Child India

March 2021

Monthly e-Newsletter of Indian Academy of Pediatrics

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Editor's Note

Dear colleagues,

The March issue of Child India is dedicated to Tuberculosis (TB) as each year, we commemorate World Tuberculosis (TB) Day on March 24 to raise public awareness about the devastating health, social and economic consequences of TB, and to step up efforts to end the global TB epidemic. The date marks the day in 1882 when Dr Robert Koch announced that he had discovered the bacterium that causes TB, which opened the way towards diagnosing and curing this disease.

TB remains one of the world's deadliest infectious killers. Each day, nearly 4000 lose their lives to TB and close to 28,000 people fall ill with this preventable and curable disease. Global efforts to combat TB have saved an estimated 63 million lives since the year 2000. With a quarter of the global burden of tuberculosis (TB) occurring in India, children in this country are at high risk of tuberculous infection and TB disease. The National Tuberculosis Elimination Program (NTEP) is the Public Health initiative of the Government of India that organizes our country's anti-Tuberculosis efforts. It functions as a flagship component of the National Health Mission (NHM) and provides technical and managerial leadership to anti-tuberculosis activities. As per the National Strategic Plan 2012–17, the program has a vision of achieving a "TB free India", and aims to provide Universal Access to TB control services.

The theme of World TB Day 2021 - 'The Clock is Ticking' –conveys the sense that the world is running out of time to act on the commitments to end TB made by global leaders. This is especially critical in the context of the COVID-19 pandemic that has put End TB progress at risk, and to ensure equitable access to prevention and care in line with WHO's drive towards achieving Universal Health Coverage.

IAP President 2021, Dr Piyush Gupta, our HSG Dr Basavaraja and all of us at Child India are thankful to the contributors to this issue on Pediatric Tuberculosis.

Regards and wishes,

Dr Jeeson C Unni
Editor-in-Chief

President's Address

Dear friends,

The excellent feedback regarding the academic content of the first two issues of Child India for this year have been overwhelmingly positive and I thank all my dear IAP members for the encouragement and support to this monthly e newsletter of IAP.

This month we celebrate 2 issues that concern children of our country.

March 21st is World Down Syndrome Day and I am sure all of you are gearing up with programs that work towards the empowerment of these lovely children. March 20th (Saturday) 6.00 to 7.30 pm we request you all to log on to a program for all of us and the public with participation of parents of children with Down Syndrome, children with Down syndrome and Down syndrome support groups.

March 22nd (Monday) - 7.30-9.30pm we will be airing a program for doctors with participation of our faculty and Dr Surekha Ramachandran, President, Down Syndrome Federation of India (former President, Down Syndrome International) with the theme ' Justice delayed is Justice denied'.

Both programs will be available on dIAP and are organised by the IAP Neuro-development Chapter.

March 24th, we celebrate World TB Day with the theme - The clock is ticking; - and we as a body need to work up a movement to support our End TB programs. This issue has articles on pediatric tuberculosis for postgraduates and practicing pediatricians so that a clear understanding of the ground reality facing pediatric TB care is created among our members.

The ECD program will get finalised after the consultative meeting this month and will be rolled out soon. Thank you for your participation in the ECD KAP study.

WIshing you all the very best,

Warm regards,

Piyush Gupta
National President, IAP 2021

Secretary's Message

Dear All,

"The best way to find yourself is to lose yourself in the service of Others."
— Mahatma Gandhi

Greetings! It has been an eventful month at the IAP Child India March 2021.

We had a very successful Administrative Meeting via Video Conferencing with the IAP Finance Committee on 2nd March 2021. My heartfelt thanks to everyone involved for participating in this meeting.

We have had many other committees that met this month like The IAP CRC Committee Meeting on 3rd March 2021, IAP SOP Committee Meeting which was held on 8th March 2021, IAP Constitutional Reforms Committee (CRC) Meeting held on 10th MArch 2021, We also had the Periodic Review Meeting of CIAP staff on 12th March 2021

We had the National ToT Via Video Conferencing on CADE (Childhood Allergic Disease Education) module National ToT on 16th & 17th March 2021. We also had the NTEP Workshop that was very well conducted along with these Workshops that were held on 7th March 2021 by Jalandhar / Punjab, the Dakshin Kannada / Karnataka held it on 13th March 2021, the Bangalore / Karnataka on 14th March 2021, on 14th March 2021 by Kottayam / on 14th March 2021 by Amritsar / Punjab, on 14th March 2021 by Ludhiana / Punjab.

I also would like to mention about the Zonal ToTs which were handled excellently were the South Zone COWIN ToT being held on 5th & 6th MArch 2021, the North Zone COWIN ToT on 8th & 9th March 2021 & West Zone COWIN ToT on 18th & 19th March 2021. Along with the Upcoming Local ToT Details with 24x7 MODULE TOTs which are being held by Chennai/ CTKK/ TamilNadu on 14th March 2021, the Salem/ Ramanathapuram/ TamilNadu on 21st March 2021, the Kanyakumari/ Kanchipuram/ TamilNadu on 28th March 2021.

The DERMA MODULE TOTs also were held by the Lucknow/ Meerut/ Uttar Pradesh State Branch on 16th March 2021, the Patna/ Purnia/ Bihar being held on 18th March 2021, the Gurgaon/ Kurukshetra/ Haryana State Branch on 21st March 2021, Pune/ Parbhani/ Maharashtra on 23rd March 2021, the North Delhi/ East Delhi/ Delhi State branch is held

Secretary's Message

on 25th March 2021, as well as the Jaipur/ Pali/ Rajasthan branch held on 27th March 2021.

I am very happy to mention that We also have the NEP-U MODULE TOTs on 16th March 2021 at Khurda/ Keonjhar/ Sundergarh/ Odisha and on 17th March 2021 at Khurda/ Keonjhar/ Sundergarh/ Odisha.

It gives me immense pleasure to inform you all that the IAP Kalaburgi, Karnataka State Branch celebrated the International Women's Day on 8th March 2021, and we look forward to having more such activities in future.

The National Project Meetings / Consultative Meet that were held this month were the IAP-WHO-UNICEF Position Paper was held on ECD 4th March 2021, Project meeting(s) on Early Childhood Development at Delhi on 21st-23rd March 2021, Inaugural Function of "IAP-WHO-UNICEF NC-ECD" and the National Consultative Meeting on Digital Wellness and Screen Time on 26th March 2021.

Finally sharing the Updates on the NRP Projects of the MOU between Indian Academy of Pediatrics and Johnson & Johnson (IAP NRP FGM Program) for the period of 3 years signed on 1st March 2021.

The Courses conducted/Upcoming in March 2021 are the District ToT of NRP FGM being held on 21st March 2021, the Basic NRP Courses conducted were 7 this month, Basic NRP Courses that are upcoming are 8 of them and the Advance NRP FGM Courses that are Upcoming are 2.

Overall, the month of March has been very fruitful and focused on academic growth for their members and we look forward to having more such activities in the coming months.

Jai IAP!! Jai Hind!!

Sincere Regards,

Dr G V Basavaraja
Hon. Secretary General 2020 & 21

World Down Syndrome Day (WDSD)

SHAJI THOMAS JOHN

United Nations General assembly in December 2011, declared 21st March as World Down Syndrome Day. So, with effect from 2012 every year, March 21st is observed as World Down Syndrome Day. The day has been decided upon because it is the 21st day of the third month; representing the trisomy of 21st Chromosome. This is a day for celebrations for people with Down syndrome all over the world.

Down syndrome (DS) is one of the most common genetic causes of mild to moderate intellectual disability. Its incidence in live births is approximately 1 in 733 to 1 in 1000; Non disjunction is the most common cytogenetic profile, followed by translocation and mosaicism. Individuals with Down syndrome often experience delay in achieving various developmental milestones. Hence proper counselling is important to guide and support the parents and motivate them to start early interventional programmes which have been proven to have a better long-term outcome. Regular screening and follow up especially for CHD and thyroid status should be emphasized as there is high incidence of both.

Antenatal diagnosis is possible and should be offered to all pregnant mothers. They are of two types: screening tests and diagnostic tests. Initially non-invasive screening should be offered to determine the probability of having a baby with DS, as it carries no risk to the mother or fetus. In the antenatal diagnostic screening tests, we have the Dual, Triple and Quadruple marker tests. The probability of having a baby with DS is calculated by combining various factors including maternal age, results of the ultrasound findings and serum markers. Now we also have the non-invasive cell free DNA test done from maternal blood, that can detect about 99 % of pregnancies with DS. If the screening tests show a high probability, diagnostic tests should be offered, but they are invasive and carry a risk of miscarriage (0.5%-1%).

