Comparison between BLOOD POLYMERASE CHAIN REACTION (PCR) and the scoring system in the Diagnosis of Pulmonary Tuberculosis in Sudanese Children

A thesis
submitted in partial fulfillment for the requirements of the Degree of Clinical MD in Paediatrics and Child Health.

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March 2008
بسم الله الرحمن الرحيم

 قال تعالى:
"... واتقوا الله ويعلمكم الله بكل شيء علم "
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➤ Appendix
To My Beloved Mother and Father

To My Brother Mohammed, My Sisters;
Iman, Intisar and Israe

To My Son Mohammed

To my Friends

For Their Love,

Encouragement and Support
Acknowledgement

I am most grateful to my supervisor Dr. Mohammed Sir K. Hashim consultant paediatrician for his encouragement, support, and valuable supervision during this work.

I am very thankful to Professor A/Tahir Awad Gasim Head Department of Institute of Endemic Diseases for supervision of the laboratory work.

My thanks extends to Omyma and Majtuba who did the laboratory work of this study.

My thanks also extends to Mr. Hassan Statistics for the ... work he did analyzing the collected data.

I am very grateful to Fadia who helped in typing the thesis.

Finally, with great appreciation, I would like to thank my family and my friends for their endless support and co-operation.
A prospective hospital based study was carried out during the period from July to September to evaluate the blood Polymerase Chain Reaction (PCR) in the diagnosis of pulmonary tuberculosis in children. 101 children in the age group 0-14 years attending to the T.B clinic in Gaafar Ibn Auf Hospital, Mohammed Elamin Hospital and Ahmed Gasim Hospital for children were included in this study. A questionnaire including information about symptoms, investigations done and final diagnosis was completed. A venous blood sample was taken for PCR.

Results showed that 56.4% of children were males and that 78.2% of them were belonging to a low socioeconomic class. Cough was the main complaint in 98%; fever was reported in 90% and weight loss in 85.1%. History of contact with an adult with T.B or chronic cough was obtained in 59.4%. BCG vaccination was reported in 92.1% of children studied. Chest x-ray was done for 94.1% of children and showed suggestive findings in 85% of them. Sputum examination were performed in 37.4% of children, of whom 28.5% showed positive results. The ESR was done for all children and 84% of them showed raised ESR. The mantoux test was done for 92% of children and 60.3% of them were positive.
91.1% of children scored ≥ 5 by scoring system denoting positive results. The blood PCR was done for all children and only 40.6% showed positive results.

On comparing the results of the PCR with the scoring system, the sensitivity of blood PCR was calculated to be 42.4%, specificity 77.7%, positive predictive value 95.1 and negative predictive value 11.6%. Blood PCR showed significant association with raised ESR, but no significant association was noted with chest x-ray finding, mantoux tests or sputum examination.

We recommend that blood PCR can be used with other methods to diagnose pulmonary T.B in difficult cases.
ملخص الأطروحة

بدأ في العاصمة Bitry، يُذكر في الجريدة الحكومية، 2007

Alberto يرجى إتخاذ إجراءات لفحص التهاب الدهون مستوى

العمرية 10-14 سنة من طفولة، كما أظهر US، KA، وST،

للطفال في عام، حيث أن %56.4 من الأطفال الذين يتكونون

من هذا الطلب، و%78.2 من الأطفال الذين يعانون هذه الظروف.

القيد والأدوية، 90% من الذين أعيدت تلقائياً، 90% من الذين

الحالة و%85 من الذين ثبتت في الجملة، 85% من الذين

الحمى، و%37.4 من الذين عازبة، 84% من الذين اعتباراً من

%60.3 من الذين تمكنت،ـ%92 عائلة.
سجل 91.1% للأطفال

نتائج شكل جهاز على أكثر أو درجات إجابة نتائج وظهرت البوليميرسلسلة بتفاعل الأطفال لجميع الدم عينة إختبار وجرى الإجابة نسبة على 40.6% ناجمة جهاز شكل نسبة 77.7% CATEGORY %42.4 كاذبة وظائفية النسبه 05% قوة نتائج

11.8 نهج للجهاز 95.1 وندرج

كيف يمكن في optimistic بهذى الأشخاصات فيما تظهر إختبار الاستخدام ب능 وراء النوبة عدم التحكم في الأعراض وجرى والإجابة.

الدم كريات ترسب معالفة الإجابة النتائج ومعالفة بالنوعية والحساسية 77.7% النسبة الإجابة 95.1 النسبة.

الجهاز الإيجابية وتسارع 16.8 متى بالإمكان الألم وراء الأعراض والحساسية والجراحة في الأحياء.

لا يمكن وصول إختبار انتفاخ الحفرة أثر النوبة.

لقد أظهر النتائج المختلفة في الأشخاص المصابين، وجرى الإجابة النسبية 

.10 زائف.لا يمكن بالتحديد إلى 50% إذا أثر في 50

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List of Abbreviations

ADA   Adenine Deaminase Test  
AFB   Acid Fast Baccillus  
BAL   Bronchoalveolar Lavage  
CT    Computed Tomography  
EMRO  Eastern Mediterranean Regional Office  
GL    Gastric Lavage  
INH   Isoniazid  
IUTLD International Union Against Tuberculosis and Lung Disease  
MTB   Mycobacteria Tuberculosis  
MDR   Multi-drug Resistance  
NAA   Nucleic Acid Amplification  
NTP   National Tuberculosis Control Programme  
PBMC  Peripheral Blood Mononuclear Cells  
PCR   Polymerase Chain Reaction  
PPD   Protein Purified Derivative  
PTB   Pulmonary Tuberculosis  
SCR   Serial Chest Radiograph  
T.B   Tuberculosis
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Chapter One

1- INTRODUCTION AND LITERATURE REVIEW

In the last decade, tuberculosis (T.B.) has reemerged as a major worldwide public health hazard with increasing incidence amongst adults and children.

Although cases among children represent a small percentage of all T.B. cases, infected children may act as a reservoir from which many adult cases arise. T.B. diagnosis in children usually follows discovery of a case in an adult\(^{(1)}\).

Tuberculosis is one of the oldest diseases known to affect humans. The casual Microorganism is one of the best examples of how the natural selection process has allows the survival of a species that has been able to adapt to change and adverse conditions.

Although, Mycobacterium Tuberculosis is estimated to have existed for 15,300 to 20,400 years based on its infrequent loss of nucleotide diversity and its mutant capacity it is increasingly accepted that species evolved from other
more primitive microorganisms belonging to the same genus, Mycobacterium (2).

During the last decade, developed nations claim to have been affected by three epidemics.

1- The resurgence in tuberculosis first noticed in 1985.
2- Tuberculosis upsurge related to Acquired Immune – Deficiency Syndrome (AIDs).
3- Multidrug resistant (MDR) tuberculosis.

Childhood tuberculosis is a consequence of sputum positive tuberculosis in adults. Children usually acquire infection by prolonged close contact with an adult who has positive sputum for mycobacterium tuberculosis. On the other hand, T.B. of children has a very limited effect on the epidemiological situation in a community due to the small number of smear positive cases amongst children.

In other words, tuberculosis in children is paucibacillary and, to a very large extent not associated with any of the symptoms associated with tuberculosis in adults.
These are two important factors which are responsible for the difficulty in the diagnosis of tuberculosis in children\(^{(3)}\).

Diagnosis of tuberculosis in children relies on the tuberculin skin test, chest radiographs and clinical signs and symptoms. However, clinical symptoms are non-specific. Skin testing and chest radiographs can be difficult to interpret, and routine laboratory tests are usually not helpful.

Although more rapid and sensitive laboratory testing which takes into account recent advances in molecular biology, immunology and chromatography are being developed, the results for children have been disappointing. Better techniques would be especially beneficial for the good of children and infants in whom early diagnosis is imperative for preventing progressive T.B \(^{(1)}\).

During the last decade of the 20\(^{\text{th}}\) century the number of new cases of T.B. increased worldwide. Currently, 95% of T.B. cases occur in developing countries where HIV/AIDS epidemics have had the greatest impact, and, where resources are often unavailable for proper identification and treatment of T.B \(^{(4)}\).
1.1 Tuberculosis Burden in Sudan:

The annual risk of T.B. infection in Sudan is 1.8, which means that amongst a 100,000 population there are 180 T.B. cases. Sudan is now known to shoulder 8-11% of the burden of T.B cases in the Eastern Mediterranean Regional Office (EMRO) \(^{(5)}\).

The average in all cases notified during the period of (1999-2005) was 25,551 with a male : female ratio of 1.5 : 1. In the year 2004 the cure success rate was 31%, the default rate was 9.6% and the failure rate was 2.7%. In the year 2005; 1500 cases in the age group of 0-14 years were reported\(^{(6)}\). In the year 2006, 2904 cases were reported in the age group 0-14 years; of which 502 cases were reported to be extrapulmonary T.B. \(^{(7)}\).

1.2 Natural History of T.B. in Children:

The natural history of T.B. in children follows a continuum; however it is useful to consider three basic stages: exposure, infection, and disease.
Exposure, implies that the child has had recent and substantial contact with an adult who has suspected or confirmed contagious pulmonary T.B. (source case). Exposed children are usually identified during follow up investigations for persons with suspected pulmonary T.B. by public health workers; the child’s tuberculin skin test (Ts) is non reactive, the results of chest radiograph are normal, and the child is free of physical signs and symptoms of T.B. although some exposed children are infected with M. tuberculosis.

The clinician cannot know immediately which exposed children are infected because the development of the delayed type hypersensitivity to the tuberculin test may take up to 3 months.

T.B. infection is first signaled by a reactive Mantoux (TST). In this stage, there are no signs or symptoms and the results of chest radiograph are either normal or show only fibrotic lesions or calcifications in the lung parenchyma or regional lymph nodes. In developing countries T.B. infection is rarely discovered and almost never treated. In most of
industrialized countries, children with a positive TST receive isoniazid for 6-12 month.

T.B. disease occurs when signs and symptoms or radiographic manifestations caused by M. tuberculosis appear. Radiographic abnormalities and clinical manifestations in infected children are probably influenced by the host's inflammatory reaction rather than by the number of organisms present. Studies have shown that in 40% to 50% of infants with untreated T.B. infection, disease develops within 1-2 years. The risk decreases to 15% amongst older children. In 25% - 35% of children T.B. is extra pulmonary and more difficult to confirm bacteriologically.

In children, who most often have primary disease, the interval between infection and disease can be several months to several years, and radiographic abnormalities often are not accompanied by symptoms; moreover, these children are rarely infectious. The major reason for separating infection from disease in children is false the perception affects the approach to treatment.
This distinction is somewhat artificial in children since infection and primary disease are parts of a continuum.

When evaluating new diagnostic tests, the basic differences between pathophysiology of T.B. in adults and children should be considered. It will take careful consideration and investigation to determine how the results of these new tests should influence the definitions and treatment of T.B. infection and disease in children\(^8\).

Children tuberculosis is believed to be on the increase worldwide, more so in the developing countries. Because of persisting inability to confirm the diagnosis, a number of children die of undiagnosed tuberculosis. Drug resistant tuberculosis is likely to emerge as a major problem, as its extent in children reflects the drug resistance status in adults\(^9\).

1.4 Epidemiology:

1.3.1 Epidemiological chain:

As with most infectious diseases the tuberculosis epidemiological chain of transmission requires the existence of:
1.4.1.1 Causal agent capable of bringing about the disease.

1.4.1.2 Reservoir or source of infection where the microorganism is found.

1.4.1.3 A mechanism of transmission.

1.4.1.4 A susceptible host.

1.3.1.1 **Casual Agent:**

Taxonomically, the causal agent of tuberculosis belonging to the order actinomycetales and the family mycobactericae.

