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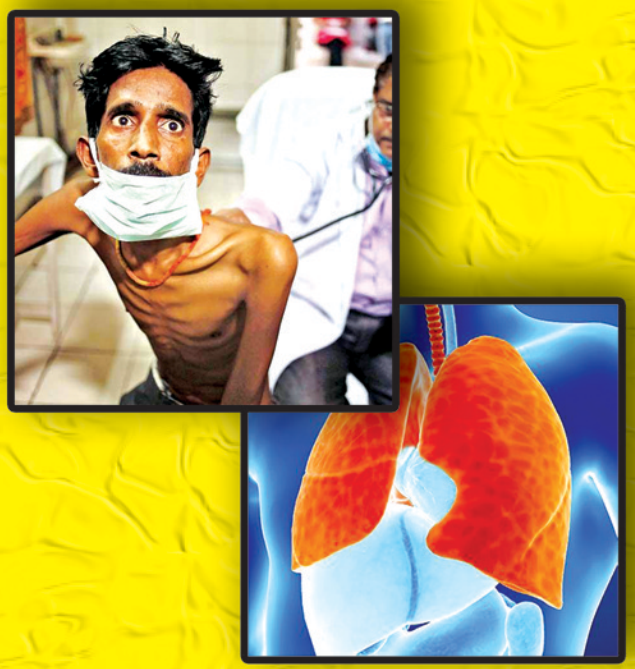
Special Issue on :

TUBERCULOSIS

& A joint initiative with ICMR-RMRC, Bhubaneswar &



The eminent popular science writer Dr. Ramesh Chandra Parida received National Award for Science & Technology Communication for the year 2021 from S&T Minister on National Science Day. We congratulate him for his achievement.

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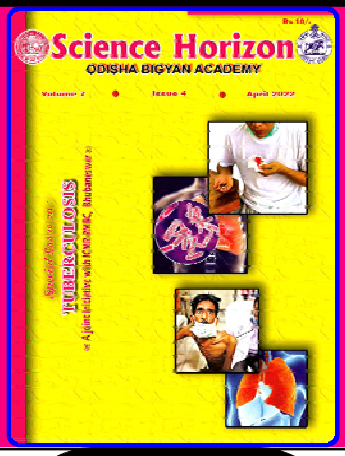

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Cover Design : ***Kalakar Sahoo***

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Editorial

TUBERCULOSIS IN INDIA

Tuberculosis (TB) is caused by bacteria, *Mycobacterium tuberculosis*, and commonly affects the lungs of humans, although it can affect other organs also. The disease is curable and can be prevented. Approximately, one fourth of the world's humanpopulation is infected with TB bacteria. However, most people infected by TB bacteria are not ill, or do not have the disease, and hence cannot transmit the infection. Although all the age groups are at risk of developing active TB disease, it mostly affects adults in their productive age group. About 95% of active TB cases and deaths occur in developing countries. In 2020, approximately 10 million people fell ill with TB worldwide, including 5.6 million men, 3.3 million women, and 1.1 million children. According to the India TB report 2020, the incidence of TB in India in 2019 was 26.9 lakhs. TB is the leading cause of severe illness and death among people living with HIV. India ranks second in the world and accounts for 9% of the global burden of HIV associated with TB infection.

In this regard, a special issue on TB has been prepared by ICMR-RMRC Bhubaneswar, along with other institutes of Odisha, to spread the scientific knowledge about TB among the general population of Odisha. It is specially tailored for the young and enthusiastic school and college students. Apart from covering the scientific aspects, the issue also focusses on the impact of TB on the mental health of the population, and other issues including the effect on the environment. This is extremely necessary to increase the scientific awareness regarding TB infection and disease among the younger generation so as to infuse the spirit of scientific excellence and requisite skills and knowledge to address such public health event in the future.

I hope the readers of this special issue will find the contents highly valuable.

Sanghamitra Pati
Guest Editor

1 EPIDEMIOLOGY OF TUBERCULOSIS: AN UPDATE

[1]Sidhartha Giri
[2]Sanghamitra Pati
[3]A.M. Khan

Tuberculosis (TB) is caused by bacteria, *Mycobacterium tuberculosis*, and primarily affects the lungs of humans, although it can affect other organs also. The disease is curable and can be prevented. Tuberculosis infection is transmitted/spread from person to person through the air. The infection spreads when a person with lung TB (pulmonary TB) coughs, sneezes, or spits, and releases substantial number of bacteria into the air. A healthy person gets infected with TB when he/she inhales the bacteria.

Approximately, one fourth of the world's human population is infected with TB bacteria. However, most people infected by TB bacteria are not ill, or do not have the disease, and hence cannot transmit the infection. For those people infected with the TB bacteria, the life time risk of developing TB disease is 5-10%. The people who fall ill with TB are primarily those who are malnourished and have weak immune system suffering from diabetes, or infected with human immunodeficiency virus (HIV), or those who use tobacco and alcohol regularly.

When a person develops active tuberculosis disease, he/she develops symptoms such as fever, cough, weight loss, night sweat, chest pain, loss of appetite, etc., which can persist for months. As the initial symptoms may be mild, there is a delay in seeking health care, and hence the symptomatic person continues to transmit the infection to other healthy people in the community especially household contacts. A person with active TB disease can transmit the infection to 5-15 healthy persons who are in close contact during a period of 1 year. In the absence of early detection and appropriate treatment, approximately 45% of HIV-negative people with TB, and almost all people with HIV and TB, will lose their life.

Who are at Maximum Risk of TB Disease?

Although all the age groups are at risk of developing active TB disease, it mostly affects adults in their productive age group. About 95% of active TB cases and deaths occur in developing countries. People who are infected with TB and HIV are 18 times more likely to develop active TB disease, compared to people who do not have HIV infection. The risk of active TB disease is 3 times higher in people who are malnourished, as poor nutrition affects the normal functioning of the immune system. In 2020, there were 1.9 million new cases of TB worldwide in those who had undernutrition.

Chronic alcohol use and tobacco smoking also increases the risk of developing active TB disease by 3.3 and 1.6 times respectively. In 2020, 0.74 million and 0.73 million new TB cases were attributed to chronic alcohol use and tobacco smoking respectively.

Impact of TB Worldwide

Tuberculosis occurs in countries across the globe. In 2020, approximately 10 million people fell ill with TB worldwide, including 5.6 million men, 3.3 million women, and 1.1 million children. In 2020, TB was the 13th leading cause of death worldwide, and the second highest infectious disease killer after coronavirus disease 2019 (COVID-19). Approximately 1.5 million people died due to TB in 2020, including 2,14,000 people with HIV (along with TB).

In 2020, 43% of all new TB cases were reported from the World Health Organization (WHO) South-East Asian region, followed by 25% from the African region, and 18% from the Western Pacific region. In 2020, 30 high burden countries contributed 86% of all the new TB cases worldwide. The top eight high burden countries accounted for two third of all the new TB cases, which included India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa.

TB is a curable disease, and active TB disease which is susceptible to drugs can be cured with a 6 months therapy using 4 anti-tubercular drugs (rifampicin, isoniazid, pyrazinamide, ethambutol). Between 2000 and 2020, approximately 66 million people have been successfully treated through proper TB diagnosis and appropriate therapy.

Anti-tubercular drugs have been used for many years, and *M. tuberculosis* bacteria strains that are resistant to one or more of these drugs have been documented. Resistance of *M. tuberculosis* bacteria to anti-tubercular drugs develops due to inappropriate use of drugs, such as incorrect prescription by doctors/ heath care workers, patients not completing the course of therapy, and poor quality medicines. Multidrug-resistant tuberculosis (MDR-TB) is caused by *M. tuberculosis* bacteria which are resistant to rifampicin and isoniazid, the two most effective anti-tubercular drugs. However, MDR-TB can be treated using other anti-tubercular drugs, although the duration of treatment can prolong upto 2 years. In 2020, only 1 in 3 people with MDR-TB accessed treatment, and hence, MDR-TB has become a public health threat with far reaching consequences. In 2018, the success rate of MDR-TB treatment was 59% worldwide.

Globally, the incidence of tuberculosis has been decreasing by approximately 2% every year, and the cumulative reduction in TB between 2015 and 2020 was 11%. TB has resulted in severe economic costs as well. Worldwide, approximately one in every two households affected with TB face costs which is higher than 20% of their total household income. In 2022, about 13 billion US dollars is required for TB diagnosis, treatment, and prevention, worldwide. Unfortunately, the funding in low- and middle- income countries (LMICs), that have almost 98% of the total TB cases, is far below the required target.

Tuberculosis in India

India has the highest number of TB cases in the world. According to the India TB report 2020, the incidence of TB in India in 2019 was 26.9 lakhs.TB is the leading cause of severe illness and death among people living with HIV. India ranks second in the world and accounts for 9% of the global burden of HIV associated with TB infection. With the rise in socio-economic status of people in India, the incidence of diabetes mellitus (DM) has increased dramatically. Evidence from modelling studies indicate that approximately 20% of all tuberculosis cases in India also suffer from diabetes. Diabetes increase the risk of TB by 3 times. Diabetes can lead to worsening of the clinical condition in TB cases, and presence of TB disease can lead to bad control of blood sugar levels in people with diabetes. In 2019, 64% of the notified TB patients had their blood sugar screened. Among all the TB patients screened for blood sugar, 7% had diabetes-TB, and 52% among these were linked to diabetic therapy.

India is the second largest consumer of tobacco worldwide, and is the third largest producer of tobacco after China and Brazil. Under the National Tuberculosis Elimination Program (NTEP), 57% of notified TB patients had their tobacco usage status known, and 14% among them were known tobacco users. Among the TB cases who were tobacco users, 24% were linked to tobacco cessation centres, in addition to brief counselling being provided to all TB patients. Undernutrition is also a strong risk factor for developing TB disease. Undernutrition contributes to about 55% of the annual incidence of TB in India. The Government of India (GoI) has committed 600 crores INR for nutritional support of Rs. 500 per month to every TB patient through direct benefit transfer into the bank account of the beneficiary. Till December 2019, approximately 38 lakh beneficiaries have been paid under the scheme.

TB is also a disease of concern during childhood and in pregnancy. Women of reproductive age group (15-49 years) contribute to a significant burden of TB in India and worldwide. In 2011, India had approximately 44,500 pregnant women with TB, and contributed to 20.6% of the global burden of TB in pregnancy. Pediatric TB is one of the 10 major causes of death worldwide in children below 15 years of age. In India, approximately 3,42,000 new cases of pediatric TB are reported every year, and accounts for 13% of overall TB in the country.

The United Nations Sustainable Development Goals (SDGs) targets to end the tuberculosis epidemic by 2030. In India, the TB National Strategic Plan (NSP) 2020-2025, is a plan formulated by the Government of India (GoI) which aims to eliminate TB in India by 2025, five years ahead of the SDG goals for 2030. The vison of NSP is to have a TB-free India, with zero deaths, disease, and poverty due to tuberculosis by 2025. The NSP emphasizes on prompt diagnosis of all TB cases using highly sensitive diagnostic tests available in the public and private sector. The

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2 MYCOBACTERIUM TUBERCULOSIS: THE BACTERIA CAUSING TUBERCULOSIS

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[3]Paresh Nath Mohanty

Mycobacterium tuberculosis is a species of pathogenic bacteria in the family mycobacteriaceae and the causative agent of tuberculosis, discovered in 1882 by Robert Koch. *M. tuberculosis* has an unusual waxy coating on its cell surface primarily due to the presence of mycolic acid. This bacterium is also known as "Kochbacillus".

Tuberculosis (TB) is caused by *M.tuberculosis*. The bacteria usually attack the lungs known as pulmonary tuberculosis. The bacteria also affect other parts of the body such as spine, kidney, brain (except hair and nail) known as extra pulmonary tuberculosis.

