A DISSERTATION ON

PREDICTIVE VALUE OF A 24 HOUR TUBERCULIN SKIN INDURATION FOR 1 TU DONE USING MANTOUX METHOD MEASURED BY PALPATION AND BALLPOINT PEN TECHNIQUE

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CERTIFICATE

This is to certify that the dissertation titled **"PREDICTIVE VALUE OF A 24 HOUR TUBERCULIN SKIN INDURATION FOR 1 TU DONE USING MANTOUX METHOD MEASURED BY PALPATION AND BALLPOINT PEN TECHNIQUE"** submitted by **Dr.V. SHANMUGAPRIYA** to the Faculty of pediatrics, The Tamilnadu M.G.R.Medical University,Chennai in partial fulfillment of the requirement for the award of M.D.Degree (Pediatrics) is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

I **Dr.V. SHANMUGAPRIYA**, solemnly declare that the dissertation titled "**PREDICTIVE VALUE OF A 24 HOUR TUBERCULIN SKIN INDURATION FOR 1 TU DONE USING MANTOUX METHOD MEASURED BY PALPATION AND BALLPOINT PEN TECHNIQUE"** has been prepared by me.

This is submitted to the **Tamilnadu Dr.M.G.R.Medical University**, Chennai in partial fulfillment of the rules and regulations for the M.D.Degree Examination in Paediatrics.

Place: Madurai

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CONTENTS

INTRODUCTION

Tuberculosis is a chronic infectious disease caused by Mycobacterium tuberculosis. Tuberculosis remains one of the major diseases afflicting children throughout the world. As the children get infection from adults with chronic pulmonary tuberculosis, the extent of the infection or disease in children is directly related to prevalence of chronic pulmonary tuberculosis in adults. Prevalence of active disease in adults in India is about 18 per 1000 population. [1]

In India, every year 1.8 million new cases of TB are reported, which accounts for one fifth of new cases in the world. In India 2 of every 5 persons in general population have latent tuberculosis.[2] The annual risk of tuberculosis infection is 1.5 in the country. The annual rate of infection in India is 20 to 25 times higher than in developed countries.[1]

Cases of tuberculosis in children represent 5-15 percent of all cases of Tuberculosis. Children have a lower prevalence rate (5-10 percent) as compared to adolescents (10-30 percent) and adults (30-50 percent). [3]

The portal of entry for *M. tuberculosis* for almost all children is the respiratory tract. Ingestion of milk laden with bovine tuberculosis can lead to a gastrointestinal primary lesion. Rarely, infection of the skin or mucous membrane can occur through an abrasion, cut, or insect bite. Transplacental transmission is very rare.

Age is an important factor in the epidemiology of childhood tuberculosis. About 60% of tuberculosis cases in children occur in infants and children less than 5 years of age. Age Between 5 and 14 years has often been called the "favored age", because children in this age group have the lowest rates of tuberculosis disease than any other age group in virtually every population. The incidence of tuberculosis begins to increase again in late childhood and adolescence, particularly for girls. There is little difference in the incidence of tuberculosis in the two sexes in early childhood.

The prevalence rate of tuberculosis is very high in children of low socioeconomic groups because of overcrowding, close contact with sputum positive cases, poverty and poverty related diseases, poor ventilation and unhygienic living conditions. Tuberculosis is often activated or precipitated by infectious diseases like measles, whooping cough, chronic diarrhea and severe malnutrition which lead to T-lymphocyte deficiency.

The incubation period varies between 4 and 8 weeks. The clinical features usually start with the development of hypersensitivity to tubercular proteins.

The clinical features of tuberculosis are vague and non specific. Over two-thirds of the children with primary complex are asymptomatic. Symptoms suggestive of tuberculosis include low grade fever for more

than 2 weeks, recent loss of appetite, poor weight gain or weight loss, night sweats, dry cough, significant lymphadenopathy. Many children with tuberculosis do not have significant cough. When cough is present children rarely produce sputum. Even when sputum is produced, organisms are sparse because they are in low concentration in the endobronchial secretions of children. In addition, young children lack tussive force necessary to suspend infectious particles of the correct size in the air, making them almost always non infective.

Childhood type of tuberculosis differs from that in adults in many ways. Children generally have a much smaller bacterial population and there is less secondary resistance. There is well marked enlargement of regional lymph nodes. Tubercle bacilli spread by lymphatic and the hematogenous route. Cavitary lesions are very rare, but children have a greater propensity for extrapulmonary disease. Healing of the lesion is mainly by calcification. Paediatric tuberculosis is usually acquired from contact with an infected adult. Unlike adults, the vast majority of children with tuberculosis are not infectious to others. Children tolerate higher doses of medication relative to body weight, with lower rates of adverse reactions.

Majority of deaths are caused by extra pulmonary tuberculosis, especially tuberculous meningitis, miliary tuberculosis or disseminated tuberculosis. Children infected prior to four years of age have a very high

rate of developing immediate clinical or radiographic manifestations or both, but are unlikely to develop reactivation disease in adulthood. In contrast, children infected in preadolescence or adolescence is more prone to develop more severe adult-type pulmonary tuberculosis soon after infection or in adulthood.

Serological test for detecting TB IgM and IgG antibody by ELISA are expensive and have low sensitivity (29-75%) and specificity (50-92%), to be useful as a confirmatory test for childhood tuberculosis. Molecular diagnostic tests such as PCR have a sensitivity of 40 to 60% and the specificity depends on the type of assay used and their results alone are insufficient to diagnose tuberculosis in children. Specimens for pulmonary tuberculosis are sputum sample, bronchoscopy, gastric lavage and pleural fluid. Specimens for extrapulmonary TB are as diverse as CSF, urine, bonemarrow aspirate, biopsies, peritoneal/pericardial fluid, etc. In these specimens, microscopy to detect AFB using Ziehl-Neelsen staining method or fluroscent microscopy using Auromine-O-dye though simple, rapid & cheap it has low sensitivity. Culture of these specimens has sensitivity between 30-50% & specificity of 100%. The disadvantage being LJ medium is slow and takes 8-12 weeks whereas radiometric BACTEC method is fast but it is costly and limited availability. Identification and isolation of the tuberculous bacilli using routine bacteriological techniques has been considered the ‘gold standard’ in

identifying a ‘case’ of tuberculosis. However, it is exceedingly difficult to isolate in majority of cases. Even in developed countries, the diagnosis is inferred on the basis of clinical and/or radiographic manifestations consistent with tuberculosis, positive tuberculin skin test, and establishing a recent link to a known infectious case of tuberculosis. Hence it is difficult to confirm or rule out the diagnosis of tuberculosis by current microbiological methods. Majority of times tuberculosis goes either overdiagnosed or underdiagnosed. Hence substantial weightage is given to indirect evidences like a positive tuberculin test.

Tuberculin test is the standard method for detecting Mycobacterium Tuberculosis infection, with a positive test (in most circumstances) signifying infection while a negative test does not rule out tuberculosis. The tuberculin skin test for indicating the presence of infection has been used extensively and predominantly in children as an important diagnostic test. Conventionally the Tuberculin reaction is read at 48 or 72 hr. This results in delay in diagnosis of infection. Strict adherence to these time limits often results in prolonged hospitalization, delayed test placement or patients interpreting their own results. Schutze et al had assessed the impact of tuberculin screening of all children during hospitalization for acute medical care and reported that nearly 30 percent of children were discharged before a 48 hr evaluation. So to overcome

these hurdles, studies have been done to know the possibility of using 24 hour mantoux reading instead of reading at 48 hour. The present study is undertaken to evaluate the relationship between mantoux readings at 24 hours and 48 hours and to see whether the Mantoux reading at 24 hour can predict Mantoux positivity at 48 hour.

REVIEW OF LITERATURE

NATURAL HISTORY AND PATHOPHYSIOLOGY:

The tubercle bacilli multiply initially within the alveoli and alveolar ducts. Some of the bacilli are ingested but not killed by macrophages that carry the organisms through lymphatic channels to the regional lymph nodes. The major groups of lymph nodes involved in children are in the hilar region, although paratracheal and subcarinal nodes also may be involved, depending upon where the organisms lodge in the lung.

The primary complex of tuberculosis consists of local reaction in the parenchyma of the lung where the organisms lodge and the inflammatory reaction of the associated lymph nodes. In most cases, the parenchymal portion of the primary complex heals completely and is of no clinical significance. Occasionally, the parenchymal lesion continues to enlarge resulting in focal pneumonitis and thickening of the overlying pleura. The foci in the regional lymph nodes develop some fibrosis but healing is usually less complete than in the parenchymal lesion. *M. tuberculosis* may persist for decades after fibrosis or calcification of the lymph nodes.

In most cases of initial tuberculosis infection, the child develops a positive tuberculin skin test, but the lymph nodes remain normal in size,

the lung parenchymal lesion is not visible on chest x-ray, and the child has no symptoms and no complications. This stage is called tuberculosis infection and most children have a normal chest radiograph. However, in some children, the lymph nodes become enlarged by the host inflammatory reaction. These lymph nodes then encroach on the regional bronchus. Partial obstruction caused by external compression may lead to hyperinflation at first in the distal lung segment. This compression occasionally causes complete obstruction of the bronchus resulting in atelectasis of the lung segment. More often, inflamed caseous nodes attach to the bronchial wall and erode through it, leading to endobronchial tuberculosis and a fistulous tract. The extrusion of infected caseous material into the bronchus transmits infection to the lung parenchyma causing bronchial obstruction and further atelectasis. The resulting lesion, which is a combination of the pneumonitis and atelectasis, is often referred to as a collapse-consolidation or segmental lesion. Occasionally, children have a picture of lobar pneumonia without impressive lymphadenopathy. If the infection is progressively destructive, liquefaction of the lung parenchyma leads to formation of a thin-walled primary tuberculous cavity.

Tubercle bacilli from the primary complex spread via the bloodstream and lymphatics to the apices of the lungs, liver, spleen, meninges, peritoneum, lymph nodes, pleura, and bone. This

dissemination can involve either large numbers of bacilli, which leads to disseminated tuberculosis, or small numbers of bacilli that create microscopic tuberculous foci scattered in the tissues. Initially, these metastatic foci are clinically inapparent but they can be the origin of both extrapulmonary tuberculosis or reactivation of pulmonary tuberculosis in later life. Massive lymphohematogenous dissemination leading to miliary or disseminated disease occurs in only 0.5 to 2% of infected children but occurs early after the initial infection. Clinically significant lymph node or lung tuberculosis usually appears within 3 to 9 months. However, lesions in bones and joints and kidneys take much longer to develop, often several years after the infection first occurs.

CLINICAL FEATURES:

The majority of children with tuberculosis infection develop neither signs nor symptoms at any time. About 25 to 35 percent of children have an extrapulmonary presentation. Pulmonary TB to extra-pulmonary TB ratio is usually around 3:1.[4]

The most common extrapulmonary form of tuberculosis is lymphatic disease accounting for about two thirds of cases of extrapulmonary tuberculosis. However, the second most common form is meningeal disease occurring in 13% of patients and, historically, occurring in three out of a thousand untreated tuberculosis infections in children < 5 years.

