these two paediatric outpatient settings; this could have been as a result of the low HIV serostatus prevalence at the time of conduct of this study. A study conducted at the Chris Hani Baragwanath Academic Hospital between 1992 to 1996, looking at the impact of increases in HIV infection in hospitalised children, found only 120 (3%) children infected out of 3,800 admitted in 1992 (55). By 1996, the number of HIV infected children had risen to 870 (19%) out of 4,694 admitted. HIV infection prevalence would be expected to be lower in children assessed in the ambulatory setting, i.e. those who were not 'ill enough' to warrant hospitalisation.

Paediatric ART coverage was low in the late 1990s, with 83% of eligible children not being able to access ART (56), and the South African National ARV roll-out only commenced in April 2004.

These factors may have contributed to medical officers not routinely doing HIV testing in patients presenting to the outpatient departments in the late 1990s.

4.1.6 Chest X-rays in the Outpatient Diagnosis of Paediatric TB

The chest x-ray findings recorded for the children diagnosed and notified as having TB in the two outpatient departments was either 'suggestive' of TB (hilar lymphadenopathy, cavitation, miliary picture), a 'lower respiratory tract infection' (bronchopneumonia, pneumonia) or 'normal'. A small percentage (15%) of children evaluated for TB in both outpatient departments did not have a chest x-ray done as part of their investigations. Two thirds of the children diagnosed with TB at CH had x-ray features suggestive of TB (Fig. 3.13), whereas only 37% had x-ray features at JGH (Fig. 3.14), P=0.004 (Table 3.2). No children were diagnosed with a lower respiratory tract infection on x-ray in the JGH outpatient setting, and more children evaluated there (51%) had normal chest x-rays compared to children seen at CH (Table 3.2). By contrast, 12% of the children diagnosed with TB at the CH outpatient department had features of 'lower respiratory tract infection' on their x-ray and only 4% of the CH cohort had normal chest x-rays. This could be a reflection of the radiology experience of the medical officers in both outpatient departments and possible closer collaboration between radiologists and outpatient staff at CH where it is evident that a radiologic diagnosis of PTB was more frequently made than at JGH. Radiological findings in PTB may not always help towards the diagnosis, particularly in small children, and can at times be confusing (57).

Interpretation of chest radiographs is a process marked by inconsistencies among different readers and between the opinions of the same reader on different occasions (7). Hilar lymphadenopathy may be difficult to detect on the antero-posterior chest radiograph and

this forms part of the radiological criteria for the diagnosis of childhood TB (39). Cavity formation is unusual in young children and more common in older children or adolescents (15). Cavities on chest x-ray are more common in HIV-infected children than in HIV un-infected children (54).

Despite the limitations of chest radiography as mentioned above, chest x-ray remains an important diagnostic tool for PTB in young children (15), and may be the only diagnostic tool in many settings (15), because obtaining specimens for microbiological assessment and confirmation outside tertiary referral centres remains a difficult task. A publication of a cross-sectional study carried out in Malawi in 2002, in 44 non-private hospitals that register and treat children with TB, reported that the diagnosis of PTB was based mainly on clinical features and radiography; less than 10% had TSTs done, or HIV serology (58).

With the rising TB/HIV epidemic, differentiating TB from HIV–related lung disease (e.g. *Pneumocystis jirovecii* pneumonia and lymphoid interstitial pneumonitis) has become a common diagnostic challenge in HIV–endemic regions (15). HIV–related lung disease and TB may co-exist and have many similar features (16), thus a high index of suspicion has become imperative to make the diagnosis of PTB (16) and this advocates further for improved specimen collection and submission for the confirmation of PTB; hence microscopy and microbiological culture evaluation should become an important part of clinical practice in the diagnosis of TB, even in the ambulatory setting.

4.1.7 TB Microbiologic Testing

Submission of specimens for microbiological assessment was not a common practice in both outpatient departments, with 95% of participants not having any specimens collected.

This could be as a result of the non-specific presentations that are commonly seen in the ambulatory environment and the difficulty in obtaining specimens for microbiology in children accessing the ambulatory health care setting.