The quality of life of people with DS have improved very much over the years; with the concept of "inclusive health" which stresses on a regular health checkup and timely intervention for medical issues as well as other therapeutic programmes, as is provided to any other child. Inclusive education and acceptance in an inclusive society have revolutionized the life and outlook of these people. They are now accepted in a normal school; are highly trainable and can stand on their own feet and live independently with a vocation of their choice.

Let's not just observe the day, let us celebrate with persons with Down syndrome.

Challenges in Pediatric Tuberculosis Care in India

Prof Subramanya NK, Bangalore
Dr Anu Rekha
Senior Assistant Professor, Dept. of Pediatrics
Govt. Mohan Kumaramangalam Medical College
Salem, Tamilnadu

Tuberculosis (TB) is one of the top ten causes of death among children worldwide till today (1).India is a high burden country.It accounts for 21% of the global burden and 13% of the overall TB burden in the country (2). Global TB targets has been set through Sustainable Developmental Goals 3.3 and it has aimed at ending tuberculosis by 2035 and by World Health Organization`s End TB strategy(3,4). Ending TB is not just a public health problem, but a developmental challenge and opportunities and it is not a "one size fits all". So, India has set a target of elimination of tuberculosis by 2025 through National Strategic Plan 2017-2025. Revised National tuberculosis control programme was renamed as National Tuberculosis Elimination Programme (NTEP) in 2020 (5).Delay in TB diagnosis and treatment initiation lead to poor outcome in children (6-9). Public health interventions designed for adult tuberculosis are not translatable to children (10). National Tuberculosis Elimination Program (NTEP) and Indian of Academy of Pediatrics have partnered to develop updated guidelines and training program for management of childhood TB in ourcountry.

This article focuses on challenges in pediatric TB because of varied symptomatology, difficulty in diagnosis of cases as well a latent TB cases, treatment, notification,and prevention.

Spectrum of disease:

In the pediatric intrathoracic TB, primary infection before 2 years of age often progresses to disease within the first 12 months (11). The risk of disease progression decreases during childhood, is least at 5–10 years of age, and increases again during adolescence (12,13). Disseminated disease and TB meningitis are usually found in very young children (age<3 years) and/ or Hu man immunodeficiency Virus(HIV)infected children (14). Mortality has a strong correlation with socioeconomic status, underlying nutritional status and immunosuppression (15,16).Varying spectrum of disease and the associated problems are the major concerns in our country.

Diagnostic challenges Challenges related to Symptomatology

Early identification of presumptive TB cases, at the first point of care be it private or public sectors is essential. TB symptoms are overlapping with other common childhood infections and are non- specific. It makes the clinical diagnosis of TB challenging in children (17). Non specificity of symptoms of extra pulmonary TB like Central nervous system TB, Abdominal TB, pleural effusion also adds to the problem.

Patient related challenges are due to late reporting to health facility which may be multi factorial (18). Underdiagnosis is often the rule at the primary care level(19).

Challenges related to Laboratory diagnosis

Major challenge of childhood TB is establishing an accurate diagnosis of MycobacteriumTuberculosis Bacilli(MTB).The national strategy for ending TB is universal Drug sensitivity testing (UDST) by culture and or molecular methods for all TB cases. Collecting an adequate sample for microbiological diagnosis presents a significant challenge, particularly for small children who cannot produce a good sputum specimen (20).Inducing sputum after hypertonic saline nebulization and the early-morning gastric aspiration or lavage are the common methods used

for collecting the respiratory samples(21).Non-sputum specimens are also important in diagnosis of TB in children as there is significantly high prevalence of Extra pulmonary TB.These procedures involve hospitalization, trained personnel, transportation delay and attention to infection control are the challenges.

Routine chest imaging must be done as initial screening test as testing of respiratory specimens from radiologically positive cases improves the yield of NAAT (22).

The diagnostic challenges and limitation of the available laboratory tests are tabulated in Table 1 & 2.

Table 1

Tests	Challenges	Limitation
Smear Microscopy	Pauci bacillary nature of cases Less than 15% are smear positive[23] Need for experienced personnel	Needs 2 specimens Non sputum specimens –not suitable
Cartridge Based Nucleic Acid AmplificationTest (CBNAAT)	Expensive Lack of access for private practioners Less number of quality control lab	Negative test cannot rule out TB Needs 131 bacilli for detection-pauci bacillary needs better test Less sensitive for ascetic and pleural fluid
Mantoux testing	Positive test indicates infection not disease False positive and false negative reading Needs 48-72 hours for interpretation Need for trained personnel	Non availability in recent times
Interferon Gamma Release Assay (IGRA)	Positive test indicates infection not disease Expensive, technically complex	reduced sensitivity in younger age (< 2years) & in immune compromised[24]
Copenhagen TB (C Tb) test([25])	New method Need for training of health care workers	Not available in India
Line Probe Assay(LPA)	Can be done only in smear positive samples or after positive liquid culture Not easily accessible	Availability only at reference laboratories
Mycobacterial Growth Indicator Tube (MGIT)/ Liquid Culture	Turnaround time -42 days[26] needs good quality specimens	High contamination rate Availability at reference laboratories

Table 2

Tests	Challenges	Limitations
Chest X Ray (CXR)	Needs a Good quality CXR Technical issues Inter/intra observer variation Artefacts	Errors in interpretation –over and under diagnosis Non specific patterns are common
Ultra Sonogram(USG)	Less sensitive in immunocompetent patients	Lack of facilities for USG guided aspiration of lymph nodes
Contrast Enhanced Computerised Tomogram (CECT)	Need for experienced radiologist Non availability at Taluk hospitals	Detects all non-specific mediastinal lymphnodes[27] High radiation exposure
Bronchoscopy	Not available at even at tertiary care hospitals	Invasive procedure

Challenges in TB management

Providing sustained, equitable access to high quality TB treatment, care and support services to all children with TB remains the challenge. Lack of uniform treatment practices and notification in private sectors, non-availability of long term outcome of treatment, high lost to follow up and death among treatment initiated children, not properly addressing of co- morbidities like malnutrition, pneumonia and HIV are the major challenges.

Challenges at Private sectors

Substantial diagnostic delays occur, and non-dependence on microbiological diagnosis and irrational and unsupported treatment of variable quality are the challenges (28). Patient treated by private providers are less commonly notified to the NTEP. Lack of awareness of private practioners upon the availability of the diagnostic facilities remains the major concern. Up take of NTEPand Private public mix schemes remains very low.

Drug Resistant TB (DRTB)

Only a limited data on the optimal treatment for children with MDR-TB (29). Diagnosis remains the challenge which requires good quality specimen. Treatment of MDR-TB is difficult as well, requiring the use of second-line medications in regimens much longer (30). Tolerability is less because of toxic second line drugs and injectable formulations. Aggressive treatment of malnutrition and HIV is needed (31). More second line drugs need trial and validation in children.

Human Immunodeficiency Virus (HIV) and TB

HIV is notorious to cause atypical pulmonary as well as vivid extra pulmonary manifestations of TB(14).HIV hastens the progression of TB infection to active disease and drives to MDRTB. TB increases the opportunistic infections in HIV and increases the mortality.Diagnosis of HIV/TB co-infection in children is still challenging. Paediatric TB and HIV have overlapping clinical manifestations, which could lead to missed or late diagnosis(32). High pill load, Adverse drug effects including Immune Reconstitution Inflammatory Syndrome(IRIS), psychosocial problems are also to be addressed.

Latent TB infection (LTBI)

In India, there are no estimates regarding the prevalence of LTBI in the general population. If untreated, 40% of LTBI children under 1 year of age develop active disease, whereas it is 24% in children of 1–10 years and 16% in those between 11 and 15 years (33).The available data on testing for LTBI as well as treatment outcomes in India are lacking (34).Implementation is fraught with challenges, including difficulty diagnosing latent TB in a highly BCG-vaccinated population, ruling out incipient active disease, and the lack of procedures for documentation and follow-up of contact screening and chemoprophylaxis in national programs.

Challenges in special circumstances COVID 19 Pandemic and TB

Longer durations of infectiousness, increased household exposure to TB infection, worsening treatment outcomes and higher levels of poverty are the impact of COVID in TB.TB case notifications fell by more than 50% during lockdown.Negative impacts include the reallocation of human, financial resources and NAAT machines from TB to the COVID-19 response.TB preventive therapy has also been affected (35)

Adolescent and TB

Adult type TB is more common including DRTB. Stigma, discrimination, identifying the Co infection like HIV are the challenges(36).Adolescents have been ignored using current age wise classification which results in sparse data. There is an urgent need for more studies to better understand tuberculosis epidemiology, prevention, and management among adolescents (37).

Neonates born to mothers with TB

Nonspecific symptoms and signs and overlapping clinical features poses problem in diagnosis and initiating treatment(38) in neonates which has substantial mortality.