PULMONARY TB:

Primary complex is the most common form of disease in infants and children, with highest prevalence in the 0-5 year group. The symptoms and physical signs of intrathoracic tuberculosis in children are often surprisingly meager considering the degree of radiographic changes observed. The physical manifestations of disease tend to differ by the age of onset. Infants have difficulty in gaining weight. Young infants and adolescents are more likely to have significant signs or symptoms, whereas school-age children often have clinically silent disease. Nonproductive cough and mild dyspnea are the most common symptoms.

EXTRAPULMONARY TB:

The most common clinically significant form of disseminated tuberculosis is miliary disease, which occurs when massive numbers of tubercle bacilli are released into the bloodstream causing disease in two or more organs. Early pulmonary involvement is surprisingly mild, but diffuse lung involvement becomes apparent if treatment is not given promptly. Miliary tuberculosis usually occurs early after the infection, within the first 2 to 6 months. Most common in infants and in malnourished or immunosuppressed patients. More often, the onset is insidious; the patient may not be able to pinpoint accurately the time of onset of the initial symptoms. Early systemic signs include malaise,

anorexia, weight loss, and low grade fever. Within several weeks hepatosplenomegaly and generalized lymphadenopathy develop in about one half of cases. About this time, the fever may become higher and more sustained although the chest radiograph usually remains normal and respiratory symptoms are few. Within several weeks, the lungs become filled with tubercles, and dyspnea, cough, rales, or wheezing occur. As the pulmonary disease progresses, an alveolar air block syndrome may result in respiratory distress, hypoxia, and pneumothorax or pneumomediastinum. Signs or symptoms of meningitis or peritonitis are found in 20 to 40% of patients with advanced disease. Choroid tubercles are present in 60 to 70% of children with radiological evidence of miliary tuberculosis and are highly specific for tuberculosis.

Tuberculous meningitis is the most serious complication in children and is uniformly fatal without treatment. The condition arises from the formation of a metastatic caseous lesion in the cerebral cortex or meninges that develops during the occult dissemination of the primary infection. This lesion, called a Rich focus, increases in size and discharges small numbers of tubercle bacilli into the subarachnoid space. The resulting gelatinous exudate may infiltrate the cortical or meningeal blood vessels producing inflammation, obstruction, and infarction of the cerebral cortex. The exudate also interferes with the normal flow of cerebrospinal fluid (CSF) in and out of the ventricular system at the level

of the basal cisterns leading to a communicating hydrocephalus. The combination of vasculitis, infarction, cerebral edema, and hydrocephalus results in this severe damage that can occur gradually or rapidly. The prognosis of tuberculous meningitits correlates most closely with the clinical stage of illness at the time of initiation of antituberculosis chemotherapy.

The majority of patients in the first stage have an excellent outcome, Where as most patients in the third stage who survive have permanent disabilities including blindness, deafness, paraplegia, and mental retardation.

Tuberculous lymphadenitis:

Tuberculosis of the superficial lymph glands is common among children in India. It is more common between 3 and 10 years of age and in young adults. Infection occurs by lymphogenous or hematogenous dissemination. Deep, upper cervical lymph nodes are most commonly involved and may be bilateral, but one side is always worse than the other.

LABORATORY EVALUATION:

Complete blood count and cell differential count are usually normal in children with tuberculosis. Pleural fluid is usually yellow, mild exudate; most typically, there are several hundred to several thousand white blood

cells/mm^3 with an early predominance of polymorphonuclear cells followed by a high proportion of lymphocytes. Acid-fast smears of the fluid are usually negative because of the relative paucity of organisms. Specific gravity is usually 1.012 to 1.025, the protein level is usually 2 to 4 g/dL, and the glucose may be low, although it is often in the low-normal range (20-40 mg/dl). Cultures are positive in only 30 to 70% of cases. The best culture specimen for pulmonary tuberculosis in the child is the early morning gastric aspirate obtained before the child has arisen and peristalsis has emptied the stomach of the pooled secretions that have been swallowed overnight. Three gastric aspirates yield *M. tuberculosis* in < 50% of cases. Mediastinal lymphadenopathy is the radiological hallmark of primary TB and the prevalence of lymphadenopathy decreases with increasing age. Radiographically, adenopathy is usually seen as discrete dense soft tissue shadow which is well circumscribed. Evidence of hilar and or mediastinal lymphadenopathy is seen in up to 83-96% children with primary TB. Adenopathy often resolves without significant radiological sequelae, although nodal calcification may result.[5] The findings of calcified hilar lymph nodes and a calcified parenchymal lesion (Ghon focus) is known as a Ranke complex. Overdiagnosis of hilar adenitis is a common mistake in clinical practice.

TUBERCULIN SKIN TEST

HISTORY:

The origin of tuberculin dates back to 1890, when a search for therapy of tuberculosis had led Robert Koch to develop a filtrate of heat-killed culture of tubercle bacilli, “old tuberculin” (OT). In 1891, Bleiker, a polish researcher, named Koch’s remedy as tuberculin. The diagnostic potential of skin response to tuberculin was identified by Epstein and Escherich. In 1934, Florence seibert extracted a new low molecular weight protein by TCA precipitation of culture filtrates using synthetic Dorset media, which was washed and re-dissolved in buffer solution to make the tuberculin solution, termed “purified protein derivative”(PPD), also called as synthetic medium old tuberculin Trichloroacetic acid precipitated (SOTT)[6]

Florence B.Seibert and John T.Glenn produced a large batch of PPD, using ammonium sulfate, which had highest degree of purity and potency, in 1939 for use as a standard for tuberculin preparation. In 1941, this material, lot number 49608, was designated as PPD-S (PPD-standard) and was accepted as a reference standard in 1952 by WHO[7]. This is the commonest PPD reference used in the United States.

Another commonly used tuberculin, PPD RT23, is a large batch of purified tuberculin produced by Seibert at Statens Serum Institute, Copenhagen and issued since July 1, 1958. Guld standardized this new tuberculin termed "RT23" in 1958.[8] All other PPDs are standardized against it. As glass and plastic adsorb tuberculin and results in variable immunogenicity of PPD, an antiadsorbant detergent, Tween 80 was added to the tuberculin and it was therefore made mandatory to be added to the subsequent formulations. Presently, only two preparations have been accepted as standard tuberculin by WHO i.e., PPD-S & PPD-RT23. The skin test is used to evaluate people with latent TB infection. It's primarily used in two situations. First, it's used in contact investigations to test close contacts of people who have active TB disease. Second, it's used as part of targeted testing activities in various groups of people who are at high risk for TB.

TUBERCULIN:

The standard solution of PPD contains 2 mg of tuberculin in 1000 ml of diluent. The tuberculin unit is defined as 0.1 ml of 1in 10,000 solution, i.e. 0.00002 mg by weight of PPD. Designated as RT-23 (1952), the standard low dose for a single or first test (1 TU) as; 0.00002 mg PPD-S + 0.000008 mg of buffer salts + 0.005% of Tween 80.

1 TU or 0.00002 mg of PPD or 1 IU (International Unit) of PPD

5 TU or 0.0001 mg of PPD

1 TU of PPD RT23 (with Tween 80) corresponds fairly well to 2.5-3 TU of PPD-S.

PRODUCT AND DOSAGE:

Tween 80 (polyoxyethylene sorbiton monocleate) is a stabilizing agent to protect the absorption of tuberculin to glass surfaces. PPD RT23 with Tween 80 was prepared by Statens Serum Institute, Denmark (SSI) from *Mycobacterium tuberculosis* and the seed-lot was supplied in freeze dried form to laboratories of the individual countries. In India, RT-23, ready to use is made up by the BCG Vaccine Laboratory Guindy, Chennai as an isotonic buffer solution. Most of the well-known studies in India have used RT-23 tuberculin and the National Tuberculosis Institute (NTI), Bangalore, uses it in all its studies. However, the production at this facility is now stopped due to lack of facilities and raw material. At present, only Span Diagnostics Limited is marketing a tuberculin caliberated against PPD RT23. Other tuberculins available in the market may not be standardized.

The differences in reactivity of those exposed and not exposed was lost at higher dosage. Hence the recommended strengths should be used for both epidemiological and clinical studies. In western studies, 5 TU PPD-S (American) and 2 TU of PPD RT23 (European) are the strength used for tuberculin testing. Whereas, in developing countries such as India, for fear of stronger reactions with higher doses; due to high BCG

coverage and high prevalence of Tuberculosis, One tuberculin unit (1TU) of *Purified Protein Derivative (PPD) RT23 with tween 80* is the recommended dose as per the WHO guidelines,[9, 10] as this is more specific in our situation and better suited to differentiate tuberculin sensitivity induced by infection with *M. tuberculosis* from that of non-specific sensitivity induced by infection with *environmental Mycobacteria i.e. Mycobacteria* other than *M. tuberculosis (MOTT).* Some other countries like USA use PPD-S (Siebert) which is also called as of Mammalian tuberculin and is considered as the international standard. All other tuberculins are standardized for biological activity against this preparation. Older preparations like old tuberculin (OT) and PPD RT22 are no longer in use.

OTHER TUBERCULINS:

Tuberculins like PPD B (Battey) and PPD-G are used only in epidemiological studies for finding the prevalence of infection with environmental mycobacteria, which are usually non-pathogenic. These antigens are not used in clinical practice in our country.

STORAGE:

Since tuberculin gets denatured by strong light, heat and storage time, it is stored in refrigerated condition so that it remains between 35 and 46 degrees Fahrenheit or between 2 and 8 degrees Centigrade, in covered containers, and is used up within the recommended time

schedule. The tuberculin should never be allowed to freeze or kept at temperatures exceeding 2 degree C except for short periods. Tuberculin vials should used before the expiry period, which is about one year after reconstitution and dilution.

A Vial of tuberculin PPD which has been entered and in use for 30 days should be discarded because oxidation and degradation may have reduced the potency.[11]

IMMUNOLOGICAL BASIS FOR TUBERCULIN REACTION:

The sensitization following infection with mycobacteria occurs primarily in the regional lymph nodes. Small lymphocytes (T lymphocytes) proliferate in response to the antigenic stimulus to give rise to specifically sensitized lymphocytes. After about 6 weeks, these lymphocytes enter the blood stream and circulate for years. Subsequent restimulation of these sensitized lymphocytes with the same or a similar antigen, such as the intradermal injection of tuberculin, evokes a local reaction caused by infiltration of these cells which release lymphokines, which further attract other lymphocytes and monocytes. These reactions along with increased permeability of the local blood capillaries lead to an induration at the test site. The erythema, at the test site due to increased vascular permeability extends beyond the induration and is not considered for interpretation.

Characteristically, delayed hypersensitivity (type IV) reactions to tuberculin begin at 5 to 6 hours, are maximal at 48 to 72 hours and subside over a period of 5 to 7 days. The skin test only measures the degree of hypersensitivity and not immunity to tuberculosis. Immediate hypersensitivity (allergic) reactions to tuberculin or to constituents of the diluent may also occur, but these allergic reactions have no diagnostic importance.

MODES OF APPLICATION:

The Mantoux method (Charles Mantoux, 1908), using a syringe to administer a measured dose at the desired depth, is preferred over the scarification test (von Pirquet, 1907), patch test (A. Moro, 1908) and a variety of multipuncture test techniques which came in vogue as and when improvisations were made, which have less sensitivity and specificity than the Mantoux, and should not be used.

If a patient can't return within the 48- to 72-hour time period, do not administer the test. Instead, schedule another time that allows the patient to come for both the test and the return appointment.