Mycobacterium tuberculosis is a bacillary shaped (rod like) organism, highly resistant to cold, freezing and drying, and very sensitive to heat sunlight and ultraviolet radiation.

Tuberculosis is caused by one of the four microorganisms comprising the so called mycobacterium tuberculosis complex, which includes mycobacterium tuberculosis, Mycobacterium Bovis and Mycobacterium Africanum and Mycobacterium microti. From a health care perspective tuberculosis produced by Mycobacterium Tuberculosis is the most important.

Tuberculosis caused by M. bovis is less frequent in industrialized countries owing to the existence of effective control of T.B. in live-stock and the pasteurization of milk.
However, M Bovis remains an important problem in developing countries. M. Africanum is in turn responsible for a smaller number of T.B. cases in Africa, owing possibly to its lesser virulence. Infection due to M. microti (the causal agent for T.B. in rodents’ has recently been described in humans mainly immunosuppressed subjects.

A single microorganism may cause tuberculosis from the moment it gains access to the host, it behaves as a polyvalent germ in the course of its growth.

The metabolism of mycobacterium tuberculosis is dependent on variations in the \( \text{O}_2 \) partial pressure and the pH of the infected organ system. The chemical structure of mycobacterium tuberculosis comprises of protein, carbohydrate, vitamins belonging to the B complex and minerals such as phosphorus magnesium and calcium.

The protein component is the fundamental substrate responsible for delayed hypersensitivity reactions and rapidly induces the so called tuberculin reaction. The Mycobacteria has a lipid rich wall which is responsible for staining characteristics and resistance to macrophage action and
drying. The Mycobacteria is unable to produce toxins which results in the lack of primary toxicity, and is characterized by a very slow rate of division which explains the lack of specificity in clinical presentation, and the very slow development of the disease, so there is no need to administer the medications several times a day.

The growth of mycobacterium tuberculosis is affected by the partial pressure of oxygen and the surrounding pH level. If the favourable pH of 7.4 and PO\textsubscript{2} partial pressure of 100 – 140 mmHg are met the multiplication will be very slow occurring once every 14-24 hrs.

When mycobacterium tuberculosis does not encounter a favourable environment it enters dormant state and multiplication can be postponed from days to many years, this latent state is also responsible for the maintenance of the disease.

1.3.1.2 **Source of Infection:**

Humans are the fundamental reservoir or host for mycobacterium tuberculosis. Healthy infected individuals are
one of the main factors that contribute to the perpetuation of T.B., because they do not show signs or symptoms of the disease, so they act as silent carriers of tubercle bacilli until their death and only a number of them, at some point, develop tuberculosis especially if they have acquired some form of immunodeficiency. However Cattle are the main reservoir for M-Bovis.

The most infectious presentations correspond to pulmonary tuberculosis where the host capacity to spread bacteria is greatest. Amongst such individuals the potential for becoming contagious is greatest amongst those with the highest bacterial load, patients who show cavities on chest radiographs and those with positive smear microscopy results.

1.3.1.3 Mechanism of transmission:

The airborne route is responsible for almost all cases of T.B. transmission, when speaking, singing, laughing sneezing and especially coughing. The infected patient expels microdroplets in the air which contain the Mycobacteria.

The largest microdroplet > 10 µm in diameter contains the largest number of bacteria, which tends to be deposited in
the upper airways because of their greater weight and thus possess a lower potential for infection.

Aerosolized droplets measuring 5-10 µm reach the more proximal portions of the upper airways of the new host where the conditions are not optimal for multiplication.

Microdroplets that measure 1-5 µm in diameter and that are formed from the larger droplet as a result of condensation after losing part of their water content typically contain 1-5 bacilli per microdroplet which are highly infectious and deposit within the alveolar spaces.

Initially macrophages followed by lymphocytes migrate towards the region of Mycobacterial deposits and in the majority of cases are able to arrest Mycobacterial multiplication, when this initial defense mechanism fails primary T.B. develops.

There are other less frequent transmission routes such as gastrointestinal tract by ingestion of food or milk infected with M. Bovis. Mucocutaneous route inoculation and placental transmission particularly in cases of maternal military T.B. leading to congenital T.B are known alternative routes.
The potential of patient to infect others depends on the following factors.

1- Extent of disease: patient with positive smear microscopy and radiographic evidence of pulmonary cavities are highly infectious.

2- Severity and frequency of coughing.

3- The quality and volume of respiratory secretions scanty viscous sputum often constitutes an ideal aerosolized vehicle and therefore is more contagious.

4- Antituberculous chemotherapy, provided patients who receive such therapy are infectious.

5- Characteristic of exposure: small closed room and bad ventilation in addition to increased duration of exposure, all increase the risk of transmission.

Socioeconomic status and poverty has been strongly associated with the incidence of T.B. by crowded living conditions, thus reducing the access to health services thus prolonging the period of infectivity of
T.B. and further increasing the risk of infection among contacts of such patient(2).

1.4 The Susceptible Host (Risk Factors):

Children under the age of 5 years and elderly subjects older than 65-70 yrs are more vulnerable to T.B. This is partly because immunity is slightly reduced in these age groups. Worldwide, T.B. affects men more than women. Individuals who are exposed to the same risks differs in their capability of developing T.B. disease when infected(2).

Immunodeficient individual have a 100 fold increase in the risk of developing T.B. as compared with normal immunocompetent individuals.

Other relative risk factors include jejunocaecal shunts, solid tumours, silicosis, head and neck neoplasms, haemodialysis, haematological neoplasms, immunosuppressive drugs, haemophilia, gastrectomy, low body weight, diabetes mellitus and heavy smoking.

There are certain HLA types that are associated with increased risk of T.B. e.g. HLA A\textsubscript{11}, B\textsubscript{1}, DR\textsubscript{2} and blood groups AB and B are more affected by T.B. than 0 or A group(2).
Malnutrition and measles increase the susceptibility to developing T.B.

1.5 Tuberculosis and HIV Infection:

Impact of HIV infection:

HIV may alter the epidemiology of T.B. in 3 different ways:

- Endogenous reactivation of pre-existing infection with mycobacterium tuberculosis in persons who became infected with HIV.

- Progression to infection with mycobacterium tuberculosis to tuberculosis in persons who have became infected with HIV.

- Transmission of tubercle bacilli to the general population from T.B. patients who developed T.B. because of HIV infection \(^{(2)}\).

1.5.1 T.B. and HIV in sub-Saharan Africa:

The tuberculosis epidemic in a large number of sub-Saharan African countries has been seriously affected by the HIV epidemic. It has been estimated that approximately one third ranging from 0 – 72% of T.B. cases between 1986 – 1993
would have not occurred in sub-Saharan Africa if the pre-1985 trend had continued.

Large increases in T.B. notifications attributed, at least partially, to HIV have also been reported from Kenya Zambia, Zimbabwe and other countries\(^{(2)}\).

By the end of 2000 about 11.5 million HIV infected people worldwide were co-infected with mycobacterium tuberculosis. 70% of all co-infected people were in sub-Saharan Africa, 20% in south East Asia and 4% in Latin America and the Caribbean.

HIV increases the risk and the rate of progression of recent or latent mycobacterium tuberculosis infection to disease, HIV is the most powerful factor known to increase the risk of tuberculosis.

There is limited data on the outcome of T.B. therapy and overall mortality in HIV infected children with culture confirmed T.B. In the absence of antiretroviral therapy HIV infected children with confirmed T.B. have poor outcome on antiTB therapy and are at high risk of death during and after
completion of anti T.B. therapy especially due to non T.B. related causes (10). There is an urgent need to optimize and monitor anti T.B. therapy in HIV infected children and to improve access to T.B. clinics and other preventative therapies(11).

A study was done to investigate the impact of INH prophylaxis on mortality and incidence of T.B. in children with HIV. The conclusion is that early INH prophylaxis improved survival and reduce incidence of T.B. in children with HIV(12).

1.6 Diagnosis of Pulmonary T.B.:

About one million children develop T.B. annually worldwide, accounting for 11% of all T.B. cases. Children with T.B. differ from adult in their immunological and pathophysiological response in ways that may have important implications in the diagnosis of T.B. in children.

There is an urgent need to improve the diagnosis and management of children with T.B., and prevention of T.B by ensuring their inclusion under the implementation of the stop T.B. strategy by National T.B. Programmes.
Critical areas for further research include epidemiology, vaccination, and the development of better diagnostic techniques; new drugs development and optimal formation of dosing of first and second line T.B. drugs.

Diagnosis of T.B. in children relies on a careful and thorough assessment of all the evidence derived from a careful history, clinical examination, and relevant investigations e.g. tuberculin skin test, chest radiographs and sputum examination.

A trial of treatment with T.B. medications is not generally recommended as a method to diagnose T.B. in children, so new diagnostic tests are clearly needed.

1.6.1 **Recommended approach to diagnose T.B. in children:**

Careful case history including history of contact with T.B. case and symptoms consistent with T.B.

- **Contact:** A close contact is defined as living in the same household or in frequent contact with a source case (e.g. caregiver) with smear positive sputum. Source cases who are sputum smear negative but culture positive are also infectious
to a lesser degree. Children especially those under 5 years of age who have been in close contact with a case of smear positive T.B. must be screened for T.B.

1.6.2 Symptoms:

Children with symptomatic disease develop chronic symptoms in most cases. The commonest symptoms are chronic unremitting cough, fever and weight loss. The specificity of symptoms for diagnosis of T.B. depends on how strict the definitions of the symptoms are:

- **Chronic cough:** an unremitting cough that is not improving and has been present for > 21 days (3 wks)
- **Fever:** of 38°C or more for 14 days after exclusion of common causes such as malaria or pneumonia.
- **Weight loss** or failure to thrive, and a look for the child’s growth charts.

1.6.3 Clinical examination:

There are no specific features on clinical examination that confirm that the presenting illness is due to pulmonary T.B.
• Physical signs highly suggestive of extrapulmonary T.B. include
  • Gibbus, especially of recent onset.
  • Non painful enlarged cervical lymphadenopathy with fistula formation.
• Physical signs requiring investigation to exclude extrapulmonary T.B.
  • Meningitis not responding to antibiotic treatment with a subacute onset or raised intracranial pressure.
• Pleural effusion.
• Pericardial effusion.
• Distended abdomen with ascites.
• Non painful enlarged lymphnodes without fistula formation.
• Non painful enlarged joint.
• Signs of tuberculin hypersensitivity.
• Phylycetenular conjunctivitis, erythema nodosum.
• Documented weight loss or failure to gain weight especially after being treated in a nutritional rehabilitation programme, is a good indicator of chronic disease in children and T.B. may be the cause\(^{13}\).

The diagnosis of T.B. refers to the recognition of an active case. Beyond the diagnosis of T.B. disease, the type of T.B. case should also be defined to enable appropriate treatment and to evaluate the outcome. The case definition is determined by

- Site of disease
- Result of any bacteriological tests
- Severity of T.B. disease.

All children with T.B. should be registered with the National Tuberculosis Control Programme (NTP) as smear positive or smear negative pulmonary T.B. Pulmonary T.B. or extrapulmonary T.B. and as a new case or previously treated case\(^{14}\).
A study was done in South Africa to assess the refined symptom based approach to diagnose pulmonary tuberculosis in children. The conclusion of the study was that pulmonary T.B. can be diagnosed with a reasonable degree of accuracy in HIV uninfected children using and simple symptom based approach. This offers the exciting prospect of improving treatment availability for children, particularly in resource limited setting, where current access to anti T.B. treatment is poor.\textsuperscript{(15)}

Another study done in South Africa, with the aim to evaluate the prevalence of symptoms associated with pulmonary T.B. in randomly selected children from a highly burdened community. It concluded that children from this highly burdened community frequently reported symptoms associated with tuberculosis. These symptoms have limited value to differentiate children diagnosed with tuberculosis from those without T.B. improved case definitions and symptoms characterization are required when evaluating the diagnostic value of symptoms\textsuperscript{(16)}. 
A study was done in Sudan by Dr. Asma Alsony to describe the variation in clinical features of individuals presenting to health facilities with chest symptoms according to their ultimate diagnosis and concluded that tuberculosis patients has a constellation of presenting symptoms with the principal symptom being cough for more than 3 weeks. The accompanying symptoms with greatest practiced significance were weight loss, malaise and night sweats\(^{17}\).