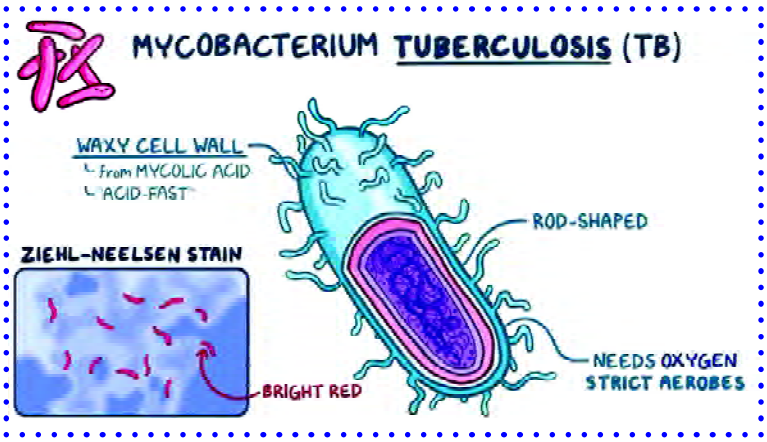

Figure-1

Physiology

Mycobacterium tuberculosis is an intracellular organism, obligate, highly aerobic and require high level of oxygen. *M. tuberculosis* is straight and slightly curved

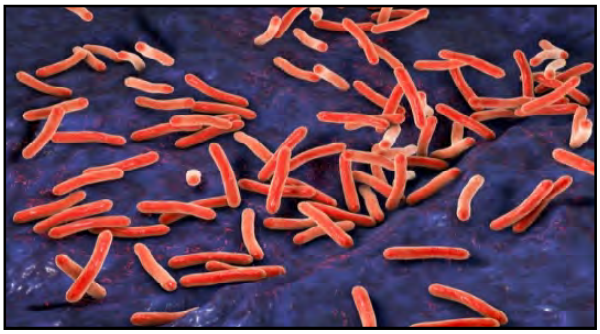

Figure-2

rod measuring about 1 to 4 µ long and 0.2 to 0.8 µ wide. It may be arranged in groups or single, pairs, beaded form or in clusters.

Pathophysiology

Humans are the only known reservoirs of*M.tuberculosis*. A misconception is that M. tuberculosis can be spread by shaking hands, making contact with toilet seats, sharing food or drink, or sharing toothbrushes. Kissing could be a

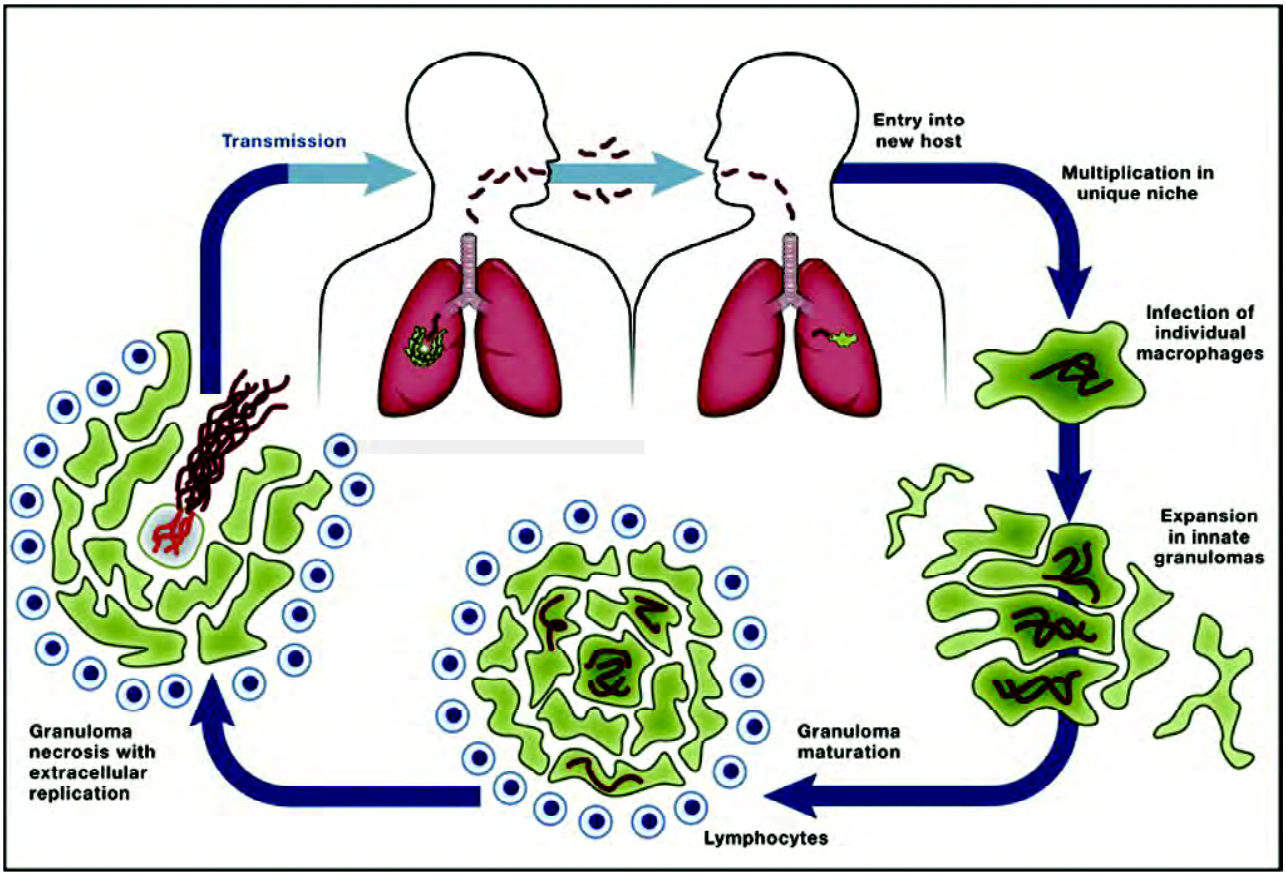

Figure-3

possible route of transmission if the person is excreting many mycobacteria through the sputum. However, the major spread is through air droplets originating from a person who has the disease either through coughing, sneezing, speaking, singing, or laughing.

When in the lungs, *M.tuberculosis* is phagocytosed by alveolar macrophages (pneumocyte Type I & II), but they are unable to kill and digest the bacterium. Its cell wall prevents the fusion of the phagosome with the lysosome, which contains a host of antibacterial factors. Specifically, *M. tuberculosis* blocks the bridging molecule, early endosomal autoantigen however, this blockade does not prevent fusion of vesicles filled with nutrients. Consequently, the bacteria multiply unchecked within the macrophage.

Microscopy

Other bacteria are commonly identified with a microscope by staining them with Gram stain. However, the mycolic acid in the cell wall of *M. tuberculosis* does not absorb the stain. Instead, acid-fast stains such as Ziehl–Neelsen stain, or fluorescent stains such as auramine are used. Cells are curved rod-shaped and are often seen wrapped together, due to the presence of fatty acids in the cell wall that stick together. This appearance is referred to as cording, like strands of cord that make up a rope. *M. tuberculosis* is characterized in tissue by caseating granulomas containing Langhans giant cells, which have a "horseshoe" pattern of nuclei.

Culture

M. tuberculosis can be grown in the laboratory. Compared to other commonly studied bacteria, *M. tuberculosis* has a remarkably slow growth rate, doubling roughly once per day. Commonly used media include liquids such as Middlebrook 7H9 or 7H12, egg-based solid media such as Lowenstein-Jensen, and solid agar-based such as Middlebrook 7H11 or 7H10. Visible colonies require several weeks to grow on agar plates. It is distinguished from other mycobacteria by its production of catalase and niacin.

Signs & Symptoms

Symptoms of *M. tuberculosis* include coughing that lasts for more than three weeks, hemoptysis (blood in cough), chest pain when breathing or coughing, weight loss, fatigue, fever, night sweats, chills, and loss of appetite. *M. tuberculosis* also has the potential of spreading to other parts of the body.

Antibiotic Resistance (ABR)

Resistance to antibiotics in *M. tuberculosis* typically occurs due to either the accumulation of mutations in the genes targeted by the antibiotic or a change in titration of the drug. *M. tuberculosis* is considered to be multidrug-resistant (MDR TB) if it has developed drug resistance to both rifampicin and isoniazid, which are the most important antibiotics used in treatment. Additionally, extensively drug-resistant *M. tuberculosis* (XDR TB) is characterized by resistance to both isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Genome

The genome of the H37Rv strain was published in 1998. Its size is 4 million base pairs, with 3,959 genes; 40% of these genes have had their function characterized, with possible function postulated for another 44%.

Evolution

The *M. tuberculosis* complex evolved in Africa and most probably in the Horn of Africa. In addition to *M. tuberculosis*, the *M. tuberculosis* complex (MTBC) has a number of members infecting various animal species, these include *M. africanum*, *M. bovis* (Dassie's bacillus), *M. caprae*, *M. microti*, *M. mungi*, *M. orygis*, and *M. pinnipedii*.

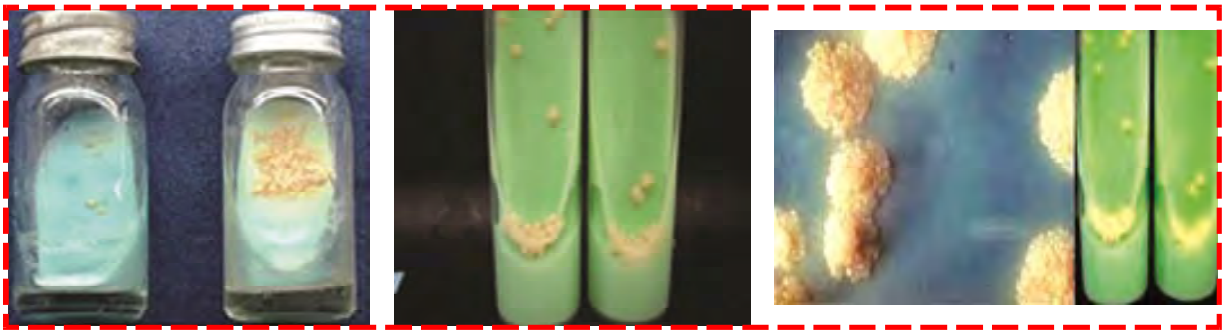

Figure-4 Figure-5 Figure-6

TST Vs. IGRA

TST	IGRA
Good for serial testing	Not as good for serial testing
Inexpensive Universally accessible	More expensive Skill, equipment and timeframe needed limit accessibility
Low specificity in certain populations (BCG-60%)	High specificity in all populations
Two visits	One visit
Variability in test interpretation by reader *** reader	Low variability in test interpretation by

Tests for TB Infection

The screening of groups with a high risk for developing tuberculosis (TB) is a priority in order to control this disease. Since there is no gold standard for the diagnosis of latent TB infection (LTBI), both the tuberculin skin test (TST) and the interferon-gamma release assays (IGRA) have been used for this purpose.

Identification of the *M. Tuberculosis* complex by the Molecular Line probe Assay

Polymerase chain reaction (PCR) was invented by Karry Mullis in 1983. It is a technique that takes a small amount of a specific DNA sequence and amplifies it for further testing. It is also called "Molecular Photocopier".

Hybridization – Detection Steps

Reverse Hybridization – Unlabeled probe specific for *Mtuberculosis* complex or other mycobacterial species are bound to the strips. Biotin labeled target DNA binds to the complementary probe on strip.

Probe target complex is detected- Streptavidin conjugated reagent detects biotin labeled target probe complex.

