Updated National Guidelines for Pediatric Tuberculosis in India, 2012†

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1. INTRODUCTION

Pediatric tuberculosis (i.e., Tuberculosis (TB) among the population aged less than 14 years) has traditionally received a lower priority than adult TB in National TB programmes because of its considered non-infectious, is difficult to diagnose, cases have been thought to be few and it was wrongly assumed that effective control of adult TB and use of BCG by itself could prevent childhood TB. Contrary to traditional National TB programmes, pediatric tuberculosis (*i.e*., TB among the population aged less than 14 years) has always been accorded high priority by Revised National Tuberculosis Control Programme (RNTCP) since the inception of the programme in our country.

In India, there are about ~400 million children who constitute about 34% of the total population [1]. The extent of childhood TB in India is unknown due to diagnostic difficulties; it is estimated to be 10.2% of the total adult incidence [2]. The maximum risk of a child getting TB is between 1-4 years when there is an increased risk of progression from infection to disease. Globally, about 1 million cases of pediatric TB are estimated to occur every year accounting for 10-15% of all TB [3]; with more than 100,000 estimated deaths every year, it is one of the top 10 causes of childhood mortality. Though MDR-TB and XDR-TB is documented among pediatric age group, there are no estimates of overall burden, chiefly because of diagnostic difficulties and exclusion of children in most of the drug resistance surveys.

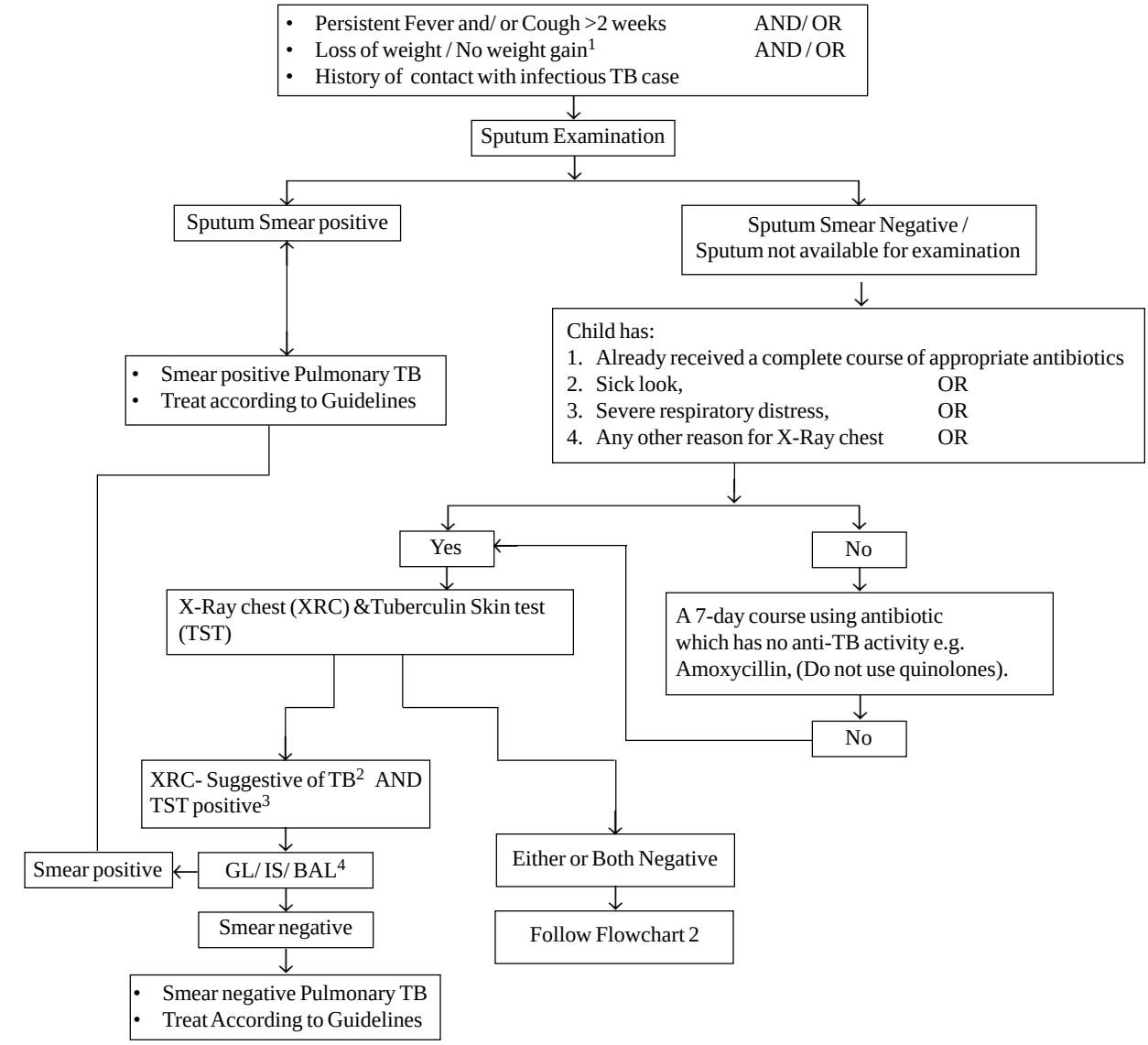
The proportion of pediatric TB cases registered under RNTCP has shown an increasing trend, from 5.6% (59846 cases) in 2005 to 7% (84064 cases) in 2011 [4]. RNTCP in association with Indian Academy of Pediatrics (IAP) has described criteria for suspecting TB among children; has separate algorithms for diagnosing pulmonary TB and peripheral TB lymphadenitis and a strategy for treatment and monitoring patients who are on treatment. In brief, TB diagnosis is based on clinical features, smear examination of sputum where this is available, positive family history, tuberculin skin testing, chest radiography and histopathological examination as appropriate. As in adults, children with TB are classified, categorised, registered and treated with intermittent short-course chemotherapy (thrice-weekly therapy from treatment initiation to completion), given under direct observation of a treatment provider (DOT provider) and the disease status is monitored during the course of treatment. Based on their pre- treatment weight, children are assigned to one of pre-treatment weight bands and are treated with good quality anti-TB drugs through ''ready-to-use'' patient wise boxes containing the patients' complete course of anti-TB drugs are made available to every registered TB patient according to programme guidelines. India was the first country to introduce pediatric patient-wise boxes.