Challenges in preventive aspects

Isoniazid(INH) preventive therapy

Treatment of all LTBI children is not practically feasible in high burden country like India. Longer

duration of monotherapy may add to the problem of drug resistance; shorter duration of therapy is not yet validated in children.There are no clear consensus on the treatment of LTBI children 6 to 18 years of age

BacilleCalmitte Guerin (BCG) vaccine

BCG vaccine do not offer protectionagainst the development of adult pulmonary TB (39). However,BCG vaccine has been shown to be protective against disseminatedforms of TB in young children, with a protective estimate of 73% (range, 67%–79%) against TB meningitisand 77% (range, 58%–87%) against miliary disease (40).The development of new TB vaccines has been identified as a priority by WHO Initiative for Vaccine Research. There is a need for development of vaccine which would prevent adult tuberculosis and in containing the drug resistant forms.

Conclusion

Systematic symptom analysis, maximal attempt for microbiological diagnosis of MTB, collecting appropriate specimens, treatment adherence, reduction of adult TB are needed thereby can help in ending TB. Isoniazid prophylaxis for latent TB infection should be rigorously done. Co-ordinated public private partnership and repeated training of health care workers, good effective vaccine against preventing adult TB will help us achieving the TB elimination by 2025.

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INDIA TB REPORT 2020
Some facts about TB in India
Pediatric TB data

Compiled for Child India by Dr Jeeson C Unni

India is the highest TB burden country in the world having an estimated incidence of 26.9 lakh cases in 2019 (WHO)

Surveillance

2019 marks another milestone year for TB surveillance effort in India, with a record high notification of 24 Lakh cases; an increase of over 12% as compared to 2018. Of the 24 lakh TB cases 90% (N=21.6 lakhs) were incident TB cases (New and Relapse/ Recurrent). This translates to an incident notification rate of approximately 159 cases/lakh against the estimated incidence rate of 199 cases lakh population; thus, closing the gap between the estimated and notified incident cases to just 40 Cases per lakh population, or an approximate of 5.4 lakh missing cases across India.

Crucial contribution that the private sector can make to the national TB programme by mandatory TB notification and providing quality TB care, he added that with both collaborative and regulatory steps, the country has notified 6,64,584 TB patients in 2019 in the private sector which amounts to a 22% increase in TB notification as compared to the year 2018

2020 for the first time Central TB Division (CTD) introduced a quarterly ranking on TB elimination efforts by all the states and UTs. Treatment linkage of drug resistant TB patients, HIV testing of TB patients, Nutritional assistance to TB patients in the form of NIKSHAY Poshan Yojana (DBT), Universal Drug Susceptibility Testing (UDST) coverage among notified TB patients, TB Preventive Therapy (TPT) coverage and Financial expenditure are included in the assessment criteria

Over 700 TB Forums have been established at the State/UT and District level involving all stakeholders. These TB Forums will provide a multi-sectoral and community-led response to addressing the challenge of TB

ORGANOGRAM OF National TB Elimination Programme

Ministry of Health & Family Welfare
↓
Central TB Division
↓
National committees National institutes
↓
State TB Cells (36 states/UTIs)
STDC ↓ .
District TB Centre (767 Districts)
↓
TB Unit (One per 1.5 – 2.5 lakh population)
↓
Designated Microscopy Centre (One per 1 lakh population)
↓
Peripheral Health Institutes

Of the reported 21.02 lakh cases in 2018, reported treatment success was 80% (N=16.79 lakhs), Death rate was 4%, Lost to follow-up after treatment initiation was 4%, Treatment failure and regimen change was together about 2%, and an overall of 7% cases was not evaluated after notification.

Active Case Finding

Active Case Finding (ACF) to implement systematic screening for tuberculosis among selected high-risk groups. The burden of undetected tuberculosis is large in many settings, especially in high-risk groups which are identified under the country's National Strategic Plan (2017-25).

Treatment Services

National TB Elimination Program (NTEP) envisages to reach every TB patient for free provision of diagnosis and evidence-based treatment. During 2019, out of the notified TB patients, 94% of TB patients were initiated on TB treatment. During 2019, 58% of total notified TB patients were offered Universal Drug Susceptibility Test (UDST)

Major initiatives and policy decisions for drug resistant TB

Introduction of injection free regimen for MDR RR TB patients in 2019 National TB Elimination Programme has envisaged to have injection free regimen for all TB patients (including Drug Resistant TB patients). After implementation of all oral H mono/poly DR TB regimen, all oral longer regimen was introduced during 2019. As per the recommendations of National Technical Expert Group (NTEG) on Treatment of TB, all Multi Drug Resistant /Rif Resistant (MDR RR) TB patients those who are not eligible for Shorter MDR TB regimen, an all-oral longer regimen have to be prescribed as per the Guidelines for Programmatic Management of Drug Resistant Tuberculosis (PMDT) in India-2019 (Pre-final text). Appropriate modification in the drug composition of all oral regimen, based on the DST result, is being carried out to ensure appropriate regimen is prescribed to the MDR RR TB patient. After introduction of all oral longer regimen, the sole regimen which contains injectables is Shorter MDR TB regimen and rest all are injection free regimen even for XDR TB patients.

Expansion of Delamanid use in 6 to 17 yrs of age group

After successful implementation in initially selected 7 States/UT's (Chandigarh, Kerala, Karnataka, Lakshadweep, Orissa, Punjab & Rajasthan) for adult MDR RR TB patients, the access has been expanded to the rest of the states in the country especially for the eligible patients in 6 to 17 years of the age-group. In these states, Delamanid is indicated for use as part of an appropriate combination regimen for pulmonary MDR-TB in adult and adolescent (6-17 years) patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Childhood Tuberculosis

Paediatric Tuberculosis (TB) is one of the ten major causes of mortality globally among children (population age less than 15 years). Globally, in 2018, an estimated 11 lakh children became ill with TB and 2,50,000 children died of TB (including children with HIV associated TB). In India, about 3,42,000 incident cases of paediatric TB are estimated to occur every year accounting for 31% of the global burden and 13% of the overall TB burden in the country.

Guidelines on Paediatric TB management in India have been updated with the support of the Indian Academy of Paediatrics and other stakeholders. Recently, the Central TB Division has signed a Memorandum of understanding with Indian Academy of Paediatrics (IAP) in

October 2019 to build capacity in Public and Private sector through 300 district level training and to notify TB cases and offer public health action for TB case management in children less than six years of age.

The proportion of paediatric TB cases registered under National TB Elimination Programme has been constantly increasing in the past five years. In 2019, a total of 1,51,286 paediatric TB patients (only 44% of estimated) were notified in India, which included new and relapse paediatric TB patients.

Trend of Paediatric TB cases out of all New TB cases under National TB Elimination Programme

Contact Tracing and Chemoprophylaxis

Under the programme, contact screening is undertaken as a regular activity to augment intensified case finding efforts across the country. All household members who are contacts of the family member suffering from active TB disease are screened for TB and the children less than 6 years of age among those are provided isoniazid (INH) chemoprophylaxis once active TB has been ruled out amongst them. Widespread implementation of this activity is being done with support from the general health system. Reverse contact tracing with the Paediatric index TB case is carried out to identify the source of infection.

Nearly 4 lakh household contacts <6 years were screened for TB as part of household contact investigation in 2019. Among the child household contacts nearly 4.2 lakhs contacts (78%) of TB cases aged less than 6 years were offered preventive therapy in 2019.

Treatment outcome of Paediatric TB patients notified in 2018 (Total)

Pediatric TB patients Notified - 128331

Microbiologically Confirmed Pediatric TB – 21186

Cure Rate - 14134 (67%)

Success Rate - 108280 (84%)

Death Rate - 1368 (1%)

Treatment Failure Rate - 602 (0%)

% Lost to follow up - 3625 (3%)

% Regimen Change - 455 (0%)

% Not evaluated - 14001 (11%)

Contact Tracing and Isoniazid Chemo-prophylaxis in Household Contacts < 6 years

Children in the household - 540013

Screened - 399357

Presumptive symptomatic cases identified – 15550

Presumptive symptomatic cases tested - 9412

TB Cases diagnosed - 4691

TB Cases Treated - 3419

Children Eligible for Isoniazid Chemoprophylaxis - 536594

Eligible children given Isoniazid Chemoprophylaxis - 417643 (78%)

Laboratory Diagnosis of Tuberculosis

Dr. V. Anil Kumar
Professor & Head, Microbiology
Amrita Institute of Medical Sciences, Kochi, Kerala

Dr. Swathy Thulasidharan
Second year Resident , Microbiology,
Amrita institute of Medical Sciences, Kochi, Kerala

The laboratory diagnosis of tuberculosis can be broadly divided into two – direct and indirect. Direct method includes microscopy, culture, antigen detection and molecular methods whereas indirect method includes tuberculin skin testing (TST), interferon gamma release assay and other methods like detection of volatile organic compounds and beta-lactamase.

