National Consultation on diagnosis and treatment of Pediatric Tuberculosis

The National consultation on diagnosis and treatment of pediatric TB was conducted on 31st January 2012 and 1st February 2012 at LRS Institute of TB and Respiratory Diseases with the following objectives:

- To review the evidence base and advances in pediatric TB diagnosis and treatment
- To arrive at a consensus for updating the Revised National Tuberculosis Control Programme (RNTCP) guidelines on Pediatric TB diagnosis and management

The list of the participants who attended the consultation and the agenda of the meeting isannexed at the end of the report. After extensive deliberations and detailed discussions on various issues related to the management of tuberculosis in children, the following key decisions were taken.

1. **Diagnosis of Pediatric TB*:**A new diagnostic algorithm was developed for pulmonary TB and the commonest type of extra pulmonary TB (Lymph node TB) addressing the concerns of RNTCP and pediatricians. For other types of extra-pulmonary TB, it was decided that the existing guidelines in the IAP consensus statement 2010 would be adopted and used in RNTCP.
    a. The pulmonary TB suspect and Lymph Node (LN) TB suspect definitions were revisited and amended for greater clarity and updated guidance. Clear definitions of 'weight loss/no weight gain" were agreed upon. Loss of weight was defined as a loss of more than 5% of the highest weight recorded in the past three months.The algorithms for the diagnosis of pulmonary TB and Lymph node tuberculosis are provided in Annexure 1. The consultation accepted to derive the guidelines for diagnosis of other types of extra pulmonary TB from the existing IAP guidelines (Detailed at Annexure 1).
    b. The group recommended that all efforts should be made to demonstrate bacteriological evidence for the diagnosis of pediatric TB. In cases where sputum is not available for examination or sputum microscopy fails to demonstrate AFB, alternative specimens (Gastric lavage, Induced sputum, broncho-alveolar lavage) should be collected, depending upon the feasibility, under the supervision of a pediatrician. ***It was decided that RNTCP will enhance the capacity of the microscopy centres at the district hospital to process these alternative samples.***

*0-14 years

c. ***Standard Operating Procedures (SOPs) would be developed and the laboratory technicians at the district hospital would be trained in these SOPs.***

d. Clear definitions of "X-ray suggestive of TB" were developed. A positive Tuberculin skin test / Mantoux's test positive weredefined as 10mm or more induration.However, non-availabilityof a standardized tuberculin in the country was identified as a cause of concern and it was decided that research is required to be done on priority to test commercially available tuberculin and reach a consensus on the optimal strength of tuberculin (1,2 or 5 TU) to be used for diagnosis in children. It was also agreed that till more evidence is collected no more than 5TU (RT23 or equivalent)should be used while 2TU dosage was considered more appropriate for routine diagnostic use.

   It was strongly agreed upon that there is no role for inaccurate/inconsistent diagnostics like serology (IgM, IgG, IgA antibodies against MTB antigens), various in-house or non-validated commercial PCR tests and BCG test. The group concurred with WHO guidance in the matter which strongly discourages serologyand non-validated commercial NAATs.

   The group also concluded that the current evidence does not support the routine use of IGRAs in clinical practice for the diagnosis of TB. However, the role of Interferon Gamma Release Assays, (IGRAs) (e.g. Quantiferon Gold, T-SPOT) in the diagnosis of TB in high endemic areas like India needs further evaluation.While acknowledging the fact that it may be difficult to localize the site of TB in few cases, the group strongly advocated against the usage of "therapeutic trial".

e. **Shared Care:** The RNTCP training manual will emphasize that treatment of pediatric patient will be a joint responsibility of referring physician/pediatrician and RNTCP. While drugs will be given through DOT centre, the patient will be referred back to the treating pediatrician at regular pre-defined intervals through a defined mechanism for monitoring the response and drug toxicity. The referring doctor will also be able to monitor growth, help in immunizationand treat other co-morbidities.

2. **Intermittent versus Daily regimen:** The available scientific evidence, advantages and disadvantages, risks and benefits were deliberated extensively and it was decided that intermittent therapy will remain the mainstay of treating pediatric patients till emergence of evidence against this mode of therapy. The group agreed that the missing doses in thrice weekly regime can adversely affect its efficacy. The group also emphasized that amongseriously ill admitted children or those with severe disseminated disease/neuro-tuberculosis, the likelihood of vomiting or non-tolerance of oral drugs is high in the initial phase. There was, therefore, an agreement that this select group of seriously ill admitted patients should be given***dailysupervised therapy during their stay in the hospital***using daily drug dosages.After discharge they will be taken on thrice weekly DOT regimen (with suitable modification to thrice weekly dosages). The mechanism to make the necessary drugs available would be developed by RNTCP.

   The group identified the urgent need to generate data on intermittent versus daily therapy.Though there is no strong evidence, anecdotal clinical experiences and initial findings from pharmacokinetic studies conducted at National Institute for Research on Tuberculosis (NIRT) suggest that daily TB treatment may be of benefit in HIV-infected children, at least in the intensive phase. This issue was widely debated, though, a consensus could not be achieved; this issue was flagged as an issue of concern which requires further discussion in future meetings involving pediatricians involved in care of HIV-infected children.

3. **Case definitions** for pediatric patients were discussed and it was agreed that following definitions will be incorporated in the RNTCP manuals.
   a. Failure to respond: A case of pediatric TB who fails to have bacteriological conversion to negative status or fails to respond clinically / or deteriorates after 12 weeks of compliant intensive phase shall be deemed to have failed response provided alternative diagnoses/ reasons for nonresponse have been ruled out.
   b. Relapse: A case of pediatric TB declared cured/completed therapy in past and has (clinical or bacteriological)evidenceof recurrence.
   c. Treatment after default: A case of pediatric TB who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months or more and has active disease (clinical or bacteriological).

d. Forprogrammatic purposes of reporting, all types of retreatment cases where bacteriological evidence could not be demonstrated,but decision to treat again was taken on clinical grounds,would continue to be recorded and reported as "OTHERS" for surveillance purposes.

4. **Drug dosages:** Based on available guidance, concerns with under dosing and current experience, the group recommended following dosages: Rifampicin 15 (12-17) mg/kg, Isoniazid 15 (12-17) mg/kg, Ethambutol 30 (25-30) mg/kg, PZA 35 (30-40) mg/kg and Streptomycin 15 mg/kg for use under RNTCP thrice weekly regime. In order to ensure that no child gets either under dosed or over dosed, it was decided to create new weight bands and keep them sufficiently narrow to avoid large fluctuations at the ends of the weight band. It was also decided to attempt to create generic boxes for each of the weight band instead of the current practice of having to combine the boxes which significantly increases the pill burden in children with body weight of ≥18kgs. However, specific guidance could not be developed in the two days of consultation. ***A core group of experts (Dr GR Sethi, Dr Varinder Singh, Dr SK Kabra, Dr RakeshLodha, DrSangeeta Sharma) was created to work out the most optimal weight bands and share the recommendations with Central TB Division.*** This was later developed with inputs from all the participants in an online consultation and a consensus was achieved. According to the new proposal, there will be six weight bands and three generic patient wise boxes will be used in combination to treat patients in the six weight bands. The details of the new weight bands and the new generic boxes are provided inAnnexure 2 (Table 1). The group was informed by CTD thatat-least 2 years will be needed to provide new formulations as time is needed for developing technical specifications of the new products (generic boxes with higher dosages and restructured weight bands), approval by technical specifications committee and the process of procurement and supply of these products under RNTCP. Till the new products are made available, an interim guidance was needed to optimize the use of the existing patient wise boxes and alignthem as much as possible to the new dosing recommendations. This guidance has also been developed and is provided in Annexure 2 (Table 2). To ensure that every child gets correct dosages, weighing of the patient in minimal clothing (as appropriate) using accurate weighing scales is essential. The group also recommended shifting to next weight band if a child gains a kilogram or

more, above the upper limit of the existing weight band. The group also agreed upon the following daily doses (mg per kg of body weight per day) Rifampicin 10-12 mg/kg (max 600mg/day), Isoniazid 10mg/kg (max 300mg/day), Ethambutol 20-25mg/kg (max 1500mg/day), PZA 30-35mg/kg (max 2000mg/day) and Streptomycin 15 mg/kg (max 1gm/day).