A study was done in Peru to evaluate the clinical and epidemiological characteristics of Peruvian children presenting with pulmonary T.B. It concluded that the typical presentation of pulmonary T.B. in Peruvian children includes symptoms of active disease similar to those in adults. This result differs significantly from that reported in developed countries where many children have minimal or no symptoms at the time of presentation. The diagnostic criteria for paediatric pulmonary T.B. must be modified in hyperendemic developing country environments where features may differ from those described in the US: The triad of cough lasting \( \geq 2 \) wks, fever and Mantoux \( \geq 10 \) mm was highly predictive for culture positive
pulmonary T.B. among children in the low income conditions\textsuperscript{(18)}.

\section*{1.7 Investigations Used to Diagnose Pulmonary Tuberculosis in Children:}

\subsection*{1.7.1 Routine methods:}

\subsubsection*{1.7.1.1 Mantoux test and other tuberculin skin test:}

Is one of the most valuable tests for demonstrating tuberculosis infection in children both symptomatic and asymptomatic. However, its application and interpretation is often undermined by difficulties\textsuperscript{(19)}.

Mantoux test is done with one Tuberculin Unit (TU) of Protein Purified Derivative (PPD) RT 23 with the Tween 80 and is the standard method for detecting infection by mycobacterium tuberculosis.

The skin test reaction is measured per millimeter of induration after 48-72 hrs in the transverse diameter of the forearm. Though it is the only way to determine the presence of a symptomatic infection in children, a negative mantoux
test can not rule out tuberculosis in a child. In general tuberculin test should not be interpreted in the same manner in individuals who are BCG vaccinated (20).

Interpretation of the test may be difficult in certain cases as it is often affected by the boosting effect of prior BCG vaccination. Malnutrition, recent viral illness and severe infection with M. tuberculosis like miliary or meningeal disease or generalized tuberculosis.

In addition there is little uniformity in the tuberculin used and the cut-off point between positive and negative reactions (21).

A standard procedure may be strictly respected in performing and interpreting the test, and the factors that can increase or decrease the intensity of the response must be taken into account (22).

The tuberculin test has limited value in clinical work especially in high prevalence countries. The tuberculin test is however, important in non BCG vaccinated children under 5 yrs of age, where a positive test is more likely to reflect recent
infection with tuberculosis and a much higher risk of developing the disease \(^{(23)}\).

Natural infection under 2 yrs of age is suggestive of recent infection and should be treated accordingly. Beyond 2 yrs of age, natural infection in association with history of contact or symptoms and signs or presence of risk factors increases the risk of the disease.

If a specific, patient presents late, but within 7 days of the test, a reaction above 10 mm it is still considered positive. However, if the reaction is less than 10 mm in these late comers, then repetition of the test need to be done on the other forearm and test may be repeated a few weeks or months after the first test \(^{(24)}\).

A study was done in Uganda to estimate the induration size demarcating positive from negative results in a group of children with suspected tuberculosis, and to compare this cut off with available guidelines for interpretation of the mantoux test in the diagnosis of T.B. in children. The conclusion of that study was cut-off induration diameters of 5 mm was
appropriate for this group of patients, in agreement with current guidelines\textsuperscript{(19)}.

Another study from India studied the role of mantoux and contact history in various forms of childhood tuberculosis and concluded that mantoux positivity in various forms of tuberculosis studied was found to be 34.7%. The positive mantoux test was highest in lymph node T.B 53%, and lowest with CNS TB 21.2%, with T.B abdomen it was 36.4%, in skeletal T.B it was 44.4% and it was 30.3% in pulmonary TB. Contact positivity was 30.4% in the standard sample\textsuperscript{(25)}.

A study was done to evaluate the use of one tuberculin unit (TU) mantoux test in the assessment of tuberculosis infection in children following neonatal BCG vaccination. The conclusion is that the use of 1 tuberculin unit (1 TU) mantoux test has reduced the number of children receiving treatment by 36% and there was no increase in the later development of tuberculosis\textsuperscript{(26)}.

A comparison of mantoux test with diagnostic BCG was studied in paediatric patients with pulmonary tuberculosis and concluded that in paediatric age group, diagnostic BCG
test has a definite edge over mantoux test in the diagnosis of tuberculosis\(^{(27)}\).

A study was conducted in healthy school children aged 4-6 yrs. The BCG skin reaction in mantoux – negative children was compared between children with and without BCG scar. After the mantoux and BCG test, the analysis of vaccine was done as per protocol. The conclusion of the study indicated that normal healthy children may have a mild exaggerated BCG test response ie induration up to 8 mm because of prior BCG vaccination, therefore BCG test, though important should not be the only criteria for start of chemotherapy of T.B in children.

An induration up to 8 mm after BCG test can be normal in India due to exposure to mycobacterium in the environment and BCG vaccination\(^{(28)}\).

1.7.1.2 Chest x-ray:

With increasing interest in childhood T.B, the difficulties in making the diagnosis of intrathoracic T.B are becoming increasingly clear. In adults chest radiography plays a small part in the diagnosis of T.B.
Chest radiograph is one of the most commonly used tests in the diagnosis of T.B, but it has its own inherent problem due to variability in interpretation.

**Basics of chest radiograph interpretation:**

Chest x-ray is the corner-stone of the diagnosis of intrathoracic tuberculosis but it should be accompanied by clinical history and examination, and tuberculin skin test, a balanced view is needed to ensure that there is no over or under diagnosis.

- **Radiological features of different types of pulmonary tuberculosis:**

  - **Uncomplicated primary disease:**

    Is the most common form of T.B seen in clinics, the radiological picture is that of primary focus in the lung with accompanying mediastinal lymph gland enlargement. The primary focus can occur in any lobe and is not limited to upper lobes as in adults, it tends to occur 1-2 cm from pleura, and poorly circumscribed and is less than 1 cm in diameter. The mediastinal lymph gland enlargement is most commonly seen in the hilar regions of the lung, and usually unilateral.
Lateral chest x-ray often useful in visualizing hilar lymph gland enlargement.

Firebase complex with mediastinal lymph gland enlargement not visible:

It appears as airway compression commonly left or right main branches. Airway compression due to lymph gland enlargement is more common in younger infants. In a minority of cases the diagnosis is enabled by observing a calcified Gohn focus.

Complicated primary pulmonary disease:

It follows the involvement of the infected lymph nodes and the adjacent large airways mainly the bronchi and leads to narrowing of the airway and form lymphobranchial T.B. This type can be classified into:

- Large airway obstruction: which mimic asthma but responds poorly to bronchodilators and clears on medical treatment.

- Unilateral hyperinflation: Narrowing of the airway acts as a check valve allowing air to be trapped in the affected lobe or lung.
- *T.B expansible pneumonia:* with complete occlusion of the airways which appears on radiography as densely consolidated lobe or lung without any visible airway bronchograms and may be associated with mediastinal shift. This type of lesion may lead to cavitation, lung fibrosis and bronchiectasis.

- *Lobar or segmental collapse:* Occurs with complete obstruction of the airways by the infected lymph gland, collapse of the segment or lobe occurs. The lobes affected are usually the right middle lobe or the lower lobes.

- *Tuberculosis bronchopneumonia:* It occurs due to spread of tuberculous material throughout the lung from ulcerating lymphnodes or cavitating lesions. This occurs usually in young children who are acutely ill.

- *Combination of the above complications or with other radiological pictures like military T.B or pleural effusions.*
- **Unrecognizable radiological patterns:** In a minority of cases, the pathogenesis and chest radiographs are impossible to explain, the underlying pathology becomes clear while in follow up.

- **Pleural disease:** common in adolescence, pleural effusions are the result of a hypersensitive immune response to the tuberculoprotein in the pleural cavity which occurs due to rupture of primary focus in pleural cavity. Children present with fever and an insidious onset of shortness of breathing.

  The effusion can vary in size from complete opacification of the whole hemithorax to a small effusion with only obliteration of the costophrenic angle.

  The diagnosis of T.B pleural effusion can be made by combining the clinical and radiological pictures, and strengthened by diagnostic tapping. T.B pleural effusion is characterized by predominance of lymphocytes in the fluid. In nearly all cases of the T.B effusion clears up rapidly on treatment.
**Miliary tuberculosis:**

Dissemination of a large number of organisms into the blood circulation follows the involvement of blood vessels by the primary complex. These large numbers of bacilli are then spread throughout the body and lead to the development of granulomas in all the involved organs.

**Congenital and neonatal tuberculosis:**

With an increasing HIV epidemic, the number of infants presenting with congenital or neonatal T.B is increasing. Neonates infected shortly after birth develop bronchopneumonia which is very non specific; hilar or mediastinal lymph node enlargement is often not seen. In infants, gland compression of the airways is common either tracheal or bronchial.

**T.B pericardial effusion:** represent less than 1% of children with T.B. They present with an insidious onset of shortness of breath and signs of congestive cardiac failure. The radiographic pictures of the chest are that of a large water bottle shaped heart and visible signs of congestive cardiac failure (29).
A study was done in Uganda aiming to define the role of Serial Chest Radiographs (SCR) in the management of children with a clinical suspicion of pulmonary tuberculosis and to determine the interval at which they should be taken. The conclusion is that serial chest x-rays are useful in monitoring response to treatment and detection of onset of secondary infectious and complications. HIV positive patients carry a poor prognosis. Based on the results of the study, pre-treatment, 2 months after onset of treatment and at the end of therapy radiographs are recommended as routine in children with a clinical suspicion of P.T.B\(^{(30)}\).

A study was conducted in Japan to assess the role of chest x-ray in diagnosis of pulmonary tuberculosis in children, and concluded that radiographic findings of the chest radiographs and enhanced CT scan play an important role in making the diagnosis of T.B in children\(^{(31)}\).

Another study done in Australia to find the specificity and sensitivity of chest radiographs in the diagnosis of paediatric pulmonary tuberculosis and the value of additional high kilo volt radiographs.
The frequency of radiograph findings in this study compared favourably with other reports. No statistically significant differences for the detection of radiographic features consistent with PTB, or for the diagnosis of PTB, were demonstrated between the two settings. Specificity increased from 74.4% to 86.6% with the addition of the high kilovolt view and sensitivity remained constant at 38.8%. This study does not support the use of frontal high kilovolt radiographs for the diagnosis of PTB, and confirms the findings of others that standard chest radiographs are a poor indicator of PTB in children (32).

A study was done to identify special features of radiological lesions associated with pulmonary T.B in Congolese HIV infected children between the age of 18 months to 15 years in the period of 1994 to 2004, and the findings indicate that the presence of diffuse parenchymal lesions in both lungs is a characteristic radiological finding of pulmonary T.B in HIV infected children, and that there is high frequency of miliary and mediastinal adenopathy (33).
The WHO guidelines categorizes children assessment of probable and confirmed cases of tuberculosis, based on documented exposure and/or infection, poorly defined symptoms and Chest X-Ray Interpretation (CXR).

The fact that chest radiography is mostly unavailable and the subjective x-ray interpretation. Hilar adenopathy is regarded as the hallmark of primary tuberculosis but the natural history of the disease show that asymptomatic hilar adenopathy is a transient phenomenon in the majority of children. Following recent primary infection; in the absence of suspicious symptoms, hilar lymphadenopathy is more indicative of primary infection than active disease.