The standard tuberculin test involves intradermal injection of '1TU PPD RT23 with Tween 80'. The preferred site is mid-volar surface of the forearm. Other test sites are carefully avoided for reasons of unreliability and increased frequency of strong, bullous reactions.

The area selected should be free of any barriers to placing and reading the skin test such as muscle margins, heavy hair, veins, sores, or scars. If the patient has any of these at the site, then you should use the other arm or the standard alternative site. After choosing the injection site, clean the area with an alcohol swab by circling from the center of the site outward. Allow the site to dry completely before the injection.

A tuberculin syringe is required to be absolutely airtight since lot of pressure is required to be exerted on the plunger for intradermal injection. If the syringe is not air tight, the amount of tuberculin injected will not be precise. A glass tuberculin syringe or a disposable tuberculin syringe can be used. No other syringe like insulin syringe should be used for the purpose.

Because some of the tuberculin solution can adhere to the inside of the plastic syringe, the skin test should be given as soon as possible after the syringe is filled.

The Mantoux test is performed by injecting 0.1 ml of the recommended PPD dilution into the upper folds of the skin (intradermal) at a predetermined test site 2 to 4 inches below the elbow by using a non-leaky (tight) tuberculin syringe fitted with a short (1 ½ cm), 26 or 27 gauge needle. The syringe is held between thumb and index finger with needle bevel facing up and the syringe parallel to the forearm. Insert it slowly at a 5- to 15-degree angle while the skin is slightly stretched in the

opposite direction. The 5- to 15-degree angle is very important because this layer of skin is very thin. For an intradermal injection, the needle bevel is advanced through the epidermis, the superficial layer of skin, approximately 3 mm so that the entire bevel is covered and lies just under the skin. The injection will produce inadequate results if the needle angle is too deep or too shallow. A tense, pale wheal that's 6 to 10 mm in diameter with discernible hair follicles appears over the needle bevel. Remove the needle without pressing or massaging the area. It's not unusual for a drop of blood to appear at the injection site, even when the needle is inserted properly. Should this happen, lightly blot the blood away with a 2x2 gauze pad or cotton ball. Do not cover the site with an adhesive bandage because the adhesive could cause irritation and interfere with the test. If leakage occurs at the insertion site, the needle bevel may not have been inserted far enough for the bevel to be covered by the skin.

If the test is unsatisfactory i.e., the correct amount has not been injected or injection has been made into the sub-cutaneous tissue or if no wheal forms or if it is less than 6 mm in diameter, the then another injection can be given. If the tuberculin test must be repeated, use another site at least 2 inches, or 5 cm, from the original site or the other arm. The site chosen for the second test should be appropriately recorded. Tell the patient to avoid scratching the site, keep the site clean and dry, and avoid

putting creams, lotions, or adhesive bandages on it and is also advised to return for reading of the test result. Also mention that getting the site wet with water is not harmful, but the site should not be wiped or scrubbed.

Sufficient care is taken to draw tuberculin in a syringe for immediate use only; tuberculin left standing in a syringe for more than an hour is preferably discarded and fresh tuberculin drawn before injection. The test must be performed by *trained persons.* Every aspect of the norm laid down, e.g., storing of tuberculin using recommended syringes, making the test with 0.1 ml at the desired depth must be adhered to, because slackness in any aspect though individually insignificant, will collectively add on to bring out different response.

ADVERSE EFFECTS:

In some atopic individuals, an urticarial wheal may appear within minutes of injection. It usually disappears in 1-2 hours.

CONTRAINDICATIONS:

Allergy to any component of Tuberculin Purified Protein Derivative or allergic reactions to a previous test of tuberculin PPD are contraindications to the use of tuberculin PPD

There is no age contraindication to tuberculin skin testing of infants.

READING OF THE TEST:

The test is usually *'read'* on the 2nd or 3rd day of the injection. Reading should be made in good light with the forearm slightly flexed at

the elbow. The margins of the induration should be determined by sight and by gently stroking with the finger and by using a pen.

When palpating for margins, be careful not to confuse a margin of induration with a margin of muscle on the forearm. To check this, raise the patient's arm to a 45-degree angle and palpate again. You should still be able to palpate the margins of induration. The diameter of the induration is measured across the forearm; from the thumb side of the arm to the little finger side of the arm or vice versa. Reading consists of the careful measurement of the largest palpable transverse diameter in millimetres of the induration at the test site by using a transparent measurer. Erythema is disregarded, but the degree of severity e.g., oedema (O), vesicle (V), bullae (B) or necrosis (N) may be recorded as additional information. Since PPD RT23 with tween 80 has been found to result in softer reactions, the small indurations may be missed if not sought carefully.

Ballpoint-pen technique:

With this technique, a medium point ballpoint pen was used to draw a line starting 1 to 2 cm away from the skin reaction along the long axis of the forearm and moving towards its center. When the pen reached the margin of the induration, an increased resistance to further movement was felt and the pen was lifted. The procedure was repeated on the opposite side of the skin reaction. The distance between the ends of the

opposing lines at the margins of the induration was measured. The ballpoint pen technique is more reproducible when compared with the palpation technique.[13]

The test result should never be recorded as ‘positive’ or ‘negative’ and must always be recorded in millimeter of size. Indurations up to 40 mm in diameter are found in practice.

TYPES OF TUBERCULIN REACTION:

1) Turgid Koch’s type of response: if any 3 of the following changes were recorded.

1. Hard induration.

2. Well delineated.

3. Painful

4. Skin changes – vesiculation or bullae, necrosis

2) Non-turgid Listeria type of response: based on the following criteria

1. Soft induration.

2. Not well delineated.

3. Not painful

“Variant reactivity” defined as induration of < 10mm at 72 hrs that, when reassessed at 6 days, increases in size to 10mm or greater. Variant reactivity has been described as a predictor of booster positivity.[14]

INTERPRETATION OF TUBERCULIN TEST

The reaction to tuberculin skin test is interpreted as follows:

Size of induration with 5TU PPD-S/1TU PPD with Tween 80

< 10 mm - Test negative /Non-infected/Non-reactor

≥ 10 mm - Positive / infected / reactor

≥ 15 mm - strongly positive

strongly positive are likely to have disease in early childhood or develop disease 4 to 5 times more commonly in the next 5 years.

1. Not all reactions to tuberculin are attributable to infection with tubercle bacilli. Tuberculin is more specific in younger age group, i.e. 0 to 9 years.

2. Larger the size of induration at the test site, higher is the probability of presence of infection with tubercle bacilli. This is supported by the observation that tuberculosis morbidity increased with the size of induration.[15]

3. Almost all reactions with induration of 15 mm or more in size may be considered attributable to infection with tubercle bacilli, irrespective of the presence or absence of BCG-scar.

4. The formation of vesicles, bullae or necrosis at the test site indicates high degree of tuberculin sensitivity and thus presence of infection with tubercle bacilli.[12]

5. The reactions with induration of less than 5 mm in size usually indicate lack of tuberculin sensitivity and thus absence of infection either with tubercle bacilli or with environmental mycobacteria. Simple trauma of the needle has been observed to give rise to induration usually in the range of

1-4 mm. However, some individuals infected with tubercle bacilli but suffering from severe degree of immune-suppression may show induration in this range.

6. Among children without BCG-scar, the majority of reactions with indurations in the range of 5-9 mm are attributable to cross-sensitivity to environmental mycobacteria. Some of these children rnight actually have been vaccinated with BCG but do not show the BCG-scar. Thus, in a proportion of children without BCG-scar, the indurations in this range may be attributable to BCG-vaccination. Among children with BCG scar, the reactions with indurations, in this range may be attributable to BCG vaccination and/or infection with environmental mycobacteria.

7. A reaction with induration between 10 to 14 mm could be attributable to infection with tubercle bacilli or due to cross sensitivity to environmental mycobacteria and/or BCG-induced sensitivity. *interpretation of reactions in 10-14 mm range requires more careful interpretation.* Induration in this range is more likely to be attributable to infection with tubercle bacilli among high risk contacts.

8. The tuberculin reaction may be suppressed in the presence of immuno suppressive states. The mean reaction size of tuberculin test has also been found to decrease with increasing grade of undernutrition[16], cancer, Hodgkin's disease, sarcoidosis, cortico-steroid therapy and during HIV

infection. This does not imply that the test should not be carried out in the presence of these conditions.

9. The hypersensitivity takes about 4-8 weeks to develop after initial infection and thus infection with tubercle bacilli may be missed in the *window period'*. Therefore, there should be a minimum period of 8 weeks between exposure and tuberculin test for detecting infection.

10. The interpretation of tuberculin test also depends on *the purpose of the test.* In case the test is used for screening apparently healthy children for subjecting to further investigations for diagnosis of tuberculosis, it is more desirable to have a higher sensitivity by deciding on a lower cutoff point of 10-mm. For a decision on preventive chemotherapy, it is desirable to have a higher cut-off point of 15 mm, to be more specific.

The presence of infection is not synonymous with disease and only about 10% of the infected children break down into disease over their lifetime.[17] Half of this risk occurs within one to two years of getting infected.

A negative tuberculin test does not exclude tuberculosis. In 25 to 50% of children with tuberculosis, the tuberculin test is negative. Thus, *tuberculin test should never be the sole criteria for diagnosing tuberculosis.*

11. Once acquired, tuberculin sensitivity tends to persist. Mantoux testing is not recommended for people who have had a past Mantoux reaction of 15 mm or greater or in people who have had previous TB disease.

False positive reactions:

1. Infection with nontuberculous mycobacteria

2. Recent vaccination with BCG

3. Errors in administering the test

4. Reading the results (erythema measured)

False Negative reactions:

1. Overwhelming TB disease e.g., tuberculous meningitis or miliary tuberculosis.

2. Very recent TB infection and test done in the incubation period of tuberculosis (takes 4-8 weeks for positive reaction)

3. Severe malnutrition depresses the hypersensitivity.

4. Intake of corticosteroids, immunosuppressive drugs.

5. Less than 6 months because their immune systems are not fully developed.

6. Recent viral infections (mumps, measles, chickenpox, HIV infection) and attenuated viral vaccination (measles, mumps, polio)

7. Faulty technique: subcutaneous injection

8. Loss of potency due to prolonged exposure to heat or light or prolonged storage after dilution.

9. Bacterial contamination of PPD solution.

10. Errors in recording.

It is impossible to discover with certainty whether a negative result is a true or a false one. For this reason, a negative Mantoux not absolutely exclude LTBI or TB disease. Anergy testing is not recommended as a method to discover whether the negative Mantoux result is a true or a false negative, either in HIV positive or non-HIV subjects.

INFECTION WITH ENVIRONMENTAL MYCOBACTERIA

Infection with environmental mycobacteria like M.Scrofulaceum, M.vaccae, M.nonchromogenicum, etc. also leads to sensitization of the host. The sensitivity induced by these generally non-pathogenic mycobacteria cross reacts with tuberculin and is known as non-specific sensitivity (NSS). This non specific sensitivity is highly prevalent in most parts of India as in other tropical countries. However, sensitivity induced by these mycobacteria will lead to smaller reactions to tuberculin than from true infection with tubercle bacilli. Therefore, most of the individuals harbouring tuberculous infection usually elicit a larger reaction to tuberculin. In this country, the infection due to *M.bovis* is rare as compared to *M. tuberculosis* because of the practice of boiling milk before consumption.