5. **Drug formulations:** Since the number of tablets is too many to consume and younger patients have difficulty in swallowing tablets,***the group strongly recommended using dispersible tablet formulations under the programme.****In the interim, DOT centres will be provided with pestle and mortars for crushing the drugs.* It will be the responsibility of the DOT provider to supervise the process of drug consumption by the child and in case any child vomits within half an hour of period of observation, fresh dosages for all the drugs vomited will be provided to the caregiver. The issue of using fixed dose combinations (FDC) under RNTCP was debated, but a consensus could not be reached due to concerns on bioavailability of individual drugs in FDC especially Rifampicin. This was flagged for further discussions in future meetings.
6. **Cat III regimen:** Though, there is utility of Cat III regimen in some pediatric TB cases, in view of: the fact that the programme has already implemented the new treatment categories; evidence of a relatively high INH resistance in studies from NIRT and increasing evidence of safety of Ethambutol in the doses used under RNTCP, the group agreed that the decision of abolishing Cat III need not be revisited. Hence, there will be only two treatment categories – one for treating 'new' cases and another for treating 'previously treated cases'. The treatment regimens are summarized in Annexure 2 (Table 3).
7. **TB Meningitis (TBM) :** The group felt that *Streptomycin can be safely replaced by Ethambutol in intensive phase of TBM*because of (a) current evidence favoring safety and efficacy of Ethambutol, (b) lack of any value addition in efficacy using Streptomycin over Ethambutol, and (c) need to avoidproblems of injection based treatment (lack of adequate muscle mass in malnourished, risks of unsafe Injections, need for a trained personnel, unpleasantness of the treatment). While ethambutol was considered a better

option than streptomycin in the treatment of new cases of childhood TB, streptomycin continues to be recommended as the additional fifth drug in the retreatment regime.

8. **Extending intensive and continuation phase:** Children who show poor or no response at 8 weeks of intensive phase shouldbe given benefit of extension of IP for one more month. In patients with TB Meningitis, spinal TB,miliary/disseminated TB and osteo-articular TB, the continuation phase shall be extended by 3 months making the total duration of treatment to a total of 9 months. It may be further extened for 3 more months in continuation phase (making the total duration of treatment to 12 months) on a case to case basis in case of delayed response and at the discretion of the treating physician/ pediatrician.
9. **Making DOT patient-friendly:** The group recommended that RNTCP may explore and ***pilot test the feasibility and effectiveness of alternate approaches like "Mother or care giver at home as DOT provider"*** in selected areas and if found useful can be accepted as strategy and scaled up.
10. **TB preventive therapy:** The dose of INH for chemoprophylaxis was recommended to be 10 mg/kg (instead of currently recommended dosage of 5 mg/kg) administered daily for 6 months. TB preventive therapy should be provided to:
    a. All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG or nutritional status.
    b. Chemoprophylaxis is also recommended for all HIV infected children who either had a known exposure to an infectious TB case or are Tuberculin skin test (TST) positive (>=5mm induration) but have no active TB disease.
    c. All TST positive children who are receiving immunosuppressive therapy (*e.g.* Children with nephrotic syndrome, acute leukemia, *etc.*).
    d. A child born to mother who was diagnosed to have TB in pregnancy should receive prophylaxis for 6 months, provided congenital TB has been ruled out. BCG vaccination can be given at birth even if INH chemoprophylaxis is planned.

The suggestion of introducing syrup formulations for infants due to difficulty in breaking tablets was debated. Given issues of bioavailability in syrup formulations and in the light of increased dose, it was decided to manage with 100 mg tablets instead of syrup

formulations.The issue of providing pyridoxine tablets for 6 months during chemoprophylaxis was discussed and it was decided that this was not required routinely.

The group also raised concern about the poor contact screening among household contacts of smear positive cases under the programme. In order to strengthen the implementation of contact screening and chemoprophylaxis and to enable monitoring at the state and national level, ***modifications in RNTCP recording and reporting***was agreed upon.

11. **Management of drug resistant TB:** The existing guidance under RNTCP on identifying MDR-TB suspects, methods of investigation to diagnose MDR-TB, treatment regimen, dosages and programmatic management of drug resistant TB (PMDT) was discussed in detail. However, it was felt by the group that the existing guidance needs to be modified to emphasize the special needs of the children. *A group was constituted (Dr GR Sethi, Dr Varinder Singh, Dr SK Kabra, Dr RakeshLodha, Dr Sangeeta Sharma, Dr Prahlad Kumar) to work on this guidance which can then be incorporated into the PMDT guidelines.*A meeting will be convened by CTD to discuss and finalize the guidance. Two key decisions are worth noting here.
    a. At least one pediatricianwho has experience in MDRTB managementis to be represented in the National DOTS-Plus committee and all the DOTS-Plus site committees.
    b. In select pediatric TB cases, where bacteriological evidence of MDR-TB is not possible to be established, the DOTS-plus site committee should be empowered to take a decision based on clinical evidence to treat the case as *"Probable MDR-TB"* with a full course of MDR-TB regimen.
12. **Research:** Several knowledge gaps and priority areas for research were identified during the deliberations. These are summarized in Annexure 3.
13. **Involvement of private sector through Indian Academy of Pediatrics (IAP):** The group strongly felt the need to sensitize and involve the pediatricians in the private health sector to follow the national guidelines for diagnosis and treatment of tuberculosis in order to prevent over diagnosis and ensure uniform and standardized management of pediatric TB across the country.

a. A training module will be developed for pediatricians by a group consisting of experts from IAP and RNTCP.

b. A programme to sensitize all pediatricians across the country based on the existing successful models would be planned with timelines, deliverables and budget by IAP in consultation with Central TB Division.

c. To conduct CME programmes on RNTCP guidelines in the annual conferences of Indian Academy of Pediatrics. IAP President committed full support to RNTCP in disseminating the consensus guidelines through all its forums including their journal - Indian Pediatrics.

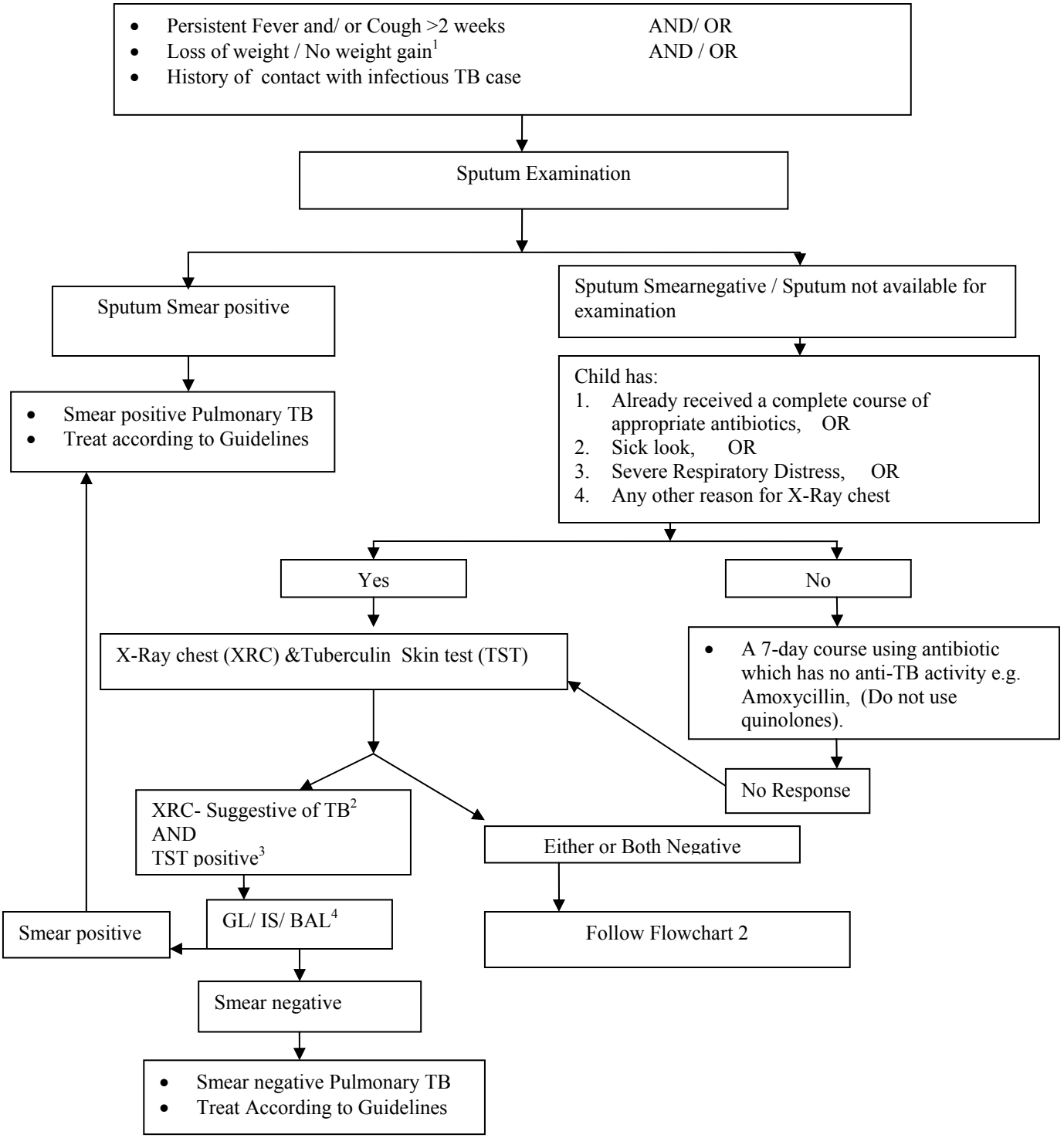
d. In order to extend RNTCP services like adherence support, retrieval of patients interrupting treatment and monitor the treatment outcome among patients managed in the private sector, the need to make TB nationally notifiable disease was discussed but no decision could be taken due to lack of consensus, Notification will enable the country to quantify the problem of pediatric TB and helps in proper planning and implementation of TB control strategies. The RNTCP's national strategic plan for 2012-17 is focused on achieving universal access which will be impossible to achieve unless TB is made a notified disease. DDG-TB informed the group of the initiative by the Central TB Division and developments in this direction at the highest level in the health ministry.