Specimen collection and processing

In pulmonary TB two sputum samples are required- a spot sample collected on the same day under supervision and an early morning sample collected the next day (spot-early morning specimen). Two spot samples collected at least one hour apart can also be used (spot-spot specimen). The sample collected must be at least 2-5 ml and mucopurulent, without any blood. Do not collect samples for culture in formalin. Collect separate samples for histopathological examination. Samples collected have to be digested to liquefy thick pus cells and for homogenization, decontaminated to inhibit normal flora and concentrated to increase the yield (not required for extrapulmonary samples collected aseptically from sterile sites like CSF or those samples meant for molecular diagnosis). The commonly used methods for processing the samples are Modified Petroff's method where the sample is mixed with equal amounts of 4% sodium hydroxide, centrifuged and the sediment obtained is neutralised with phosphate buffer saline (recommended for solid culture) and the one using NALC (N-acetyl-L-cysteine) and 2% sodium hydroxide recommended for automated liquid cultures. The digestion of sputum with bleach before smear preparation has shown an increase in TB detection.

Direct Methods for Detection of TB

MICROSCOPY

Microscopy serves as the basis of detection of TB in developing countries like India. Sputum samples should be examined within 48 hours of collection and smears are prepared from the mucopurulent part of the sputum or from the sediment obtained after concentration. The regularly used methods for staining are Ziehl-Neelsen (ZN) technique employing carbol fuschin and fluorescent staining methods using auramine or rhodamine dyes. In ZN method, M. tuberculosis appears as long, slender, beaded, less uniformly stained pink coloured acid fast bacilli. A smear is reported as negative if no bacilli is seen after examining at least 100 oil immersion fields. In fluorescent staining the bacilli appear brilliant yellow against a dark background. Limit of detection is 10,000 bacilli/mL. Fluorescent microscopy is preferred as much larger area of smear can be examined rapidly. Microscopy cannot differentiate live bacilli from dead nor can it predict MDR TB or presence of non-tuberculous mycobacteria. A fluorescent

viability marker like flourescein diacetate (FDA) which only stains live, cultivable bacteria can be combined with smear microscopy for TB treatment monitoring. Automated microscopic technologies are now available which can robotically load stained slides and use high-resolution digital analysis to give results within minutes.

CULTURE

Culture is still considered the gold standard for diagnosis of TB offering several advantages like increased sensitivity, indication of viability and detection of drug susceptibility. Culture can be done the conventional way using egg based solid media like Lowenstein-Jensen (LJ) medium or it can be automated using agar based liquid cultures Middlebrook 7H10/11.

Conventional method for TB culture

LJ medium the most commonly used medium for TB culture is a selective medium developed by Lowenstein who incorporated congo red and malachite green to inhibit unwanted bacteria. It was later modified by Jensen into a glycerated egg based formulation that eliminated congo red and used a moderate concentration of malachite green. This prevented growth of the majority of contaminants and brought about the earliest possible growth of mycobacteria. The LJ medium is composed of potato starch, L-asparagine (sources of nitrogen and vitamins) mono-potassium phosphate, magnesium sulphate (enhance organism growth and act as buffers), malachite green (prevents the growth of contaminants), glycerol egg suspension (provide fatty acids and protein required for the metabolism of mycobacteria) and distilled water. The albumin present in egg coagulates and provides a solid surface for inoculation. Glycerol acts as a source of carbon and favours the growth of the human type tubercle bacillus while being unfavourable to the bovine type. MTB produces typical rough, tough and buff coloured colonies on LJ medium. The limit of detection is 100 bacilli/mL but the growth takes about 4-8 weeks.

Automated method for TB culture (MGIT 960)

Automated systems for TB culture include automatic liquid culture systems like BACTEC MGIT 960 and MB/BacT. The MGIT or mycobacterial growth indicator tube system is a fully automated system based on a non-radiometric detection method that measures the consumption of oxygen by fluorescence. The MGIT tube has a ruthenium pentahydrate oxygen sensor embedded in silicon at the bottom and contains 8 ml of modified Middlebrook 7H10/11 broth which fluoresces following the oxygen reduction induced by aerobically metabolizing bacteria in the medium. The medium is supplemented with OADC (oleic acid, albumin, dextrose and catalase) and PANTA antibiotic mixture (polymyxin B, amphotericin B, trimethoprim and azlocillin) prior to inoculation to promote mycobacterial growth and inhibit other organisms present in the specimen. A total of 960 tubes can be loaded into the MGIT 960 system which incubates the tubes at 37°C and monitor each hour for fluorescence development for 42 days or until a positive signal is developed. Growth usually occurs in about 9-16 days. Total duration of incubation is 6 weeks. The drawbacks include high rates of contamination, requirement of biosafety facilities and trained technicians.

Species identification of culture isolates can be done using conventional biochemical methods (niacin test, nitrate reduction, para-nitrobenzoic acid) or immunochromatographic tests using MPT64 antigen (specific antigen secreted during growth of MTBC).

ANTIGEN DETECTION

Lipoarabinomannan (LAM) which is an immunogenic glycolipid and a major virulence factor found in cell wall of mycobacteria can be detected using ELISA or dipstick method. But the test is not recommended for diagnosis of TB except in HIV patients.

MOLECULAR METHODS

Molecular methods can detect nucleic acid of both live and dead bacilli, take lesser time, are more sensitive especially in case of extrapulmonary samples and can detect genes coding for drug resistance. Current methods include cartridge-based nucleic acid amplification test (CBNAAT – Xpert and Truenat), line probe assay (LPA), loop mediated amplification (LAMP) and whole genome sequencing (WGS).

GeneXpert

Cepheid's GeneXpert is the CBNAAT system endorsed by WHO in December 2010 for the diagnosis of pulmonary, extrapulmonary and paediatric TB. CBNAAT is a semi-quantitative nested real-time PCR which can simultaneously detect MTB and resistance against rifampicin. The earlier version detected MTB using five overlapping, fluorescent, molecular probes (probes A–E) collectively complementary to entire 81 bp rpoB core region. M. tuberculosis identified when at least two of the five probes give positive signals with a cycle threshold (CT) of ≤38 cycles. The difference between the first (early CT) and the last (late CT) CT values is used to detect rifampicin resistance (>3.5 cycles - resistant, </= 3.5 cycles - sensitive and first probe CT >34.5 cycles and last probe CT of >38 cycles – indeterminate). The sputum is liquefied and inactivated after which 2 mL of the sample is transferred into a cartridge and loaded onto the GeneXpert machine. The turn-around time is an impressive 2 hours with analytical limit of 131 CFU/ mL and presence of NTM does not confound the result. But some disadvantages include lower sensitivity with smear-negative pulmonary samples and extra-pulmonary samples and false positive and false negative results in the prediction of rifampin resistance (RIF-R) in paucibacillary samples. Nevertheless, GeneXpert is the first point of care assay for TB and 23 million Xpert tests have been procured in 130 countries and have led to a 3- to 8-fold increase in testing for MDR TB worldwide. The sensitivity of a single Xpert MTB/RIF test in smear-negative culture-positive patients was 72.5% and this increased to 90.2% when three samples were tested. The specificity of Xpert MTB/RIF was 99%.

Xpert MTB/RIF Ultra assay (Ultra) is a next-generation assay for TB and RIF-R detection and is an advanced version of Xpert MTB/RIF assay. Ultra assay cartridge is redesigned to 50 µl volume capacity (older version had 25µl capacity PCR tube) and it uses four relatively long sloppy molecular beacon (SMB) namely rpo1, rpo2, rpo3, rpo4 and two additional probes a TaqMan probe targeting the M. tuberculosis multicopy IS6110 gene and a molecular beacon targeting multicopy IS1081 gene. There is a 10-fold increase in analytical sensitivity of Ultra for detection of M. tuberculosis H37Rv thereby identifying more cases of smear negative and culture-positive TB as well as more TB cases overall. For "trace call", one or both of the probes for the multi-copy targets are positive with Cts less than 37 cycles and no more than one rpoB probes have a Ct less than 40 cycles. MTB is reported as NOT detected if neither of the multi-copy target probes are positive and the sample processing control is positive with a Ct less than 35 cycles. If MTB is detected with a "trace call", then no interpretation can be made regarding rifampicin resistance and results are reported as MTB detected, trace, RIF indeterminate. Ultra also has improved ability to detect resistance in mixed samples. But this increased sensitivity may predispose to false-positive results due to

sample cross contamination and increased false-positive results in subjects with recent a history of TB. Other issues are failure to detect INH mono-resistance and differentiate between live and dead bacilli, and false RIF positive results and RIF resistance indeterminate results. When compared to Xpert MTB/RIF, in CSF sensitivity increased to 95% and in respiratory samples in children it increased to 71%. The sensitivity of Xpert MTB/RIF Ultra assay in smear-negative culture-positive patients was >90% and for smear-positive culture-positive patients >98%. The specificity of Xpert MTB/RIF Ultra assay is >98%.