BCG – INDUCED SENSITIVITY:

In BCG vaccinated children, the reaction to tuberculin ranges from 3 to 10 mm even in the immediate post-vaccination period i.e., during infancy and second year of age.[18]

The presence or size of post vaccination tuberculin skin test reaction does not reliably predict the degree of protection afforded by BCG because it is a hypersensitivity reaction. Tuberculin skin reactivity to BCG wanes with time (80 to 90% negative by 2-3 years). Therefore, higher the age of the child, lesser the probability of the reaction could be attributable to BCG.

ISONIAZID THERAPY:

Isoniazid treatment of tuberculosis in children had no significant effect on tuberculin sensitivity.

HIV INFECTION:

Tuberculin testing is indicated in HIV-seropositive children and in such tuberculin negative children, annual testing is recommended. This is to enable timely detection and treatment of tuberculosis in HIV-infected children because of the progression of HIV infection to disease(AIDS) on one hand, renders the patient anergic (to tuberculin), on the other hand, in patients with clinical disease(AIDS) tuberculosis presents in atypical forms which is difficult to diagnose.

DRUG INTERACTIONS

Reactivity to the test may be depressed or suppressed for up to 6 weeks in individuals who are receiving corticosteroids or immunosuppressive agents[19] or viral vaccines. Therefore testing should be postponed for 4-6 weeks.[20, 21]

REPEAT TEST

It is usually unnecessary to repeat the test unless the test injection or reading was performed unsatisfactorily. The repeat test should be given at a different site within 1 week of the first test.[22] The repeated testing of uninfected persons does not sensitize them to tuberculin. [23]

BOOSTER PHENOMENON:

This is because the small amount of tuberculin injected for the first test can boost the size of the second test though it per-se does not sensitize the individual. This results from 'recall' of sensitivity induced by BCG vaccination or infection with environmental mycobacteria. The booster phenomenon may be seen when the second test is given 1 week to 1 year after the first test. Booster phenomenon increases with age. Repeating the test with higher doses may result in larger reactions which are attributable to non-specific sensitivity is of no value for detection of infection with tubercle bacilli.

TWO- STEP TESTING:

Two-step testing should be performed on the initial testing if tuberculin testing will subsequently be conducted at regular intervals, for instance among health-care workers, to minimize the likelihood of interpreting a boosted reaction as a conversion. Two-step testing is

performed when there is a need to establish a true baseline Mantoux. If the first test showed either or no reaction or a small reaction, the second test should be performed one to four weeks later. Both tests should be read and recorded at 48 to 72 hours. Patients with a second tuberculin test (booster) response of 10 mm or more should be considered to have experienced past or old infection; this probably represents a boosted reaction and is the correct one – that is, the result that should be used for decision-making or future comparison.[24]

Persons who do not boost when given repeat tests at one week, but whose tuberculin reactions change to positive after one year, should be considered to have newly acquired tuberculosis infection in the preceeding interval and managed accordingly. Boosting is maximal if the second test is placed between one and five weeks after the intial test and it may continue to be observed for up to two years.

Two-step-testing is not necessary for contacts of infectious cases who will have already been re-sensitised if transmission has occurred, or for anyone who has been Mantoux tested in the previous two years.

MANTOUX CONVERSION:

This is defined as when the second of two Mantoux tests increases by 10mm or greater over the first test. This is most useful in providing evidence of infection in exposed contacts but does not apply if vaccination takes place in the meantime. If a person is exposed to

infectious TB who has a documented Mantoux test result within the past 12 months, then only one test is necessary to detect conversion. People who demonstrate Mantoux conversion should be investigated for latent TB infection or active disease.

Recent converters are defined on the basis of both size of induration and age of the person being tested:

An individual whose tuberculin reaction changes from < 10 mm in diameter to > 10 mm in diameter & increases by 6 mm within a 2-year period is classified as a recent convertor for persons < 35 years of age.

MANTOUX REVERSION:

This is defined as a reduction in Mantoux response following a previous test that is the change to a negative Mantoux result following a previous positive result. Generally the phenomenon is uncommon in healthy individuals, occurring in less than 10% of such people with a previously positive Mantoux.

Reversion is more common:

- when the initial mantoux is < 14mm
- in those where the initial positive reaction was a boosted result (identified by two-step testing)
- in older adults (estimated at 8% per year).

This in other words means that if the test is known to be positive in any individual, say a treated case, the repeat evaluation for any relapse or failure of therapy can not be based on the skin reactions to PPD.

BCG TEST:

Termed the BCG test[25], 0.1 ml of BCG vaccine is injected intradermally as in direct vaccination method to children clinically suspected to have severe type of tuberculosis disease and yet showing a false negative reaction to the initial tuberculin test. In contrast to healthy children, such children will produce induration of 5mm and above in 24-48 hours at the vaccinal site, pustule by day 5, ulcer by day 7, which heal with scab in about 10-15 days. The accelerated response is measured usually between 24-48 hours and reactions larger than 5 mm are taken as positive. Demonstration of this new type of allergy was first pointed out by A.de Assis, who named it infra-tuberculin allergy. But the BCG test as a diagnostic tool is *not recommended or practised universally* as it has neither superior value nor has valid reason for using it instead of the tuberculin test. It does have the major drawback that once it is given, the tuberculin test can not be reliably used in near future to judge recent infection of tuberculosis since it will be falsely positive due to vaccination.

ALTERNATIVES TO TUBERCULIN TESTING:

The limited sensitivity of the established tuberculin skin-test in identifying people with latent infection represents a major obstacle to better tuberculosis control. Recently developed in vitro tests such as whole-blood assays like QuantiFERON-TB Gold have approved by U.S. Food and Drug Administration as an aid for diagnosing Mycobacterium tuberculosis infection in people with active tuberculosis. It detects the release of IFN-gamma from sensitized persons when their fresh heparinised whole blood is incubated with mixtures of synthetic peptides representing two proteins present in M.tuberculosis: early secretory antigenic target-6(ESAT-6) and culture filtrate protein-10(CFP-10)

AIM AND OBJECTIVES

AIM:

To observe the induration of Mantoux test at 24 hours.

OBJECTIVES:

1) To see whether reading Mantoux test at 24 hour can predict Mantoux positivity at 48 hour and its usefulness in detecting Tuberculous disease.

2) To study the influence of age, sex, BCG scar status and symptomatology to Mantoux positivity.

MATERIALS AND METHODS

Study design:

Prospective observational study

Study centre:

The study was conducted in the Institute of Child health and Research centre, Government Rajaji Hospital, Madurai.

Study period:

The study was carried out prospectively from December 2007 to June 2009 over the period of 1 year and 6 months.

Methodology:

Children between 6 months to 12 years with clinical suspicion of tuberculosis were administered Tuberculin skin test as per Mantoux method.

Inclusion criteria:

Children in the age of 6months to 12 years with any of the following:

1. Positive contact history: Household exposure to known/suspected case of adult TB on ATT or taken ATT in the past 2 years.

2. Low weight for age (less than 80 % of expected/ recent Wt loss of 10%)

3. Persistent fever for > 2 weeks

4. Cough for > 2 weeks

5. Significant lymphadenopathy: Cervical and axillary nodes of more than 1 cm, inguinal nodes of more than 1.5 cm with or without matting and not responding to antibiotic therapy for 2 weeks.

Exclusion criteria:

1. Recent vaccination

2. Recent viral illness

3. Prior Mantoux positivity

Tuberculin used:

Study used SPAN's tuberculin PPD (Code NO: 18411). It is a diluted and ready to use solution for performing mantoux test. Source material is calibrated against Batch RT 23 manufactured by Statens Serum Institute, Denmark. It is diluted with a buffer containing Tween-80 as a stabilizer. All children were given 0.1 ml of 1TU PPD RT 23 with

Tween 80 intradermally over the mid-volar aspect of left forearm using tuberculin syringe after cleansing the area with spirit. Plastic disposable Tuberculin syringe with 27 gauge needle was used. The skin of the arm is lightly stretched lengthwise and the pointer of the needle is inserted lengthwise, with bevel upward, intradermally. After injection, a pale wheal of 6-10mm was taken as correct intradermal administration. In case of faulty administration test was repeated in the right forearm.

Caregivers and children were educated not to wipe/scrub/massage/apply cream over the test site. They were specially advised about the importance of reporting at 24 hour and 48 hour for reading the test. 24 hour and 48 hour readings were taken in all cases that turned-up for reading. Transverse diameter of the induration was palpated and marked by Ball point pen technique (Sokal method) and measured meticulously with a transparent ruler in mm by the same observer in all cases. Data was collected on pretested proforma with clinical details.

Children whose Mantoux reading at 48 hour $\geq$ 10 mm was considered as tuberculin positive and details regarding age, sex, BCG status, contact history, past history of Mantoux test, past history of ATT, symptoms like fever and its duration, cough and its duration, hemoptysis, significant lymph node enlargement and its group, low weight for age or weight loss were rechecked and further investigation like chest x-ray, FNAC, sputum or gastric juice AFB, pleural fluid and CSF analysis, HIV

status carried out based on clinical diagnosis. Children whose Mantoux readings at 48 hour < 10 mm were considered as tuberculin test negative. The diagnosis of TB in children is nearly always presumptive. The bacteriological confirmation is not always possible. Hence those children who have been started on ATT were noted and they were considered as having active disease irrespective of mantoux positivity since there is no single gold standard test to diagnose tuberculosis.

ETHICAL CLEARANCE : obtained

CONSENT : An informed consent was obtained from the Parents of each child

ANALYSIS : Data was entered in excel spread sheet and analysed using simple descriptive statistics

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2008).**

Using this software range, frequencies, percentages, means, standard deviations, chi square and 'p' values were calculated. Kruskul Wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's test for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship. Sensitivity, specificity, accuracy, positive predictive value and negative predictive values were calculated using the following formulae

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + False negative}} \times 100$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{False positive + True negative}} \times 100$$

$$\text{Positive predictive value} = \frac{\text{True positive}}{\text{True positive + False positive}} \times 100$$

$$\text{Negative predictive value} = \frac{\text{True negative}}{\text{True negative + False negative}} \times 100$$

CONFLICT OF INTEREST : Nil

FINANCIAL SUPPORT : Nil

OBSERVATION, ANALYSIS AND RESULTS

BASELINE DATA:

6560 children with clinical suspicion of tuberculosis were given mantoux test. Among them, 5904 cases (90%) turned up for reading at 24 hour and 48 hour. 206 cases (3.48%) were more than 10 mm at 48 hr and were considered mantoux positive cases.

Table - 1

Mantoux given cases	Follow- up both 24 and 48 hours		Mantoux positive cases	
	No	%	No	%
6560	5904	90	206	3.48

Table - 2

AGE DISTRIBUTION OF 206 POSITIVE CASES

Age group	Cases	
	No.	**%**
6month - 1 year	9	4.4
1- 5 year	90	43.7
5 – 10 year	82	39.8
> 10 year	25	12.1
Total	206	100
Range	11 months – 12 years	
Mean	6.1 years	
S.D.	3.2 years	

Out of the 206 mantoux positive cases, 90 cases (43-7%) were between 1-5 years, 82 cases (39.8%) were between 5-10 years, 25 cases (12%) were > 10 years and 9 cases (4.4%) were < 1 year. Mean age of mantoux positivity was 6 years.