14. **Recording and Reporting:** It was recommended that there should be disaggregated reporting of children with TB by two age groups (0-4 and 5-14 years). It was also recommended that treatment cards for pediatric TB patients should be visually enhanced by adding colour and pictures to alert the DOT providers to the special considerations for the childhood cases.

15. **National Technical Working Group on Pediatric TB, a mechanism for continuing consultation:** *It was decided that a national technical working group of 10-12 experts on pediatric TB would be constituted with clearly defined terms of reference.* This would provide a forum for continuing consultations with experts and an opportunity to evolve the guidelines based on evolving evidence.

Diagnostic Algorithm for Pediatric Pulmonary Tb

Flowchart 1



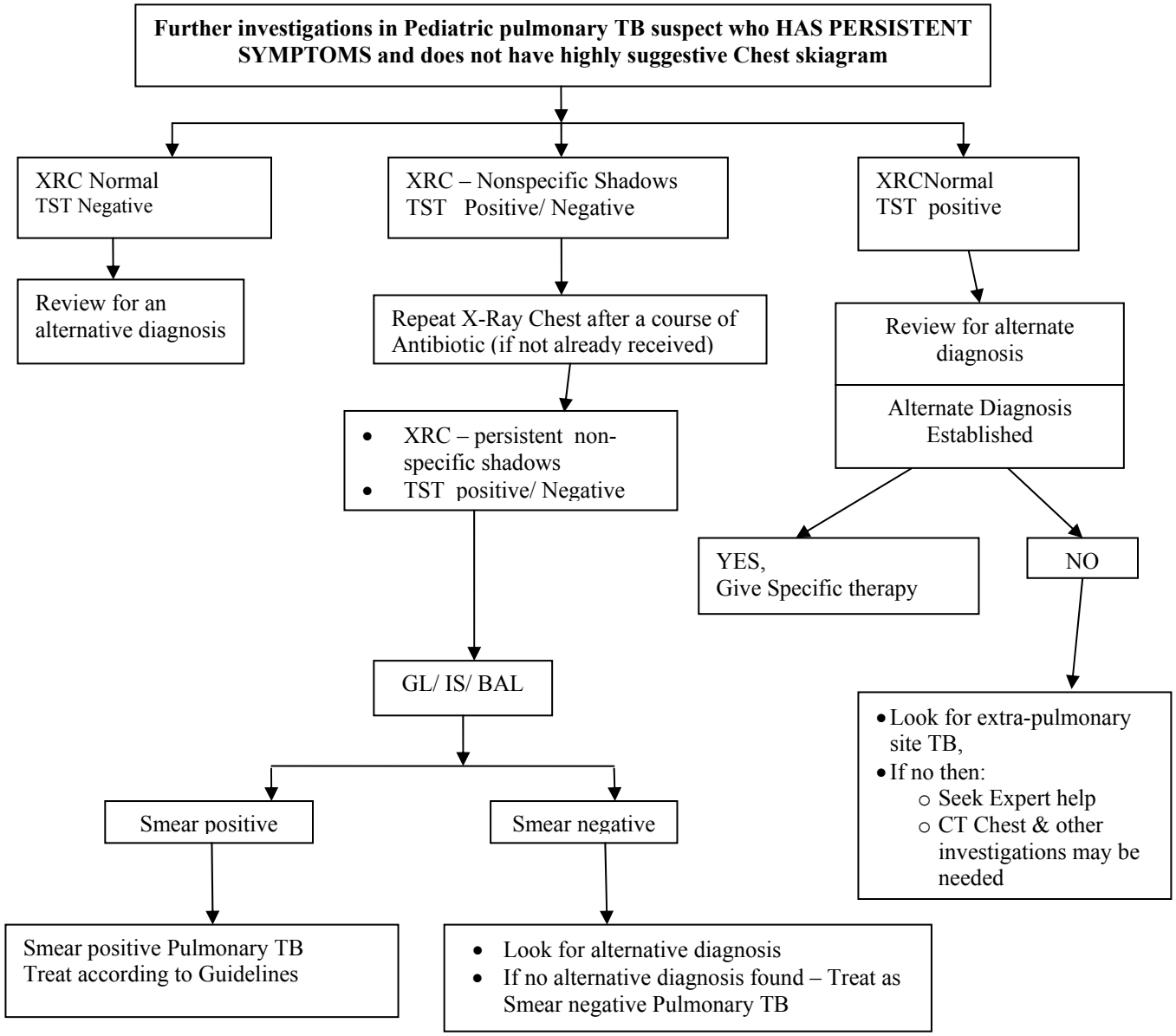
[1] History of unexplained weight loss or no weight gain in past 3 months; Loss of weight defined as loss of more than 5% body weight as compared to highest weight recorded in last 3 months.

[2] Radiological changes highlysuggestive of TB are Hilar/paratracheal lymphadenitis with or without parenchymal lesion, Miliary TB, fibrocavitary pneumonia,.

[3] If the radiological picture is highly suggestive of TB, then proceed to do further investigations irrespective of the TST result as the sensitivity of the test is not 100%.

[4] All efforts including Gastric Lavage (GL)/ Induced sputum (IS) or Bronchoalveolar lavage (BAL) should be made to look for Acid fast bacilli (AFB) depending upon the facilities.

Flowchart 2


Further investigations in Pediatric pulmonary TB suspect who HAS PERSISTENT SYMPTOMS and does not have highly suggestive Chest skiagram
XRC Normal
TST Negative
XRC – Nonspecific Shadows
TST Positive/ Negative
XRCNormal
TST positive
Review for an alternative diagnosis
Repeat X-Ray Chest after a course of Antibiotic (if not already received)
Review for alternate diagnosis
Alternate Diagnosis Established
XRC – persistent non-specific shadows
TST positive/ Negative
YES,
Give Specific therapy
NO
GL/ IS/ BAL
Look for extra-pulmonary site TB,
If no then:
Seek Expert help
CT Chest & other investigations may be needed
Smear positive
Smear negative
Smear positive Pulmonary TB
Treat according to Guidelines
Look for alternative diagnosis
If no alternative diagnosis found – Treat as Smear negative Pulmonary TB

When to suspect pulmonary TB?