	Xpert MTB/RIF	**Xpert MTB/RIF** Ultra
Diagnosis	MTB complex	MTB complex
Resistance	Detects rifampicin resistance	Detects rifampicin resistance
Molecular targets	Single target: rpoB core region	Multi copy target: rpoB core region Insertion elements: IS6110 & IS1081
Resistance detection	Real-time PCR; 5 probes for rpoB region.	Melting curve analysis; 4 probes for rpoB region.
Sample volume	2 ml	2 ml
PCR reaction volume	25 µl	50 µl
Assay duration	112 minutes	65-87 minutes
Limit of detection	131 cfu/ml	16 cfu/ml
Cost	Rs.2200	Rs.2200

Truenat MTB Plus

Another automated nucleic acid amplification test is Truenat MTB Plus which is a new chip-based, micro real-time polymerase chain reaction (PCR) test that detects tubercle bacilli in sputum samples in approximately one hour. When a positive test result is obtained an "add-on" chip Truenat MTB-RIF can be used to detect RIF-resistance, which takes another one hour. The test is done on the battery-powered Truelab system, which includes a sample preparation device which extracts and purifies DNA from sputum sample and a PCR analyser device with modules that can load one, two or four samples. As Truenat is a portable point of care assay it is a good choice for peripheral centres. The sensitivity for the Truenat MTB Plus is 80% and specificity is 95%. Truenat MTB-RIF has a sensitivity of 87.5 per cent and specificity of 99.5 per cent for detecting rifampicin resistance.

Line Probe Assay (LPA)

Line probe assays are a family of DNA strip-based tests that determine the drug resistance profile of a MTBC strain through the pattern of binding of amplicons (DNA amplification products) to probes targeting the most common resistance associated mutations to first- and second-line agents and to probes targeting the corresponding wild-type (WT) DNA sequence. It can be performed on smear positive sputum specimens or culture isolates after DNA extraction and PCR amplification.

GenoType MTBDRplus Version 2 targets specific mutations in the Rif-resistance determining region (RRDR) of the rpoB gene (from codon 505 to 533) to detect Rif resistance, and mutations in the inhA promoter (from -16 to -8 nucleotides upstream) and the katG (codon 315) regions to identify Isoniazide (INH) resistance. The second version of GenoType MTBDRsl includes the quinolone-resistance determining region (QRDR) of gyrA (from codon 85 to 96) and of gyrB (from codon 536 to 541) (16) genes for detection of resistance to fluoroquinolones and the rrs (nucleic acid position 1401, 1402 and 1484) and the eis promoter region (from -37 to -2 nucleotides upstream) for detection of resistance to second line drugs.

The turn-around time of LPA is 5-6 hours but the entire procedure generally takes about 3 days. It has good sensitivity and specificity but are complex and require skilled laboratory personnel as well as adequate facilities. Although

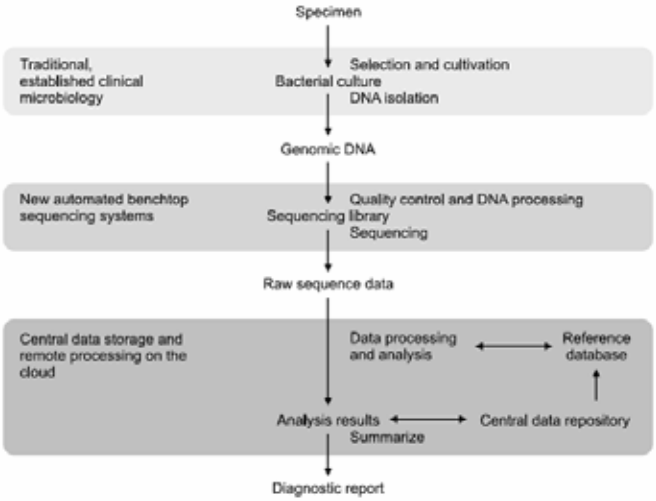
LPA can detect the mutations that are most frequently identified in resistant strains, some mutations that confer resistance are outside the regions covered by the test and therefore resistance cannot be completely excluded even in the presence of all WT probes. First Line-LPA showed a sensitivity and specificity for the detection of Rif resistance of 96.7% and 98.8%, respectively, and for the detection of INH resistance, a sensitivity and specificity of 90.2% and 99.2%, respectively. Second Line-LPA (GenoType MTBDRsl V1) showed a pooled sensitivity and specificity for the detection of fluoroquinolone resistance by direct testing of 86.2% and 98.6%, respectively, and a pooled sensitivity and specificity for the detection of second-line injectables drugs resistance of 87.0% and 99.5%, respectively.

Loop-mediated isothermal amplification (TB-LAMP)

TB-LAMP is a simple isothermal DNA amplification method which is rapid, cost-effective and uses 4 different primers specifically designed to recognise 6 distinct regions of the gyrB and 16srRNA genes. Amplification and detection of gene can be completed in a single step with a detection limit of 5-50 copies of purified DNA with results being ready within 35 minutes for a solid medium culture and 60 minutes for a liquid medium culture. The sensitivity for the TB-LAMP is 78% and specificity is 98%.

Whole Genome Sequencing

Whole genome sequencing involves sequencing the entire genome of MTB and help identify microevolution within MTB lineages as they are transmitted between hosts. It identifies single nucleotide polymorphisms (SNPs), which can be used to predict susceptibility to first-line and second line drugs and distinguish between different strains and lineages. There are two types of sequencers, the first generation sequencer and the second generation (widely known as the next-generation sequencer [NGS]). The first generation sequencer is relatively slow, but has a high throughput and low cost while the second generation has a lower throughput, higher cost and is able to sequence multiple genomes in less than a day. WGS is superior to Xpert MTB assay as it can detect various types of mutations better than the Xpert and can avoid false positives when a polymorphism in the rifampicin-resistance determining region (RRDR) of rpoB is detected. It can be done on direct clinical samples (both smear positive and negative) as well as culture isolates. Thus WGS can guide treatment, identify true multidrug resistant cases thereby avoiding unnecessary exposure to second line drugs and help identify mono-resistance avoiding discontinuation of all first line drugs. The drawback is that the test is very expensive, only a limited number of centres perform the test and it takes about 15 days for generating the report.



INDIRECT METHODS FOR DETECTION OF TB

Indirect methods include tuberculin skin testing, interferon-gamma release assay and detection of volatile organic compounds and beta lactamase.

The tuberculin skin testing

The tuberculin skin testing also known as Mantoux test is one of the few investigations dating from the 19th century that is still widely used as an important test for diagnosing tuberculosis. Though very commonly used, its interpretation always remains difficult and controversial as various factors like age, immunological status coexisting illness etc influence its outcome and interpretation. The test involves intradermal injection of purified protein derivative (PPD) of MTB in the forearm. A positive test is development of a 10 mm or more induration after 48-72 hours. But BCG vaccination can also produce a similar reaction at the TST site limiting its usefulness in vaccinated children and adults who are repeatedly tested.

Interferon-gamma assay

In interferon-gamma assay, T-cells sensitised with MTB and culture filtrate protein (CFP-10) release interferon-gamma which are detected based on enzyme-linked immunosorbent assay (ELISA). QuantiFERON-TB Gold Plus (QFT-Plus) is the latest generation of interferon gamma release assays (IGRAs) to receive approval from the U.S. FDA. It is an in-vitro assay which gives a positive result only with TB infected individuals and not by BCG-vaccinated or healthy unvaccinated individuals making it highly specific. The result is available within 24 hours and doesn't require a second visit by the patient. The drawbacks include inability to clearly distinguish latent TB from active TB, reduced sensitivity in immunocompromised patients, and lack of adequate positive predictive value for progression to active TB. Also the sample needs to be incubated 8-16 hours thereby requiring a portable incubator or faster transport facilities.

Summary

Test	Turnaround time
Solid culture	Up to 60 days
Liquid Culture	14- 42 days
Line Probe Assay first & second line	48 h
Smear AFB ,LED based fluorescent microscopy	1 day
Loop-mediated isothermal amplification (TB-LAMP)	60 min
Xpert MTB/RIF	112 min
Xpert MTB/RIF Ultra assay	65-87 min
Truenat MTB Plus	60 min
Whole Genome Sequencing	15 days

WHO Diagnostic algorithms

Algorithm 1 relies on molecular WHO-recommended rapid diagnostics (WRDs), as the initial diagnostic tests, and is appropriate for all settings, although the choice of which molecular WRD to use may differ in a setting with high MDR/RR-TB prevalence (e.g. a test that detects MTBC and RIF resistance may be needed) or with high HIV prevalence (e.g. a more sensitive test may be needed).