Bacteriological confirmation of PTB is rarely achieved in resource–limited settings where most cases present, and where mycobacterial culture infrastructure is limited (15). WHO advises the confirmation of the diagnosis of TB in children by using whatever specimens and laboratory facilities are available (36). Appropriate specimens should be submitted for microscopy and for mycobacterial culture and histopathological examination from the TB-affected sites where laboratory facilities permit. Appropriate clinical specimens may include expectorated or induced sputum, gastric aspirates, fine needle aspiration, lymph node biopsy or any other specimen that is biopsied (Appendix 2, Box 2).

A prospective study carried out in a primary health care facility in Cape Town between March 2007 and June 2009 demonstrated the feasibility of sputum induction for the diagnosis of TB in children in a community setting. Eleven percent of child participants had positive TB microbiology (smear- and/or culture-positive) (29), a yield similar to that observed in adult TB suspects. The same study demonstrated that TB microbiologic testing can in fact enhance the certainty of the TB diagnosis: 17% of children with 'Probable' TB at initial evaluation were confirmed microbiologically. Microbiologic yield was substantially higher (44%) in children with a history of adult TB contact. An increment in the diagnostic yield (22%) was also found in children who had not been diagnosed clinically, but were diagnosed by sputum induction. A second sputum induction test increased the diagnostic yield by 34% (29). These results show that it is possible to conduct microbiological

assessments to help make and confirm the diagnosis of TB in children, and detect patients in whom the diagnosis may have been missed clinically. Microbiological confirmation resulted in almost a quarter more children being treated than would have been treated on clinical grounds (29).

In children who have complicated or severe TB disease, HIV infection, suspected drug-resistant TB, or an uncertain diagnosis, microbiological confirmation is preferred, even mandatory, in order to guide therapy (36). Studies show that HIV infection and immune suppression do not reduce the yield from smear microscopy for AFB in children with TB (15, 59).

4.1.8 TB Score Charts

The diagnosis of TB in children relies on careful and thorough assessment from a careful history, clinical examination and relevant investigations, i.e. TST, chest x-ray, sputum smear microscopy, or the collection of appropriate clinical specimens for microbiological assessment. Existing diagnostic tests for TB in children have their shortcomings, and the full range of diagnostic tests are often not available in settings where the vast majority of TB cases are diagnosed (36), prompting the need for classification systems such as that promulgated by the WHO (41,36). As a result of the difficulty of confirming TB in children, some countries have adopted the use of score charts (36), but these are difficult to validate because of a lack of a diagnostic gold standard (15, 60). Score charts have been found to perform particularly poorly in children with 'Suspect' PTB (36), and in children who are also HIV-infected (61). A prospective study conducted at a mission hospital in Zambia in 1999, found that the paediatric TB score chart that was developed for resource-poor countries

showed very low specificity (25%) (61), which led to over-diagnosis of TB and unnecessary use of costly anti-tuberculous drugs (61).

4.1.9 WHO TB Classification

The majority of children evaluated at the two outpatient departments had 'Probable' TB, as defined by the WHO classification system for childhood TB (41). This was based on the high prevalence of positive TST reactions in the cohort, and (in the CH cohort) on suggestive chest x-ray findings. Of the seven criteria suggested to guide work up of TB in a child, only five criteria were used by clinicians making a diagnosis of TB in the majority (65%) of children notified with TB at the ambulatory setting at JGH. Staff at CH exhibited a more thorough clinical approach, using six or seven criteria in their decision making process in 82% of their patients (Table 3.4).

A study from Cape Town which looked at the criteria used for the notification of childhood TB in a high-incidence area, demonstrated that the majority of children (72%) were also diagnosed with 'Probable' TB; this was based mainly on a diagnostic chest x-ray which made up 33% of their cohort (39).