The above flowcharts depict the diagnostic algorithm for childhood pulmonary TB. Fever and / or cough of recent onset lasting for > 2 weeks should arouse suspicion of tuberculosis. It is important to document fever and not depend merely on impression. Fever can be of any type and the often-described evening rise of temperature is neither specific to this etiology.

Cough can be dry or moist and may be severe. Cough persisting beyond 2 weeks, particularly as an only symptom in an otherwise healthy child can be due to viral infection and is often not due to TB. Such children, therefore, do not always warrantextensive investigations. As cough and fever are otherwise also common, it is the unabated persistence of these symptoms for over 2 weeks which makes TB more likely. Recurrent symptoms with normal intervening period are less likely to be due to tuberculosis.

Recent unexplained loss of weight is an important pointer to the suspicion of tuberculosis.
History of exposure to an infectious TB patient (smear positive) should always prompt detailed examination for presence of the disease. However, in a symptomatic child, contact with a person with any form of active tuberculosis within last two years may be significant as many a times there can be a coexisting pulmonary involvement which went unrecognized due to lack of chest symptoms.

Diagnosis is also more likely in presence of risk factors such as recent history of measles or whooping cough and immunocompromised state including steroid therapy. TB remains an important cause of persistent pneumonia not responding to antibiotic therapy in our country.

Significant superficial lymphadenopathy must be specially looked for, as it may often coexist.

Diagnosis of tuberculosis can never be reliably made only on clinical features. The subject with abovementioned clinical features- in isolation or in combination -is only a TB suspect. Further investigations are always necessary to establish the diagnosis. Therapeutic trial with anti-TB drugs is therefore, not recommended and instead every attempt must be made to prove the diagnosis.

Bacteriology

Demonstration of AFB from any body fluid or tissue is confirmatory of tuberculosis. Such a proof is often lacking in childhood tuberculosis because of difficulty in collection of sputum and due to paucibacillary primary disease in children. However, studies do report that the yield of a positive test in advanced cases may be as high as in adults. Therefore, every attempt must be made to bacteriologically prove the diagnosis in every case of suspected tuberculosis.

Sputum smear examination is the primary investigation of choice if sputum specimen is available from the child. If sputum smear is positive, patient is diagnosed as smear positive pulmonary TB and should be initiated on TB treatment.
If sputum smear is negative or not available, then the patient is prescribed a course of antibiotics for duration of seven days, and in case symptoms persist, Chest X-ray and Tuberculin skin test (TST / Mantoux test) should be performed. Care should to be taken to use antibiotics which do not have anti-TB activity.Fluoroquinolones should not be used as antibiotics at this point in time. In case the symptoms continue unabated despite antibiotics, then chest X-ray and TST should be done.
However, in a sick looking or distressed child with persistent symptoms of >2weeks duration, chest skiagram and TST test should be performed immediately along with other workup for non-TB infections.

Even where the XRC is highly suggestive of TB (Hilar/paratracheal lymphadenitis with or without parenchymal lesion, Miliary TB, fibrocavitary pneumonia) AND TST is positive, an attempt should be made for establishing bacteriological diagnosis using alternative specimens like Gastric Lavage (GL)/ Induced sputum (IS) or Bronchoalveolar lavage (BAL) depending on the facilities available. Given that the sensitivity of TST is not 100%, in any case with highly suggestive radiology, one must attempt bacteriological diagnosis (as mentioned above) even if the TST is negative. Based on the bacteriological results, case may be labeled as smear positive or negative TB and treated appropriately.

Inpediatric pulmonary TB suspect who HAS PERSISTENT SYMPTOMS and / or non-specific radiological shadows but efforts for a bacteriological diagnosis havefailed, further investigative scheme is detailed in Flowchart 2. It is broadly divided into three possible situations.

1. If both TST and X-ray findings are negative, then TB is highly unlikely and an alternative diagnosis should be looked for.
2. In situations where the CXR has persistence of non-specificshadows despite a course of antibiotics, alternative samples for TB (GA/IS/BAL) should be sent to establish bacteriological diagnosis irrespective of the TSTpositivity.In case the alternative sample is AFB positive, then classify and treat as smear positive case. In case these samples are negative, then an alternative diagnosis should be diligently looked for. If no alternative diagnosis is established, the case may be classified and treated as smear negative TB.
3. If only TST is positive and X-ray chest is not suggestive, then look forTB at an extra-pulmonarysite or an alternative diagnosis. Cases with persistent symptoms with TST positive but no evidence of TB at pulmonary/ extra-pulmonary site thus far, often need expert help and detailed investigations like CT chest, etc.

Bacteriological Investigations using following alternative specimens can be attempted:

1. Early morning gastric aspirate is a preferred specimen for most young children with suspected TB for detecting AFB or isolating *Mycobacterium tuberculosis*. The child is kept fasting for about 6 hours (at night) and an appropriate size intra-gastric tube is passed in the morning. Initially the aspirate is drawn from the stomach and then a further washing with 15-30 mL saline is taken. The contents so recovered are then immediately transferred to the laboratory. This specimen can also be collected as an ambulatory procedure after 4-6 hours fasting with some loss of yield.
2. Sputum collection is possible in older children with extensive and cavitatory disease, particularly if the patient has a wet cough.
3. Induction of sputum by 3% nebulized hypertonic saline can be tried in other children. The patient is pretreated with nebulized bronchodilators like salbutamol prior to induction. Following saline nebulisation, chest physiotherapy is done to loosen up the secretion and the samples are collected from the throat or nasopharynx using a collector attached to a suctionat one end and a catheter/tube to the other. The suction catheter provokes cough and the secretions brought up are collected via suction.
4. Bronchial washings / bronchoalveolar lavage (BAL) can also be used as a diagnostic tool though the availability is limited. Bronchoscopy and BAL is often needed for evaluatingcases of persistent pneumonia. Sometimes, there may be a co-existent peripheral lymphadenopathy, which is easily accessible and the aspirates from these can be used for bacteriological/ cytological diagnosis.

The experience shows that one needs to collect at least two samples of whatever type of the respiratory specimens one decides to choose to get the optimal yield. If the facilities are limited, these tests may be prioritized and atleast be done in all children with wet cough or children who have definite parenchymal lesion on chest skiagram.

Ziehl-Neelsen stain can reveal AFB only if sample contains > 10,000 bacilli per ml. Various culture methods such as LJ medium, Radiometric (Bactec) and Non-radiometric (MGIT) can be used for confirming diagnosis in paucibacillary state. The newer methods are capable of giving faster results and may be used if available. Mycobacterial culture and drug sensitivity assumes special significance in case of suspected drug resistance and should be attempted in cases needing retreatment (particularly the defaulters and failures but preferably in all cases).

Radiology

Chest radiograph merely localizes the site of pathology and does not define etiology. There are no pathognomonic radiological signs of tuberculosis. In relevant clinical setting, certain radiological lesions may strongly suggest tuberculosis and they include miliary, hilar or paratracheal lymphadenopathy with or without parenchymal involvement, pleural effusion and fibrocaseouscavitatory lesions. Rarely chest X-ray may be normal, such cases should be referred to an appropriate center for further detailed investigations, if the clinical suspicion and epidemiological risk (e.g. close contact of an infectious case, etc.) is high. In clinical practice, non-resolving chest shadows despite adequate antibiotic therapy in a symptomatic child raises the possibility of tuberculosis. It is worth mentioning that all persistent radiological lesions are not necessarily due to TB. Asymptomatic patients may have persistent shadows due to parenchymal scarring, pleural thickening, and healed fibro-atelectatic changes. On the other hand, a child with bronchiectasis or an interstitial lung disease may have presence of non-resolving shadows with persistent symptoms.

Ultrasonography of chest is helpful to assess pleural fluid collection; although decubitus chest *X*–ray film may also reveal similar information.

CT scan is rarely necessary and is not cost and radiation effective. ChestCT scan, however, may offer an opportunity for CT guided biopsy for tissue diagnosis.