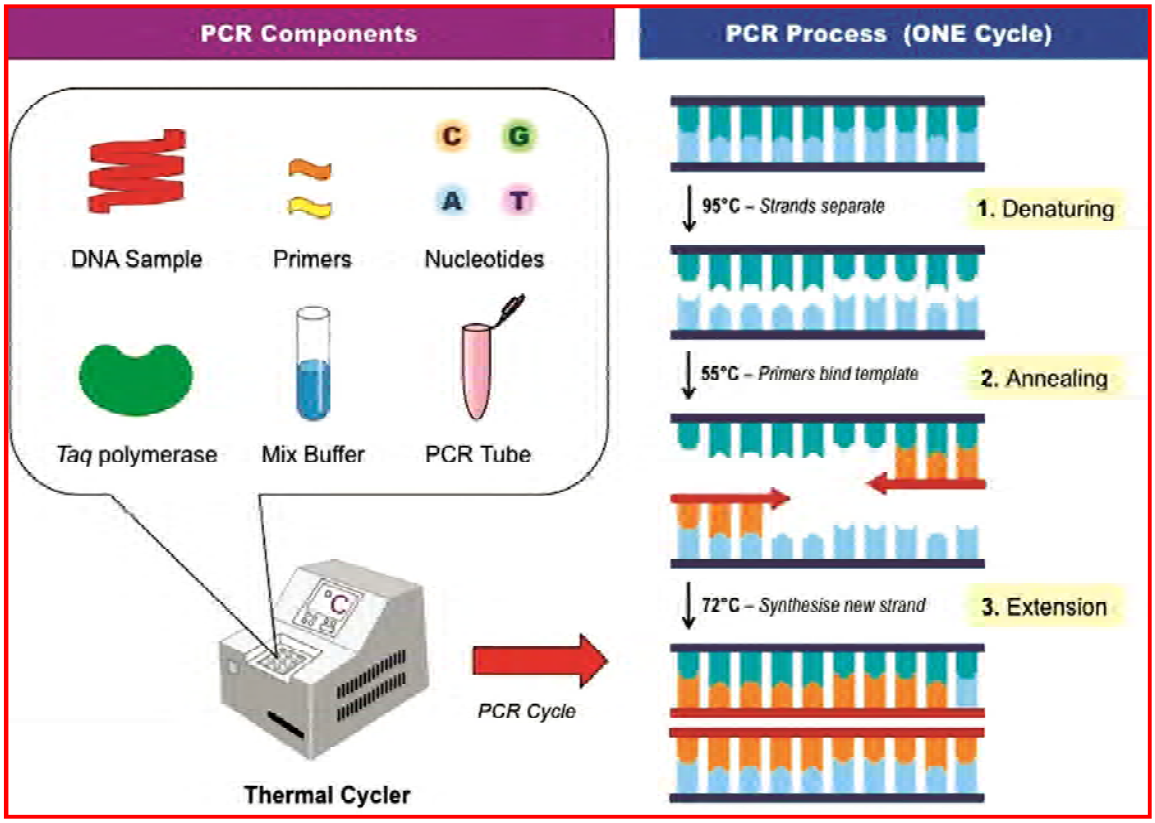

Figure-7

CBNAAT – Cartridge-Based Nucleic Acid Amplification Test

CBNAAT system detects DNA sequences for *M. Tuberculosis* and rifampicin resistance by polymerase chain reaction (PCR). It purifies and concentrates *M. tuberculosis* bacilli, from sputum samples, isolates genomic materials from captured bacteria by sonication and subsequently amplifies the genomic DNA by PCR. The process identifies clinically relevant, rifampicin resistance inducing mutations in the RNA polymerase beta (rpobeta) gene in the *M. Tuberculosis*genome in the real time format using fluorescent probes called molecular beacons. Results are obtained from unprocessed sputum samples in 90 minutes.

Liquid Culture MGIT 960

The MGIT (Mycobacteria Growth Indicator Tube) consists of liquid broth medium that is known to yield better recovery and faster growth of mycobacteria. The MGIT contains 7.0 ml of modified Middlebrook 7H9 broth base. This medium is terminally sterilized by autoclaving. An enrichment, MGIT OADC (Oleic acid, Albumin, Dextrose and Catalase) or MGIT 960 Growth Supplement, is added to make the medium complete. This growth supplement is essential for growth of many mycobacteria, especially those belonging to *M. tuberculosis* complex. Addition of the MGIT PANTA is necessary to suppress contamination.

In addition to Middlebrook 7H9 liquid media, the MGIT tube contains an oxygen-quenched fluorochrome, tris 4, 7-diphenyl-1, 10-phenonthroline ruthenium chloride pentahydrate, embedded in silicone at the bottom of the tube. During bacterial growth within the tube, the free oxygen is utilized and is replaced with carbon dioxide. With depletion of free oxygen, the fluorochrome is no longer inhibited, resulting in fluorescence within the MGIT tube when visualized under UV light. The intensity of fluorescence is directly proportional to the extent of oxygen depletion.

MGIT tubes may be incubated at 37ºC and read manually under a UV light or entered into a MGIT 960 instrument where they are incubated and monitored for increasing fluorescence every 60 minutes. Growth of bacteria as well as mycobacteria increases the fluorescence. In case of *M. tuberculosis*, at the time of positivity, there are approximately 105 – 106 colony- forming units (CFU) per ml of medium. The instrument declares a tube negative if it remains negative for six weeks (42 days). The detection of growth can also be visually observed by the presence of a non-homogeneous light turbidity or small granular/ flaky appearance in the medium. Growth of some non tuberculous mycobacteria or NTM (most commonly rapid growers) results in light turbidity, while contaminating bacteria generally produce heavy turbidity.

Drug susceptibility testing can be performed based on the same principle. Two MGIT tubes are inoculated with the test culture. A known concentration of a test drug is added to one of the MGIT tubes, and growth is compared with the MGIT tube without the drug (growth control). If the test drug is active

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3 IMMUNOLOGICAL CONCEPTS IN TUBERCULOSIS

[1]Sonalika Rath
[2]Ira Praharaj

Although *Mycobacterium tuberculosis (M.tuberculosis)* is one of the oldest bacterial pathogens known to man and grown in culture, the understanding of immunity to this pathogen is still evolving with newer methods of investigation. Proper understanding of the immunological aspects of tuberculosis is vital in the endeavour to develop effective vaccines against the pathogen and disease.

The BCG vaccine, a live attenuated bacterial vaccine has been around for more than 100 years now and has been used worldwide but has not been effective in reducing the burden of TB disease.

Spectrum of TB disease

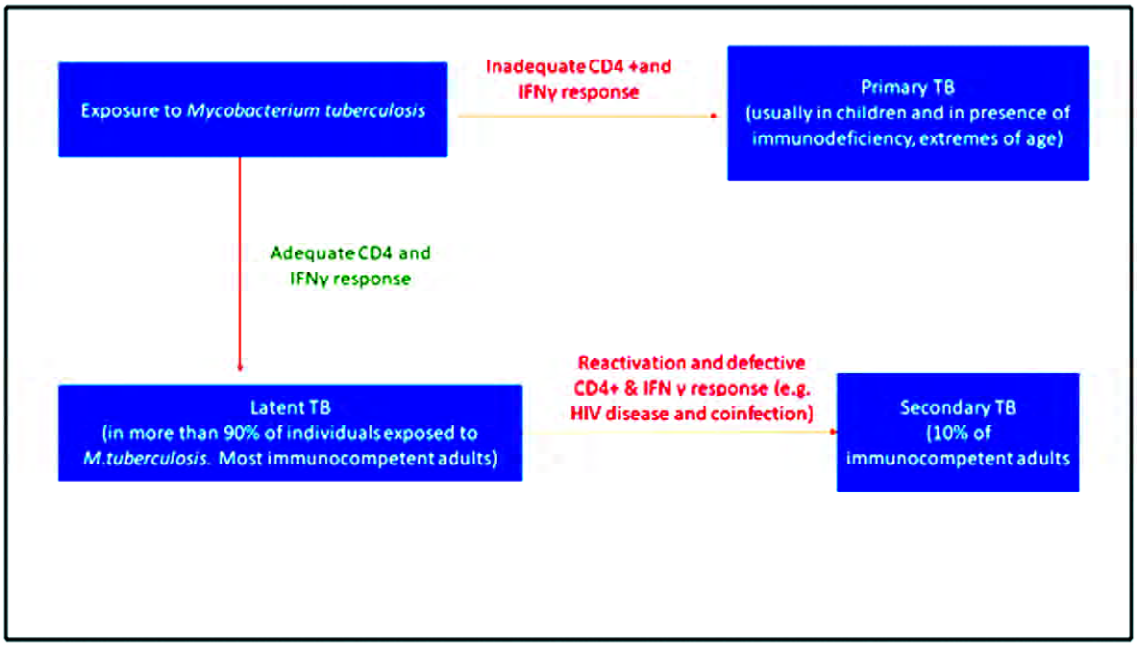

Fig.1:Simple representation of the spectrum of tuberculosis disease and association with cell-mediated immunity, especially the role of CD4+ T lymphocytes and IFNγ

Primary Tuberculosis

Primary tuberculosis is characterized by granulomas in the lungs. TB granulomas are comprised of lymphocytic infiltration, consisting of both T and B lymphocytes, in addition to macrophages which surround them

as well as fibroblast cells. The major role played by the granuloma is in containing the *M.tuberculosis* infection which in many endemic areas occurs early on in life.

Latent Tuberculosis

After infection with *M.tuberculosis*, in a number of instances, the bacteria are not completely eradicated from the body inspite of immune responses, both cell mediated and humoral. A latent state of existence in the body is seen in a considerable proportion of individuals infected with tuberculosis. This has been estimated to be as much as one-third of the global population. Of them, only 5-15% of individuals with latent tuberculosis ever progress to active disease during their lifetime.

Mycobacterium tuberculosis as a paradigm of an intracellular pathogen

The capacity to survive and multiply inside cells and especially macrophages is considered one of the important virulence factors for *M.tuberculosis*.The bacteria persist in phagosomes that prevent fusion with lysosomes.*M.tuberculosis* targets macrophages, especially the alveolar macrophages in primary infection, which although engulf the bacteria do not kill them and may in fact lead to their persistence and multiplication intracellularly.*M.tuberculosis*, once internalized by macrophages prevents phagolysosomal fusion and infact persists in the phagosomes.

The pathogen has a highly evolved mechanism for evading the host immune response against it and multiplying even in the presence of substantial host immune response.

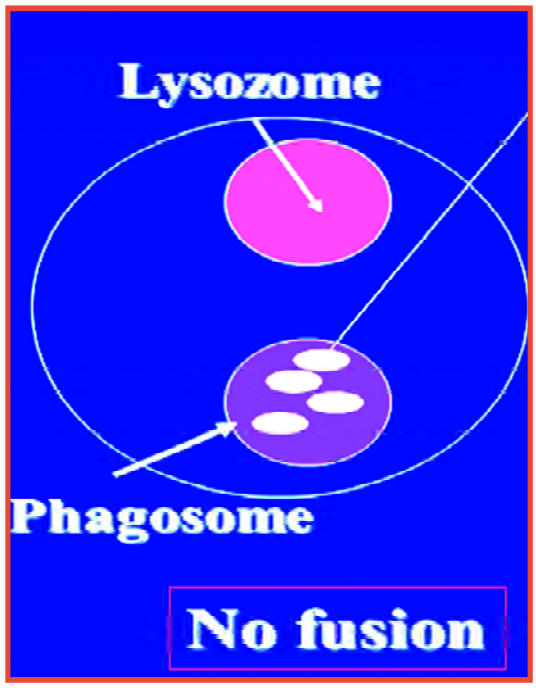

Fig. 2: Depicting the persisting of *M.tuberculosis* bacteria intact in macrophages (phagosomes) without phago-lysosomal fusion

The intracellular location protects the organism from antibody mediated immune response and cell mediated immune response with different effector T-cell populations need to be in force for clearing the organism. Cell mediated immunity plays an especially important role in tuberculosis.