Algorithm 2 incorporates the most recent WHO recommendations for the use of the LF-LAM assay as an aid in the diagnosis of TB in PLHIV, and may be most relevant to settings with a high HIV prevalence. However, Algorithm 2 is applicable to any patient living with HIV who meets the testing criteria, regardless of the underlying prevalence of HIV in that setting.

Algorithm 3 and Algorithm 4 are for follow-up testing to detect drug resistance other than RIF resistance: Algorithm 3 is used when the purpose is to detect resistance to second-line drugs in patients with RIF resistance;

Algorithm 4 is used when the purpose is to detect resistance to INH in patients at risk of Hr-TB and with RIF susceptibility.

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NIKSHAY

NI-KSHAY-(Ni=End, Kshay=TB) is the web enabled patient management system for TB control under the National Tuberculosis Elimination Programme (NTEP). It is developed and maintained by the Central TB Division (CTD), Ministry of Health and Family Welfare, Government of India, in collaboration with the National Informatics Centre (NIC), and the World Health Organization Country office for India.

Nikshay is used by health functionaries at various levels across the country both in the public and private sector, to register cases under their care, order various types of tests from Labs across the country, record treatment details, monitor treatment adherence and to transfer cases between care providers. It also functions as the National TB Surveillance System and enables reporting of various surveillance data to the Government of India.

Report all cases via Niikshay Sampark – 1800 11 6666 or Nikshay web portal/mobile app

Submit hard copies to District TB Officer - Agents liaison between the private practitioner and the program

Nikshay Poshan Yojana

Parents ger Rs 500/mth throughout duration of treatment

Private provider incentive (to doctor reporting the case)

Rs 500 at notification

Rs 500 for reporting treatment outcome

Rs 1000 at completion of treatment

Latent Tuberculosis Infection in Children - Recent Changes

Dr. Jijo Joseph John
Pediatric Pulmonologist
Associate Professor

Dr. Reny Joseph
Consultant Pediatrician
MGM Muthoot Hospital

Believer's Church Medical College Hospital, Kozhencherry

DEFINTION: Latent Tuberculosis (LTB) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis (M. Tb) antigens, with no evidence of active tuberculosis infection.

Household contact is defined as a person who shared the same enclosed living space as the index patient for one or more nights or for frequent or extended daytime periods during the three months before the start of the current treatment.

Following an infection by M. Tb, around 5 – 10% patients will develop active TB disease, mostly within the first 5 years after initial infection. The risk for active disease depends on several factors, the most important of which is the immunological status of the patient. The risk of developing an active disease decreases by almost 90% after taking TB preventive therapy in patients with LTB infection.

Prevention of active TB by treatment of LTBI is a critical component of WHO End TB strategy. LTBI management is one of the key activities under the 'Prevent' component of the National Strategic Plan 2017 – 2025, for TB Elimination by 2025.

ELIGIBILITY CRITERIA

1. Children under 5 years of age who are household contacts of microbiologically confirmed pulmonary TB may continue to be given TB preventive therapy (TPT) after ruling out active TB, according to current National guidelines.

2. A child born to a mother who was diagnosed to have TB in pregnancy should receive TPT, provided congenital TB has been ruled out.

3. Children and adolescents (5 – 15 years), who are household contacts of microbiologically confirmed pulmonary TB, should be systematically tested for LTBI. If found to have LTBI, they should be offered TPT.

4. Children and adolescents (12 months – 15 years) living with HIV should be given TPT after ruling out active TB.

5. Children living with HIV, (< 12 months) should also be given TPT if they are contact of a pulmonary TB, after ruling out active TB.

6. Children and adolescents (5 –15 years) planned to be initiated on anti- TNF α treatment, receiving dialysis, preparing for organ or hematological transplant, on immunosuppressive drugs for a longer duration (>2 mg/kg/day oral steroids for > 2 weeks) should be systematically tested for LTBI. If found to have LTBI, offer treatment after ruling out active TB.

7. Apart from these conditions, children and adolescents (5-15 years) on any chronic immunosuppressive conditions as decided by the pediatrician, should be tested and treated for LTBI.

TESTING FOR LTBI

1. LTBI testing is not a requirement for initiating TB preventive treatment for children and adolescents living with HIV, and household contacts aged < 5 years.

2. For all other eligible children and adolescents, Interferon gamma release assay (IGRA) shall be used for diagnosis of LTBI.

3. In the absence of free availability of IGRA, commercially available Mantoux test or PPD may be used, with careful understanding of the test and ensuring correct technique.

RULING OUT ACTIVE TB DISEASE

Active TB disease should be ruled out in any children or adolescents before initiating LTBI treatment.

1. Apart from history and clinical examination, Chest X ray shall be taken for ruling out active TB. If the chest X-ray shows any abnormality, the child shall be further evaluated for TB as per the national guidelines.

2. Clinical examination for signs of extra-pulmonary TB such as significant lymphadenopathy shall be made.

3. A clinical committee shall be constituted at district level to take decisions regarding doubtful cases.

TREAMENT FOR LTBI

1. All eligible children and adolescents (<15 years), who were diagnosed to have LTBI, shall be provided treatment with 3 month daily dose

TREATMENT REGIMEN FOR LTBI TREATMENT

Treatment Regimen	Dose
INH plus Rifampicin daily for 3 months	**Isoniazid** Age 10 years & older: 5 mg/kg/day Age <10 years: 10 mg/kg/day (range, 7–15 mg) **Rifampicin** Age 10 years & older: 10 mg/kg/day Age <10 years: 15 mg/kg/day (range, 10–20 mg)

USE OF INH PLUS RIFAMPICIN FDC AS PER WEIGHT BAND

Weight band	4–7 kg	8–11 kg	12–15 kg	16–24 kg	>25 kg
RH 75/50 mg (FDC)	1	2	3	4	Use adult formulations

of Isoniazid plus Rifampicin, after ruling out active TB.

2. Isoniazid plus Rifampicin has lower risk of adverse effects as compared to longer duration of INH alone, probability of adherence is increased due to the shorter duration, and as child-friendly, fixed dose combinations are available. This regimen is also safer to use in a setting with lower drug resistance to Rifampicin and in places where adequate systems are there to rule out active TB.

3. The current recommendations will be reconsidered once INH plus Rifapentine regimens are available in the market.

CONTACTS OF DRUG RESISTANT TUBERCULOSIS

- Close contacts of index cases with proven DR-TB should be monitored closely for signs and symptoms of active TB.

- Assess the intensity of exposure, certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events.

- An individualized preventive therapy shall be offered to high risk (e.g. children ≤ 5 years, people on immunosuppressive therapy and people living with HIV) household contacts of bacteriologically confirmed MDR cases, using drugs as per the drug sensitivity profile of index case.

- All such cases should be referred to district clinical committee and decision should be made by this committee.

- Informed consent should be also taken from the parents before starting the treatment.

PYRIDOXINE SUPPLEMENTATION

- Individuals at risk for peripheral neuropathy, such as malnutrition, children living with HIV, renal failure or diabetes should receive Pyridoxine supplementation while on Isoniazid containing regimens.

- Exclusively breast fed infants should also be given Pyridoxine supplementation while on INH therapy.

- Standard dose of Pyridoxine for prevention of neuropathy is 10 – 25 mg/day.

CONTRAINDICATIONS TO TPT

- Contact of drug resistant TB- treatment to be individualised based on drug susceptibility testing

- Acute hepatitis and peripheral neuropathy – weigh risk vs. benefits of starting TPT.

BASELINE ASSESSMENT

At base line assess for the following to guide decision making

- History of drug allergy, other medications

- Contact with DRTB

- Potential contraindications to LTBI drugs

- Assessment of other comorbidities

- Assessment of social and financial situation of the family, to arrange essential support in co-ordination with primary health care system

- Treatment supporter: Assess if a treatment supporter outside family is needed. If required it shall be arranged in coordination with primary health care team

• Testing of Liver Enzymes at baseline to be done

ADVERSE EVENTS MONITORING, ADHERENCE AND TREATMENT COMPLETION:

Efficacy of LTBI management is greatest if atleast 80% of doses are taken within the stipulated time.

• Treatment shall be under supervision. A treatment supporter from family is preferred

• Treatment Supporter shall look for adverse events and monitor adherence daily

• The Treatment Supporter needs to mark √ against each dose in the LTBI treatment card

• The LTBI treatment card shall be reviewed every week by the primary health care team and the information will be updated in LTBI application

• Retrieval actions shall be taken by the primary health care team if a treatment interruption occurs

• Child/adolescent on LTBI treatment shall be seen by a Medical Officer at least once in a month to look for the following

o Signs and symptoms of TB disease

o Adverse reactions especially symptoms and signs of hepatitis

o Adherence to the prescribed regimen. Elicit reasons for any missed dose and extend necessary support to enable future adherence to LTBI management.

• Any adverse drug reactions shall be recorded in the treatment card. Adverse events also need to be reported through the pharmacovigilance program of India.