Tuberculin test

The standard tuberculin skin test recommended for use is the Mantoux's test. Commercially available tuberculin in the country are of the strength of 1, 2 and 5 Tuberculin Unit (TU) PPD (RT23 equivalent). It is important to raise a wheal of about 6 mm after the intra-dermal injection and the test is read 48-72 hours after an injection. Ballpoint or palpatory methods are used to read the induration. The width of reaction (induration) in the horizontal plane is noted for interpretation. **Mantoux's test or PPD skin test is considered positive if the induration is 10 mm or more.** This cutoff was recommended using a 1 TU PPD RT23. **It is recommended that the 10mm cutoff may be continued to use for strengths of PPD only up to 5TU, however,2TU PPD RT23 was considered to be the most suitable strength.** In no case strength higher than 5 TU should be used. Degree of reaction, including necrosis and ulceration, may not necessarily differentiate infected from diseased. Prior BCG vaccine has minimal influence on PPD reaction.

If the patient returns for reading beyond 72 hours but by 7th day, a positive test can still be read. A repeat test may be needed, if there is an induration less than 10mm and the suspect reports for reading beyond the stipulated time of 72hours post injection.Repeat tuberculin test when required should preferably be done on the other arm. The reading of the repeat test should be interpreted as in any other individual.

Status of othertests in vogue for diagnosing active tuberculosis in children:

1. **BCG Test:** BCG test is **not recommended** in diagnosis of tuberculosis.
2. **Serodiagnostic Tests:** As mycobacterial antigens overlap in different stages of infection and disease, there are no specific antigens that can confirm natural infection or active disease. Commercial antigen tests are not easily available or well evaluated. Commercial TB antibody tests share similar problems of interpretation and as they cannot differentiate natural infection from BCG vaccine induced infection and active disease from old healed disease. **These tests are not recommended for use.**
3. **Interferon Gamma Release Assays (IGRAs):** Newer generations of tests which measure the production of interferon gamma by the peripheral mononuclear cells have been developed to identify the patients with TB disease or latent infection. These use two antigens, early secretion antigen target (ESAT 6) and culture filtrate protein 10 (CFP 10), which are specifically present only in mycobacterium tuberculosis and not in other mycobateria or the BCG vaccine strain. These tests though have a principle similar to skin test but do away with the need for a repeat visit by the patient for reading purposes.QuantiferonGold™ and T-spot™ are two of the commercially available IGRAs. These are being used in place of the skin test in low prevalence countries to detect latent TB infection. However, these expensive tests do not differentiate the TB infection from disease. Theexact advantage of these tests in high burden situation is still not clear**. Hence, these are not recommended for use in the diagnostic algorithm for Tuberculosis in India.**
4. **PCR Tests and Gene Expert ®:** The inhouse Nucleic acid amplification tests (NAAT) and several commercial tests have poor sensitivity for diagnosing TB in smear negative samples. The laboratory contamination is a real risk. Thesetests are, therefore, not recommended for the diagnosis of childhood TB. NAATs are preferred for rapid identification of the culture isolates rather than using them directly over clinical specimens.
   However, Heminested, cartridge based real time PCR marketed as Xpert MTB/RIF™ is now endorsed by WHO as a likely point of care te**s**t using clinical specimens. This may be used, where available, particularly in previously treated cases or cases who are contacts of chronic/ MDR TB adults. The test has ability to detect Mtb as well as rifampin resistance in a matter ofhours. Being cartridge based, real time technology, and the risk of cross contamination is also less. The utility of this test for extra-pulmonary specimens is being established.

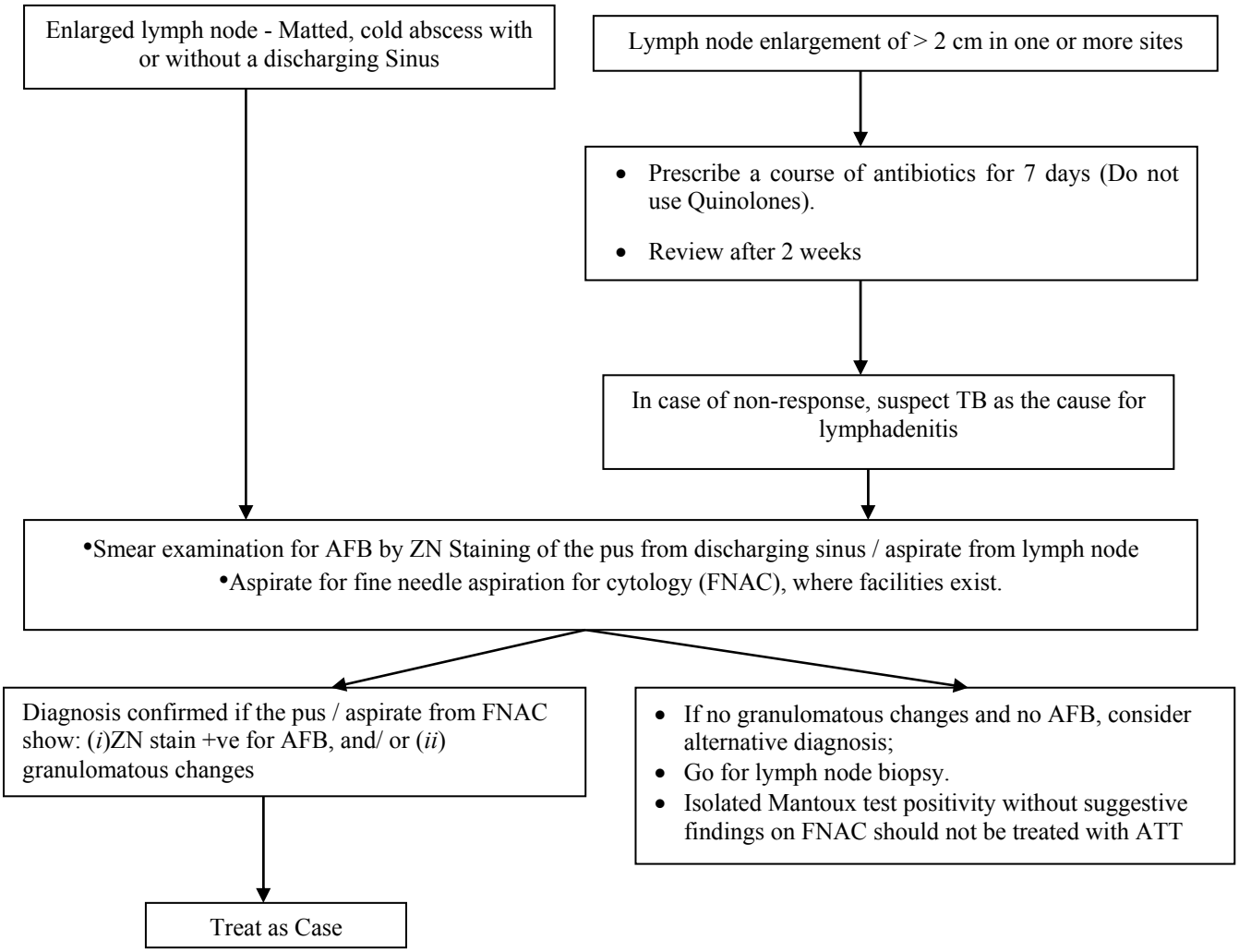
Extra-pulmonary Tuberculosis

TB lymphadenitis

This is most common form of extra pulmonary tuberculosis. Clinical correlate of diagnosis includes progressive enlargement of lymph node for more than 2 weeks, firm, minimally tender or not tender, sometimesfluctuating, may be matted and may have chronic sinus formation.

The diagnostic algorithm is shown below. Fine needle aspiration cytology (FNAC) is usually adequate for accurate diagnosis and it correlates well with biopsy in >90% of cases. Histopathology typically shows necrosis and epitheloid granuloma. It is important to look for AFB in FNAC specimen and it may be positive in 20-70% of patients. When FNAC is inconclusive, biopsy is necessary for confirmation of diagnosis. In children, lymphadenopathy is common due to recurrent tonsillitis and URIs as well. Such reactive lymphadenitis may clinically mimic tuberculosis but does not warrant anti-TB drugs. Persistent lymphadenopathy of significant size (say more than 2cm in the neck) should however, be investigated.TST is mostly positive in a significant proportion, but isolated skin test positivity is not enough to establish a diagnosis of TB. Hence anti-TB drugs should not be given unless the diagnosis of TB is confirmed by FNAC or histopathology.