It is concerning that so few children (4%) were diagnosed with 'Suspect' TB in the cohort described in our study; this may imply that children with little clinical evidence of the disease may have had a missed diagnosis of TB. The lack of definitive diagnostic tests for childhood TB remains a dilemma for both the clinician and the epidemiologist and this will remain a major setback in identifying and confirming TB in children with 'Suspect' TB, and will continue to contribute to the high morbidity and mortality of childhood TB if such children have a missed or delayed diagnosis. Failure to confirm a diagnosis of TB in

suspected cases remains a major constraint in paediatric TB research including the epidemiology, pathogenesis, treatment, and chemoprophylaxis (57). The graduated approach to diagnosing childhood TB formulated by WHO (7,41) helps to ascertain a level of certainty with which the diagnosis can be made (39) and may hence assist with the challenges of diagnosing childhood TB, particularly in developing countries.

4.2 Limitations of this study

This study was carried out in two paediatric outpatient departments in Johannesburg, and the findings described are a reflection on how TB was diagnosed and notified in tertiary ambulatory settings at the end of the 1990s. Considering the fact that rapid microbiological techniques e.g. GeneXpert diagnostic assay, and specialist resources to assist with interpretation of paediatric chest x-rays have become more widely available, the study findings may not be applicable to current TB diagnosis in these facilities, or at lower level hospitals and primary healthcare facilities. With the availability of more improved diagnostic techniques, any nursing professional or doctor working in the ambulatory setting should be trained in the collection of sputum, nasopharyngeal aspirates or gastric aspirates. With planning, all of these specimens can be collected at primary, secondary or tertiary level. For adenitis, which is the other form of TB seen in the ambulatory setting, a fine needle aspirate should be done and sent for cytology and TB culture. A greater awareness of the role which HIV plays in predisposing children to TB disease has emphasised the importance of HIV screening, and interpretation of CXRs and TST responses in the light of HIV test results,

which was not the case in this study in the outpatient departments in the late 1990s. This study can lead on to a current audit of ambulatory paediatric TB diagnosis.

The signs and symptoms commonly used to aid in the diagnosis of childhood TB are not specific, especially in areas where TB is endemic and complicated by poor socio-economic environments. The study cohort may have been enriched for children whose immunological and nutritional profiles would have resulted in TST positivity, and a diagnosis of 'Probable TB' based on this finding.

The TST is an important component in the diagnosis of childhood TB, particularly in the ambulatory setting. Problems in the reliability of the test can occur if technique is poor, and with differing potency of tuberculin antigens. Although there is mixed uniformity in tuberculin which may affect interpretation (32), the product used by the Paediatric facilities in Johannesburg is obtained from one source (Statens Serum Institut, Copenhagen, Denmark) and so would not be expected to have affected TST interpretation at the study outpatient departments.

Microbiological isolation (i.e. culture) of MTB from sputum, gastric aspirates or lymph node aspirates forms the gold standard test through which a diagnosis of TB can be made. In children, confirmation of the diagnosis by this method has been a cumbersome and difficult task and is rarely done in outpatient departments. Furthermore, the finding of organisms on direct smear from gastric aspirates has a low specificity since false positives may be produced by other mycobacteria or acid-fast organisms (32).

Interpretation of chest radiographs is also a process marked by inconsistencies among different readers and between the opinions of the same reader on different occasions (7).

Reliability will be dependent on those reading the x-rays. Hilar lymphadenopathy may be difficult to detect on the chest radiographs and this is a major radiological criterion for the diagnosis of childhood TB (39). A lateral film is of great assistance, and should be taken when PTB is suspected (62).

Incomplete clinical notes and difficulties in retrieving patient folders from hospital records departments may impact negatively on the quality of data, especially when undertaking retrospective studies. In this study, records for each of the patients were obtained for review, but inconsistent reporting by different clinicians would be expected to have impacted on the consistency of the data. Furthermore, by basing the study cohort finding strategy on review of notification booklets, we may have missed a subset of children diagnosed with TB but who were not notified with the condition at hospital-based notification centres.