TREATMENT OUTCOME

• Treatment completion: A child/adolescent initiated on LTBI management who completed at least 80% of recommended dose (68/84) within 120% of planned LTBI management duration (100 days) for 3HR

• Treatment Failed: A person initiated on LTBI Management who developed TB disease, any time while on LTBI Management course.

• Died: A person initiated on LTBI Management who died for any reason while on LTBI Management course.

• Lost to follow-up: LTBI Management interrupted for four consecutive weeks or more for 3HR.

• LTBI Management discontinuation due to toxicity: A person whose LTBI management is discontinued by clinician due to adverse events or drug to drug interactions, without completing the treatment.

• Not evaluated: such as records lost, transfer to another health facility without record of LTBI management completion.

MONITORING INDICATORS FOR TPT AMONG CHILDREN < 5 YEARS

• Proportion of children < 5 years who are household contacts of pulmonary TB cases who have been initiated in TB preventive therapy

• Proportion of children < 5 years who are household contacts of pulmonary TB cases who have completed a course of TB preventive treatment

MONITORING INDICATORS FOR TPT AMONG CLHIV

• Proportion of eligible children and adolescents living with HIV who were started

on TB preventive Treatment

- Proportion of eligible children and adolescents with HIV who completed a course of TPT.

LONG TERM FOLLOW UP

- All children and adolescents who are household contacts of pulmonary TB shall be followed up every quarter by the primary healthcare team, to assess active symptoms of TB.

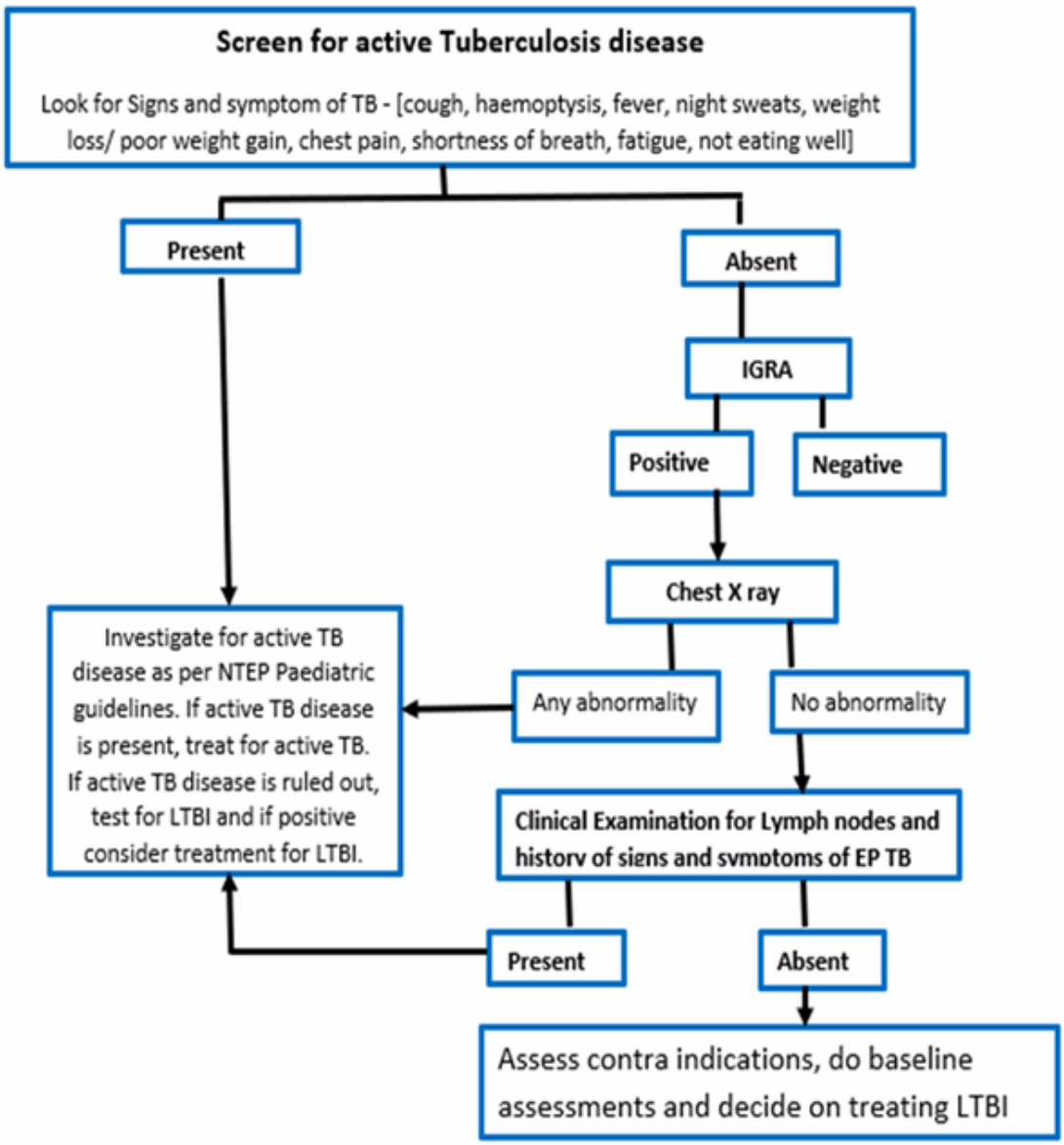
- The same vigil shall continue even after completion of treatment of LTBI.

- If any child initiated on LTBI develops TB later, tests for INH or Rifampicin resistance will be offered at the baseline if a biological specimen is available.

Diagnostic Algorithm for diagnosis and treatment of LTBI among HIV negative eligible children and adolescents aged 5-15 years.

FURTHER READING

1. World Health Organization. The end TB strategy. World Health Organization; 2015.



RNTCP to NTEP; The End Game of TB in India

Dr Ranjit Baby Joseph
Pediatrician and Allergy Specialist
Senior Specialist, Aster Medcity, Kochi

It was in 1962 that India has started her war against tuberculosis. Since then it has re-organized itself two times; first into the Revised National Tuberculosis Control Program (RNTCP) in 1997 and then into the National

Tuberculosis Elimination program (NTEP) in 2020.

National TB Program- NTP (1962-1997)

The National TB Programme (NTP) was launched by the Government of India in 1962 in the form of District TB Centre model involved with BCG vaccination and TB treatment. A joint review of NTP was done by Government of India, World Health Organization (WHO) and the Swedish International Development Agency (SIDA) in 1992 and some shortcomings were found in the programme such as managerial weaknesses, inadequate funding, over-reliance on x-ray, non-standard treatment regimens, low rates of treatment completion, and lack of systematic information on treatment outcomes. Among them the main road block for the Indian government at that time was the lack of financial funding to meet the public health goals which later got resolved to a great extent with support from WHO and UN in 1992. Around the same time in 1993, the WHO had declared TB as a global emergency, devised the directly observed treatment – short course (DOTS), and recommended to follow it by all countries.

Revised National TB Control Program- RNTCP (1997-2020)

With assistance from international agencies, NTP was revitalized and the large scale implementation of the first phase of Revised National TB Control Program (RNTCP-I) was started in 1997. It was identified that an appropriate treatment strategy could cure majority of TB cases once diagnosed. The RNTCP thus officially formulated, adopted the internationally recommended DOTS strategy, as the most systematic and cost-effective approach to control TB in India. Adoption of smear microscopy for reliable and early diagnosis was introduced in a decentralized manner in the general health services. Supply of drugs was also strengthened to provide assured supply of drugs to meet the requirements of the system.

The RNTCP was held responsible for carrying out the Government of India five year TB National Strategic Plans (NSP). Both diagnosis and treatment of TB are provided free of cost through RNTCP without much waiting period. Major additions to the RNTCP, over and above the structures established under the NTP, was the establishment of a sub-district supervisory unit, known as a TB Unit, with dedicated RNTCP supervisors posted, and decentralization of both diagnostic and treatment services, with treatment given under the support of DOT providers. Large-scale

implementation of the RNTCP began in late 1998.

The initial objectives of the RNTCP in India were:

- To achieve and maintain a TB treatment success rate of at least 85% among new sputum positive patients.
- To achieve and maintain detection of at least 70% of the estimated new sputum positive people in the community.

The RNTCP was then expanded across India until the entire nation was covered by the RNTCP in March 2006. At this time the RNTCP also became known as RNTCP II. RNTCP II was designed to consolidate the gains achieved in RNTCP I, and to initiate services to address TB/HIV, MDR-TB (DOTS+) and to extend RNTCP to the private sector. The second phase aimed to maintain at least a 70% case detection rate of new smear positive cases as well as maintain a cure rate of at least 85%, in order to achieve the TB-related targets set by the Millennium Development Goals for 2015. The design of the RNTCP II remained almost the same as that of RNTCP I. Systematic research and evidence building to inform the programme for better design was also included as an important component. The Advocacy, Communication and Social Mobilization were also addressed in the design. The challenges imposed by the structures under NRHM were also taken into account.