Diagnostic algorithm for diagnosis of Lymph Node Tuberculosis



Pleural Effusion

If chest X-ray is suggestive of pleural effusion, pleural aspiration should always be performed for biochemical, cytologicaland smear examination by ZN stain to confirm the diagnosis. Typically, a tubercular effusion fluid is straw colored (pus, if aspirated, is very rarely due to TB etiology) has large numbers of cells (in hundreds; predominantly mononuclear), with high proteins (>3g/dL). Adenosine Deaminase (ADA) levels over 60 IU/L may be suggestive of tuberculous pleural effusion but is not diagnostic of TB.Pleural biopsy may be performed, where available, particularly when the fluid aspirate findings are inconclusive.

Tubercular meningitis (TBM)

Children with TBM present with a rather longer (>1 week) duration of fever, with vague CNS symptoms such as behavior changes, irritability, drowsiness, headache, vomiting and seizures. Physical examination reveals typically global encephalopathy with focal deficits, hydrocephalus and movement disorder. Risk factors for TBM include age < 5 years, contact with an adult suffering from tuberculosis, PEM grade III and IV, and HIV infection.

1. Typically CSF is clear to opalescent, usually does not show very high cell count (under 500 cells/mm^3) with lymphocytosis. Biochemical investigations reveal increased proteins and mild reduction in glucose. The typical CSF picture may, however, not always be seen. Furthermore, the typical CSF picture described above can also be mimicked by partially treated pyogenic meningitis. In such a situation, reassessing after 48-72 hours of treatment with a fresh set of broad spectrum potent antibiotics to evaluate improvement in clinical status as well as in CSF can be useful.
2. Efforts should be made to establish the diagnosis by collecting more supportive evidence using TST, chest skiagrams. Bacteriological diagnosis from appropriate samples including CSF is diagnostic. Many a time concomitant TB lesions elsewhere in the body (say, pulmonary) co-exist and can clinch the diagnosis. Mycobacterial culture from CSF should also be attempted but CSF culture has poor sensitivity (16%) though specificity is high (90%).
3. Neuroimaging is an important diagnostic modality. It may reveal one or more of the following findings: basal meningeal enhancement; hydrocephalus with or without peri-ventricular ooze; tuberculoma(s); or infarcts may be seen in different areas, especially in basal ganglia.
4. Normal CT scan does not rule out TBM and in case of strong clinical suspicion of diagnosis, a repeat follow-up CT scan after few days may show newly developing lesions. CSF abnormalities in TBM may take variable time up to few months to return to normal.
5. Besides routine CSF examination, CSF ADA is high in TBM. Various studies have a cut-off point between 7 and 11.3 IU/L for diagnosis. This may offer supportive evidence in favor of TBM but should not be taken in isolation.
6. CSF antigen and PCR tests are neither routinely available nor reproducible. They are, therefore, not recommended. CSF antibody tests have poor sensitivity and specificity and hence are not useful.

Tuberculoma

Often seen in older children, it may present as a focal seizure in supra-tentorial cortical lesion or with symptoms and signs of raised intracranial tension with multiple localizing signs and hydrocephalus in posterior fossa lesion. It may sometimes also be seen as a part of TB meningitis. Differentiation from other ring lesions, especially neurocysticercosis (NCC) is difficult in cortical lesion. A ring enhancing lesion is not pathognomonic of tuberculoma. A larger lesion >20 mm, disc lesion or ring lesion with thicker rim with central nodule favors tuberculoma while multiple, smaller, thin rim with epicentric nodule favor NCC. MR spectroscopy may help in diagnosis of tuberculoma as it shows lipid peak.

Abdominal tuberculosis

It may present as localized disease such as mesenteric lymphadenopathy, intestinal disease, peritoneal involvement or systemic disseminated disease presenting as hepatosplenomegaly. Large matted lymph node mass may be clinically evident and ultrasound guided biopsy may help in confirming the diagnosis.

1. There are no standard guidelines for sonography diagnosis of abdominal tuberculosis. However, corroborative evidence includes: echogenic thickened mesentery with lymph nodes > 15mm in size; dilated and matted bowel loops; thickened omentum, and ascites. None of these findings, however, is specific to TB alone.
2. Barium follow-through examination may be suggestive of intestinal disease but is not confirmatory.
3. Exudative peritoneal disease presents as ascites that is often clinically evident. The ascitic tap should always be done in such situations and the fluid tapped is an exudate, typically showing lymphocytic predominant cellular response with high proteins (>3g/dL).

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Table 1: New weight bands and generic patient wise boxes with drug dosage delivered and pill burden

Body Weight	RIF	INH	PZA	ETB		mg/kg of body weight					PILL BURDEN		
						R	H	Z	E		2 drug FDC	3 drug FDC	individual drugs
				Product 1									
6	100	100	250	200		17	17	42	33		3	2	4
7	100	100	250	200		14	14	36	29		3	2	4
8	100	100	250	200		13	13	31	25		3	2	4
				Product 2									
9	150	150	400	300		17	17	44	33		3	2	4
10	150	150	400	300		15	15	40	30		3	2	4
11	150	150	400	300		14	14	36	27		3	2	4
12	150	150	400	300		13	13	33	25		3	2	4
				Product 3									
13	200	200	500	400		15	15	38	31		3	2	4
14	200	200	500	400		14	14	36	29		3	2	4
15	200	200	500	400		13	13	33	27		3	2	4
16	200	200	500	400		13	13	31	25		3	2	4
				Product 1+2									
17	250	250	650	500		15	15	38	29		6	4	8
18	250	250	650	500		14	14	36	28		6	4	8
19	250	250	650	500		13	13	34	26		6	4	8
20	250	250	650	500		13	13	33	25		6	4	8
				Product 2+2									
21	300	300	750	600		14	14	36	29		6	4	8
22	300	300	750	600		14	14	34	27		6	4	8
23	300	300	750	600		13	13	33	26		6	4	8
24	300	300	750	600		13	13	31	25		6	4	8
				Product 3+3									
25	400	400	1000	800		16	16	40	32		6	4	8
26	400	400	1000	800		15	15	38	31		6	4	8
27	400	400	1000	800		15	15	37	30		6	4	8
28	400	400	1000	800		14	14	36	29		6	4	8
29	400	400	1000	800		14	14	34	28		6	4	8
30	400	400	1000	800		13	13	33	27		6	4	8

Table 2: Revised Dosing and Weight bands according to existing Pediatric Patient wise boxes (PWB)

Weight	New	Tab	Rif del-r	INH del-r	PZA del-r	ETHAM del-r	RIF/ kg	INH/ kg	PZA/ kg	ETHAM / kg
6	PC13	1	75	75	250	200	13	13	42	33
7	PC13	1	75	75	250	200	11	11	36	29
8	PC13 + half of PC13	1.5	112.5	112.5	375	300	14	14	47	38
9	PC13 + half of PC13	1.5	112.5	112.5	375	300	13	13	42	33
10	PC13 + half of PC13	1.5	112.5	112.5	375	300	11	11	38	30
11	PC13 + half of PC13	1.5	112.5	112.5	375	300	10	10	34	27
12	PC14	1	150	150	500	400	13	13	42	33
13	PC14	1	150	150	500	400	12	12	38	31
14	PC14	1	150	150	500	400	11	11	36	29
15	PC14	1	150	150	500	400	10	10	33	27
16	PC14 + half of PC13	1 +1/2	187.5	187.5	625	500	12	12	39	31
17	PC14 + half of PC13	1 +1/2	187.5	187.5	625	500	11	11	37	29
18	PC14 + PC13	1 each	225	225	750	600	13	13	42	33
19	PC14 + PC13	1 each	225	225	750	600	12	12	39	32
20	PC14 + PC13	1 each	225	225	750	600	11	11	38	30
21	PC14 + PC13	1 each	225	225	750	600	11	11	36	29
22	PC14 + PC13	1 each	225	225	750	600	10	10	34	27
23	PC14	2	300	300	1000	800	13	13	43	35
24	PC14	2	300	300	1000	800	13	13	42	33
25	PC14	2	300	300	1000	800	12	12	40	32
26	PC14	2	300	300	1000	800	12	12	38	31
27	PC14	2	300	300	1000	800	11	11	37	30
28	PC14	2	300	300	1000	800	11	11	36	29
29	PC14	2	300	300	1000	800	10	10	34	28
30	PC14	2	300	300	1000	800	10	10	33	27