The complete lack of HIV infection status data collection in this study reflects the prevailing clinical practice in South African outpatient departments in the late 1990s. As childhood TB is commonly associated with HIV co-infection, it is problematic that this important data field was not available for analysis in this study. The high prevalence of positive TST reactions in the cohort of children described in this study would suggest that many children were probably HIV-uninfected: at the time of study conduct, in the late 1990s, there was no South African ART rollout infrastructure, and very few HIV-infected children in need of ART were receiving this therapy. HIV-infected children with TB at the time that this study was conducted would be expected to have had severe immunosuppression, and may not have produced a robust TST response to tuberculin. They may also have bypassed the outpatient setting, and have been diagnosed with TB as inpatients.

4.3 Conclusion

Analysing the data extracted from the patient records from the two paediatric outpatient departments, this study has been able to conclude that criteria being used to diagnose childhood TB are in accordance with the recommended WHO criteria suggested for the diagnosis of childhood TB. However, there is evidence suggesting that clinical staff at CH were more compliant with the WHO algorithm than were the staff at JGH. Children notified for TB at CH tended to have a more thorough work-up (with at least 82% being evaluated using at least six or seven clinical parameters recommended to guide child TB diagnosis). The majority of children in both outpatient departments (CH, 90%; JGH, 96%) were classified as 'Probable' TB cases, and the proportion of 'Confirmed' TB cases in both outpatient departments was minimal (CH, 4%; JGH, 2%). These findings indicate that the WHO recommended approach (Appendix 1) is being practised and followed up with the investigatory tools that are available in the two outpatient departments.

That few of the children had an outpatient diagnosis of 'Suspect' TB is concerning, and may indicate that a TB diagnosis was missed in children who may have had the disease but whose clinical presentation did not alert clinicians to a possible diagnosis of the condition.

Mantoux responses and chest x-ray features tended to steer clinicians towards a diagnosis of TB in this cohort. TSTs done and which came out positive (CH, 88%; JGH, 84%) indicate that, at the time of study conduct in the late 1990s, TST was the major identifying diagnostic tool in the two outpatient departments to diagnose 'Probable' TB. The use of chest x-rays in the two departments varied, highlighting the discrepancies and

inconsistencies in radiological diagnosis of paediatric PTB. Lack of microbiologic confirmation of TB was a major short-coming in both outpatient departments, in which the majority of children did not have specimens submitted (CH, 92%; JGH, 98%).

Increasing awareness of ancillary diagnostic tools, e.g., HIV testing in child TB suspects, and microbiologic confirmation of MTB disease using sputum induction and/or gastric aspiration and fine needle aspiration in outpatient environments will help in improving the diagnostic practices for confirming TB.

Morbidity and mortality due to childhood TB has increased with the HIV epidemic; there is now a need to increase efforts of using more reliable methods and diagnostic tools to diagnose paediatric TB infection and/or disease in the outpatient setting. Strategies such as contact tracing, by targeting families 'at risk' for TB (as identified by a sentinel adult or child TB case), would be expected to enhance the identification of TB suspects.

4.4 Recommendations

Successful management of the TB epidemic in children relies on careful diagnosis with thorough assessment of all evidence derived from a careful history, clinical examination and relevant investigations. This, straightforward approach is now under threat in settings with a high HIV prevalence as interpretation of diagnostic methods used at the time of this study will require greater awareness in interpreting these results as a lot of overlap is seen in clinical presentation between children with TB and HIV, and HIV confounds the TST and chest x-ray based diagnosis of childhood TB. This calls for the following recommendations:

a) An updated audit, interrogating ambulatory paediatric TB diagnosis at the facilities investigated in this study;
b) Adopting standardised approaches to the management programmes based on best available evidence and recent research to assist in streamlining diagnostic methods for childhood TB;
c) Engagement and training of all healthcare workers who provide care to children (including paediatricians, medical officers, nurses and allied medical staff) regarding the diagnostic approach to childhood TB in the outpatient setting;
d) Improve current existing practices in the prevention programmes and screening programmes to enable earlier detection of possible TB cases and utilize INH preventive therapy for eligible clients , e.g. TB contact tracing;
e) Identify areas where criteria being used to diagnose childhood TB in the ambulatory settings could be improved;
f) Encourage use of recent advances in diagnostic techniques such as the GeneXpert diagnostic assay on sputum and gastric aspirates and fine needle aspirates;
g) Community education and involvement to increase awareness of signs and symptoms of TB;
h) Primary healthcare integration of TB services;
i) Frequent updates of National TB programmes and guidelines, in order to keep abreast of developments in the field of TB case management;