National Strategic Plans

There have been a number of National Strategic Plans since the start of RNTCP, the latest of which is the National Strategic Plan 2017-2025.

National Strategic Plan (NSP) 2012 - 2017

The NSP 2012 - 2017 had the aim of achieving universal access to quality diagnosis and treatment. Before this there was little treatment available through the RNTCP for the treatment of drug resistant TB. A number of significant improvements were made during the five years of the plan with a long term vision for a 'TB free India'. These included:

- Complete geographical coverage: Complete geographical coverage for diagnostic and treatment services for MDR TB was achieved in 2013. Also, the National AIDS Control Organisation (NACO) had collaborated with the RNTCP and had made HIV-TB collaboration effective. Most TB patients registered by the RNTCP were receiving HIV screening and 90% of HIV positive TB patients were receiving antiretroviral treatment.
- Notification by the private sector: A government order in May 2012 made it compulsory for health care providers to notify every TB case diagnosed.
- Banning of sero-diagnostic tests: In June 2012 the GoI prohibited the import and sale of serodiagnostic tests for TB. It is now believed that this has saved countless people from having inaccurate results.
- Development of Nikshay: The Central TB Division developed a case based and web based system called "Nikshay" in 2012. This helped with the reporting of all TB cases even from the remotest health institutions.
- Established standards for TB care in India: The Standards for TB Care in India was also developed and it was published in 2014. The Standards describe what should be done, and the TB treatment and care that should be provided throughout India, including what should be provided in the private sector.

However, to eliminate TB in India by 2025, five years ahead of the global target, a framework to guide the activities of all stakeholders including the national and state governments, development partners, civil

society organizations, international agencies, research institutions, private sector, and many others whose work is relevant to TB elimination in India is formulated by RNTCP as National Strategic Plan for Tuberculosis Elimination 2017-2025.

National Strategic Plan (NSP) 2017 – 2025

In 2017 it was announced that the national goal was now the elimination of TB in India by 2025. At the same time the launch took place of the next 5 year plan, the NSP 2017 - 2025. The Vision of this NSP is TB free India with zero deaths, disease and poverty due to tuberculosis and the goal is to achieve a rapid decline in the burden of TB, mortality and morbidity, while working towards the elimination of TB in India by 2025.

The targets of the National Strategic Plan are set out as consisting of both outcome and impact indicators. There are also four main "thrust" or priority areas in the NSP which are:

- Private sector engagement
- Plugging the "leak" from the TB care cascade (i.e. people with TB going missing from care)
- Active case finding among key populations and
- Prevention of development of active TB among people in "high risk" groups with latent TB.

According to the NSP TB elimination has been integrated into the four strategic pillars of "Detect – Treat – Prevent – Build" (DTPB).

- Detect: The aim is to detect all those people with drug sensitive TB as well as those with drug resistant TB. The emphasis is to be on reaching TB patients seeking care from private providers and also finding people with undiagnosed TB in "high risk" or key populations. This is to be done through:
  - Scaling up free, high sensitivity TB diagnostic tests such as CB-NAAT;
  - Scaling up private provider engagement approaches;
  - Universal testing for drug resistant TB and
  - Systematic screening of high risk populations.

Notification of all TB patients from all health care providers is made mandatory by Government of India since 2012. All health care providers (clinical establishments run or managed by government (including local authorities), private, or NGO sectors, and /or individual practitioners) should notify every TB case to local health authorities (district health officer, chief medical officer of a district, and municipal health officer of a municipal corporation/ municipality) every month. With its amendment in 2015, all laboratories are also included to notify TB cases. From March 2018, all chemists will also inform about TB patients for whom they have dispensed the TB drugs. TB patients themselves are also encouraged to notify themselves. Every TB patient will be attempted to reach out by the local public health authority, namely, District Health Officer or Chief Medical Officer of a District and Municipal Health Officer of urban local bodies, so that the incentives and support to patients, families and communities can be properly extended. "Nikshay" can also be used by both government and private health care facilities to facilitate TB notification.

The Technical & Operational Guidelines for TB Control (TOG) describes how various tests should be used to diagnose anyone who has signs and symptoms suggesting that they might have TB. The tests to be used are sputum smear microscopy, chest X ray and the new CB-NAAT test. The CB-NAAT test is beginning to be made available throughout India. There is a diagram, or set of rules, which shows which tests should

be used for different groups of people.

For promotion of public-private mix in TB prevention and care, private providers are provided incentives for TB case notification, and for ensuring treatment adherence and treatment completion. The incentives are provided through direct beneficiary transfer.

- Treat: Initiate and sustain all patients on appropriate anti TB treatment wherever they seek care with patient friendly systems and social support right from starting of treatment till the patient is cured. Anti TB drugs are given free in the form of daily fixed dose combinations (FDCs) for all TB cases with the support of directly observed treatment (DOT).

All patients are screened for rifampicin resistance (and for additional drugs wherever indicated). For drug sensitive TB, daily FDCs of first-line anti-tuberculosis drugs in appropriate weight bands for all forms of TB and in all ages should be given. First line treatment of drug-sensitive TB consists of a two months intensive phase with four drug FDCs followed by a continuation phase of four months with three drug FDCs.

- Prevent: Preventing the emergence of TB in susceptible populations. This is to be done through

o Scaling up air-borne infection control measures at health care facilities

o Providing treatment for latent TB infection for the contacts of people with confirmed TB and

o Addressing the social determinants of TB through an approach across different sectors. The social determinants of health are generally considered to be the conditions in which people live and work that affect their health.

Air borne infection control measures: TB infection control is a combination of measures aimed at minimizing the risk of TB transmission within population and hospital and other settings. The foundation of such infection control is:

- Early diagnosis, and proper management of TB patients.
- Health education about cough etiquettes and proper disposal of sputum by patient.
- Houses should be adequately ventilated.
- Proper use of air borne infection control measures in health care facilities and other settings

Contact tracing: -Since transmission can occur from index case to the contact any time (before diagnosis or during treatment) all contacts of TB patients must be evaluated. These groups include:

- All close contacts, especially household contacts
- In case of paediatric TB patients, reverse contact tracing for search of any active TB case in the household of the child must be undertaken.
- Particular attention will be paid to contacts with the highest susceptibility to TB infection

Isoniazid Preventive Therapy (IPT): Preventive therapy is recommended to Children < 6 years of age, who are close contacts of a TB patient. Children will be evaluated for active TB by a medical officer/ pediatrician and after excluding active TB he/she will be given INH preventive therapy

In addition to above, INH preventive therapy will be considered in following situation:

- 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.

- All TST positive children who are receiving immunosuppressive therapy (e.g. Children with nephrotic syndrome, acute leukemia, etc.).
- A child born to mother who was diagnosed to have TB in pregnancy will receive prophylaxis for 6 months, provided congenital TB has been ruled out. BCG vaccination can be given at birth even if INH preventive therapy is planned.

Close contacts of index cases with proven DR-TB (drug resistant-TB) will be monitored closely for signs and symptoms of active TB as isoniazid may not be prophylactic in these cases.

BCG vaccination: It is provided at birth or as early as possible till one year of age. BCG vaccine has a protective effect against meningitis and disseminated TB in children.

Addressing social determinants of TB like poverty, malnutrition, urbanization, indoor air pollution, etc. require inter departmental/ ministerial coordinated activities and the programme is proactively facilitating this coordination.

- Build: Build and strengthen relevant policies to strengthen the health system for TB control under the National Strategic Plan 2017-2025. Provide extra capacity for institutions and extra human resources capacity. This can be done through

o Translating high level political commitment into action;

o Restructuring the RNTCP and other institutional arrangements;

o Building supportive structures for surveillance, research and innovations. Providing a range of interventions based on the local situation;

o Scaling up technical assistance at national and state levels and

o Preventing the duplication of partner activities

National TB Elimination Program- NTEP (2020-till date)

Consolidating a series of rapid and progressive advancements in RNTCP from 2016 onward, and with Government of India's commitment to achieve the END TB targets 5 years earlier than global targets, RNTCP was re-named as the National TB Elimination Program. The change came into effect from 1st January 2020. The intent behind this is to align the program with India's goal of eliminating TB by 2025 and this change of name is expected to give huge thrust to the people working for elimination of tuberculosis from top to bottom and the general population.

Suggested reading

1. Guidelines on Pediatric TB, tbcindia.gov.in
2. RNTCP government program, tbfacts.org

Dr. R. Remesh Kumar, National President Elect, honoured at Mangalore Pedicon 2021.
He delivered the prestigious Dr. M.R. Shenoy Oration : Pediatric Allergic Disorders - Face the Challenge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