Despite these reservations, chest radiographs remains the most widely used diagnostic test in clinical practice providing an accurate diagnosis in most of the children when interpreted by an experienced clinician (34).

The diagnosis of T.B reactivation, reinfection is based on the isolation of the agent in the sputum, primary T.B is difficult to diagnose, usually established by indirect signs of low epidemiological specificity, symptoms, CXR, and the
tuberculin test. Interpretation of CXR is important in this context. CT chest is recommended if chest x-ray is equivocal, other modalities can be used e.g. ultrasound and MRI\textsuperscript{(35)}.

**1.7.1.3 Sputum examination:**

In low income and high tuberculosis prevalence countries, sputum smear microscopy is likely to remain for the future the only cost effective tool for diagnosing patients with infectious tuberculosis and to monitor their progress in treatment. Sputum smear microscopy is a simple, inexpensive and appropriate technology method, which is relatively easy to perform and to read.

The International union against tuberculosis and lung diseases recommends collecting three sputum samples in the early morning which are morning specimens of all sputum produced one or two hours after waking and to be sent directly to the lab for microscopy and culture and the diagnosis is made if at least 2 positive sputum smears in a patient presenting with respiratory symptoms\textsuperscript{(36)}.

A study done in south Africa aiming to investigate whether sputum induction can be successfully performed in
infants and young children and to determine the ability of induced sputum compared to Gastric Lavage (G.L.) for the diagnosis of pulmonary tuberculosis in HIV infected and uninfected children. The conclusion is that sputum induction can be safely and effectively performed in infants and young children. Induced sputum provides a satisfactory and more convenient specimen for bacteriological confirmation of pulmonary tuberculosis in HIV infected and uninfected children (37).

Another study was done in Uganda aiming to compare sputum obtained by nasopharyngeal aspiration and by induction for staining and culture of mycobacterium tuberculosis and concluded that nasopharyngeal aspirate is a useful, safe and low cost technology method for confirmation of pulmonary tuberculosis and like sputum inductions can be taken in outpatient clinics (38).

A study was done in India to evaluate the sensitivity of gastric lavage specimen for observation of acid-fast bacilli and isolation and mycobacterium in patients proved to be suffering from pulmonary tuberculosis. The conclusion of the study that
gastric lavage can be a valuable alternative specimen instead of sputum for diagnosis of tuberculosis in children and elderly patients if both smear and culture results are applied\(^{(39)}\).

A study conducted in South Africa to compare the sensitivity of both sputum and gastric lavage, and the result showed that diagnosis of tuberculosis in young children can be confirmed by a straightforward sputum test rather than the conventional and invasive procedure of gastric lavage. Samples from induced sputum and gastric lavage were positive in 87% and 65% of children respectively. The yield from one sample from induced sputum was similar to that from three gastric lavage. In addition, almost half of all culture positive sputum samples were also smear positive, enabling rapid diagnosis and initiation of treatment. There was no difference in reliability of diagnosis between HIV positive patients and HIV negative children. Sputum induction was useful even in young infants, with almost 40% of children with a positive sputum culture being less than one year of age\(^{(40)}\).

A study done in USA concluded that children rarely produce sputum samples adequate for examination and
typically have low bacterial loads which makes the mycobacterial identification by smear difficult. Acid fast stains of early morning gastric washings also have a low yield. The best specimens for culture are the early morning gastric washings containing aspirated respiratory secretions. Bronchoscopy can be useful to demonstrate endobronchial lesions or airway compression\(^{(41)}\).

Comparative study was performed in India to study the sensitivity of diagnostic tests for tuberculosis in children. The sensitivity of various tests against gastric lavage was done. The statistical significance of gastric lavage AFB positive is 70.3% of patients and its p value is significant over ESR, TB IgG and Adenine Deaminase (ADA) test. Therefore, gastric lavage test can be considered as one of the diagnostic tests for suspected or problematic cases of childhood tuberculosis\(^{(42)}\).

### 1.7.1.4 Erythrocyte Sedimentation Rate (ESR):

It is a non specific screening test that indirectly measures how much inflammation is in the body.
The test can be used to monitor inflammatory or cancerous diseases and is useful in detecting and monitoring tuberculosis.

Normal values by westergren method
New born 0-2 mm/hr.
Neonate to puberty 3-13 mm/hr.

An increased ESR rate may be due to anaemia, kidney disease, tuberculosis, osteomyelitis, pregnancy, rheumatoid arthritis SLE and other inflammatory conditions.

Conditions that cause lower than normal levels occur in congestive heart failure, hyperviscosity syndrome, hypofibrogenaemia polycythemimia, and sickle cell anaemia and low plasma proteins\(^{(43)}\).

A study was done in USA to determine the usefulness of ESR in children with no specific symptoms and concluded that ESR may be a useful screening test to help to rule out serious illness in a child with non specific symptoms or non specific clinical findings on clinical examination\(^{(44)}\).

Another study in South Africa done to determine whether raised ESR measurement indicates active P TB in HIV
infected children and concluded that a raised ESR is not indicative of PTB in children with advanced HIV disease, but it is associated with diagnostic dilemma in HIV infected children with advanced disease (45).

A consensus statement of a working group in India status report on diagnosis of childhood tuberculosis stated that CBC/ESR has no value in either diagnosis or follow up of childhood tuberculosis. ESR is a test which is influenced by several factors extraneous to the patient and disease, therefore, is not recommended (46).

Although an elevated erythrocyte sedimentation rate, may be expected in children with tuberculosis, a recent study found that one third of children with T.B had a normal ESR at the time of diagnosis, suggesting little value in using ESR as a diagnostic test for childhood T.B (47).

1.7.2 **Polymerase Chain Reaction (PCR):**

Diagnostic (PCR) is a technique of DNA amplification that uses specific DNA sequences as a marker for microorganisms. In theory this technique can detect a single organism in a specimen such as sputum gastric aspirate, pleural fluid,
cerebrospinal fluid or blood. Recent publication shows that various PCR techniques, most using the mycobacterial insertion element IS 6110 as DNA marker for mycobacterial complex organisms, have a sensitivity and specificity greater than 90% for detecting pulmonary T.B in adults. However, these tests are not performed correctly in all clinical laboratories and may offer a little advantage over high-quality microscopic examination of sputum.

The cost involved and the need for sophisticated equipment and scrupulous techniques to avoid cross contamination of specimens preclude the use of PCR techniques in many developing countries. PCR may have a special role in the diagnosis of pulmonary and extra pulmonary T.B in children, since sputum smears are usually unrevealing in these cases.

Use of PCR in children has not been extensively evaluated. It appears that PCR may have a useful but have a limited place in evaluating children for T.B. A negative PCR results never eliminates T.B as a diagnostic possibility, and a positive result does not confirm it.
PCR major use will be in evaluating children with significant pulmonary disease where the diagnosis is not easily established by clinical or epidemiological grounds.

PCR may be particularly helpful in evaluating immuno-comprised children with pulmonary disease and aid in the diagnosis of extrapulmonary T.B. However performing PCR on gastric aspirates is not a useful test to distinguish between T.B infection and disease (48).

For diagnosis of T.B; many different DNA amplification targets have been used such as: gene encoding the 32 KDa, 38 KDa or 65KDa antigens, those genes are group specific with species identification requiring subsequent restriction enzymes treatment or hybridization. However, the target most frequently amplified IS980 or IS6110 repetitive element, which is present in multiple copies in most strains of MTB complex. DNA from bacteria present in clinical specimens have been extracted by numerous methods using from simple boiling or shaking with glass bead or more complex extraction procedures (49).
Despite the obvious advantages of the procedures of DNA amplification technology in diagnostic microbiology laboratory, the accuracy and reproducibility of PCR assay depend on the technical expertise of the operator. Specificity of the test may be affected by contamination of the specimen during lab processing, if non specific primers are selected for the assay or if PCR conditions are not optimal allowing nonspecificity of a low inoculation of the microorganism is present in the clinical specimens\(^{(50)}\).

Diagnostic techniques based on PCR have two major problems, false positive reaction due to contamination, and the second is false negative due to inhibitors that interfere with PCR.

The results obtained by PCR were consistent with those obtained from culture, which is the gold standard PCR is a useful technique for rapid diagnosis of T.B at various sites\(^{(51)}\).

A present amplification of MTB can not replace the classical diagnostic techniques due to their lack of sensitivity in the absence of specific internal control for detection of inhibitor of the reaction. Furthermore, isolates are needed for
suspected studies. The technique may be useful for rapid detection of MTB in particular circumstances, as well as for the rapid detection of most Rifampicin resistant isolates. The introductions of diagnostic amplification techniques into a clinical lab implied a degree of proficiency for excluding false negative results\(^{(52)}\).

PCR based tests have definitive value in routine species identification, molecular epidemiology and the rapid detection of mutations associated with drug resistance. With increased awareness of the emerging drug resistant species offers the most relevant application to date\(^{(53)}\).

The role of PCR in day to day clinical practice need to be defined. A negative PCR never eliminates the possibility of T.B and a positive result is not always confirmatory. The PCR may be useful in evaluating children with significant pulmonary disease when diagnosis is not readily established by other means, in evaluating immunocompromised children e.g. HIV with pulmonary disease\(^{(54)}\).

A study was conducted to evaluate a rapid diagnostic method based on amplification by PCR of a fragment of IS6110
insertion element for detection of MTB in children. The specificity was found to be 100%, sensitivity 83.3%, and it concluded that if appropriate lab methods are used DNA amplification is a reliable method for early diagnosis of T.B in children and appear to be very helpful in clinical practice when the diagnosis of active T.B is difficult and need to be rapidly confirmed\(^{(55)}\).

Another study for assessment of PCR results showed that sensitivity of this test is 88.3% and specificity 100%. Negative results of Nucleic Acid Amplification (NAA) similarly to the negative results by microscopy do not preclude T.B\(^{(56)}\).

Another study found that specificity of PCR is highest on sputum that is positive by acid fast staining. Results have been disappointing using NAA on gastric aspirates from children. The high false positive rate suggests that NAA should be only used when T.B disease is suspected by abnormalities in the chest radiographs\(^{(57)}\).

The conclusion of another study was that the sensitivity of PCR is comparable to that of culture for detection of MTB in children, and may strengthen and hasten the clinical
diagnostic in culture negative patients. However, because of limitations in specificity the result of PCR alone are insufficient to diagnose T.B in children. Although ongoing refinements in PCR techniques should improve the specificity for this test, epidemiologic and clinical information continue to be the most important consideration in the diagnosis of T.B in culture negative children \(^{(58)}\).

Another study was done to evaluate the use of Roche Ampiclor for mycobacterium tuberculosis PCR test in comparison to culture results and final clinical diagnosis. This study showed that sensitivity was 66.7% specificity was 91.7% and the results were available approximately after 6.5 hours after specimen receipt in the lab \(^{(59)}\).

Ampiclor MTB will provide rapid, valuable information for diagnosis and control of tuberculosis.

Another study conducted to evaluate a heminested IS6110 PCR as a tool for diagnosis of T.B in children. Specimens were gastric aspirate, nasopharyngeal aspirate and sputum samples, results of PCR were compared with those of culture, clinical assessment and a scoring system. The
sensitivity of PCR was 67% and it was comparable to that of culture method (71%) and was significantly higher than that of lowenstein-Jensen culture (54%) or AFB stain (42%) for children with highly probable T.B. PCR detection rate for culture positive was 100% for smear positive samples, and 76.7% for smear negative samples. Specificity of PCR was 100% in control children\(^{(60)}\).

A study was done aiming to analyze the yield of bronchoalveolar lavage fluid (BALF) smear and PCR in patients with confirmed pulmonary T.B.

BALF smear was positive in 47%, BALF, PCR in 78% and BALF smear and/or PCR was positive in 83% combined use of BALF smear and MTB complex. PCR has a good diagnostic yield in patients with sputum smear negative T.B with or without sputum production\(^{(61)}\).