The characteristic pathological hallmark of tuberculosis infection is the tubercular granuloma. It is an aggregate of different inflammatory and immune cell types such as macrophages, other mononuclear cells, lymphocytes and characteristic giant cells called as “Langhans Giant Cells”. Although long considered essential for control of tuberculosis infection, recent concepts about tubercular granulomas have seen a shift in the perception of their role as niches

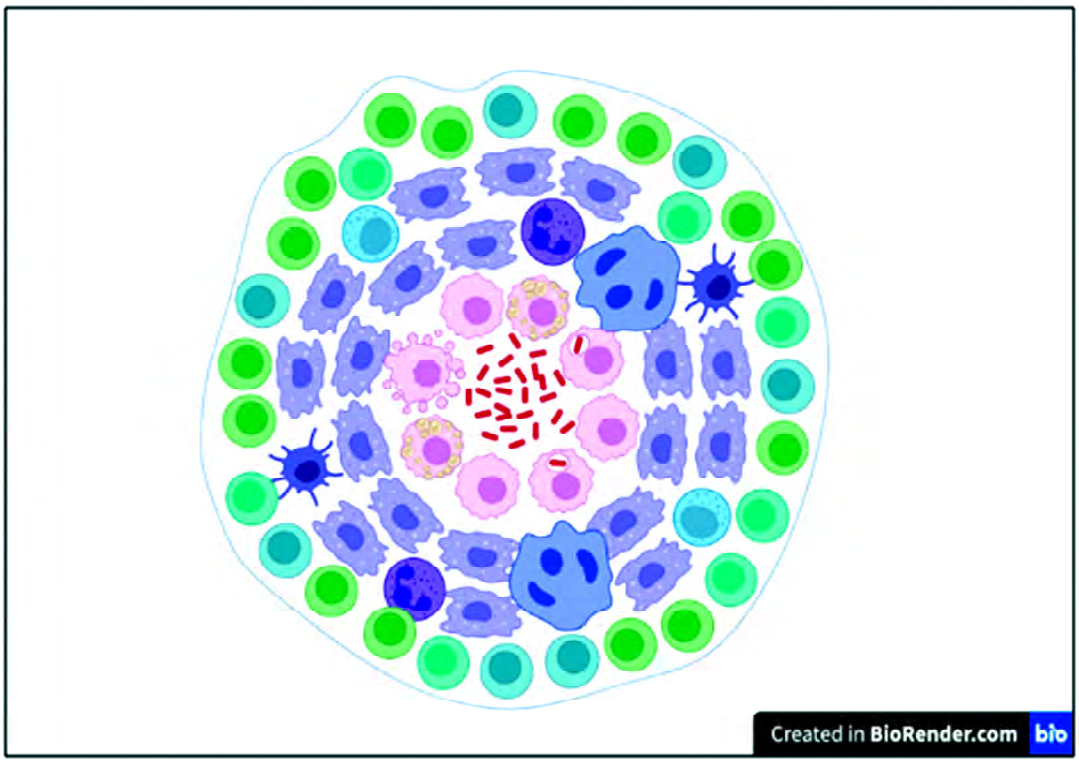

Fig.3. The tuberculous granuloma -is characteristic of primary tuberculosis and consists of infiltration with inflammatory cells such as macrophages, epithelioid cells, lymphocytes and characteristic "giant cells" known as Langhans giant cells as depicted in the tuberculous granuloma contains both "helper" T lymphocytes, otherwise known as CD4 T lymphocytes as well as "cytotoxic" T lymphocytes

for survival of the bacteria from which it may later disseminate.

Role of Cell-mediated Immunity in Tuberculosis

Since *M.tuberculosis* is an intracellular pathogen, cell mediated immune responses are more important although there is considerable role played by the innate immunity as well. After an individual is exposed to *M.tuberculosis*, either the innate immune response or the T cell immunity as an acquired immunity component can help contain it.

Role of T Lymphocytes-the Central Mediators of Protection Against Tuberculosis

The most important cellular components for the control of TB infection are the CD4+ T lymphocytes and mycobacteria specific CD4+ T lymphocytes typically are T helper (Th1) cells and produce IFNã. Although CD4+ T lymphocytes play the major role in the control of the disease process after infection with *M.tuberculosis* and have been the focus of much research regarding the immunity to *M.tuberculosis*, several studies in animals and humans have indicated the substantial role of CD8+ T lymphocytes or the cytotoxic T cell subset in recognizing certain class of antigens from *M.tuberculosis* and contributing to control of *M.tuberculosis* infection.

Cytokine Response and Pathogenesis of Tuberculosis

Cytokines are small protein or peptide molecules which play a very important role

in cell to cell signaling and in the immune response to different pathogens by enabling communication between different cell types. In case of tuberculosis, protection and control of TB disease is conferred by a specific kind of immune response known as the Th1 response which leads to a proinflammatory response important for killing of intracellular pathogens like *Mycobacterium tuberculosis*. IFN-ã is also the cytokine type majorly responsible for the cross-talk between T-lymphocyte subsets and the effector cells, i.e. macrophages. The major cytokines responsible for a Th1 type of response are IFNã and IL-12. The IFNã response is also the basis of some common diagnostic tests for TB infection and exposure such as the Interferon Gamma Release Assay (IGRA).

The other important cytokine in the pathogenesis and control of TB is TNF-á which is important in granuloma formation and hence controlling the disease. It is also the cytokine responsible for destruction of lung tissue due to host response against *M.tuberculosis*.

Tuberculosis and HIV

Human Immunodeficiency Virus (HIV) disease is one of the major risk factors for active tuberculosis diseases as well as TB reactivation. The Human immunodeficiency virus specifically affects particular subsets of the cell-mediated immunity in the human body, i.e. the CD4 T lymphocytes, otherwise known as the “helper” T cells.

HIV disease not only increases the propensity for developing active TB disease but also changes the clinical presentation. HIV positive individuals and patients with active disease have a higher likelihood of developing extrapulmonary TB or TB which affects organs other than the respiratory system. Therefore, screening for TB infection and disease is very important in HIV positive individuals.

Immunity to TB, Current TB Vaccine and Translation to Newer TB Vaccines

The oldest vaccine against tuberculosis, Bacillus Calmette Guerin (BCG) developed over 13 years between 1908 and 1921 is a weakened or attenuated strain of *Mycobacterium bovis*, closely related to *Mycobacterium tuberculosis*. BCG vaccine has been used in many countries but has not been effective in preventing many forms of tuberculosis including the severe manifestations of tuberculosis. The efficacy of the BCG vaccine can range from 0 to 80% with some protection for childhood manifestations of tuberculosis such as tuberculous meningitis. The vaccine efficacy for BCG appears to be closely related to the geographical location and is lowest in areas of the world where the TB burden is high and the population is exposed frequently and early to *M.tuberculosis* as well as multiple species of environmental non-tuberculous mycobacteria. Owing to the many limitations of the BCG vaccine and its limited efficacy in preventing most forms of TB in adults in many parts of the world, there is considerable emphasis on novel TB vaccines and vaccine strategies aimed at both preventive TB vaccines which should be administered early on in life in infancy before exposure to *M. tuberculosis* or environmental mycobacteria, as well as

therapeutic vaccines which are aimed at being used along with the anti-TB chemotherapeutic agents/drugs and to prevent recurrent disease. The major types of preventive TB vaccines include whole-cell vaccines, subunit vaccines and inactivated vaccines. Although a number of TB vaccine candidates, numbering more than 20 have progressed through clinical studies and clinical trials in the last 2 decades, for a number of them the disappointing results have only revealed the lack of complete understanding of the immune response to tuberculosis and its complexity in different host conditions.

Among the different new-age vaccines in various stages of development are vaccine candidates using whole-cell, viral vector vaccines and vaccines using recombinant proteins.One of the major hurdles faced in pre-clinical phases for TB vaccine development is the absence of appropriate animal models in which these vaccines can be tested before being tested in humans. Lack of clinical/immunological correlates of protection makes the process of evaluating efficacy of newer tuberculosis vaccines difficult.

Going forward, the evolving concepts in immune response to tuberculosis as well as better animal models and relevant correlates of protection against TB disease need to be incorporated in the quest to develop effective vaccines against this organism.

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against the isolated mycobacteria, it will inhibit the growth and thus there will be suppression of fluorescence, while the growth control will grow uninhibited and will have increasing fluorescence. Growth is monitored by the BACTEC 960 instrument which automatically interprets results as susceptible or resistant.

TrueNaT

Detection of rifampicin resistance in *M. tuberculosis*usingTruenat MTB/MTB Plus aids in the diagnosis of MDR-TB. This test detects the presence of major mutations (SNPs) in the MTB genome that are known to cause resistance to rifampicin.

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SYMPTOMS OF TUBERCULOSIS

4

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Introduction

Tuberculosis (TB) is caused by a bacteria called *Mycobacterium tuberculosis*. Medical science has advanced a lot in the 21st century but clinical history still holds the pride of place and symptomatology remains the key to approach for the diagnosis of tuberculosis. Application of the knowledge regarding the symptoms & signs by the common man can save tremendous resources in respect of finances, equipment and personnel requirement for case finding campaign particularly in a huge population like India. Based on patient's clinical symptoms and other investigations, doctor can understand the nature, severity and extent of TB.

However, clinical approach has its limitation. At times clinical evidence may be absent or insufficient or at times even misleading. Doctor used to apply his/her clinical skill with help of different investigations for the diagnosis & proper management of TB. Demonstration of TB bacteria in patient samples will confirm the definite diagnosis.

Clinical History

Family history of TB, particularly infant & children,are important but may not always be present. Other possible source of infection from close contact other than family member should be kept in mind which helps the doctor to treat TB in a precise way. TB patients should provide details of previous illness (like diabetics, peptic ulcer, HIV, chronic kidney diseases, cancer, emotional stress etc.), drug history (steroid, other immunosuppressive drug, cancer treatment) to treating physicians as, exposure to diseases/ drugs could be a potential source for decreased immunity in patients leading to development of TB disease. Even past history of any anti TB drugs with duration of treatment should be explained by the patient or by previous document which helps the physician for prescribing proper anti TB medication. A patient's past & present occupation (e.g. coal mines), working environment, nature of work may predispose his/her susceptibility to TB. Patient's general pattern of life comprising his/her habits, recreation and behavior may influence his/her health. Malnutrition, excessive drinking, smoking, indifferent family life, inadequate rest also undermine health and decreases the immunity of patients, which lead to development of TB. Doctors usually

ask the patient to tell his/her history in his/her own words, as many important links in the chain of evidence may thus be discovered which may otherwise be missed.

Symptomatology

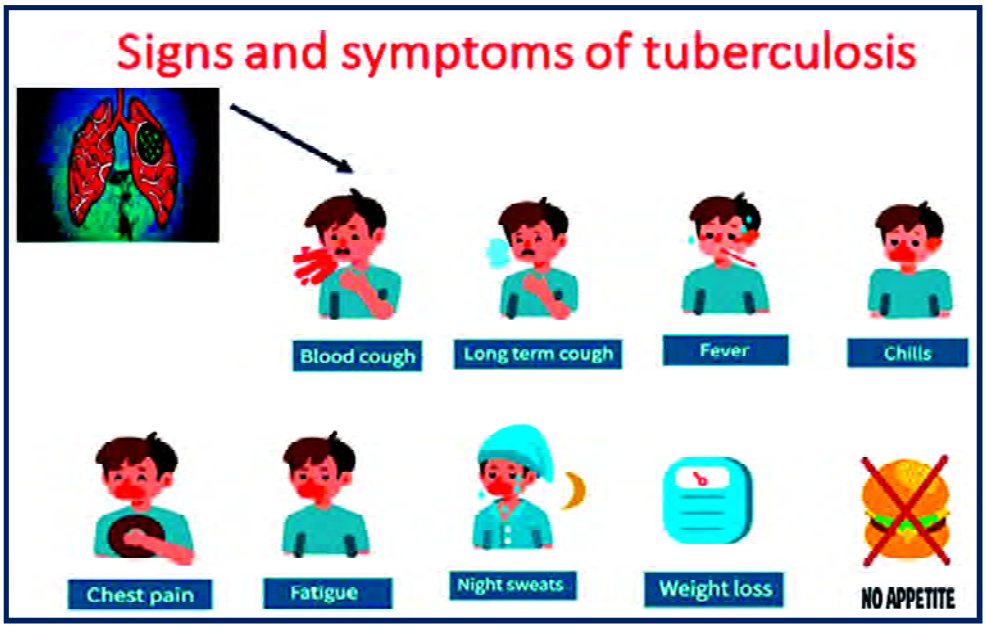
Symptoms of Pulmonary TB (TB inside lung) do not provide a clear-cut diagnosis; as they are common to many non-tuberculosis conditions affecting the lungs. Symptoms may be absent, not only during the early phase of development of disease but at times even in advanced stage of the disease. Appearance of symptoms, early or late, depends not only upon the extent and situation of the lesion but also primarily upon the human body's response to the disease. High immunity of patient may inhibit the activity of TB bacteria and prevent any tissue reaction or, as usually happens, the disease may progress slowly. Moreover, symptoms may persist even after the lesion is healed.