TABLE 3: Treatment Categories and Regimens for Childhood Tuberculosis

Category of treatment	Type of patients	TB treatment regimens	
		Intensive phase	Continuation phase
New cases	• New smear-positive pulmonary Tuberculosis (PTB) • New smear-negative PTB • New extra-pulmonary TB.	$2H_3R_3Z_3E_3$*	$4H_3R_3$
Previously treated cases	• Relapse, failure to respond or treatment after default • Re-treatment Others	$2S_3H_3R_3Z_3E_3$ +$1H_3R_3Z_3E_3$	$5H_3R_3E_3$

H=Isoniazid, R= Rifampicin, Z= Pyrazinamide, E= Ethambutol, S= Streptomycin

**The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week.*

Pulmonary TB refers to disease involving lung parenchyma. Extra Pulmonary TB refers to disease involving sites other than lung parenchyma. If both pulmonary and extra pulmonary sites are affected, it will be considered as Pulmonary for registration purposes. Extra Pulmonary TB involving several sites should be defined by most severe site.

***Smear positive**: Any sample (sputum, induced sputum, gastric lavage, broncho-alveolar lavage) positive for acid fast bacilli.*
***New Case**: A patient who has had no previous ATT or for less than 4 weeks.*
***Relapse**: Patient declared cured/completed therapy in past and has evidence of recurrence.*
***Treatment after Default**: A patient who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months and has active disease.*
Failure to respond: A case of pediatric TB who fails to have bacteriological conversion to negative status or fails to respond clinically / or deteriorates after 12 weeks of compliant intensive phase shall be deemed to have failed response provided alternative diagnoses/ reasons for non-response have been ruled out.
***Others**: Cases who are smear negative or extra pulmonary but considered to haverelapse, failure to respond or treatment after default or any other case which do not fit the above definitions.*

In patients with TB meningitis on Category I treatment, the four drugs used during the intensive phase can either be HRZE or HRZS. The present evidence suggests that Ethambutol can be used in children.

Children who show poor or no response at 8 weeks of intensive phase may be given benefit of extension of IP for one more month. In patients with TB Meningitis, spinal TB, miliary/disseminated TB and osteo-articular TB, the continuation phase shall be extended by 3 months making the total duration of treatment to a total of 9 months. A further extension may be done for 3 more months in continuation phase (making the total duration of treatment to 12 months) on a case to case basis in case of delayed response and as per the discretion of the treating physician.

Under Revised National Tuberculosis Program (RNTCP, all patients shall be covered under directly observed intermittent (thrice weekly) therapy. The supervised therapy is considered as the most optimal treatment and is followed under RNTCP. It is important to ensure completion of treatment in every case put on treatment to prevent emergence of resistance, particularly to Rifampicin. In the rare circumstances where a patient is given daily therapy, observation and completion of therapy remains as important. It is the duty of the prescriber to ensure appropriate and complete treatment in all cases.

Research Priorities in childhood Tuberculosis

Operational research

1. Evaluation of existing already recommended new diagnostics for children in the programmatic context (operational/implementation research), e.g. Xpert etc.
2. Evaluate data already existing in some states to improve the documentation of the burden of childhood TB.
3. Models to improve notification of pediatric TB cases from private sector.
4. Evaluate trends in case detection of childhood TB (changes after training of staff etc)
5. Assess NTP performance with reference to childhood TB using the standard indicators for case detection and treatment outcomes.
6. Is the program seeing only certain types of TB and missing the more serious forms in younger ages?
7. Assess the effectiveness and feasibility of using family members as DOT providers
8. Assess the effectiveness/feasibility of intensified TB case finding in high-risk populations like malnourished children (Anganwadis, Nutritional rehabilitation centres)
9. Document the role of the private sector in all aspects of the management of childhood TB and the extent to which existing public/private partnerships are aware of childhood TB and its particular problems.

Scientific research

Disease burden (Epidemiology)

1. Determine prospectively the incidence of childhood TB in different communities making use of standardized consensus diagnostic criteria.
    a. Geographically representative
    b. covering all age groups (0-14) and socioeconomic strata
    c. pulmonary (smear-positive and smear-negative) and extrapulmonary TB
    d. HIV-infection
    e. drug-resistance
2. Epidemiologic studies (classical and molecular epidemiology) to study TB transmission in community
3. Carry out a prospective evaluation of the incidence of disseminated BCG disease (in HIV high prevalence districts)

Diagnosis

1. Development of new diagnostics suitable for child specimens
2. Test for latent TB with ability to predict disease progression
3. Point of care test with good accuracy for childhood TB
4. Evaluate and validate the new (clinical) diagnostic algorithm
5. Evaluate newer diagnostic tests in child TB suspects (egXpert Rif, urine LAM, MODS, LPA etc)
    a. Stratified by age, type of TB and HIV status
    b. Define gold standard – culture confirmation

    c. International consensus definition to be used against which to validate new diagnostics (JID March 2012)
6. Comparison of different specimens for pulmonary TB (IS, GL, string test, NPA) and number of specimens
7. Role of ultrasound in Intrathoracic Lymphadenopathy
8. Standardization of Mantoux test (Indian)
9. Evaluation of new skin test based on ESAT6 antigen (Diaskin, Russia)
10. Evaluate in multicentric fashion, Indian innovations eg breath analysis, antigen assays

Treatment

1. Investigate shorter, child-friendly regimen for both, infection and disease
2. Pharmacokinetic studies with newly revised RNTCP dosage schedule – all ages, HIV positive and neg, types of TB
3. Pharmacokinetic studies of second-line drugs.
    a. Population PK (follow cohorts)
    b. Outcomes important to document
4. Study drug-drug interactions and drug toxicity, particularly in HIV-infected children who frequently receive multiple drugs other than antituberculosis agents.
5. Evaluate rates of treatment failure and recurrence (disaggregated by HIV status): multicentric cohort study
6. Standard 6 month therapy: daily versus intermittent
7. Pilot the new dosing recommendations
8. Evaluate 3- and 4-month treatment regimens in paucibacillary forms of childhood TB
9. Evaluate necessity for longer periods of treatment in HIV-infected children.
10. Participate in trials of new TB drugs/regimens

Prevention

1. Development of Vaccines to prevent infection and disease in children and adults
2. Assess the accuracy of classification of cases as smear-positive pulmonary TB, smear- negative pulmonary TB and extrapulmonary TB, and the quality of management of cases.
3. Carry out epidemiological studies to determine the numbers of HIV-infected and non-infected children in contact with both sputum smear-positive and smear- negative adults, both HIV-infected and non-infected, who might qualify for chemoprophylaxis in different communities.
4. Assess the value of standard isoniazid prophylaxis and compare it to shorter multidrug chemoprophylaxis in both HIV-infected and non-infected children.
5. Contact Tracing and Chemoprophylaxis
6. Study the effectiveness different strategies (treatment card, new register, training etc) for improving contact-tracing and chemoprophylaxis in children – document outcomes
7. Collaborate in the establishment of vaccine trial sites for the evaluation of new TB vaccines.

Drug resistant tuberculosis

1. Validation of Consensus definition for MDRTB in children (confirmed and probable cases)
2. Evaluate the treatment of drug-resistant TB in children and determine the most effective regimens (fully oral regimen?).

3. Prevalence of infection and disease among childhood contacts of DRTB patients
4. Study chemoprophylaxis for the childhood contacts of adults with sputum smear- negative and smear-positive drug-resistant TB.