A study examines the diagnostic utility of the PCR in samples of bone marrow aspirate in patients with diverse clinical symptoms. Tubercular aetiology was detected in 33% of patients clinically suspected of T.B while culture on the Lowenstein-Jansen - medium grow MTB in only one patient.
None of these patients had been diagnosed by microscopy. Clinical improvement with antituberculous therapy was observed in 85% of patients with positive PCR. PCR demonstrated much higher sensitivity specificity and early therapeutic decision for suspected extrapulmonary T.B\(^{(62)}\).

A study performed to determine the usefulness of the Ampiclor mycobacterium tuberculosis PCR test in diagnosing T.B in tissue and body fluids other than respiratory secretions, concluded that the sensitivity was 76.4%, specificity was 99.8%, positive predictive value was 92.8% and negative predictive value was 99.2%. The results were available within 8.5 hours\(^{(63)}\).

PCR is used to detect mycobacterium tuberculosis from sputum, CSF and pleural fluid samples and recently from the Buffy coat of peripheral blood sample of patients with pulmonary T.B. This approach appears to be more useful with HIV infection than in immunocompetent patients and confirmatory studies are needed\(^{(64)}\).
Although PCR tests are much faster than conventional T.B screen methods, they have a low sensitivity and specificity when used with peripheral blood mononuclear cells (65).

A study to evaluate the clinical value of detection of mycobacterium tuberculosis DNA (MTB-DNA) in peripheral blood mononuclear cells (PBMC) for diagnosis of pulmonary tuberculosis. The conclusion is that PCR Triton X-100 technique method is rapid, simple, specific and sensitive. The accuracy could be increased in combination with sputum MTB examination.

Detection of MTB – DNA in PBMC is of value in diagnosis of pulmonary T.B (66). PCR test based on insertion sequence IS1081 was developed to detect mycobacterium tuberculosis complex organisms in the peripheral blood. The method was applied to blood samples from immunocompetent individuals with localized pulmonary T.B. Seven out of 16 (43.75%) blood samples were found to be positive for circulating DNA copies of MTB complex (67).

The overall sensitivity and specificity and accuracy of PCR assay was 40%, 100%, 60%, respectively. There is a
correlation between PCR positivity and sputum smear results. The study concluded that detection of mycobacterium tuberculosis DNA from peripheral blood by PCR technique is useful for the rapid diagnosis of tuberculosis patients with HIV negative. Haematological dissemination was important in tuberculosis patients and peripheral blood samples were suitable and easy materials. However, standardization of the PCR method must be encouraged for the diagnosis of tuberculosis\(^{(68)}\).

In certain cases of tuberculosis it is difficult to get the sample from the site of infection. Some researchers have tried to detect DNA of MTB complex from the blood of those patients. The purpose of this study is to determine the diagnostic efficacy of peripheral blood based PCR for diagnostics of pulmonary T.B. The overall sensitivity and specificity of the PCR assay was 20% and 94.4%, respectively and positive and negative predictive values were 85.71% and 41.46%, respectively. The overall efficacy of the test was 47.91%. because of the low sensitivity, a negative PCR assay does not rule out the disease. However, this test may be
helpful in cases where specimens from the site of infection are not available\textsuperscript{(69)}.

1.7.3 **Scoring system:**

A study was conducted to develop a scoring system for screening children for T.B. and for selecting suspects for further investigation in tuberculosis control programmes. Based on contribution from 10 countries on the use of diagnostic criteria in childhood tuberculosis, criteria were selected to be used as elements in the score model. Data were collected by standardized questionnaire on 899 subjects aged under 15 years; 794 of them were considered probable or confirmed cases of T.B. by the diagnosing doctors. From each record, the criteria, procedure used in the diagnosis of probable or confirmed T.B. and regarded by the doctors as relevant criteria were selected. Bacteriology, histology, and chest radiography were used either as singles or collectively as the definitive reference (gold standard) against which the more subjective criteria cited as a relevant were then ranked and further explored for inclusion in the score model.
The relative importance for each criterion to every other criterion on the list was expressed as weights, determined by employing a logarithmic least squares method to solve the ratio scales estimation problem which underlies decision making involving more than one criterion. The resultant values were then assigned to each criterion in the final score model. As a conclusion the model provides for epidemiological differences between target populations and should prove successful as a screening tool to select children for further investigation by radiography and bacteriology. The conclusion of the study is that there is no consistency in the number of cases identified as T.B. by the different methods used. The scoring system for high T.B. prevalence regions result in over-diagnosis and the cases diagnosed by it do not match with bacteriologically or radiologically labeled positive cases. Undue, weightage given to symptoms there is high consistency between prevalence of malnutrition, tuberculin positivity and history of contact among the bacteriologically positive cases. Bacteriological and radiological confirmation
can not be taken as gold standard in children. The scoring method can be used as a screening tool for further investigations and keeping the child under observation till the diagnosis is confirmed\(^{(71)}\).

Another study evaluated the applicability of Keith Edwards score system for the diagnosis of childhood tuberculosis and concluded that in any select population with indicative clinical features Keith Edwards score can be a definitive guideline for diagnosis of childhood T.B \(^{(72)}\).

A retrospective case control evaluation of a score system adopted by Ministry of Health, Brazil in the diagnosis of pulmonary T.B in childhood was performed. Among the variables analyzed the radiological status had the greater impact into the diagnosis, followed by exposure to an adult with T.B. and tuberculin skin test > 10 mm.

The sensitivity of the scoring method was 88% and specificity 86.5% \(^{(73)}\).

Evaluation of some available scoring system concluded that they have high sensitivity and low specificity, which may lead to over diagnosis and unnecessary treatment of non T.B.
patients. They are not currently recommended for diagnosis but further research could be taken to evaluate the existing scoring charts (74).

An evaluation of proposed diagnostic scoring system for pulmonary T.B in Brazilian children, cases had gastric lavage cultures positive for MTB and recovered with treatment, while the controls had negative cultures and recovered with treatment other than anti tuberculosis. Radiologic aspect, contact with adult T.B, tuberculin skin test > 10 mm was associated with pulmonary T.B diagnosis. The sensitivity of the score ranged from 58% - 89% and specificity from 98% to 86%. The scoring system may be a useful diagnostic method in areas with high prevalence of T.B (75).

Development and multicentric field evaluation of paediatric scoring system, may lead to over diagnosis by the scoring system but we will not get children coming back with severe multisystem disease later. There are children who attend outpatient department repeatedly for respiratory tract infections with negative CXR (76).
In scoring systems more weightage is given to laboratory tests e.g. acid fast bacilli, tubercles in biopsy, suggestive radiology, and tuberculin test > 10 mm induration. These scoring systems need validation in individual countries. There is definite need for a scoring system based on clinical features for making a diagnosis of T.B in children. However, feasibility of achieving the same scoring system remains doubtful(77).

A study was done in the Republic of Congo to evaluate the agreement between 8 scoring systems and clinical diagnosis and concluded that the clinical presentation of T.B in HIV infected and non infected children was quite similar but HIV infected children were more likely to have a prior history of T.B. Correlation between clinical scoring systems was poor with some disagreement in the decision of whom to treat, and under scoring. There is a need for improved childhood diagnostics(78).

A score sheet has been developed to improve the diagnosis of childhood T.B by MRC National Tuberculosis Research Programme and Centre for epidemiological research
in south Africa, Eritrea, and the International Union Against Tuberculosis And Lung Disease (IUATLD).

Scoring criteria for the diagnosis of childhood T.B adopted by the National Tuberculosis Programme of Sudan\(^5\).

**Table 1:** Scoring criteria for diagnosis of childhood TB adopted by the National Tuberculosis Programme of Sudan

<table>
<thead>
<tr>
<th>Criteria</th>
<th>score points in &lt; 5 yrs</th>
<th>score points in &gt; 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of contact</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Skin test</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>&gt; 5</strong></td>
<td><strong>&gt; 5</strong></td>
</tr>
</tbody>
</table>

A study done in Sudan with objectives to study the pattern of disease and criteria used by different paediatricians for screening children for tuberculosis and comparing them to suggested criteria by IUATLD assesses the reliability of
immune-chromatographic test (ICT) in detecting children with T.B, recognize treatment regimens used by paediatricians and compare them to suggested protocol by the NTP and assess the knowledge and attitudes of parents to the child illness.

The conclusion of the study was that the criteria used by paediatricians for screening children were compatible with those suggested by IUATLD group; they include; weight loss, fever, cough, history of contact, tuberculin test. A scoring system has been suggested for screening children for tuberculosis(79).

Another study was carried out at Wad Medani children Teaching hospital with objectives of applying the scoring criteria developed by the MRC National Tuberculosis Research programme and Centre For Epidemiological Research and IUATLD to Sudanese children as cases of pulmonary tuberculosis, to develop a valid scoring criteria for Sudanese children, and to apply the new scoring criteria again to all patients(80).
Application of the scoring system (adopted by the NTP of Sudan for patients showed that 89.1% of the patients fulfill the scoring criteria for diagnosis of pulmonary T.B. So this scoring system can be used confidently in selection of patient suspected of having pulmonary T.B for further investigation and management.

A new scoring system was developed from patients with positive skin test, and then was applied to all of patients and it was found that only 36% of all patients fulfill the new scoring criteria for diagnosis of pulmonary tuberculosis. This newly introduced scoring system needs further study to assess its feasibility versus the already used methods for the diagnosis of pulmonary T.B\(^{(81)}\).
JUSTIFICATIONS

- Tuberculosis is one of the major health problems affecting Sudanese children.
- Diagnosis of pulmonary tuberculosis in children is difficult and time consuming which usually leads to delay in the diagnosis. Thus an easier and efficient diagnostic method is a necessity in developing countries.
- The National Tuberculosis Programme (NTP) of Sudan is not using a single method for diagnosis of pulmonary tuberculosis in children. They use the routine diagnostic methods (CXR, mantoux test, ESR, sputum examination and the scoring system). When the diagnosis is a dilemma, other modalities are used, like computed tomography of the chest (CT), and polymerase chain reaction.
- PCR is one of the tests that are used to diagnose pulmonary tuberculosis. It is usually done on sputum,
gastric lavage and pleural effusion fluid samples which is difficult to obtain in children.

- A blood sample for PCR is easier to obtain.
- No study has been done to assess the role of blood PCR in the diagnosis of pulmonary tuberculosis in Sudanese children.
OBJECTIVES

- **General Objectives:**
  To evaluate the blood PCR as a method in diagnosis of pulmonary tuberculosis in children.

- **Specific Objectives:**
  - To determine the sensitivity and specificity of blood PCR in the diagnosis of pulmonary tuberculosis in children in comparison with the scoring system.
  - To compare the blood PCR with the scoring system in the diagnosis of pulmonary tuberculosis in children and also with other routine methods used to diagnosis pulmonary tuberculosis in children.
  - To compare the blood PCR with the clinical diagnosis of pulmonary tuberculosis in children.
2- PATIENTS AND METHODS

2.1 Nature of Study: This is a prospective hospital based study.

2.2 Study Area:

This study was conducted in T.B. clinics of the following hospitals: Gaafar Ibn Auf Children’s Hospital, Mohamed Elamin Children’s Hospital Omdurman and Ahmed Gasim Teaching Hospital.

2.3 Study Period: This study was conducted during period of 3 months from July – September 2007.

2.4 Study Population:

This study included children from 0 – 14 years of age attending T.B clinics in the 3 hospitals with suspicion of pulmonary tuberculosis.

2.5 Sample Size: All children attending the T.B. clinic in the three hospitals in the period of the study.
2.6 **Inclusion Criteria:**
- All children ages 0-14 yrs who are attending T.B. clinics with suspicion of pulmonary tuberculosis whose caretakers accepts inclusion in the study.