The following symptoms are common in TB; cough, fever, weakness, weight loss, chest pain, loss of appetite, haemoptysis(coughing up blood) etc. Of the above symptoms, the most common symptoms are cough for more than two weeks. Even some other respiratory disease can be cause of cough, still TB should be suspected as two diseases may also be present simultaneously. Blood in sputum may occur due to other diseases, but TB is more common than other diseases. Blood in sputum may be due to healed TB too. TB can affect any organ of body except nail & hair, but in about 80% of TB cases, the lungs are affected. So, chest symptoms are commonly encountered in TB patients. TB which affects lung is called as Pulmonary TB, whereas TB outside the lung is called as extra-pulmonary TB. Symptoms of extra-pulmonary TB depend on the site of affected organ. Out of extra-pulmonary TB, TB in lymph node (usually neck swelling), pleural effusion (accumulation of water outside the lung but inside the chest) are common.

Lassitude (physical or mental tiredness, lack of energy) is one of the earliest symptoms. In the beginning, it is experienced only towards the end of the day and disappears after a short rest. Gradually, the patient begins to feel tired earlier and more easily. Even the night's rest may not relieve him/her. Digestive disturbances are sometimes prominent. They are characteristically vague and of the nature of dyspepsia, such as fullness after meals, flatulence. Loss of weight, slow but progressive, is frequent. Every case of Pulmonary TB exhibits some degree of fever. In early phases, the fever is slight and of short duration, usually occurring in the late afternoon or evening.

Signs

Though Pulmonary TB is more common, still extra-pulmonary TB is frequently associated with it. So, a thorough general physical examination is required covering all the systems (respiratory, cardiac, digestive, neurological, etc). It helps the physician not only in the identification of other sites of TB, but also in the detection of other non-tubercular diseases (Chronic Kidney Diseases, Diabetics Mellitus, etc) which may require modification of patient management.Through general examination, physician can identify; anemia (low hemoglobin), cyanosis (bluish



discoloration of finger/lip/tongue), clubbing of fingers(swelling of dorsal surface of distal end of finger), edema (swelling of body/feet) etc. Physical examination of the chest, like any other diagnostic measure, has its value as well as limitation. None of the observed physical signs is pathognomonic of tuberculosis. Many clinical findings like; pleural rub, pericardial friction, bronchospasm, localized wheeze help physician in precise diagnosis which may be missed by other investigations. Clinical examination also helps physician for further exploration during treatment, which may not be possible by other investigations particularly in low resource settings; for example, identification of ideal site for aspiration of fluid from pleural space in pleural effusion(fluid outside lung but within chest). Physical examination usually enhances the doctors' ability to interpret the varied and different investigation reports. Pulmonary tuberculosis mostly occurs in apical and posterior segments of upper lobes and apical segments of lower lobes of the lungs. Thus early physical signs are usually found posterior over those regions.

Skeletal deformities, poor expansion of chest, asymmetrical abnormalities in chest wall, retraction or prominence of any part of chest can be appreciated by physician by only observing the patient without touching him/her. Displacement of trachea (wind pipe), apex beat of heart suggest the nature of underlying pathology. Pattern of swelling of lymph node (consistency, size, conglomeration) at times helps physician for further effective mode of investigation for firm diagnosis of tuberculosis. Type of appreciation of voice sound by hand by physician over chest wall of patients gives many information of underlying lung pathology. Changes in percussion note over chest wall gives many physiological or pathological information of lung condition. Finally, stethoscope helps physician for identification of underlying lung physiology or pathology by listening to the type of breath sound, adventitious sound, voice sound, whispered sound over chest wall.

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5 LABORATORY DIAGNOSIS OF TUBERCULOSIS

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Tuberculosis (TB), is a highly infectious disease caused by *Mycobacterium tuberculosis* (M.tb) and primarily affects the lungs.According to the World Health Organization (WHO), 1.5 million people died from the disease in 2020. TB is usually curable and preventable under the right conditions and with appropriate therapy. A variety of TB strains exist, and some of these have become resistant to available anti-tubercular drugs.

TB is transmitted from person to person by respiratory droplets.Almost one in four people in the world are infected with TB bacteria. People with well-functioning immune systems may not experience TB symptoms, even if they are infected with the bacteria, and this is known as latent or inactive TB infection. Latent tuberculosis infection (LTBI) itself progresses to active disease in approximately 5% to 10% of infected persons. The rate of progression is much greater in immune compromised individuals such as HIV, advancing age, diabetes or other immune compromising illnesses.

Strategies to combat tuberculosis aim, first, to identify and treat persons who have active disease. Tools for the diagnosis of active disease include clinical suspicion, response to treatment, chest radiographs, staining and microscopy for detection of for acid-fast bacilli (AFB), culture for mycobacteria, and, more recently, nucleic acid amplification (NAA) assays.

An ideal test for tuberculosis would provide rapid results (available within 1 day), would have high sensitivity and specificity, low cost, and robustness (ability to provide reproducible results in a variety of settings), would be highly automated or easily performed without the need for excessive sample preparation or technical expertise, and would be able to provide drug-susceptibility data. Ideally, such a test would also be able to distinguish between LTBI and active disease.

Did you know?

Researchers have traced Tuberculosis or TB back to the days of the ancient Egyptian civilization, more than 5,000 years ago. However, the first written documents describing TB were found in India and in China. In 1720, for the first time, the infectious origin of TB was conjectured by the English physician Benjamin Marten, in

his publication "A new theory of Consumption". Both terms consumption and phthisis were used in the 17th and 18th centuries, until in the mid-19th century when Johann Lukas Schönlein coined the term "tuberculosis" in the 1834.

Currently Available Diagnostics Can be Classified as Those That

- Directly detect the actively growing bacilli or the nuclei acids of bacilli.
- Indirectly detect the immune response against the bacilli.

Direct Methods of M. Tuberculosis Detection

Direct detection of TB infection includes microscopy, culture, antigen detection and nucleic acid detection methods, whereas indirect methods of detection include detection of immune response by tuberculin skin testing (TST) and interferon gamma release assays (IGRAs).

Microscopy

Sputum smear microscopy forms the backbone for diagnosis of TB. The most regular practice is acid fast staining using carbol fuschin, Ziehl–Neelsen (ZN) method and fluorochrome dyeauramine/rhodamine Fluorescence microscopy (FM). In ZN staining, the bacilli appear pink in a blue background while in auramine staining, the bacilli appear as bright yellow luminous rods, against a dark background. Microscopy is relatively fast, inexpensive and specific for TB in high incidence areas. Sputum microscopy has varied sensitivity and can detect the bacilli in sputum when the load of bacilli is 5000-10000 bacilli/ml. Routine microscopy cannot differentiate between live and dead bacilli and hence it is not suitable to monitor TB treatment response. It can neither be used to predict drug resistance nor the presence of non tuberculous mycobacteria (NTM).

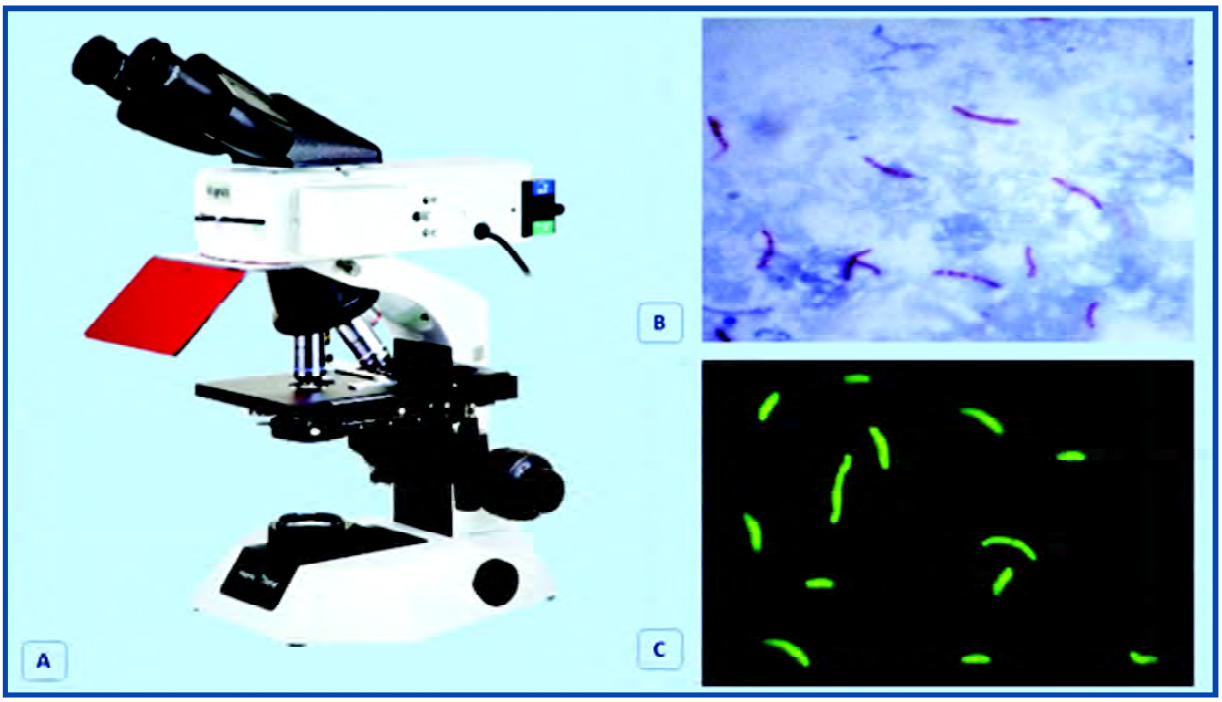

Figure 1: Microscopy: A) Microscope; B) ZN stain; C) FM Microscopy

Did you know?

The famous scientist Robert Koch was able to isolate the tubercle bacillus. He used methylene blue staining recommended by Paul Ehrlich and identified, isolated and cultivated the bacillus in animal serum. Finally, he succeeded in reproducing the disease by inoculating the bacillus into laboratory animals. This result was presented by Robert Koch on 24th March 1882 to the Society of Physiology in Berlin, marking a milestone in the history of fight against TB and this date is now commemorated annually as the World TB Day. Koch was awarded the Nobel prize in Medicine in 1905 for his contribution to the elucidation of the infectious etiology of TB and for his scientific results.

In his early studies on the bacteria, Koch noted that this organism was much more difficult to stain than other bacteria that he had previously discovered, including Bacillus anthracis. We now know that M. tuberculosis resists staining because of its exceptionally resilient cell wall structure containing mycolic acids, long chain hydrocarbons akin to paraffin wax. This observation led to development of a special staining method by Franz Ziehl, which was later modified by Friedrich Neelsen. This method also known as the Ziehl-Neelsen (ZN) stain, and the method uses heat to allow stain to penetrate the waxy surface of mycobacteria. Use of a strong acid as a decolorizer removes the stain from all organisms without such a waxy coat and gives the method its common name "acid-fast staining." The Ziehl-Neelsen method was further improved on by Joseph Kinyoun, who omitted the heating step, therefore limiting the infectious risk inherent with aerosolization of M. tuberculosis. Later, by the 1930s, E. Lowenstein and K. Jensen (their first names appear to have been lost to history) developed selective media containing malachite green, now known as Löwenstein-Jensen (LJ) medium, which is still commonly used for culture of mycobacteria.