National Consultation on diagnosis and treatment of Pediatric TB
31st January and 1st February 2012
Venue: LRS Institute of TB and Respiratory disease,Mehrauli Road, New Delhi, India

Objectives:

To review the evidence base and advances in pediatric TB diagnosis and treatment
To arrive at a consensus for updating the RNTCP guidelines on Pediatric TB diagnosis and management

Agenda

Day 1	*31st January 2012 (Tuesday)*	
09.00 – 09.30	Registration	
09.30 – 10.00	**INAUGURAL SESSION**	
	Welcome and Objectives Address Address Address Vote of thanks	Dr. Ashok Kumar,DDG-TB,CTD Dr. RohitAgarwal,President, IAP Dr. D Behera,Director, LRS Dr. PuneetDewan, MO-TB, WHO-SEARO Dr. Devesh Gupta, ADDG(TB),CTD
	SESSION 1: **OVERVIEW OF NATIONAL AND GLOBAL GUIDELINES** Rapporteur: Dr. Ajay Kumar MV, CTD	Chairs: Dr Ashok Kumar, DDG-TB Dr RohitAgarwal, President, IAP Dr P Kumar, Director, NTI
10.00 – 10.30	Overview of Pediatric TB management under RNTCP – Achievements and Challenges	Dr. Devesh Gupta, CTD
10.30 – 11.00	Global guidelines on Pediatric TB	Dr. SoumyaSwaminathan, NIRT
11.00 – 11.30	Comparison and global and national guidelines on Pediatric TB	Dr Sangeeta Sharma, HOD Pediatrics, LRS
11.30– 12.00	Tea Break	
	SESSION 2: **DIAGNOSIS OF PEDIATRIC TB** Rapporteur: Dr GR Sethi, Professor of Pediatrics, LNJP, Delhi	Chairs: Dr. D Behera, Director, LRS Dr Piyush Gupta, Editor-in-chief, Indian Pediatrics Dr. RajeswarDayal, Professor of Pediatrics, Agra
12.00–12.30	Advances and challenges in diagnosis of Pediatric TB	Dr. SushilKabra, Professor of Pediatrics, AIIMS, Delhi
12.30– 13.00	Open forum discussionon diagnosis issues	
13.00–14.00	Lunch Break	
	SESSION 3: **TREATMENT OF PEDIATRIC TB** Rapporteur: Dr GR Sethi, Professor of Pediatrics, LNJP, Delhi	Chairs: Dr. SoumyaSwaminathan, Senior Deputy Director, NIRT

14.00–14.30	**Advances and challenges in Treatment of Pediatric TB**	**Dr. Varinder Singh, LHMC, Delhi**
14.30 – 14.40 **14.40-15.00**	**Pharmacokinetics of anti-TB drugs in children:** **AIIMS experience** **Pharmacokinetics of anti-TB drugs in children: Indian and Global evidence**	**Dr. SushilKabra, Professor of Pediatrics, AIIMS, Delhi** **Dr. GeethaRamachandran, NIRT**
15.00 – 15.30	**Open forum discussion on treatment issues**	
15.30 – 16.00	**Tea Break**	
16.00 – 17.00	**Discussion on Treatment Issues continued**	
17.30 – 20.30	**Core Group Meeting (Consolidation of discussions and preparing proposed diagnostic algorithm and treatment related recommendations)**	
Day 2	***1st February 2012 (Wednesday)***	
	SESSION 3: **RECOMMENDATIONS TO RNTCP**	**Chairs:** **Dr. Ashok Kumar, DDG-TB** **Dr. SoumyaSwaminathan, NIRT**
09.30 – 10.00 **10.00 – 11.00**	**Proposed consensus diagnostic algorithm and other related recommendations** **Discussion on the presentation**	**Dr GR Sethi, Professor of Pediatrics, LNJP, Delhi**
11.00 – 11.30	**TeaBreak**	
11.30 – 12.15 **11.30 – 13.00**	**Proposed treatment dosing and other related recommendations** **Discussion on the presentation**	**Dr GR Sethi, Professor of Pediatrics, LNJP, Delhi**
13.00 – 14.00	**LunchBreak**	
14:00 – 14:30 **14:30 – 15:00**	**Knowledge gaps in Pediatric TB management and priority research agenda** **Discussion**	**Dr. SoumyaSwaminathan, NIRT**
15.00 – 15.30	**TeaBreak**	
15.30 – 16.30	**Open Forum Discussion on any other issues** **Summary and Next steps**	

List of participants and their contact details

S.No	Name	Designation	Email	contact phone number
1	Dr Ashok Kumar	DDG-TB, Central TB Division, Dte.GHS, MoHFW	ddgtb@rntcp.org	011-23063226
2	Dr Devesh Gupta	Addnl DDG-TB, Central TB Division, Dte.GHS, MoHFW	guptadev@rntcp.org	011-23062781 / 09811033031
3	Dr SoumyaSwaminathan	Senior Grade Deputy Director, NIRT, Chennai	doctorsoumya@yahoo.com	9444057478
4	Dr GeethaRamachandran	Researcher in Pharmacokinetics, NIRT, Chennai	geetha202@rediffmail.com; geethar@trcchennai.in	044-28369648 / 09790835712 Fax no:-044-28362528
5	Dr D Behera	Director, LRS Institute of TB and respiratory diseases	dirlrsi@gmail.com; directorlrsi@yahoo.co.in; dirlrsi@bol.net.in	9790835712
6	Dr Prahlad Kumar	Director, National TB Institute	nti@ntiindia.org	080-23362431/ 23441192-93/ 09341262352
7	Dr Sangeeta Sharma	HOD Pediatrics, LRS Institute of TB and respiratory diseases, Delhi	sharmasangeeta2000@gmail.com	9341262352 / 080-23362431
8	Dr Varinder Singh	Professor of Pediatrics, LHMC, Delhi	4vsingh@gmail.com	9899666510
9	Dr RakeshLodha	Associate Professor of Pediatrics, AIIMS, Delhi	rakesh_lodha@hotmail.com; rlodha1661@gmail.com	011-26593621 / 09868397533
10	Dr SushilKabra	Professor of pediatrics, AIIMS, Delhi	skkabra@hotmail.com	011-26594610 / Fax no:-011-26588941
11	Dr Rewari BB	NPO-ART, NACO	drbbrewari@yahoo.com	011-43616667 / 09811267610 Fax no:- 011-26429099
12	Dr Rohit C Agarwal	Mumbai (IAPpresident)	drrohitag@hotmail.com	022-25153643/ 022-25133062/ 09821096353
13	Dr GR Sethi	Professor of Pediatrics, LNJP, Delhi	grsethi56@gmail.com	011-27867019, 9968604305
14	Dr PuneetDewan	MO-TB, SEARO	dewanp@searo.who.int	9871389967
15	Dr Sreenivas A	NPO-TB, WHO-India Office	sreenivasa@searo.who.int	9313058578
16	Dr RanjaniRamachandran	MO-TB Labs, SEARO	ramachandranr@searo.who.int	9650296363
17	Dr Ajay Kumar MV	TB-HIV Consultant, CTD	kumaramv@rntcp.org	9311384574
18	Dr. Santosh K. Talwar	Consultant Pharmaceuticals, EPW, MoHFW	talwar.dr@gmail.com	011-23061175
19	Dr. BhaskarShenoy	Head of the paediatrics department, Manipal hospitals, Bangalore - 560 017	bshenoy@gmail.com	080-25023263 / 09845036174 Fax no:-080-25266757

S.No	Name	Designation	Email	contact phone number
20	Dr. Meenu Singh	Professor Pediatrics, PGIMER Chandigarh	meenusingh4@gmail.com	0172-2755306 / 9914208306, 9814117152
21	Dr RajeshwarDayal	Prof &HOD-pediatrics, SN Medical College Agra	r_dayal123@rediffmail.com	9837022899
22	Dr KiranRade	Consultant Epidemiologist, Central TB Division	radek@rntcp.org	9810104609
23	Dr Piyush Gupta	Editor in chief, Indian Pediatrics	prof.piyush.gupta@gmail.com	9811597172
24	Dr AnandVasudev	Executive Officer, IAP	asvasudev@yahoo.com	011-22779484 / 09811074973
25	Dr. RohitSarin	DTCD.MD.FNCCP Vice chairman Tuberculosis Association of India	drsarin@yahoo.com drsarin_tai@yahoo.com	011-26517827 / 011-26854922 Fax no:-011-26568227
26	Dr. RupakSingla	MBBS, MD, DNB Head, Deptt. Of TB & chest Diseases	drrupaksingla@yahoo.com	011-26517826/30 Fax no:-011-26517834
27	Dr. Tariq Wali	CST Dvsn , NACO	drstwali@gmail.com	9720192030