Table - 3

SEX DISTRIBUTION OF 206 POSITIVE CASES

Sex	**Cases**	
	No.	**%**
Male	105	51
Female	101	49
Total	206	100

Among the 206 positive cases, 105 cases (51%) were male and 101 (49%) were female.

Table -4

CONTACT HISTORY FOR 206 POSITIVE CASES

Contact History	Cases	
	No.	%
Present	63	30.6
Absent	143	69.4
Total	206	100

Out of the 206 mantoux positive cases, 63 cases (31%) had positive contact history with open cases of pulmonary TB.

Table – 5

B.C.G. SCAR

B.C.G. Scar	Cases	
	No.	%
Present	166	80.6
Absent		
a) BCG given	22	10.7
b) BCG not given	18	8.7
c) Total	40	19.4
Total	206	100

Among 206 positive cases, B.C.G. scar was absent in 40 cases (19.4%). 22 cases (10.7%) received B.C.G. but scar not seen.

Table -6

GRADING OF NUTRITIONAL STATUS

Nutritional Grade	CASES	
	No.	%
Normal	24	11.7
Grade I	51	24.8
Grade II	67	32.5
Grade III	56	27.2
Grade IV	8	3.9
Total	206	100

Out of the 206 cases, 11.7% were of normal grade, 24.8% belong to grade I malnutrition, 32.5% belong to grade II, 27% belong to grade III and 4% grade IV.

Table -7

X - RAY FINDINGS

X- ray findings	Cases	
	No.	%
Normal	166	80.6
Abnormal	40	19.4
Total	206	100

Among the 206 positive cases, 40 cases (19.4%) had features of TB in X-ray like pleural effusion, pneumonia, hilar adenopathy, minor fissure opacification, etc.

Table - 8

CLINICAL FEATURES

Clinical features	Cases	
	No.	%

Fever		
< 1 week	42	20.4
1-2 weeks	26	12.6
2-3 weeks	2	1.0
> 3 weeks	9	4.3
Total	79	38.3
Cough		
< 1 week	45	21.8
1-2 weeks	41	19.9
2-3 weeks	6	2.9
> 3 weeks	32	15.6
Total	124	60.2
LN		
Cervical group	42	20.4
Submandibular	5	2.4
Axillary	1	0.5
Total	48	23.3
Others	55	27.1

Majority had cough, fever and lymphadenopathy as predominant symptom.

Table - 9

INDURATION VALUES AT VARIOUS TIME INTERVALS FOR 206 POSITIVE CASES

Induration in mm	Time interval			
	24 hour		48 hour	
	No	%	No	%
0 mm	5	2.4	-	-
1-4 mm	6	2.9	-	-
5-9 mm	64	31.1	-	-
10 mm & above	131	63.6	206	100
Total	206	100	206	100
Range	0-30		0-40	
Mean	11.53		16.61	
S.D.	5.11		3.85	
/p/	0.0001 (Significant)			

Among the 206 positive cases, 131 cases (63.6%) had induration > 10 mm at 24 hours, 64 cases (31.1%) were between 5-9 mm at 24 hours, 6 cases (2.9%) were between 1-4 mm and only 5 cases (2.4%) had no induration at 24 hours.

Table - 10

CONTACT HISTORY AND POSITIVITY AT 24 HOURS

Contact history	Total cases	Positivity at 24 hours			
		Positive		Negative	
		No.	%	No.	%
Present	63	36	57.1	27	42.9
Absent	143	95	66.4	48	33.6
'p'		0.729 Not significant			

Out of the 206 mantoux positive cases, 57% with positive contact history had positive mantoux test and 42% with positive contact history had negative mantoux test.

Table – 11

COMPARISON OF RESULTS AT 24 HOURS WITH RESULTS AT 48 HOURS FOR ALL CASES

48 hr induration	24 hr induration	
	≥ 10 mm	< 10 mm
≥ 10 mm	131	75
< 10 mm	0	5698

True positive = 131

False positive = Nil

True negative = 5698

False negative = 75

Sensitivity = 63.5

Specificity = 100

Positive predictive value = 100

Negative predictive value = 98.7

On comparing 24 hour reading to 48 hour mantoux reading it was observed that sensitivity was 63.5, specificity and PPV was 100 & NPV was 98.7%.

Table - 12

INDURATION VALUES FOR ALL CASES AT VARIOUS TIME INTERVALS

Induration in mm	Time interval			
	24 hour		48 hour	
	No	%	No	%
0-4	5139	87.0	5203	88.1
5-9	634	10.8	495	8.4
10 & above	131	2.2	206	3.5
Total	5904	100	5904	100
Range	0-30		0-40	
Mean	2.37		2.39	
S.D.	2.89		3.39	
'p'	**0.0014 (Significant)**			

Among the 5904 cases, 131 cases had ≥ 10 mm at 24 hour compared to 206 cases at 48 hours. 634 cases were between 5-9 mm at 24 hour compared to 495 cases at 48 hour. 5139 cases were between 0-4 mm at 24 hour compared to 5203 cases at 48 hour.

Table- 13

COMPARISON OF INDURATION VALUES AT 24 HOURS WITH ATT TREATMENT FOR 206 MANTOUX POSITIVE CASES

24 hr induration (mm)	ATT given		ATT not given	
	No.	%	No.	%
0-4	8	3.8	3	1.45
5-9	53	25.1	11	5.3
≥ 10	126	61.1	5	2.4
Total	187	90.7	19	9.2

Among the 206 mantoux positive cases who received ATT, 61% had > 10 mm induration at 24 hour, 25% had induration between 5-9 mm, and 3.8% had induration between 0-4 mm. Out of the 206 positive cases 9% were not started on ATT.

Table:-14

VALIDITY OF 48 HOUR INDURATION IN PREDICTING ACTIVE DISEASE

48 hr induration	ATT started	ATT not started
≥ 10 mm	187	19
< 10 mm	63	5635

Sensitivity = 74.8 %

Specificity = 99.6%

PPV = 90.7%

NPV = 98.8%

When mantoux reading was done at 48 hour, the sensitivity of the test was 74.8 %, specificity was 99.6%, PPV was 90.7% and NPV was 98.8%.

Table - 15

VALIDITY OF 24 HOUR INDURATION IN PREDICTING ACTIVE DISEASE

24 hr induration	ATT started	ATT not started
≥ 10 mm	126	5
< 10 mm	124	5649

Sensitivity = 50.4%

Specificity = 99.9%

PPV= 96.1%

NPV= 97.85%

When mantoux reading was done at 24 hour, the sensitivity of the test was 50.4 %, specificity was 99.9%, PPV was 96.1% and NPV was 97.8%.

Table -16

COMPARISON OF VALIDITY OF 24 HOUR AND 48 HOUR MANTOUX TEST

	24hr	48hr
Sensitivity	50.4	74.8
Specificity	99.9	99.6
PPV	96.1	90.7
NPV	97.85	98.8

On comparing the parameters of validity at 24 hour and 48 hour it was found that 24 hour reading has sensitivity of 50 compared to 74.8 at 48 hours and NPV 97.8 compared to 98.8.

DISCUSSION

The tuberculin skin test has been the traditional method of diagnosing infection with mycobacterium tuberculosis. Tuberculin skin test and quantiFERON-TB (QFT) were used to diagnose latent tuberculosis infection. The decision to select one test over the other depends upon the population to be tested, purpose of testing and resource availability. The skin test only measures the degree of hypersensitivity and not immunity to tuberculosis. The larger the reaction, greater is the probability that the responsible organism is M.tuberculosis. Tuberculin skin test is useful in the evaluation of children suspected of having tuberculosis in as much that a significant reaction supports the diagnosis.

In any population, the probability that a positive skin test represents a true infection depends on the prevalence of infection with M.tuberculosis. The tuberculin skin test has a specificity of approximately 99 percent in populations that have no other mycobacterial exposures or BCG vaccination. Specificity is lower (approx. 95%) in populations where cross reactivity with other mycobacteria is common. Therefore, the positive predictive value of a tuberculin test depends on probability of tubercular infection in a patient / prevalence of the infection in the population and the specificity of the test in that population. In a community, tuberculin test can be used to determine the overall prevalence of a positive skin reaction. The annual risk of infection

and prevalence of infection help to determine the problem of infection due to tuberculosis. The benefits of screening for latent tuberculosis has gained importance in the wake of a large number of high risk categories like concurrent infection of tuberculosis and HIV, malignancies, IV drug abuse, ESRD and the children exposed to an open adult case. The benefits of screening and preventive therapy vary widely, although the benefits outweigh the risks for all risk groups. The induration is measured by ballpoint pen technique whose accuracy is high as indicated in a study to determine the reliability of skin test measurement[31] by which says that Global intra and interobserver reliability coefficients of the ballpoint pen technique were high.

The health-care provider should inform the patient of the need to return for the reading of the test. Self reading of the test has been shown to be unreliable as said by APIC guidelines committee[32] about the responsibility for reading the tuberculin skin test. In this study, among the 6560 cases, 5904 cases (90%) only turned for reading by the single examiner at both 24 hour and 48 hour and are only analysed further as it is only reliable.

In a review by Udani et al, tuberculin testing using 1TU RT23 was positive in 52.3% (range 19.3-73.3%) of children with tuberculosis[26]. In this study, the positivity of the tuberculin skin test by mantoux method is

3.48% among children with symptoms suspicious of tuberculosis infection.

In a study at pulmonology dept[27],ICH & RC, Chennai, Mantoux positivity is 34.7% in children with tuberculosis and positivity among various forms of TB are LN TB – 53%, skeletal – 44.4%, abdomen TB-36.4%, pulmonary- 30.3%, central nervous system (CNS) -21.2%.

In a study at pondhicherry among healthy school children[28], 18.4% were tuberculin positive.

In India, the overall prevalence of tuberculin reactivity is about 30%; males 35% and females 25% as shown in the survey conducted by the National Tuberculosis Institute, Bangalore[29]. In this study also among the 206 positive cases, 105 cases (51%) are male and 101 (49%) are female. There is no significant difference in mantoux positivity based on sex of the children.

In the present study, Out of the 206 mantoux positive cases, 90 cases (43-7%) are between 1-5 years, 82 cases (39.8%) are between 5-10 years, 25 cases (12%) are > 10 years and 9 cases (4.4%) are < 1 year. Mean age of mantoux positivity is 6 years. The majority of mantoux positive cases are between 1-10 year age group.

Tuberculosis is less a disease of the individual and more strikingly a disease of the family and of the community. This is even more the case with tuberculosis in children. The household is the location where

infection is most likely to occur and the transmission is from parent to child. In a study at pulmonology dept[27], ICH & RC, Chennai, contact positivity is 30.4% with no major variation in the different forms of tuberculosis. In this study, contact positivity is 30.6% among the children with symptoms suspicious of tuberculosis infection with mantoux positivity.

In a study at Makati health center[30], it was found that 22% of sample population to have tuberculosis infection that is a positive tuberculin skin test, with 15.4% having tuberculosis exposure and 65.4% with clinical manifestations highly suggestive of tuberculosis in children. Sex, presence of clinical signs and symptoms of tuberculosis and tuberculosis exposure all showed no statistically significant correlation with results of tuberculin skin test. These are important findings to show that treatment of tuberculosis infection or disease in children must not be based solely on the presence of signs and symptoms and on the history of TB exposure. On the other hand, some TB infection may be missed because a tuberculin skin test was not done in the absence of any signs and symptoms suggestive of tuberculosis or in the absence of history of exposure. In this study also, there is no significant difference in mantoux positivity among children with and without exposure to open case of TB.