Culture

Culture remains the gold standard for diagnosis of TB, and it helps in diagnosis of drug resistance and monitoring the TB treatment response. However, *M.tb* grows extremely slowly in comparison to other bacteria as the doubling time of *M.tb* is about 18 hours. So, TB diagnosis and its DST by culture method is time consuming. Cultures are generally performed using solid and liquid culture medium. Traditional egg based (Lowenstein Jensen) and agar based (Middlebrook 7H10/11) media are widely used. The conventional egg based medium takes from 4 to 8 weeks for visible growth of bacteria. The growth rate of the bacteria is more rapid in liquid medium. The most common liquid culture method adopted by the laboratories, is using Middlebrook 7H9 broth - the mycobacterial growth indicator tube (MGIT), a non-radiometric detection method which measures the consumption of oxygen by fluorescence. As bacteria grow in the culture, the oxygen is utilized causing it to be fluorescent when placed under UV light. The

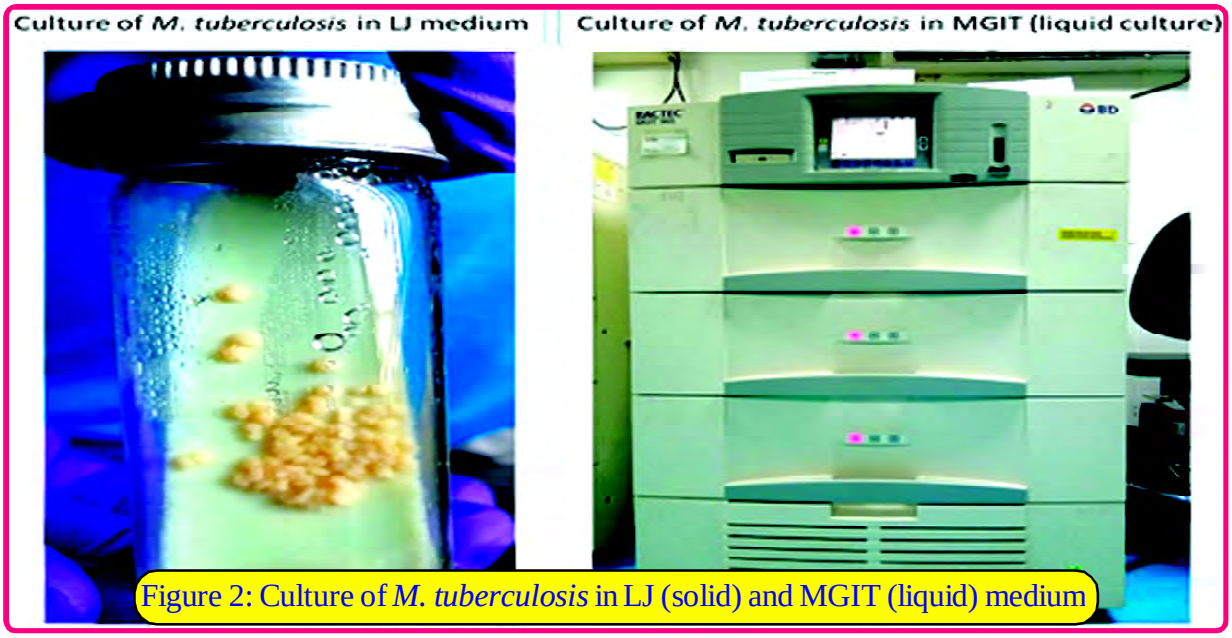

Figure 2: Culture of *M. tuberculosis* in LJ (solid) and MGIT (liquid) medium

limit of detection by culture is 100 bacilli/ml, thus increasing the sensitivity compared to sputum microscopy.

The major limitations of culture methods are requirement of bio-safety facilities that are expensive to build and maintain and specially trained laboratory technicians to perform the procedure. Hence, TB cultures are performed only at National Reference Laboratories (NRLs) or in hospital laboratories having TB containment facility in large cities.

Molecular Detection: Nucleic Acid Amplification Tests (NAAT)

Advent of Polymerase Chain Reaction (PCR) has revolutionized the area of molecular biology. The polymerase chain reaction (PCR) is used to make millions of copies of a target piece of DNA. It is an indispensable tool in modern molecular biology and has transformed scientific research and diagnostic medicine.PCR and its variations have a wide range of specialized applications and are used by scientists in all fields of biology. Gene amplification can achieve the goal of reducing the generation time of microorganisms to minutes. Most

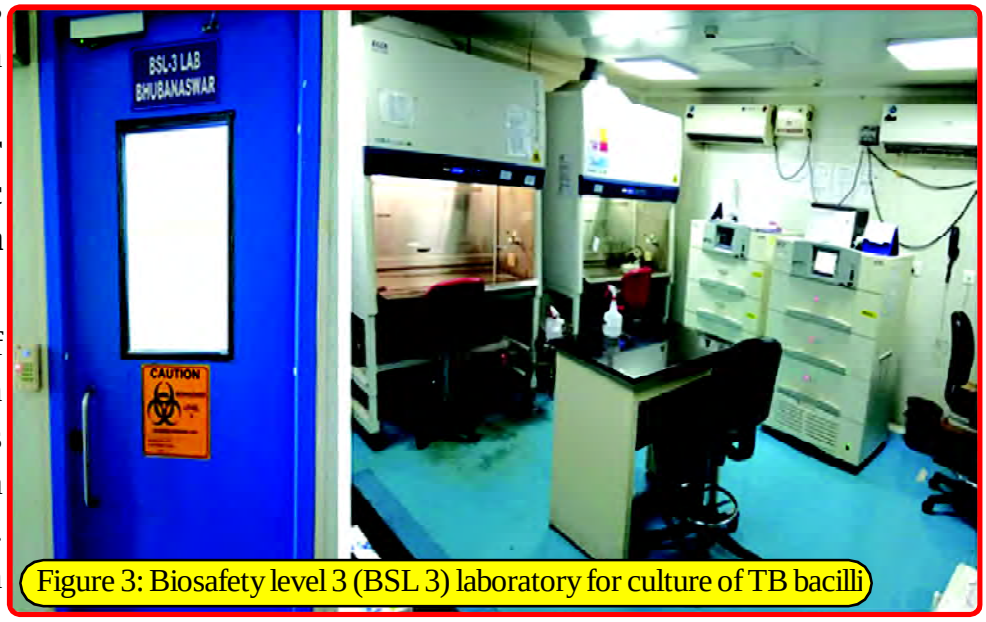

Figure 3: Biosafety level 3 (BSL 3) laboratory for culture of TB bacilli

molecular methods detect the nucleic acid (DNA) of both live and dead bacilli. Because the DNA based molecular methods also can detect the DNA of a dead bacilli, they are not suitable to monitor the TB treatment response. The major advantage of the NAAT assays is these tests are recommended for the paucibacillary samples like extrapulmonary and pediatric samples.

Xpert MTB/RIF and Xpert MTB/RIF Ultra (CBNAAT)

Xpert MTB/RIF (Cepheid, United States) often referred to as Cartridge Based Nucleic Acid Amplification Test (CBNAAT), is a rapid molecular test, for the detection of the *M. tuberculosis* complex and rifampicin (RIF) resistance screening in presumptive cases. The Xpert MTB/RIF assay uses semi-quantitative nested real-time PCR to amplify a fragment containing the 81 bp hotspot region of the *rpoB* gene (codons 507–533) that is then hybridized to five molecular beacon probes. The whole experiment is performed in a self-contained cartridge, like a mini laboratory, to minimize carryover-contamination between samples. Compared to the standard culture based DST, it significantly decreases the detection time of RIF resistance from 4 to 8 weeks (culture and DST) to only 2 hours. Recently, the next-generation Xpert MTB/RIF Ultra system (Cepheid) that has a larger amplification chamber to increase the amount of sputum and two additional targets (IS1081 and IS6110) to identify MTB has been launched. It has higher MTB detection sensitivity (16 bacilli/ml compared with 131 bacilli/ml for the current Xpert MTB/RIF cartridge) and facilitates MTB screening in

Figure 4: A) CBNAAT system; B) Sample report

specimens with low numbers of bacilli, such as sputum samples from children and from patients co-infected by HIV, and in difficult-to-diagnose cases, such as smear-negative pulmonary and extra-pulmonary TB.

in 1-, 2-, or 4-module configurations with the latter most capable of testing four samples simultaneously. Due to the portability of this testing platform, Truenat may be valuable in peripheral healthcare settings, such as

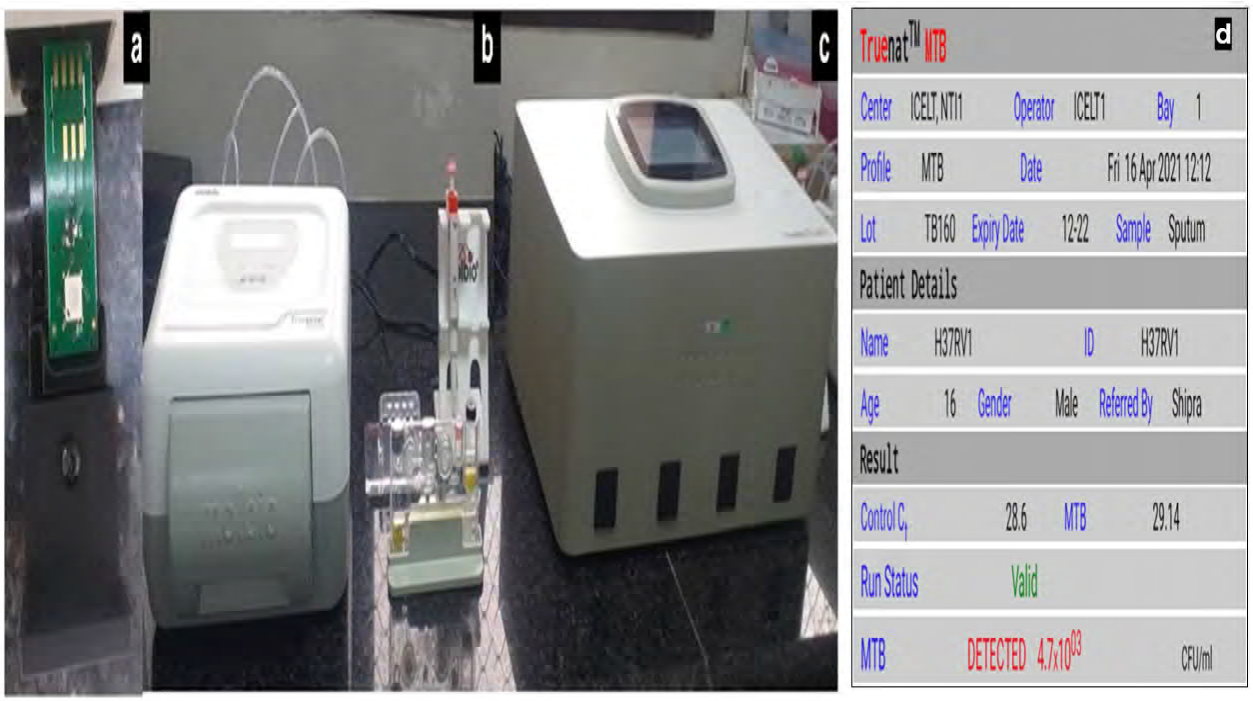

Figure 5: TrueNAT system: a) PCR microchip; b) Trueprep for DNA extraction; c) PCR analyzer; d) Sample report

Truenat

Truenat (Molbio Diagnostics/Bigtec Labs, Goa/Bengaluru, India), is a new chip-based, micro real-time -PCR test that detects tubercle bacilli in sputum samples in approximately one hour. Upon receiving a positive test result, an "add-on" chip can be used to detect RIF-resistance status, adding another one hour of test time. The test is prepared and run on the battery-powered Truelab system, which includes the sample preparation device (i.e., machine for DNA extraction and purification from the sputum sample) and the PCR analyzer device, available designated microscopy centers (DMCs) and primary healthcare facilities in India. It has a detection limit of 100 CFU/ml.