2.7 **Exclusion Criteria:**
- Children suspected to have pulmonary tuberculosis and have another chronic disease such as malnutrition, CRF, Diabetes.
- Children whose ages > 14 years
- Children or their relatives who refused to be included in the study.
- Children with extra pulmonary tuberculosis.

2.8 **Ethical Consideration:**
- Approval consent of the study was taken from our local committee of paediatric and child health, university of Khartoum.
- Written consent was obtained from the hospitals administration authorities.
Verbal consent was obtained from the parents and/or the caretaker.

2.9 Methods:

2.9.1 Questionnaire

The questionnaire was conducted for all patients. It is standardized questionnaire designed by the researcher. Information on name, age, gender, locality, complains and duration of illness, investigations and their results were included and final diagnosis.

2.9.2 Collection of a blood sample for PCR:

The blood samples were collected by the researcher. Venous blood sample of three mls was taken from each child in an Ethylene Diamene Tetra Acetic Acid (EDTA) container and kept in a temperature of about 8°C and transported to the laboratory in the same day. Each container has a label showing patient’s name and the serial number similar to that of the questionnaire. The blood sample was taken in the same day to the laboratory of the Institute of Endemic Diseases of University of Khartoum.
2.9.3 PCR Technique:


**Reagents, supplies and equipments:**

1- Red blood cell lysing solution:
   Sterile distilled H2O 1. L.
   NH4Cl 7.5 gm.
   Tris 1.0 gm.

2- Nucleic acid lysis buffer:
   10 m M Tris pH 8.2
   400 mM Nacl.
   2 mM EDTA pH 8.2 with Hcl.

3- 10% SDS.

4- Proteinase K (2 mg/ml) in H2O. stored frozen (-20).

5- 5.3 M Na Cl.

6- Cold 100% and 75% ethanol purity 99.9%.

7- Vortex, centrifuge, microfuge, water bath (65°C) pipettor with tips and polypropylene tubes.
2.9.4 **Data collection technique:**

Data was collected by the researcher by filling the preformed questionnaire.

2.9.5 **Data analysis:**

Data was entered in computer using the Statistical Package of Social Science (SPSS) system.

Frequencies were obtained for all variables and Chi square tests were computed for selected variables. The level of significance was taken as $P = 0.05$.

2.9.6 **Calculation of sensitivity and specificity of blood PCR:**

Sensitivity and specificity of blood PCR is done by grouping and classification of patients according to the scoring system and the result of PCR as shown in the table below:
### Positive test | Negative test
--- | ---
Disease present | T P | F N
Disease absent | F P | T N

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \times 100
\]

\[
\text{Specificity} = \frac{TN}{FP + TN} \times 100
\]

#### 2.9.7 Difficulties Encountered:
Refusal of caretaker of some children to be included in the study and to give a blood sample for PCR.

#### 2.9.8 Other participants:
- Two lab technicians
- Statistician
Chapter Three

3- RESULTS

3.1 Sociodemographic Characteristics and Social History of Children Included in the Study:

3.1.1 Sociodemographic characteristics of children studied:

The study group included 101 children of whom 57 (56.4%) were males and 44 (43.6%) were females, with a male to female ratio of 1.3:1 as shown in (Figure 1).

The highest occurrence of pulmonary tuberculosis was observed in the age group of 1-5 years which comprises 43.6%, followed by the age group of 10-14 years which comprise 28.7% of children studied as shown in (Table 2).

Most of children were originally from Western Sudan constituting 56 (55%) followed by children from the south 20 (19.8%), followed by children from the North 14 (13.9%), eight children were from Central Sudan and only three children
(2.9%) were originally from Eastern Sudan. This is shown in
(Table 3).
**Table 2: Distribution of children according to age groups:**

\[ n = 101 \]

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 months</td>
<td>2</td>
<td>02.0</td>
</tr>
<tr>
<td>&lt; 5 – 11 months</td>
<td>11</td>
<td>10.9</td>
</tr>
<tr>
<td>1-5 years</td>
<td>44</td>
<td>43.6</td>
</tr>
<tr>
<td>6-9 years</td>
<td>15</td>
<td>14.8</td>
</tr>
<tr>
<td>10-14 years</td>
<td>29</td>
<td>28.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>101</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Table 3: Distribution of children according to their original home

\[ n = 101 \]

<table>
<thead>
<tr>
<th>Original home</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khartoum</td>
<td>4</td>
<td>04.0</td>
</tr>
<tr>
<td>Central</td>
<td>16</td>
<td>15.8</td>
</tr>
<tr>
<td>North</td>
<td>10</td>
<td>09.9</td>
</tr>
<tr>
<td>East</td>
<td>9</td>
<td>08.9</td>
</tr>
<tr>
<td>West</td>
<td>42</td>
<td>41.6</td>
</tr>
<tr>
<td>South</td>
<td>20</td>
<td>19.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>101</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Most of children resides in Khartoum State 87 (86%), while only 8 (7.9%) reside in Gezera State.

3.1.2 Social History:

Most of children live with their families in their own houses constituting 70 (69%), while 28 (28.7%) live in rented house and two (1.9%) children were homeless. 54 (53.5%) have tap water supply, while 47 (46.5%) haven’t.

Electricity supply was available for 41 (40.5%) of children, while 60 (59.4%) haven’t. The socioeconomic status of most of the children was low constituting 79 children (78.3%), while 22 (21.7%) children belong to the moderate socioeconomic status as shown in (Figure 2).

3.2 Symptoms of Pulmonary Tuberculosis:

99 children (98%) presented to the T.B clinic with the complain of cough, 91 (90.1%) with fever and 86 (85%) with weight loss, shown in (Figure 3).
Figure 2: Distribution of patients according to socioeconomic
n = 101

78%

22%
Figure 3: The presenting symptoms
n = 101

Cough  Fever  Weight loss
98      90      86
3.2.1 The cough: The duration of cough was more than 4 weeks in 72 children (72%), 24 (24%) complained of cough for a duration of 2-4 weeks, and 3 (3%) for less than 2 weeks as shown in (Table 4).

60 of children complained (60%) of productive cough while 39% complained of dry cough, as shown in (Figure 4). Forty four (44%) of children had productive cough of whitish sputum while nine (9%) had yellowish sputum and only 7 (7%) of greenish sputum.

3.2.2 The fever: The duration of fever was more than 4 weeks in 69 children (75.8%), 20 (21.9%) had fever for 2-4 weeks duration, while only two (2.1%) had fever for less than 2 weeks as shown in (Figure 5).

56 children (61.5%) complained of high grade fever, 27 (29.7%) with moderate fever and only eight (8.8%) of low grade fever.

77 (84.6%) of children complained of nocturnal fever, 10 (10.9%) continuous, whole four (4.3%) had diurnal fever. This is shown in (Figure 6).
Table 4: Distribution of children according to duration of cough:

\[ n = 99 \]

<table>
<thead>
<tr>
<th>Duration of cough (weeks)</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>2 – 4</td>
<td>24</td>
<td>24.3</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>72</td>
<td>72.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>99</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Figure 4: Distribution of patients according to type of cough
n = 99
Figure 5: Distribution of patients according to duration of fever

n = 91

- < 2 wks: 2%
- 2 - 4 wks: 19.8%
- > 4 wks: 68.3%
Figure 6: Distribution of patients according to type of fever

n = 91

85% Nocturnal

11% Continuous

4% Diurnal
63 children (69.2%) had fever associated with sweating, while 28 (30.7%) had no sweating.

3.2.3 The weight loss: 33 children (38.3%) had marked weight loss, 30 (34.9%) with moderate weight loss and 23 (26.7%) with mild loss of weight. This is shown in (Table 5)

3.3 Contact with Tuberculous or Chronic Cough Patients:

A positive history of contact with a patient with tuberculosis or chronic cough is reported in 60 (59.4%) of all children and the nature of contact is the household in 56 (93.3%) and only four (6.7%) the contact is neighbour. This is shown in (Figure 7)

3.4 Vaccination:

93 (92.1%) of children were vaccinated with BCG and 88 (94.6%) are having BCG scar as shown in (Figure 8).
Table 5: Distribution of children according to the degree of loss of weight:

\( n = 86 \)

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked</td>
<td>33</td>
<td>38.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>30</td>
<td>34.9</td>
</tr>
<tr>
<td>Mild</td>
<td>23</td>
<td>26.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>86</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Figure 7: Distribution of patients according to contact with chronic cough or TB case
n = 60

- 55% household
- 41% No contact
- 4% Neighbour
Fig. 9: Distribution of patients according to BCG vaccination

n = 93

No
Children vaccinated without BCG scar
Children vaccinated with BCG scar

87
8
5

0
10
20
30
40
50
60
70
80
90
3.5 Investigations:

3.5.1 Chest x-ray:  
95 children (94.1%) were investigated by a chest x-ray and 81 (85.2%) of them had a chest x-ray suggestive of pulmonary tuberculosis, while the remaining 14 patients (14.8%) These findings are shown in (Figure 9).

3.5.2 Sputum examination: Sputum smear were done for 35 all children (34.7%) and it was positive in 10 (28.5%), while sputum culture was done for only one (1%0 and it was positive.

Gastric lavage was done for only 16 of all children (15.8%) and all of their results were negative.

This shown in (Table 6)

3.5.3 ESR: The (ESR) was performed for all children and, it was more than 100 mm/hr in 19 (18.8%) and ranging from 50-100 mm/hr in 42 (41.6%), t was below 50 mm/hr in 24 (23.8%) while 16 (15.8%) showed normal for age ESR results as shown in (Table 7).
Figure 9: Distribution of patients according to chest x-ray findings suggestive of T.B
n = 95

- 85%
- 15%
Table 6: Distribution of children according to type of sputum test:

\[ n = 52 \]

<table>
<thead>
<tr>
<th>Type of sputum test</th>
<th>Number of children</th>
<th>Positive results</th>
<th>Negative results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>(%)</td>
<td>No</td>
</tr>
<tr>
<td>Sputum smear</td>
<td>35</td>
<td>34.7</td>
<td>10</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>1.0</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>Gastric lavage</td>
<td>16</td>
<td>15.8</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 7: Distribution of children according to the ESR:

\[ n = 101 \]

<table>
<thead>
<tr>
<th>ESR results</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal for age</td>
<td>16</td>
<td>15.8</td>
</tr>
<tr>
<td>&lt; 50 mm/hr</td>
<td>24</td>
<td>23.8</td>
</tr>
<tr>
<td>50 – 100 mm/hr</td>
<td>42</td>
<td>41.6</td>
</tr>
<tr>
<td>&gt; 100 mm/hr</td>
<td>19</td>
<td>18.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>101</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
3.5.4 **The Mantoux test:** The mantoux test was performed in 93 of all children (92.1%) and it was more than 15 mm in 21 (22.6%), ranging from 10-15 mm in 35 (37.6%) and 6-9 in four (4.3%) and less than five in 33 (35.5%). These results are shown in (Table 8).

3.6 **The Scoring System:** 92 children (91.1%) score of five or more which was positive according to scoring system, while only 9 (8.9%) scored less than five. This shown in (Figure 10).