2. NATIONAL CONSULTATION ON DIAGNOSIS AND MANAGEMENT OF CHILDHOOD TUBERCULOSIS [5]

In order to reconcile between Global and National guidelines, to review the evidence base and update the RNTCP guidelines in consensus with Indian academy of paediatrics, a National consultation was organized in January 2012. The consultation has come up with wider recommendations that have been incorporated in the programme.

2.1 *Diagnosis of pediatric TB:* A new diagnostic algorithm is developed for pulmonary TB, the commonest type of extra pulmonary TB (Lymph node TB) and for other types of extra-pulmonary TB. The diagnostic algorithms for the diagnosis of pulmonary TB and Lymph node tuberculosis are provided in ***Fig.* 1.** The salient recommendations are:

(*a*) All efforts should be made to demonstrate



[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 highly suggestive of TB are Hilar/paratracheal lymphadenitis with or without parenchymal lesion, miliary TB, fibro-cavitatory 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.
All efforts including Gastric lavage (GL)/ Induced sputum (IS) or Bronchoalveolar lavage (BAL) should be made to look for Acid fast bacilli (AFB) or for M tb rapid culture or Gene Xpert® where ever facilities are available.

FIG.1*a* *Diagnostic algorithm for pediatric pulmonary tuberculosis*

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.