DNA Line Probe Assays

Line probe assays (LPAs) are basically DNA–DNA hybridization assays that allow the simultaneous detection of different mutations by using multiple probes. After DNA extraction and target amplification, amplicons are hybridized to specific oligonucleotide probes that are complementary to the target sequences and are immobilized on the surface of a strip. After several post-hybridization washes to remove non-specific binding, the amplicon-

Figure 6:DNA Line Probe Assay (LPA): A) GT Blot instrument; B) Sample report

probe hybrids are visualized by eye as colored bands on the strip. LPAs focus on the hotspot regions of the drug-resistance. LPAs has been developed for the simultaneous detection of MTB and screening of drug resistance to rifampicin (R), isoniazid (H), aminoglycosides, fluoroquinolones and ethambutol.

Sequencing

Sequencing is the best technology to rapidly analyze the genotype of an organism. Beside targeted gene sequencing (TGS), the development of Next Generation Sequencing (NGS) has been a major breakthrough in molecular biology because it can rapidly provide whole genome data in a single run. This allows species identification, screening of all (known and new) mutations (synonymous and non-synonymous mutations, insertions and deletions) in a sample, detecting drug resistance, and predicting the organism evolution.

Indirect Methods of *m. Tuberculosis* Detection

Tuberculin Skin Testing (TST)

Popularly known as Mantoux test, this test is used to determine whether a person is infected with *M. tuberculosis*. This test involves injecting 0.1 ml of the tuberculin purified protein derivative (PPD) of MTB intradermally in the forearm and the resulting reaction is read after 48–72 h. The test result is read in terms of millimeters of the induration or swelling. While using tuberculin test, it should be remembered that, in general, it detects only presence or absence of infection, i.e., exposure toMTB or latent TB.

Did you know?

In 1890, Robert Koch developed tuberculin (an extract of the TB bacilli) as a cure, though it proved to be ineffective. In 1907, Clemens von Pirquet developed a skin test

that put a small amount of tuberculin under the skin and measured the body's reaction. Pirquet also invented the term "latent TB infection" in 1909. In 1908, Charles Mantoux updated the skin test method by using a needle and syringe to inject the tuberculin. In the 1930s, American Florence Seibert PhD developed a process to create a purified protein derivative of tuberculin (PPD) for the TB skin test. Prior to this, the tuberculin used in skin tests was not consistent or standardized. Seibert did not patent the technology, but the United States government adopted it in 1940.

The TB skin test is still used today and has remained virtually unchanged for almost eighty years. A more recent advancement in TB testing has been the interferon-gamma release assays (IGRAs).

Interferon Gamma Release Assay (IGRA)

Interferon-Gamma Release Assays (IGRAs) are whole blood tests which can help in the diagnosis of *M. tuberculosis* infection. However, the test cannot differentiate between active tubercular disease and latent tuberculosis infection (LTBI). IGRAs measure the reactivity of a person's immune system to

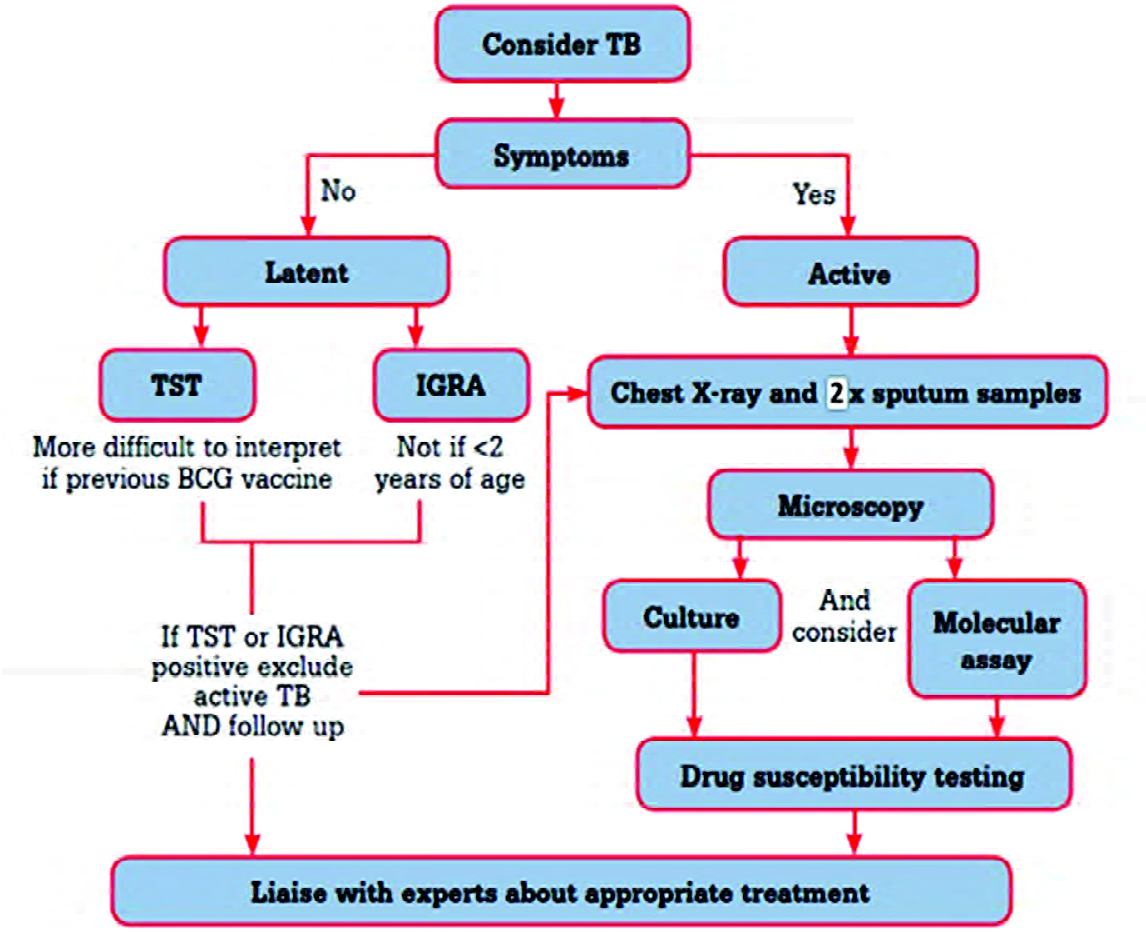

Figure 7: Flow chart for laboratory diagnosis of TB

M. tuberculosis. The white blood cells (WBCs) of most people infected with *M. tuberculosis*, will release interferon-gamma (IFN-g) when mixed with antigens (substances which can induce an immune response) derived from the *M. tuberculosis* bacteria. For the test, fresh blood sample collected from a person is mixed with antigens and controls. The test requires a single patient visit, and the results can be available within 24 hours. Another advantage of IGRA test is that prior BCG vaccination does not cause a false positive test result.

Did you know?

Diagnosis of TB by any microbiological tools and treatment for TB are available FREE of cost at all health facilities under National Tuberculosis Elimination Program (NTEP), India to both public and private sector patients by Government of India (GOI). Treatment adherence to regular and complete treatment is important for successful treatment outcome and relapsefree cure from TB. The TB patients are traced and treated under NTEP and are monitored by dedicated NTEP treatment supervisors. In May 2012, Government of India issued a gazette notification which makes it mandatory for private practitioners to notify any case of TB that they diagnose or treat. The mechanisms provided for notification include both paper and case-based web based online reporting system called NIKSHAY. Under the scheme NIKSHAY Poshan Yojana all notified TB patients are provided incentive of Rs 500 per month during anti-TB treatment for Nutritional support in cash or in-kind support through Direct benefit transfer (DBT).

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network of laboratories for TB diagnosis under the NTEP includes 6 National Reference Laboratories (NRLs), 31 Intermediate Reference Laboratories (IRLs), 50 certified laboratories for liquid culture and drug susceptibility testing (DST) services, 64 certified laboratories for line probe assay (LPA) services, along with 20356 designated microscopy centres.

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TREATMENT OF TUBERCULOSIS

6

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The basis of treating tuberculosis lies on killing the Mycobacteria and preventing development of drug resistance by the organism for which appropriate combination of atleast three effective drugs in correct dosage for stipulated duration and directly observed therapy (DOTS) provided by treatment supporter (ASHA) is essential and ensured under TB control program (NTEP) with an objective to "cure" and prevent "relapse".

DOTS: Directly Observed Treatment Short course ensures "no missed doses" and compliance as the treatment supporter or observer directly observes the medication intake by the patient. Patient-centered care involves shared management of the illness by the patient and health care workers

The most important drugs used for the treatment of drug susceptible TB are Isoniazid(H), Rifampicin(R), Pyrazinamide(Z), and Ethambutol(E) called as first line anti tubercular drugs available in fixed-dose combination (FDC) i.e., all the drugs to be consumed are contained in a single pill at fixed doses thereby reducing the number of pills to be taken per day. The number of pills depends on weight of the patient according to weight band. Both new as well as previously treated cases of drug susceptible TB are treated with same regimen (2HRZE+4HRE) contrary to previous guidelines as the present guideline simplifies the treatment regimen in to "drug susceptible" or "drug resistant" category. To know about the drug resistance pattern of the TB bacilli, rapid molecular testing methods (CBNAAT or TrueNat) are utilized and carried out at designated centers in every corner of the country and states. Besides rapid molecular tests which give results in hours,there are other confirmatory tests like culture and DST (both solid culture and liquid culture) with turnaround time in weeks available at IRL(STDC), Cuttack and RMRC, Bhubaneswar.

Phases of Treatment

Drug susceptible tuberculosis treatment has two phases

i) An initial 2 months of Intensive Phase (IP) with combination of usually 4 drugs (H,R,Z,E) to eliminate most of microorganisms and reduce the risk of treatment failure.

ii) The second phase named as Continuation Phase (CP) of 4 months duration with a combination of usually 3 drugs (H, R, E) to ensure cure.

Weight bands and Pill numbers:

wt band (kg)	Daily tablets (4FDC) for 2 months-IP	Daily tablets(3FDC) for 4 months-CP
25-34	2	2
35-49	3	3
50-64	4	4
65-75	5	5
>75	6	6

When to start TB treatment

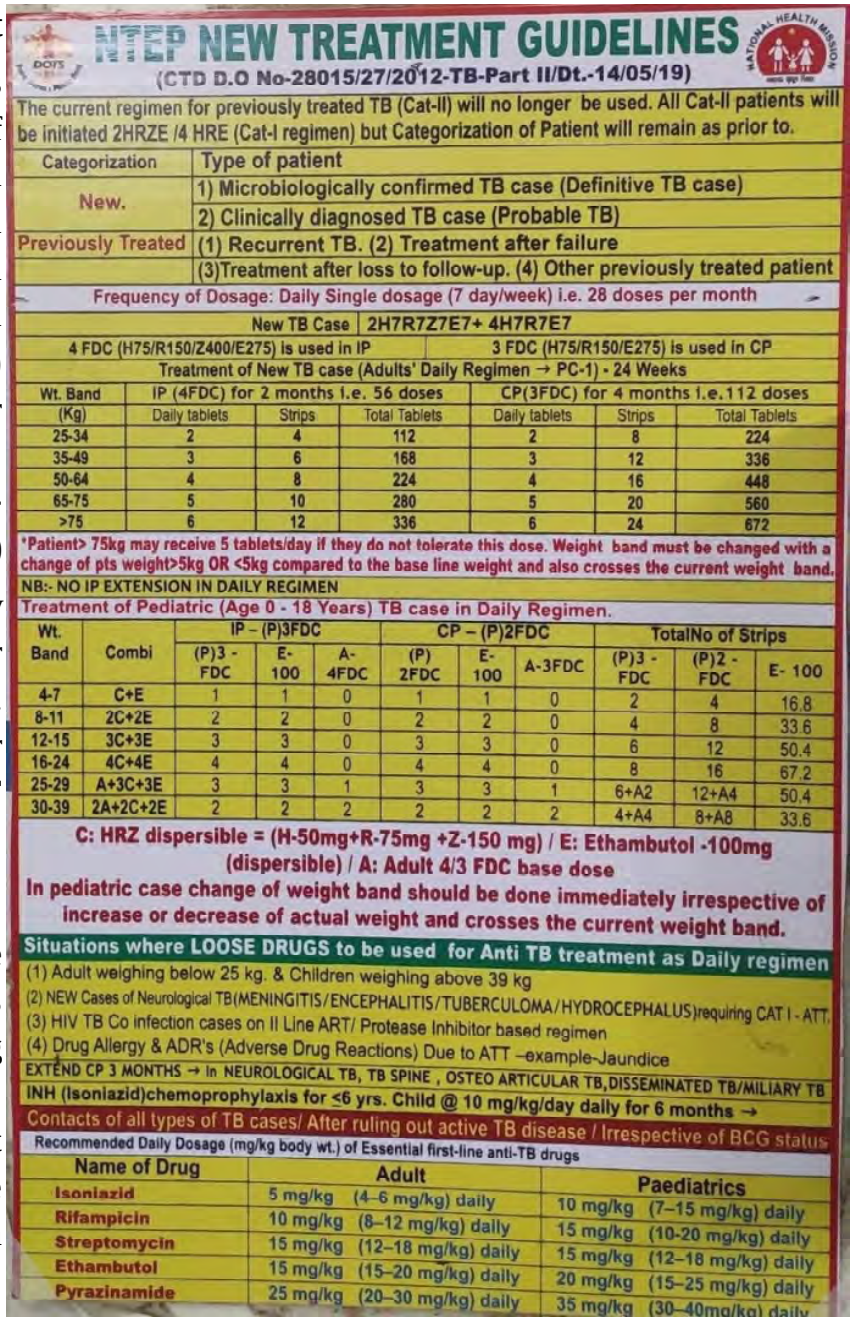
It should be as soon as possible after the diagnosis of TB is made whether with bacteriological confirmation (microbiologically confirmed TB) or on physician's decision (clinically diagnosed TB) irrespective of immune status or comorbidity of the patient.