In a study at Pondicherry among healthy school children[28], B.C.G scar is present in 77.4% of healthy school children with positive

tuberculin skin test. In this study also, BCG scar is present in 80.6% of mantoux positive cases and is absent in 40 cases (19.4%) out of which 22 cases (10.7%) received B.C.G. vaccination but scar not seen. Most B.C.G scars are distinctive but it is not true for all of them. Likelihood permanent scar formation after BCG vaccination depends on the nature of immune response in young infants. Most patients with absent scars even after BCG vaccination have shown in vitro evidence of cell mediated immunity against tuberculosis.

Most symptoms in children with primary complex are constitutional in the form of mild fever, anorexia, weight loss, decreased activity. Cough is an inconsistent symptom. Children with progressive pulmonary disease may present with high grade fever and cough. Expectoration of sputum and hemoptysis are usually associated with advanced disease. Tuberculous pleural effusions are uncommon in children younger than 5 years of age and they have fever, cough, dyspnea, pleuritic pain on the affected side and there is usually no expectoration. In a study at Makati health center[30], the most common clinical manifestations noted by parents that were suggestive of tuberculosis were poor weight gain, decreased or poor appetite and prolonged cough and colds. In this study, majority of mantoux positive cases are having cough, fever and lymphadenopathy as predominant symptom.

Malnutrition may suppress a tuberculin test even in children with active tuberculosis due to depressed cell mediated immunity. In the present study, out of the 206 cases, 11.7% are of normal nutrition, 24.8% belonged to grade I malnutrition, 32.5% belonged to grade II, 27% belonged to grade III and 4% grade IV. So it is seen that mantoux positivity can occur in all grades of nutritional status although positivity is less with severe grades on malnutrition. Among the 206 positive cases, 40 cases (19.4%) had features of TB in X-ray like pleural effusion, pneumonia, hilar adenopathy, minor fissure opacification, etc. This shows that absence of radiological features of tuberculosis does not exclude pulmonary tuberculosis. Other features should be taken into account before excluding tuberculosis. But if there is radiological evidence of tuberculosis in a child with symptoms suspicious of tuberculosis, it forms the mainstay of diagnosis and assessment of treatment of tuberculosis.

In a study by Oztwik[33] which evaluates the predictive value of a 24 hour induration, the mean (SD) size of the induration at 24 hours was less than that of the induration present at 48 and 72 hours. Differences were statistically significant ($p < 0.001$). There was no difference between 48 and 72 hours reading ($p > 0.5$).

In a study at Pondicherry among healthy school children[28], it was found that when the tuberculin reaction was 0–9 mm, a significant difference was noted between the 24- and 72-h reading ($p = 0.0001$).

There was no difference in the size of the tuberculin reaction between the 24- and 72-h readings when the reaction size was ≥ 10 mm ($p > 0.05$).

In this study, the mean size of induration at 24 hours (11.53) was less than that of induration present at 48 hours (16.61) with a significant p value (P = 0.0001). The difference was significant especially when the induration at 24 hour was between 0-9 mm and there is little difference when the induration was more than 10 mm at 24 hours.

In a study at pulmonology dept[27], ICH & RC, Chennai, It was found that sensitivity of mantoux was 51% and specificity 71.7%.the positive predictive value of the test was 52.6% and negative predictive value was 70.4%.the percentage of false negatives was 49% and the percentage of false positive was 28.3%. Thus mantoux test has low sensitivity and specificity and high false negative rates.

In a study at Pondicherry among healthy school children[28], the positive and negative predictive value for induration ≥ 10 mm at 24 hr was estimated as 96.7 and 99.5 % respectively. Even in children who had a reaction of 0-9 mm at 24 hr, the tendency to remain negative was very high as indicated by the positive and negative predictive values of 98.5% and 96.7% respectively.

In a study by Oztwik[33] which evaluates the predictive value of a 24 hour induration, any induration 24 hours after placement of the tuberculin test had a sensitivity of 94% and' a specificity of 75%. At 24 hours,

induration of any size had a relatively low positive predictive value (63%), although induration > 5 mm had a higher (86%) positive predictive value and also demonstrated that it will not always be possible to tell whether any induration (> 5 mm) will develop into a positive test but if there is no induration especially in children younger than 13 years, it is highly possible (98%) that the tuberculin test will be negative.

In this study, it is found that on comparing 24 hour reading to 48 hour mantoux reading it was observed that sensitivity was 63.5, specificity and PPV was 100 & NPV was 98.7%. There is no false positive and the false negative is 75. Among the 206 mantoux positive cases who received ATT, 61% had > 10 mm induration at 24 hour, 25% had induration between 5-9 mm, and 3.8% had induration between 0-4 mm. Out of the 206 positive cases 9% were not started on ATT. When mantoux reading was done at 48 hour to predict active tuberculosis, the sensitivity of the test was 74.8 %, specificity was 99.6%, PPV was 90.7% and NPV was 98.8%. When mantoux reading was done at 24 hour to predict active tuberculosis, the sensitivity of the test was 50.4 %, specificity was 99.9%, PPV was 96.1% and NPV was 97.8%. On comparing the parameters of validity at 24 hour and 48 hour it was found that 24 hour reading has sensitivity of 50 compared to 74.8 at 48 hours and NPV 97.8 compared to 98.8

An early study by Howard and Solomon[34] showed that size of induration at 24 hours was highly predictive of eventual findings at 48 to 72 hours. In children the positive predictive value of any induration (> 1mm) reading at 24 hours was relatively low (63%) when a cut off of > 10 mm was used, but increased to 86% if the size of induration was > 5 mm at 24 hours.

In this study, the induration of > 10 mm at 24 hours remained > 10 mm at 48 hours and there is no single case which becomes < 10 mm at 48 hours when the induration is > 10 mm at 24 hours. All of the strongly mantoux positive cases have their induration at 24 hours itself. This study shows that a mantoux positive at 24 hours will remain positive at 48 hours and a negative mantoux test at 24 hours has to be seen again at 48 hours to confirm the negativity of mantoux test.

CONCLUSIONS

1. 63.6% of mantoux positive cases at 48 hrs had more than 10 mm induration at 24 hour itself. Only 2.4% of cases had no induration at 24 hours.
2. Tuberculin positivity in this study among children with symptoms suspicious of tuberculosis is 3.5%.
3. Validity of reading mantoux at 24 hours instead of 48 hours have high specificity and PPV but decreases in sensitivity (24 hr – 50.4% ; 48 hr – 74.8%). So mantoux positivity at 24 hours will remain positive at 48 hrs but negativity at 24 hours has to be verified at 48 hours.
4. Contact history is positive in 30.6% of mantoux positive cases.
5. BCG scar is absent in 19.4% mantoux positive cases
6. Grade IV nutritional status also had mantoux positivity (3.9%)
7. X-ray is abnormal in 19.4% of mantoux positive cases.

LIMITATIONS

1) Though measures have been taken to increase follow up for reading the test result, the drop out was 10%.
2) From this study, it is not able to give a cutoff value at 24 hrs to denote positivity at 48 hrs.
3) Qualitative evaluation of tuberculin test responses was not studied.
4) The study used 1 TU only. The results are not analysed for other higher tuberculin strength.

RECOMMENDATIONS

1. Tuberculosis skin test which is a traditional method to diagnose tubercular infection still remains gold standard to detect latent TB infection.
2. Children with symptoms suspicious of tuberculosis should be administered tuberculin test to detect infection since strongly positive mantoux is indicative of tuberculosis.
3. Validity of reading mantoux at 24 hours instead of 48 hours have high specificity and PPV but decreases in sensitivity (24 hr – 50.4% ; 48 hr – 74.8%). So mantoux positivity at 24 hours will remain positive at 48 hrs but negativity at 24 hours has to be verified at 48 hours.
4. There is no significant difference in mantoux positivity among children with and without exposure to open case of TB. Hence some TB infection may be missed because a tuberculin skin test was not done in the absence of any signs and symptoms suggestive of tuberculosis or in the absence of history of exposure. That is treatment of tuberculosis infection or disease in children must not be based solely on the presence of signs and symptoms and on the history of TB exposure, strongly positive tuberculin skin test also plays a role especially in young children.

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PROFORMA

Name :

Age :

Sex :

Weight :

Nutritional grade:

Prior Mantoux test done: Yes/No

If Yes; When:

Result:

H/O BCG vaccinaton and Scar:

Contact history:

H/O fever:

< 1 wk 1-2wk 2-3wk >3wk

H/O cough:

< 1 wk 1-2wk 2-3wk >3wk

Loss of weight:

Chest infection not responding to antibiotics:

Hemoptysis:

Lymphnode:

Cervical submandibular axillary

Steroids:

Viral infection:

Lung signs:

Mantoux reading:

24 hr

48 hr

72 hr

HIV status for positive cases:

WBC count: TC

DC

X-ray chest:

FNAC of LN:

Sputum / Gastric juice AFB:

Pleural fluid analysis:

CSF analysis:

ATT: started / not

ABBREVATIONS

AIDS – ACQUIRED IMMUNODEFICIENCY SYNDROME

AFB - ACID FAST BACILLI

ATT – ANTI- TUBERCULOUS THERAPY

BCG – BACILLE CALMETTE GUERIN

CSF – CEREBROSPINAL FLUID

CFP - CULTURE FILTRATE PROTEIN

ESAT – EARLY SECRETORY ANTIGENIC TARGET

ESRD – END STAGE RENAL DISEASE

HIV – HUMAN IMMUNODEFICIENCY VIRUS

FNAC – FINE NEEDLE ASPIRATION CYTOLOGY

IFN - INTERFERON

OT – OLD TUBERCULIN

PCR – POLYMERASE CHAIN REACTION

PPD – PURIFIED PROTEIN DERIVATIVE`

PPV – POSITIVE PREDICTIVE VALUE

NPV – NEGATIVE PREDICTIVE VALUE

QFT – QUANTI-FERON-TB TEST

SSI – STATENS SERUM INSTITUTE

TU – TUBERCULIN UNIT

MASTER CHART ABBREVIATIONS

Sex:
- m - male
- f – female

Contact history:
- p – positive
- n – negative

BCG scar:
- p – present
- a – absent

HIV status:
- neg – negative

Nutritional status:
1- normal
2- grade I
3- grade II
4- grade III
5- grade IV

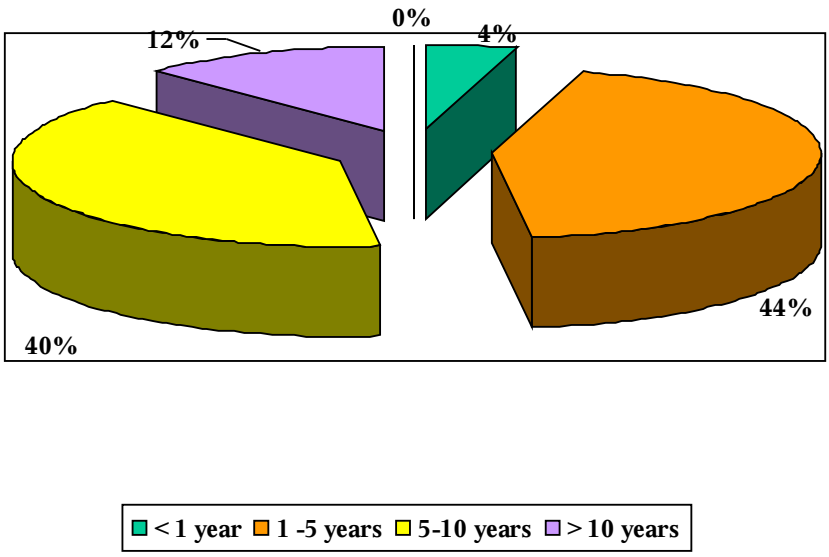
Fever:
1- less than 1 week
2- one to two week
3- two to three week
4- more than three week