3.7 **Diagnosis:**

77 children (76.2%) were diagnosed as pulmonary tuberculosis by doctors in TB clinics, 10 (9.9%) were considered as suspected but no pulmonary tuberculosis, while 13 children (12.9%) were considered as suspected who were offered trial of treatment and only one (1%) was suspected with for whom INH prophylaxis was offered. This is shown in (Figure 11).
<table>
<thead>
<tr>
<th>Mantoux test</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 15 mm</td>
<td>21</td>
<td>22.6</td>
</tr>
<tr>
<td>10 – 15</td>
<td>35</td>
<td>37.6</td>
</tr>
<tr>
<td>6 – 9</td>
<td>04</td>
<td>4.3</td>
</tr>
<tr>
<td>&lt; 5</td>
<td>33</td>
<td>35.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>93</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>
Figure 10: Distribution of patients according to scoring system

n = 101

Negative < 5
Figure 11: Distribution of patients according to diagnosis

n = 101

- T.B. case: 77.2%
- Suspect No. T.B: 9.9%
- T.B suspect with trial treatment: 2.9%
- Suspect with I.N. treatment: 1.1%
3.8 PCR:

The Polymerase Chain Reaction (PCR) was positive in 41 (40.6%) of children as shown in Figure (12), the males were 22 (53.7%), while the females were 19 (46.3%). Forty of them (97.6%) were complaining of cough while only one (2.4%) hadn’t complained of cough; P Value of 0.7. 38 (92.7%) complained of fever while only three (7.3%) hadn’t; P value of 0.47. 35 of children (85.4%) complained of weight loss while 6 of children (14.6%) haven’t weight loss; P value of 0.9. This shown in (Table 9)

Nine of the children (22%) who were positive by PCR had normal ESR for age while 32 (78%) of them showed raised ESR; P value of 0.037. 21 (51%) of those positive by PCR had a positive mantoux test; P value of 0.073, while the rest had a negative mantoux test. 29 of children (70.7%) with positive PCR showed chest x-ray findings suggestive of pulmonary tuberculosis; P value of 0.31. These findings shown in (Table 10). Only two children (4.9%) who had a score less than 5, were having positive PCR, while 39 (95.1%) whose score was more than 5 had positive PCR results. This shown in (Figure 13)
Figure 12: Distribution of patients according to PCR result
n = 101
### Table 9: Clinical presentation in children with positive PCR

<table>
<thead>
<tr>
<th>Presenting symptom</th>
<th>Children with positive PCR</th>
<th>Children with negative symptoms PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive symptoms</td>
<td>Negative symptoms</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Cough</td>
<td>40</td>
<td>97.6</td>
</tr>
<tr>
<td>Fever</td>
<td>38</td>
<td>92.7</td>
</tr>
<tr>
<td>Weight loss</td>
<td>35</td>
<td>85.4</td>
</tr>
</tbody>
</table>
Table 10: Comparison between PCR positivity and the findings of other investigations 

(n = 41)

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Positive findings</th>
<th>Negative findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>29</td>
<td>70.7</td>
</tr>
<tr>
<td>ESR</td>
<td>32</td>
<td>78.0</td>
</tr>
<tr>
<td>Mantoux test</td>
<td>21</td>
<td>51.0</td>
</tr>
</tbody>
</table>
Figure 13: The scoring system of children with positive PCR
30 children (73.2%) who were positive by PCR were diagnosed as having pulmonary tuberculosis. Seven (17.1%) were considered as suspected but not having pulmonary tuberculosis, 3 (7.3%) received trial of treatment and only one child (2.4%) received INH prophylaxis as shown in (Table 11)
Table 11: The diagnosis tuberculosis in children with positive PCR

\[(n = 41)\]

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No of children</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive PCR</td>
<td>(%)</td>
</tr>
<tr>
<td>Pulmonary T.B</td>
<td>30</td>
<td>73.2</td>
</tr>
<tr>
<td>Suspected No T.B</td>
<td>07</td>
<td>17.1</td>
</tr>
<tr>
<td>Suspected with trial of treatment</td>
<td>03</td>
<td>07.3</td>
</tr>
<tr>
<td>Suspected with INH prophylaxis</td>
<td>01</td>
<td>02.4</td>
</tr>
</tbody>
</table>


Chapter Four

4- DISCUSSION

Pulmonary tuberculosis (T.B) is a common clinical problem in paediatrics, its diagnosis in children is difficult because they differ from adults in their immunological and pathophysiological response. Diagnosis of T.B in children relies on a careful and thorough assessment of all evidence derived from a careful history, clinical examination and relevant investigations e.g. chest x-ray, mantoux test, ESR and sputum examination.

4.1 Sociodemographic Characteristics and Social History of Children Participating in the Study:

Among children of this study male predominance was observed, males constitute 56.4% with a male : female ratio 1.3:1. The male predominance was also observed by Al Fadil as males constitute 57.6% of all children included in his study\(^\text{(80)}\).
In Abdmoneim’s study males constitute 56.3%\(^{(81)}\) and by Alam El Din who reported a male percentage of 51.2% in his study\(^{(82)}\), male predominance was found also by Diab with a percentage of 52% \(^{(83)}\). This was in contrast with what has been mentioned that there was no or little difference between boys and girls up to puberty\(^{(84)}\). In Europe and North America when tuberculosis was common the male rate continued fairly high at all ages\(^{(16)}\).

The male predominance can be explained by higher exposure and social activities of boys.

Age of children included in the study ranges from 0 – 14 years old, 43.6% were in the age group 1-5 years. In comparison with A/Moneim study who found that children in the age group of 5 -13 years constitute 60% of children studied\(^{(81)}\). Alam El Din study showed that children under fives constitute 61%, this was also found by Elfadil.

In contrast to what has been written that the prevalence of pulmonary tuberculosis increases with age in both sexes\(^{(16)}\). Reports from India showed that the incidence of the disease rises with age and it was high in the age group 0 –
14 years\(^{(3)}\). A retrospective study in Turkey showed that 62% of children were under 6-years of age\(^{(85)}\).

The high prevalence of tuberculosis in the age group 0-5 years can be explained by their vulnerability to pulmonary tuberculosis due to nutritional problems and their close contact with affected adults.

The majority of children were originally from western Sudan 55.4% who came for consultation. Most children included in this study reside in Khartoum State and constituted 86.1% and the rest were from different states for consultation. This can be explained by migration from western Sudan due to civil war and the poor financial and environmental conditions they live in.

Children who reside in their own houses were 69.3%, 53.5% of children live in houses with tap water supply and only 40.6% had electricity supply.

Tuberculosis is a burden on the family financially, family incomes in 39.6% of children studied were less than 300 SDG. 78.2% were of low socioeconomic status. This result which is similar to A/Moneim study who found that 97% of children
with tuberculosis were of low socioeconomic status. These findings are very much reflecting the prevalence of this disease amongst low socioeconomic classes.

4.1 Symptoms of Pulmonary Tuberculosis:

4.1.1 Cough:

Cough is the main complaint and was reported in 98% of children studied. This is relatively comparable to Alfadil who found chronic cough in 89.7% of children studied\(^\text{(80)}\).

A/Moneim study showed that cough was a complain in 67% of children\(^\text{(81)}\). 1991 study showed cough was a complain in 75% of children\(^\text{(86)}\) while in the 1996 study it was found to be 93.3\%\(^\text{(87)}\).

A study done in British Colombia Canada reviewing 202 cases of pulmonary tuberculosis showed that 60% of children were asymptomatic\(^\text{(88)}\).

Another study done in Department Of Radiology, Children’s hospital Los Angles, showed that 65% of patients presenting with tuberculosis during childhood were asymptomatic\(^\text{(89)}\).
All children included in this study were symptomatic. This may be explained by the low socio-economic status, ignorance, illiteracy and lack of screening of contacts.

4.2.2 Fever: Fever was found in 90.1% of children studied; its duration was more than 4 weeks in 68% and 2-4 weeks in 19.8%, high grade fever in 55.4%. This result is similar to A/Moneim who found fever in 91.3%, and Alam who found fever in 90.5% of children studied, similarly in 1991 Zein et al, conducted study on 65 children with pulmonary T.B and fever was present in 100% of children\(^{86}\).

The type of fever suggestive of pulmonary tuberculosis is high grade more than 38ºC for a period more than 2 weeks mainly nocturnal which could be associated with night sweating, after exclusion of common causes such as malaria or pneumonia\(^{5}\).

4.2.3 Weight loss: Weight loss was the third common complain and it is found in 85.1% of children, which was marked in 38.7% of children, 34.8% moderate and mild in 26.7%. weight loss in pulmonary tuberculosis should be documented by comparing previous and present weight of the
child, this couldn’t be done in this study, children had no records of their previous weights, so weight loss in this study is rather subjective and taken asymptomatic from parents or caretaker.

In Al Fadil study weight loss was found in 96% of children.

A/Moneim study showed that 98.1% of children presented to T.B clinics complained of weight loss.

Similar results were shown by 1991 study and 1996 study. In 1991 study weight loss was present in 78% of cases. In the 1996 study weight loss was present in 96.9%.

Weight loss or failure to thrive both support the diagnosis of pulmonary tuberculosis, and is one of the criteria included in the scoring system\(^5\).

4.3 History of Contact:

Presence of contact with an adult T.B case with chronic cough is one of the important points that should be asked about when taking a history in a child with suspected T.B. Contact is one of the criteria included in the scoring system. Defining the contact or source case has an important role in
prevention and control of tuberculosis. In this study 59.4% of children have positive history of contact, in 93.3% of cases the contact is household related while in 6.7% it was contact with a neighbour.

History of contact was reported in 50.5% in A/Moneim study, 43% for the 1991 study and 64.6% for 1996 study.

Children contacts of adult T.B case screening should be activated for early detection and treatment of children, and health education is necessary in increasing benefits of screening, early detection and treatment.

4.4 BCG Vaccination:

In this study 92.1% of children were vaccinated with BCG, while 94.6% of them had a BCG scar. In comparison with A/Moneim study BCG vaccination was given to 76.7% of children, while the study done 1991 found 29.5%, in the study done in 1996; 52.3%. Another study was done in 1997 in Sharg El Neil province in a total of 1367 children aged 3 months. 15 yrs BCG vaccination was received by 82.6% of the children (90).
Alfadil found that 65.5% of children studied received BCG vaccine, and 65.4% of them had the BCG scar\(^{(80)}\).

Absence of the BCG scar in vaccinated children was explained by failure of vaccination due to improper administration or loss of potency of the vaccinate due to improper storage and transportation.

The percentage of children vaccinated without BCG scar is lower than that found by Alfadil study\(^{(80)}\).

In the mean time BCG remains an effective and safe vaccine, BCG was found have an efficacy of around 70-80%. In many studies, it prevents severe disease in the young rather than reactivation of pulmonary disease in older age groups. Use of BCG complicates the interpretation of the tuberculin skin test\(^{(91)}\).

4.5 **Investigations:**

4.5.1 **Chest x-ray**

Chest x-ray was done in 94.1% of children studied and the report of 85% of them were suggestive of pulmonary tuberculosis. In comparison with A/Moneim study, 75% of
children showed chest x-ray finding suggested of pulmonary tuberculosis.

In Alam study chest x-ray findings suggestive of pulmonary tuberculosis were detected in 88% of children while in Magda study it was 83%(81,87).

Chest x-ray is a highly sensitive technique for diagnosing pulmonary T.B in immunocompetent individuals, even though it is unspecific since T.B generates no pathogenic radiological signs, regardless of how suggestive the images may seem. Thus, while there are radiographic images highly suggestive of T.B, these findings are only aid in the diagnosis and suggest that microbiological evaluations should be carried out to confirm the diagnosis. In the same way, the prognosis and response to treatment can not be decisively assessed by the radiographic course, since lesion regression can take place in a period of 3-9 months(84).

In 94.1% of children studied chest x-ray was done and the result of 85% was suggestive of pulmonary tuberculosis. While in Dr. Abd Moneim study 75% of children showed chest x-ray findings suggestive of pulmonary tuberculosis (81).
4.5.2 **Sputum examination:**

Sputum examination was performed in 37.4% of children in this study and was positive in 28.5% of them which is a low yield as expected. This is not comparable to results of A/Moneim study in which sputum examination was performed in 21% of children and all results were negative.

Microscopy of sputum and gastric lavage were performed in 24 children in Alam Eldin study and was positive in only 3.6% of them. This low yield similar to other studies in Sudan, in 1991 study it was 5% in 1996 study 3% (82,86,87).