(*b*) A positive Tuberculin skin test/Mantoux test was

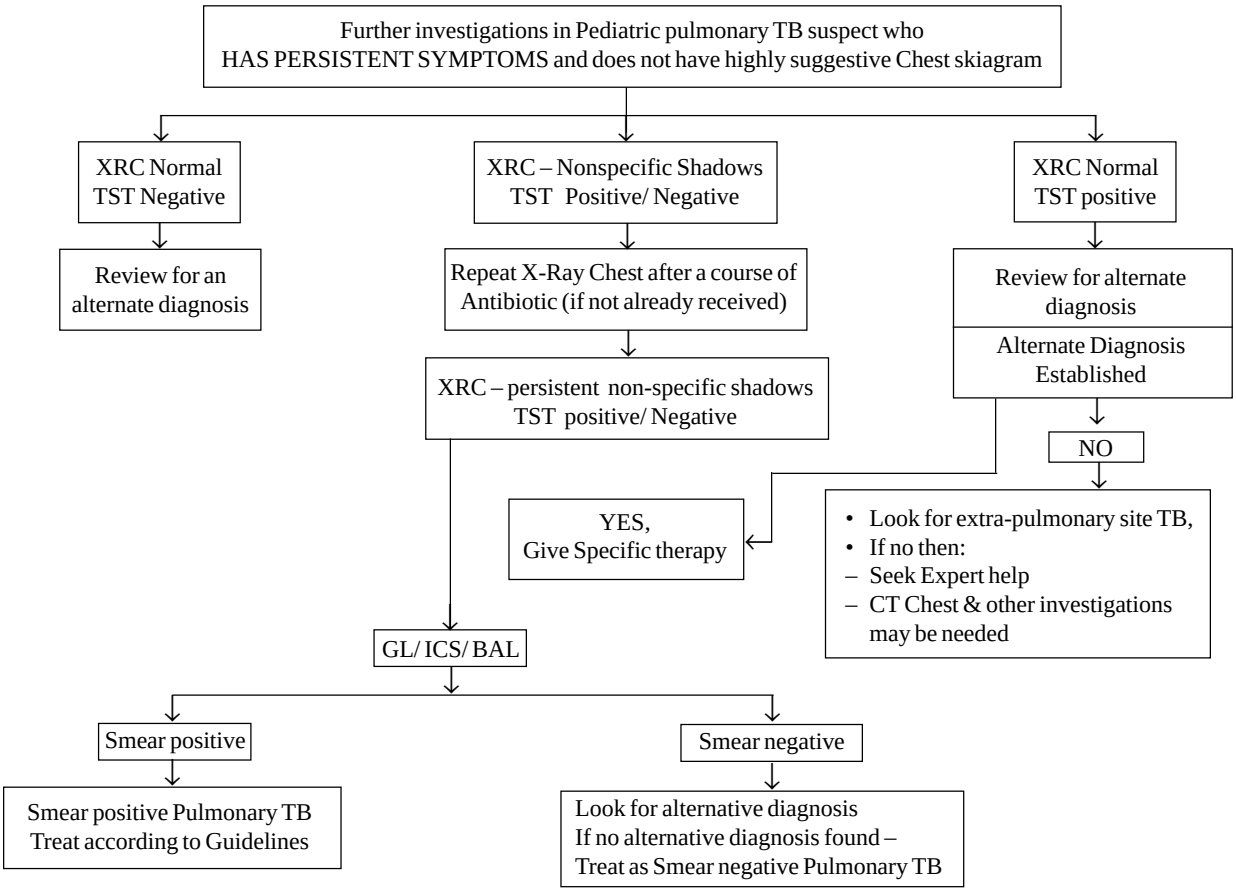


FIG.1*b* *Diagnostic algorithm for pediatric pulmonary tuberculosis.*

defined as an induration of 10 mm or more, measured 48-72 hours after Intradermal injection with Tuberculin 2 TU (RT 23 or equivalent). In HIV cases the cut off is reduced to 5 mm or more of induration.

(*c*) 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.

(*d*) There is no role of IGRAs in clinical practice for the diagnosis of TB.

(*e*) Loss of weight – often used as a clinical marker for the disease has been objectively defined as a loss of more than 5% of the highest weight recorded in the past three months.

2.2 *Intermittent versus Daily regimen:* The intermittent therapy will remain the mainstay of treating pediatric patients. However, among seriously 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. Such, select group of seriously ill admitted patients can be given daily supervised 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 following are the daily doses (mg per kg of body weight per day) Rifampicin 10-12 mg/kg (max 600 mg/day), Isoniazid 10 mg/kg (max 300 mg/day), Ethambutol 20-25 mg/kg (max 1500 mg/day), PZA 30-35 mg/kg (max 2000 mg/day) and Streptomycin 15 mg/kg (max 1g/day).

2.3 The following newer *Case definitions* for pediatric TB patients 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) evidence of 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).

For programmatic 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.

2.4 *Drug dosages:*

(*a*) To meet the pediatric fraternity concerns about under dosing and also in view of the latest WHO guidance, the drug dosages have been rationalized for childhood cases. There shall be six weight bands (6-8,9-12,13-16,17-20,21-24,and 25-30 kg) and the existing pediatric PWBs are to be used in different combinations to meet these expectations. In future, three generic patient wise boxes (instead of the existing two) will be used in combination to treat patients in these six weight bands. It would take at-least 2 years for supply of these new products under RNTCP.

(*b*) To ensure that every child gets correct dosages, weighing of the patient in minimal clothing (as appropriate) using accurate weighing scales is essential.

(*c*) It was also agreed that, all pediatric TB patients should be shifted to next weight band if a child gains a kilogram or more, above the upper limit of the existing weight band.

2.5 *Drug formulations:* Since, the number of tablets is too many to consume and younger patients have difficulty in swallowing tablets the *DOT centers 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 programme will continue to explore the possibility of using quality fixed dose combinations and dispersible tablets in future.

2.6 *Treatment regimens:* There will be only two treatment categories – one for treating 'new' cases and another for treating 'previously treated cases.' **(*Table* I)** Three drug category III regime has been since withdrawn in view of high INH resistance (>5%) in our community.

2.7 *TB Meningitis:* In the management of TB Meningitis, the group recommended 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 avoid problems 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 to replace streptomycin in the treatment of new cases of childhood TB, streptomycin continues to be recommended as the additional fifth drug in the retreatment regime.

2.8 *Extending intensive and continuation phase:*

(*a*) Children who show inadequate or no response (on smear or clinico-radiological basis) at 8 weeks of intensive phase should be given benefit of extension of IP for one more month.

(*b*) 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/ pediatrician.

2.9 *TB preventive therapy:* The currently recommended dose of INH for chemoprophylaxis is 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, TST 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 (>=5 mm 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.

TABLE I 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 have relapse, 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 should be preferred 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.

3. WAY FORWARD

These consensus National Guidelines on pediatric tuberculosis was jointly developed in consultation with Indian Academy of Pediatric and TB experts from various premier institutions in India. Keeping the interests of the Nation at large, it is urged that all the clinicians, teachers, academicians, researchers or any other person dealing with pediatric tuberculosis with in the Government or Private or non-governmental sector should adopt these guidelines for the diagnosis and treatment of pediatric tuberculosis in India.

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