Cough:
1- less than 1 week
2- one to two week
3- two to three week
4- more than three week

LN – lymphnode
1- cervical
2- submandibular
3- axillary

ATT:
- s – started
- NS – not started

AGE DISTRIBUTION OF 206 POSITIVE CASES



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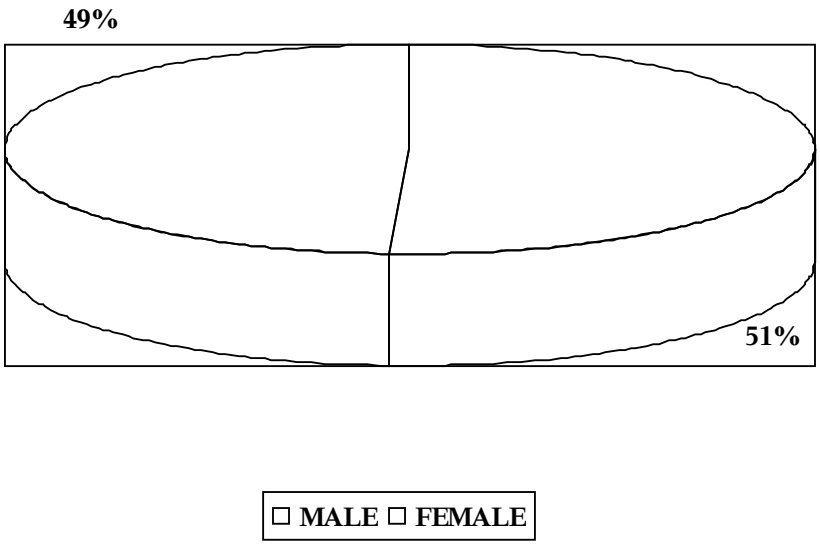
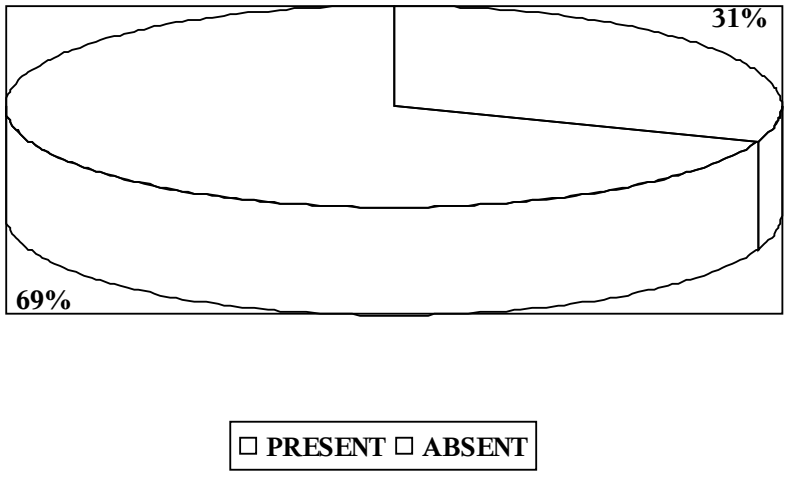
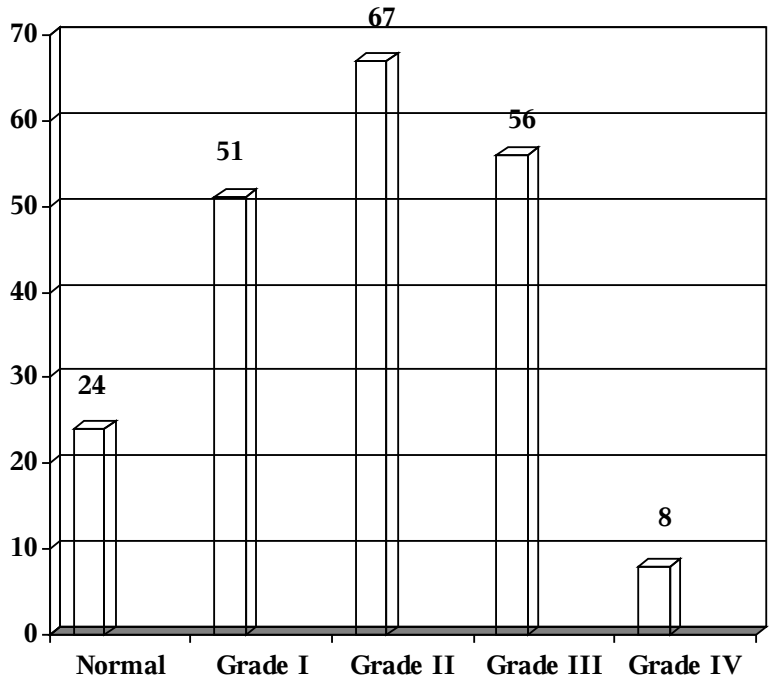