This was also the case in other parts of Africa and a south African study by Dias on 627 T.B children which showed positive AFB in 5% (92). In Lusaka the positive yield was 17% as reported by the same author (92).

The low yield of sputum or gastric lavage examination may be due to the fact that children rarely produce sputum samples adequate for examination and typically have a low bacteriological loads and also due to technical problem in laboratories (95).
4.5.3 **ESR.** In this study ESR was performed for all children, in 84% it was raised above normal ranges for age but a high ESR above 100 mm/hr was found only in 18.8% of cases. In Dr. Abd Moneim study ESR was performed for 81% of children with 44% having an ESR above 100 mm/hr. This result was comparable with Alam study in which ESR was performed in 79.8% of children and was high above 100 mm/hr in 13.1%.

A study in Gatar, India by Almarria and colleagues on 68 children with T.B showed a normal ESR in 33% of the patients and it seemed that the ESR had a little value in the diagnosis of childhood T.B\(^{(93)}\).

ESR has a low place as a screening tool in symptomatic children, it may be useful in group of patients in whom clinical evaluation has given rise to moderate suspicion of the presence of the disease.

4.5.4 **Mantoux Test (Tuberculin tests):**

Mantoux test is one of the tests to be requested in the T.B clinics for children. In this study it was performed in
92.1% of cases and it was positive in 60.3% and negative in 39.7%.

While 7.9% of children were showing negative mantoux test diagnostic BCG was performed and was positive.

In Alfaadil study mantoux test was performed for 34.5% and was positive in 44.3% of children. A/Moneim study showed that 81% of children were investigated by mantoux test\(^{(80,81)}\).

A positive test does not exclude active tuberculosis. The tuberculin test is however, important in non BCG vaccinated children under 5-years of age, where a positive test is more likely to reflect recent infection with mycobacterium tuberculosis and a much higher risk of developing the disease\(^{(23)}\).

**4.6 Diagnosis:**

Pulmonary tuberculosis was the final diagnosis in 76.2% of children studied, 9.9% were suspected cases but T.B was excluded by routine investigations. 12.9% were suspected with trial of treatment and follow up while 1% was suspected and prescribed INH prophylaxis with follow up.
4.7 Scoring System:

The scoring system has a sensitivity of 88.9% and specificity of 86.5\(^{(9)}\).

In this study applying the scoring system adopted by the national Tuberculosis Control Programme of Sudan, which was developed by National Tuberculosis Research Center South Africa.

Children who score less than 5 points were 8.9% and those who score 5 points or more were 91.1% of all children studied.

Children who score less than 56 (66.7%) were diagnosed as tuberculosis, and 3 (33.3 \%) as suspected not tuberculous while children who score more than 5 (77\%) of them were diagnosed as tuberculous, (7.6\%) as suspect not tuberculous, (14\%) as suspected with trial of treatment and (1.1\%) as suspected with INH prophylaxis.

Recently a lot of criticism has been directed to the use of diagnostic scores of paediatric T.B in chronically debilitated children including malnourished and HIV positive children. These scores being not standardized and a minority validated
or adapted to HIV or malnourished as reported by Hesseling et al\(^{(94)}\).

Alfadil evaluated the scoring system developed by the MRC National T.B research programme centre and the IUATLD for diagnosis of pulmonary tuberculosis were the same as the criteria shared by our doctors for diagnosis of pulmonary tuberculosis, by applying this scoring system to all patients studied 89.1% fulfill the scoring criteria for diagnosis of pulmonary tuberculosis so this scoring system can be used confidently in selection of patients suspected of having pulmonary tuberculosis for further investigation and management\(^{(80)}\).

A/Moneim evaluation of scoring system conducted that it has proved to be effective in screening children for tuberculosis and has a chance of more than 70% for correct diagnosis\(^{(81)}\).

**4.8 PCR:**

Blood PCR was positive in (40.6%) of children studied. Comparing the result of blood PCR with the scoring system, the sensitivity of this test was found to be 42.4%, specificity
77.7% positive predictive value 95.1% and the negative predictive value 11.6%.

Comparable to the study performed to evaluate the blood PCR in comparison with results of sputum smear examination, blood PCR sensitivity was found to be 40%, specificity 100% and an accuracy of 60% (68).

Another study evaluated blood PCR in comparison with sputum culture, it found the sensitivity to be 20% and the specificity to be 94.4% positive with a predictive value of 85.7%. The negative predictive value was 41.5% and the efficacy 47.9%.

**Fever:** Children with positive PCR complained of fever were 92.7% with a P value of 0.47 which shows an insignificant relationship between the positivity of PCR and presence of fever.

**Weight loss:** Children with a positive PCR and weight loss were 85.4% with a p value of 0.9 which shows insignificant relationship between weight loss and positivity of PCR.

**Chest x-ray:** Children with chest x-ray finding suggestive of pulmonary tuberculosis and positive PCR were 80.6% with a p
value of 0.3 which shows a insignificant relationship between positivity of PCR and the chest x-ray findings.

**Sputum examination:** Comparing the positivity of PCR and results of sputum examination, which is done for some of the children studied showed that there was no significant relationship.

**ESR:** 48% of children with positive PCR showed raised ESR results with a p value of 0.037 which reflects the correlation between PCR positivity and raised ESR.

**Mantoux test:** (51%) of children with a positive PCR were had positive mantoux test with a p value of 0.73, there is no significant relationship between the positivity of blood PCR and mantoux test.

73.2% of children with positive PCR were diagnosed as tuberculosis, 17.1% suspected and 7.3% suspected with trial of treatment and 2.4% are suspect with trial of treatment with a p value of 0.79, which indicates an insignificant relationship between them.
95.1% of children with a positive PCR were having scoring of 5 or more by a scoring system while 4.8% with a score of less than 5 had a positive PCR.

4.9 Credibility of PCR in the Diagnosis of Pulmonary Tuberculosis in Children:

Although PCR has a low sensitivity in comparison with other methods it can be used to diagnose pulmonary tuberculosis in children.
CONCLUSIONS

1- Diagnosis of childhood pulmonary tuberculosis is difficult because confirmatory tests are not commonly used due to their high cost and time consumption.

2- The routine methods used to diagnose pulmonary tuberculosis in tuberculosis clinics are not the same and are not applied to all children.

3- The scoring system is simple, easy to apply and sensitive method, but, is not commonly used in T.B clinics.

4- The blood polymerase chain reaction sensitivity was found to be 42.1%, specificity 77.7%, positive predictive value .95, negative predictive value 11.6.

5- The high ESR is related to blood PCR positivity.

6- The test is expensive, needs qualified personal and well equipped laboratory with a low sensitivity and moderate specificity.
**RECOMMENDATIONS**

1- Blood polymerase chain reaction is not recommended to be used as routine methods for diagnosis of pulmonary tuberculosis in children due to low sensitivity and moderate specificity.

2- Blood PCR is not cost effective method for diagnosis of pulmonary tuberculosis in children.

3- More usage of the scoring system should be applied in the T.B clinics.

4- Screening of children contacts to adult pulmonary tuberculosis patients should be applied routinely.

5- More research for new diagnostic methods to diagnose pulmonary tuberculosis should be pursued and advised.
References


(11) Bosch S. Outcome of HIV infected children with culture confirmed T.B. www.HIVandhepatitis.com


(32) Villiers RUP, Andronikou S, Westhuizen SV. Specificity and sensitivity of chest radiograph, in the diagnosis of paediatric pulmonary tuberculosis and the value of


(41) Zar H. Results of a South African study this week’s issue of show how a diagnosis of tuberculosis in young children can be confirmed by a straightforward sputum test, rather than the conventional invasive procedure of gastric lavage. Br Med J 2000; 82: 305-8.


University of Khartoum  
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Questionnaire

Evaluation of the Scoring System in the Detection of Tuberculosis in Children

(1) Personal data:

1.1 Name of care taker: ........................................ Tel No.: ..............
1.2 Name of the patient: ........................................
1.3 Age  1.3.1 0-4 month  □  1.3.2 < 5-11 month  □  
         1.3.3 1-5 yrs  □  1.3.4 5 < 10 yrs  □  
         1.3.5 10 – 14 yrs  □
1.4 Gender:  1.4.1 Male  □  1.4.2 Female  □
1.5 Tribe: ..............................................................................
1.6 Origin: ..............................................................................
1.7 Residence: ...........................................................................
1.8 Tap water supply:  
         1.8.1 Yes  □  1.8.2 No  □
1.9 Electricity supply:  
         1.9.1 Yes  □  1.8.2 No  □
1.10 The house:  
         1.10.1 Rented  □  1.10.3 Own house  □
1.11 Monthly income:  
         1.11.1 < 300 SDG □  1.11.2 300-600 SDG □  1.11.3 > 600 SDG □
1.12 Socio-economic status  
         1.12.1 Low □  1.12.2 Moderate □  1.12.3 High □

(2) Symptoms of tuberculosis:

2.1 Cough:
2.1.1 Yes 2.1.2 No

2.2 Duration of cough:
2.2.1 < 2 wk 2.2.2 2-4 wks 2.2.3 > 4 wks

2.3 Type of cough:
2.3.1 Dry 2.3.2 Productive

2.4 Type of sputum:
2.4.1 Whitish 2.4.2 Yellowish
2.4.3 Greenish 2.4.4 Containing blood

2.5 Fever:
2.5.1 Yes 2.5.2 No

2.6 Duration of fever:
2.6.1 < 2 wk 2.6.2 2-4 wks 2.6.3 > 4 wks

2.7 Type of fever:
2.7.1 Low grade 2.7.2 Moderate 2.7.3 High grade

2.8 What is the main time of fever?
2.8.1 Nocturnal 2.8.2 Diurnal 2.8.3 Continuous

2.9 Is the fever associated with sweating?
2.9.1 Yes 2.9.2 No

2.10 Loss of weight
2.10.1 Yes 2.10.2 No

2.11 The degree of loss of weight:
2.11.1 Marked 2.11.2 Moderate
2.11.3 Mild 2.11.4 No

2.12 Is there contact with a chronic cough case?
2.12.1 Yes 2.12.2 No

2.13 Contact is:
2.13.1 Household 2.13.2 Neighbour
2.13.3 School 2.13.4 Others:

3. Vaccination:
3.1 Is the child vaccinated with BCG?
3.1.1 Yes 3.1.2 No
3.2 BCG scar
   3.2.1 Yes □ 3.2.2 No □

(4) Investigations:
4.1 Mantoux test
   4.1.1 Yes □ 4.1.2 No □
4.2 Result of Mantoux test:
   4.2.1 0-5 mm □ 4.2.2 6-9 mm □
   4.2.3 10-15 mm □ 4.2.4 > 15 mm □
4.3 Chest x-ray:
   4.3.1 Done □ 4.3.2 Not done □
4.4 Was the x-ray findings suggestive of T.B.
   4.4.1 Yes □ 4.4.2 No □
4.5 Sputum smear
   4.5.1 Done □ 4.5.2 Not done □
4.6 Result of sputum examination:
   4.6.1 Positive □ 4.6.2 Negative □
4.7 Sputum culture
   4.7.1 Done □ 4.7.2 Not done □
4.8 Result of sputum culture:
   4.8.1 Positive □ 4.8.2 Negative □
4.9 Gastric lavage:
   4.9.1 Done □ 4.9.2 Not done □
4.10 Result of gastric lavage:
   4.10.1 Positive for AFB □ 4.10.2 Negative for AFB □
4.11 ESR result:
   4.11.1 Normal for age □ 4.11.2 < 50 mm/hr □
   4.11.3 50-100 mm/hr □ 4.11.4 > 100 mm/hr □
4.12 PCR result:
   4.12.1 Positive □ 4.12.2 Negative □