Current management programmes of TB in children still have room for improvement to decrease the morbidity and mortality in child TB cases. Further research opportunities that could be undertaken include:

a) Better understanding of the epidemiology of childhood TB, especially with the setting of the HIV epidemic;

b) Development and use of better and affordable diagnostic techniques which will show more specificity for MTB, and which will be unaffected by prior BCG vaccination or exposure to other environmental mycobacteria. The recently introduced GeneXpert diagnostic test is specific for identifying the MTB bacillus and has a far shorter turn-around time than the currently used microscopy and culture techniques; research opportunities can be undertaken to implement this method in outpatient and ambulatory settings for hastening diagnosis of childhood TB and enhancing diagnostic certainty.

c) Improve systems for implementation of current available procedures, e.g. enhancing outpatient capacity to safely conduct sputum, induced sputum, gastric aspirate and fine needle specimen collections.

Appendix 1: World Health Organization provisional guidelines for the diagnosis of pulmonary tuberculosis in children (41)

A. Suspect Tuberculosis	B. Probable Tuberculosis	C. Confirmed Tuberculosis
1.)An ill child with a history of contact with a confirmed case of pulmonary tuberculosis. 2.)Any child: 2.1 Not regaining normal health after measles or whooping cough; 2.2 With loss of weight, cough and wheeze not responding to antibiotic therapy for respiratory disease; 2.3 With painless swelling in a group of superficial nodes.	A suspect case and any of the following: 1. Positive (> 10mm) induration on tuberculin testing; 2. Suggestive appearances on chest radiograph; 3. Suggestive histologic appearances of biopsy material; **4.** Favourable response to specific antituberculous therapy	1. Detection by microscopy or culture of tubercle bacilli from secretions or tissues, OR; **2.** The identification of the tubercle bacilli as *Mycobacterium tuberculosis* by culture characteristics.

Appendix 2: WHO Recommended approach to diagnosis of TB in children, 2006 (36)
Box 1

1.	Careful history (including history of TB contact and symptoms consistent with TB)
2.	Clinical examination (including growth assessment)
3.	Tuberculin skin testing
4.	Bacteriological confirmation whenever possible
5.	Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
6.	HIV testing

Box 2

SITE OF DISEASE	PRACTICAL APPROACH TO DIAGNOSIS
Peripheral Lymph Nodes (especially cervical)	Fine-needle aspiration
Miliary TB	Chest X-ray
TB Meningitis	Lumbar puncture (and computerized tomography brain scan where available)
Pleural Effusion	Pleural tap
Abdominal TB	Abdominal ultrasound and tap ascitic fluid
Osteoarticular TB	X-ray, joint tap or synovial biopsy
Pericardial TB	Cardiac ultrasound and Pericardial tap

Appendix 3: Data Abstraction Sheet

Data extracted from patient clinical records at CH and JGH

Demographics:

Outpatient hospital file number

Date of birth

Gender

Date of attendance to the outpatient department

Residential suburb

Patient History:

Presenting complaint

Duration of presenting complaints (days/weeks)

Clinical History interrogated: fever, cough and duration, loss of appetite, weight loss, night sweats, neck swellings).

History of contact with an adult PTB case Yes / No

Clinical Examination:

Weight (kg)

Presence of clinical features:

- Fever
- Upper respiratory tract infection

- Bronchopneumonia
- Lymphadenopathy

Tuberculin Skin Test:

Tuberculin skin test done or not done

If done, on reading, diameter of induration as recorded in the clinical notes

Recorded as positive or negative on the data information sheet

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X-ray Findings:

CXR done or not done

If done, x-ray findings as recorded in the clinical notes

Microbiology Results:

Sputum or gastric washings taken from the patient as recorded in the clinical notes

If taken, microscopy & culture results as recorded in the clinical notes.

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