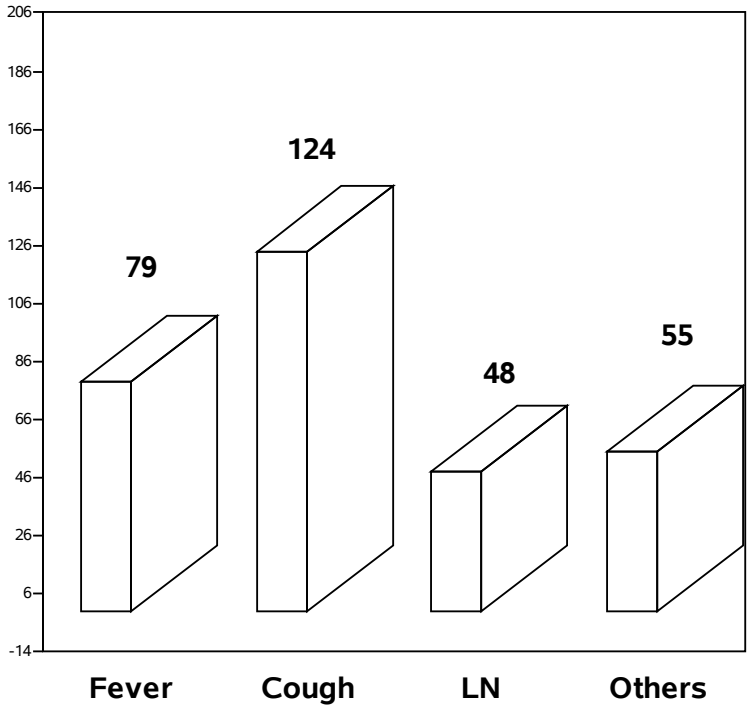
CONTACT HISTORY FOR 206 POSITIVE CASES



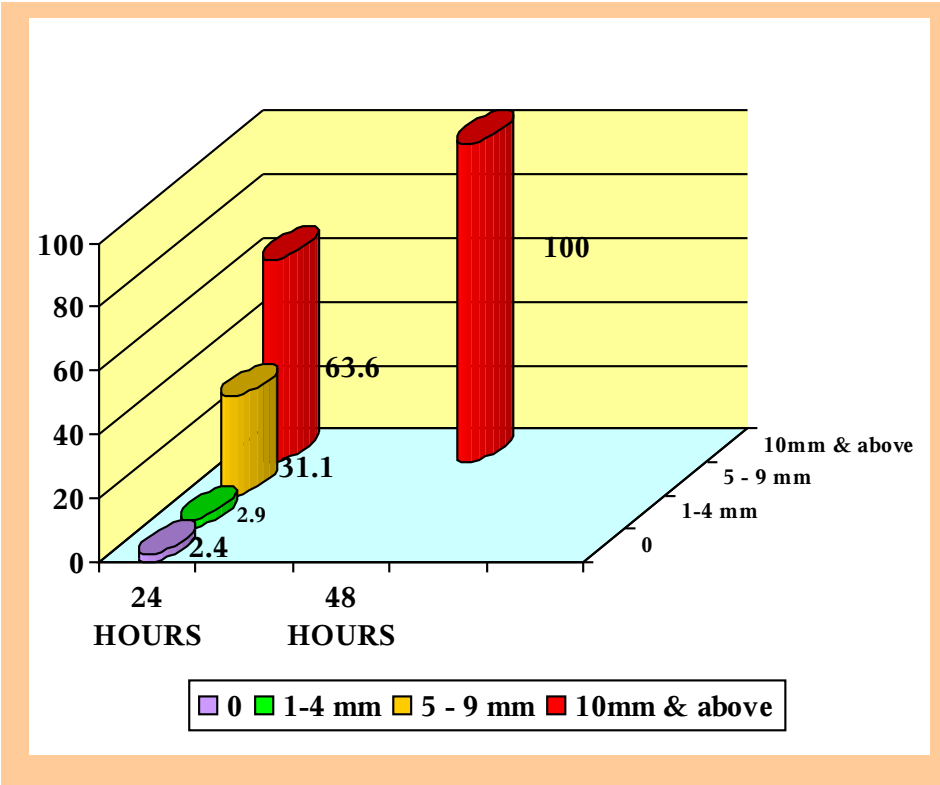
GRADING OF NUTRITIONAL STATUS



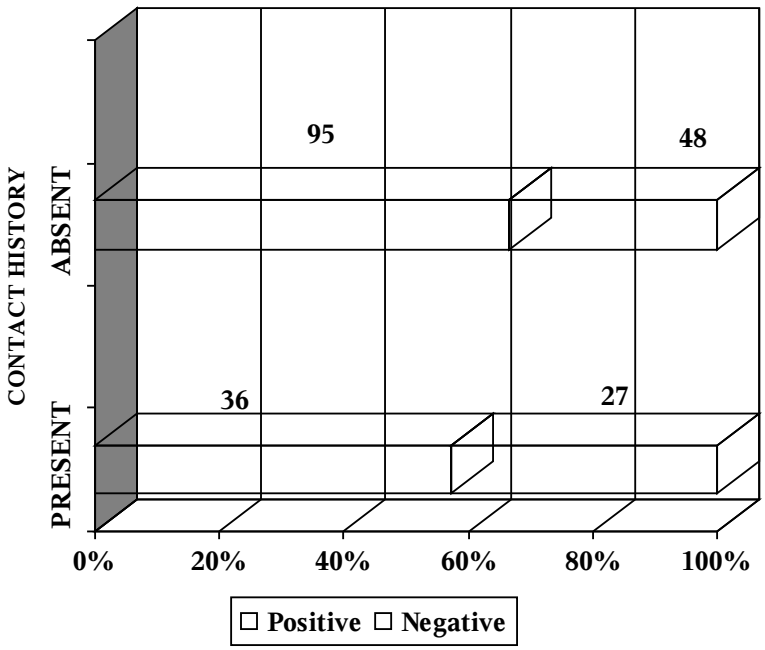
CLINICAL FEATURES FOR 206 POSITIVE CASES



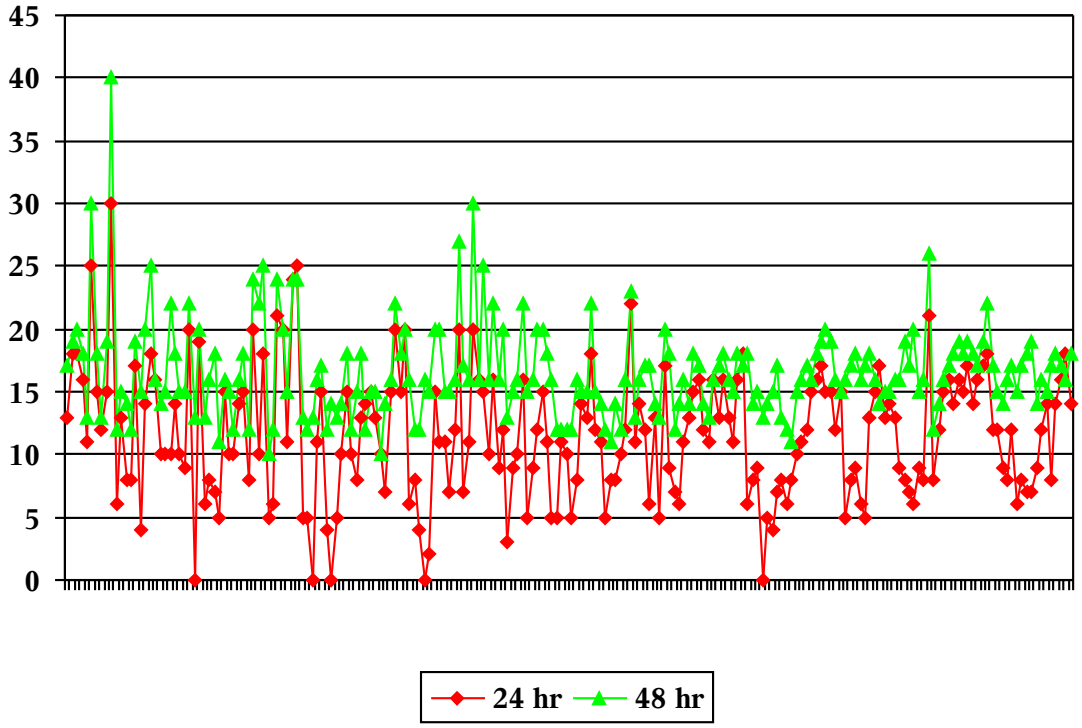
INDURATION VALUES AT VARIOUS TIME INTERVALS FOR 206 POSITIVE CASES



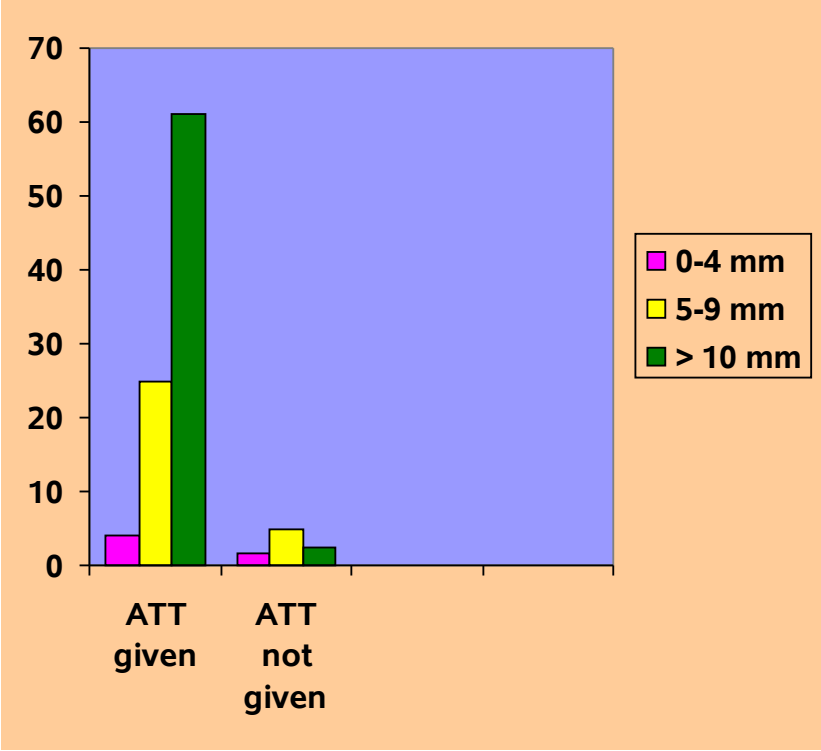
CONTACT HISTORY AND POSITIVITY AT 24 HOURS



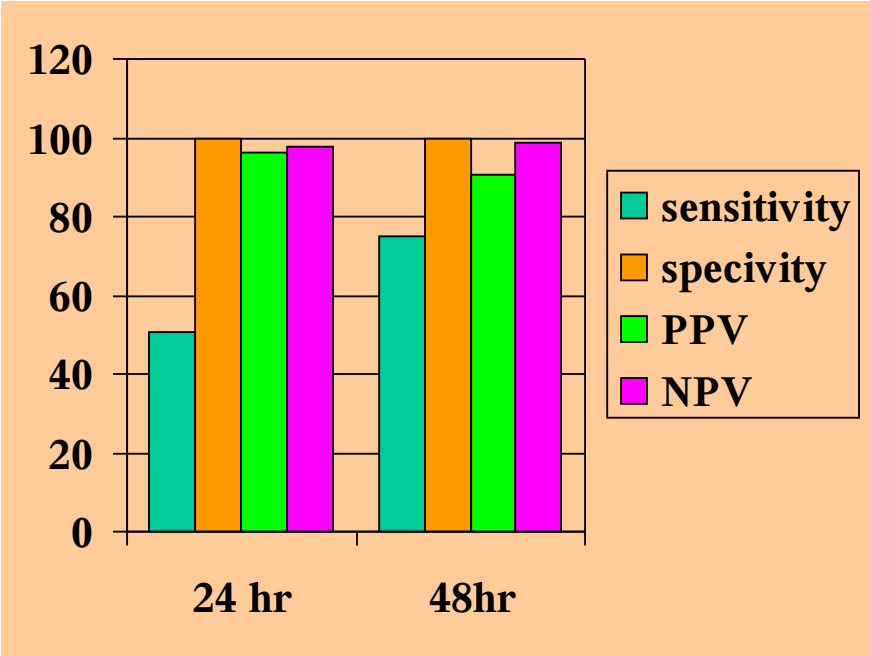
INDURATION AT 24 HR AND 48 HR



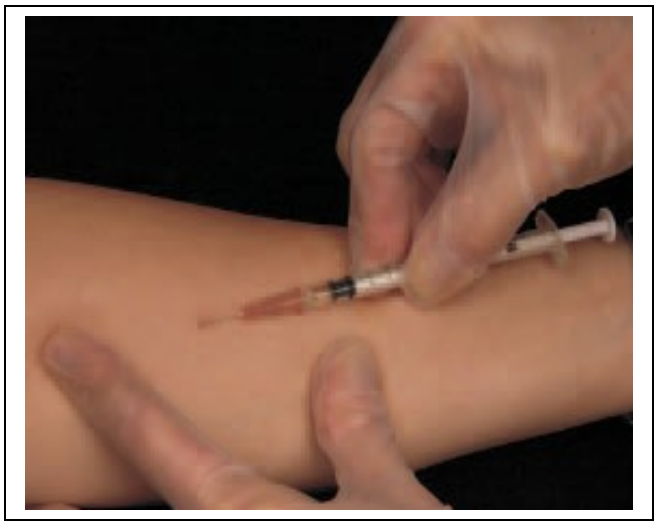
COMPARISON OF INDURATION VALUES AT 24 HOUR WITH ATT TREATMENT FOR 206 MANTOUX POSITIVE CASES

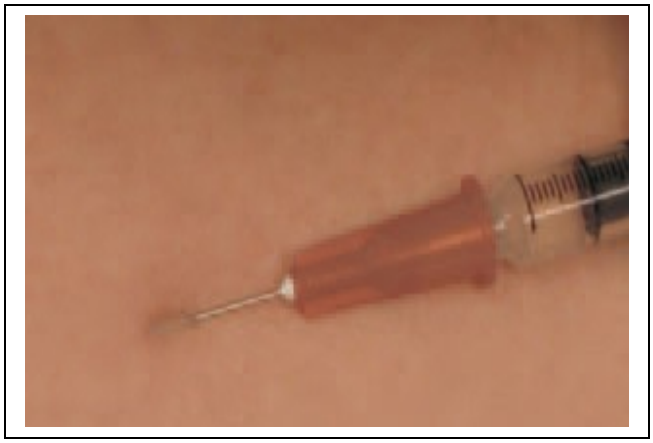


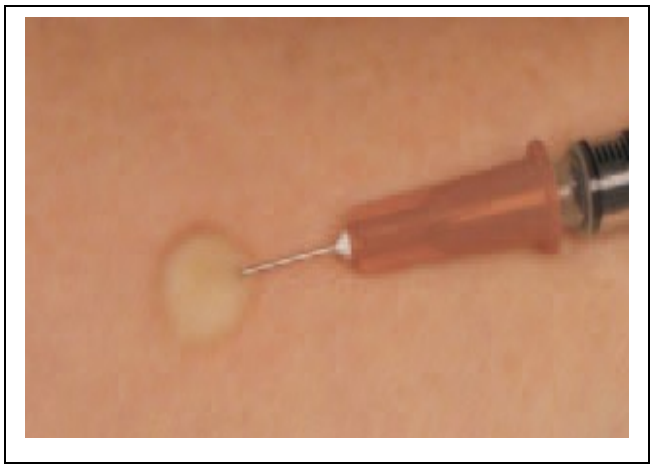
COMPARISON OF VALIDITY OF 24 HOUR AND 48 HOUR MANTOUX TEST



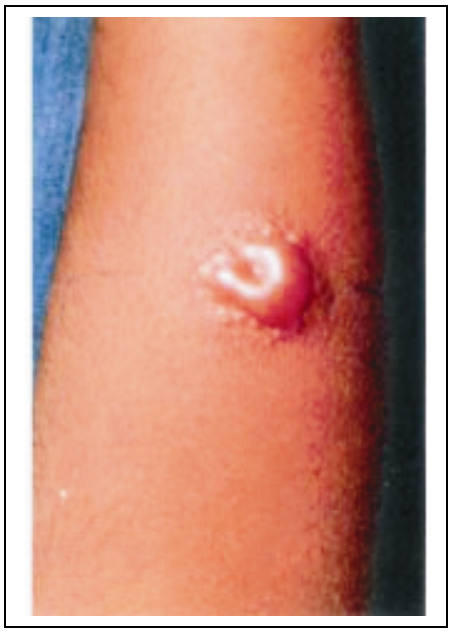
TECHNIQUE OF INTRADERMAL MANTOUX TEST







KOCH TYPE OF RESPONSE



LISTERIA TYPE OF RESPONSE