Timing of taking anti-tubercular treatment (ATT)

The pills should preferably be taken at least half an hour after breakfast with a glass of water. No food should be consumed for at least one hour after ATT consumption.

Common side effects

Nausea and vomiting are commonly reported by patients which mostly occurs with taking the drugs on empty stomach. Urine turns orange in colour that need not to be panicked. Some serious side effects include skin rash, jaundice, blindness.



NTEP NEW TREATMENT GUIDELINES

(CTD D.O No-28015/27/2012-TB-Part II/Dt.-14/05/19)

The current regimen for previously treated TB (Cat-II) will no longer be used. All Cat-II patients will be initiated 2HRZE /4 HRE (Cat-I regimen) but Categorization of Patient will remain as prior to.

Categorization	Type of patient
New.	1) Microbiologically confirmed TB case (Definitive TB case)
	2) Clinically diagnosed TB case (Probable TB)
Previously Treated	(1) Recurrent TB. (2) Treatment after failure
	(3)Treatment after loss to follow-up. (4) Other previously treated patient

Frequency of Dosage: Daily Single dosage (7 day/week) i.e. 28 doses per month

New TB Case | 2H7R7Z7E7+ 4H7R7E7

4 FDC (H75/R150/Z400/E275) is used in IP | 3 FDC (H75/R150/E275) is used in CP

Treatment of New TB case (Adults' Daily Regimen → PC-1) - 24 Weeks

Wt. Band (Kg)	IP (4FDC) for 2 months i.e. 56 doses			CP(3FDC) for 4 months i.e.112 doses		
	Daily tablets	Strips	Total Tablets	Daily tablets	Strips	Total Tablets
25-34	2	4	112	2	8	224
35-49	3	6	168	3	12	336
50-64	4	8	224	4	16	448
65-75	5	10	280	5	20	560
>75	6	12	336	6	24	672

*Patient> 75kg may receive 5 tablets/day if they do not tolerate this dose. Weight band must be changed with a change of pts weight>5kg OR <5kg compared to the base line weight and also crosses the current weight band.

NB:- NO IP EXTENSION IN DAILY REGIMEN

Treatment of Pediatric (Age 0 - 18 Years) TB case in Daily Regimen.

Wt. Band	Combi	IP – (P)3FDC			CP – (P)2FDC			TotalNo of Strips		
		(P)3 - FDC	E-100	A-4FDC	(P) 2FDC	E-100	A-3FDC	(P)3 - FDC	(P)2 - FDC	E- 100
4-7	C+E	1	1	0	1	1	0	2	4	16.8
8-11	2C+2E	2	2	0	2	2	0	4	8	33.6
12-15	3C+3E	3	3	0	3	3	0	6	12	50.4
16-24	4C+4E	4	4	0	4	4	0	8	16	67.2
25-29	A+3C+3E	3	3	1	3	3	1	6+A2	12+A4	50.4
30-39	2A+2C+2E	2	2	2	2	2	2	4+A4	8+A8	33.6

C: HRZ dispersible = (H-50mg+R-75mg +Z-150 mg) / E: Ethambutol -100mg (dispersible) / A: Adult 4/3 FDC base dose

In pediatric case change of weight band should be done immediately irrespective of increase or decrease of actual weight and crosses the current weight band.

Situations where LOOSE DRUGS to be used for Anti TB treatment as Daily regimen

(1) Adult weighing below 25 kg. & Children weighing above 39 kg

(2) NEW Cases of Neurological TB(MENINGITIS/ENCEPHALITIS/TUBERCULOMA/HYDROCEPHALUS)requiring CAT I - ATT.

(3) HIV TB Co infection cases on II Line ART/ Protease Inhibitor based regimen

(4) Drug Allergy & ADR's (Adverse Drug Reactions) Due to ATT –example-Jaundice

EXTEND CP 3 MONTHS → In NEUROLOGICAL TB, TB SPINE , OSTEO ARTICULAR TB,DISSEMINATED TB/MILIARY TB

INH (Isoniazid)chemoprophylaxis for ≤6 yrs. Child @ 10 mg/kg/day daily for 6 months →

Contacts of all types of TB cases/ After ruling out active TB disease / Irrespective of BCG status

Recommended Daily Dosage (mg/kg body wt.) of Essential first-line anti-TB drugs

Name of Drug	Adult	Paediatrics
Isoniazid	5 mg/kg (4–6 mg/kg) daily	10 mg/kg (7–15 mg/kg) daily
Rifampicin	10 mg/kg (8–12 mg/kg) daily	15 mg/kg (10-20 mg/kg) daily
Streptomycin	15 mg/kg (12–18 mg/kg) daily	15 mg/kg (12–18 mg/kg) daily
Ethambutol	15 mg/kg (15–20 mg/kg) daily	20 mg/kg (15–25 mg/kg) daily
Pyrazinamide	25 mg/kg (20–30 mg/kg) daily	35 mg/kg (30–40mg/kg) daily

Treatment of Pediatric (Age 0 - 18 Years) TB case in Daily Regimen.

Wt. Band	Combi	IP – (P)3FDC			CP – (P)2FDC			TotalNo of Strips		
		(P)3 - FDC	E-100	A-4FDC	(P) 2FDC	E-100	A-3FDC	(P)3 - FDC	(P)2 - FDC	E- 100
4-7	C+E	1	1	0	1	1	0	2	4	16.8
8-11	2C+2E	2	2	0	2	2	0	4	8	33.6
12-15	3C+3E	3	3	0	3	3	0	6	12	50.4
16-24	4C+4E	4	4	0	4	4	0	8	16	67.2
25-29	A+3C+3E	3	3	1	3	3	1	6+A2	12+A4	50.4
30-39	2A+2C+2E	2	2	2	2	2	2	4+A4	8+A8	33.6

C: HRZ dispersible = (H-50mg+R-75mg +Z-150 mg) / E: Ethambutol -100mg (dispersible) / A: Adult 4/3 FDC base dose

In pediatric case change of weight band should be done immediately irrespective of increase or decrease of actual weight and crosses the current weight band.

Treatment of TB in children and adolescents

First line treatment regimen (drug susceptible) is same as recommended for adults. Adolescents can use adult formulation and may need extra support for adherence. Severe forms of tuberculosis like TB meningitis, osteo-articular TB (bones and joints) should have longer duration of treatment (usually 9-12 months). Breastfed babies are encouraged to continue breast feed during their treatment.

Treatment of pregnant and breast-feeding women with TB

The regimen is same as other people. Breast-feeding mothers should continue to breast feed their baby during anti TB treatment preferably just before the mother consumes the drugs and few hours later.

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7

DRUG-RESISTANT TUBERCULOSIS

Baijayantimala Mishra

Tuberculosis (TB) is a disease caused by bacteria called *Mycobacterium tuberculosis*. The disease spreads from one infected person to another person through the air. TB most commonly affects the lungs, but it can affect other body organs, such as the brain, kidneys, intestine, lymph nodes, or bone.

In most cases, TB is a treatable and curable disease when treated with the right drugs for the right duration at the right time.However, it can lead to severe illness and death without proper treatment.

Drug-resistant Tuberculosis (DRTB)

Drug-resistant TB is called when the infective agent *M.tuberculosis* (MTB) bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the TB bacteria.

Burden and problems of DRTB

According to the World Health Organisation (WHO), two billion people are infected with *M.tuberculosis*, roughly a quarter of the world's population. Around 9 million new TB cases occur every year, and 1.5 million deaths occur due to TB. As per the recent WHO report, around five lakhs people develop drug resistance every year. However, around 30% of cases were not diagnosed, and >50% of drug resistance cases were not detected and reported. This indicates, many tuberculosis cases still remain undiagnosed, detection of drug resistance is also missed in a large proportion of tuberculosis cases, many do not have access to treatment, and lastly, treatment may not be successful in a large proportion of patients.

India contributes approximately 25%-30% of the world's tuberculosis cases and drug resistance, which is the highest global contribution by any country. Globally, 6.19%of TB cases had MDR-TB, including 2.84% among new and 11.62% among previously treated cases. The estimated number as of 2019 of multi-drug resistance TB (MDRTB) in India was124,000, 9.1 per 1lakh population. MDR status is the most important parameter as this is the major determinant for the type of antitubercular treatment.

So, to handle the TB menace, both early diagnosis and early detection of drug resistance are essential. Appropriate treatment can be initiated on time, and the maximum possible cure can be achieved.

The Drugs used to Treat TB

TB is primarily treated by two groups of drugs.The first line and second lines of antitubercular drugs.

First-line antitubercular drugs (FLDs)

Rifampicin, Isoniazid, Ethambutol and Pyrazinamide belong to first-line drugs. When a TB case is detected for the first time,the patient is treated with the FLDs. Of the four FLDs, rifampicin and isoniazid are the two most essential drugs.

Second-line antitubercular drugs

These are the reserved drugs used to treat TB cases resistant to the first-line drugs., Drugs belonging to fluoroquinolone and aminoglycosidesare among the major second-line antitubercular drugs.

Recently added antitubercular drugs

Bedaquiline, Delamanid and Linezolid are the recently added antitubercular drugs approved for use in multi-drug resistant cases.

The emergence of strains resistant to either of these drugs causes major concern, as it leaves the option of less effective drugs, have more toxic side effects, and result in higher death rates.

Types of DRTB

Drug resistance tuberculosis are of two types based on the status of antitubercular drug intake.

Primary drug resistance

When drug resistance is detected in a newly diagnosed patient who has not been treated previously with antitubercular drugs before, it is called “Primary drug resistance”. This is primarily due to infection with a drug-resistant MTB strain.

Secondary drug resistance

When drug resistance is developed in a TB patient who is already under antitubercular drug treatment,it is called “Secondary drug resistance”. In this case, the resistance to the drug is developed during the treatment.

How Drug Resistance Develop?

Development of drug-resistance TB can occur due to several reasons as mentioned below. However, TB drug resistance is mostly a man-made phenomenon due to mismanagement in administering antitubercular drugs, which leads to spontaneous mutations in *M. tuberculosis* that make a drug ineffective against the mutant bacteria.

Causes of DRTB development

Improper use of the antitubercular drug is the major reason for the development of drug resistance. This can be due to several causes like:

a. Drug is not taken properly as per the medical instruction

b. Inadequate dose or irregularly administered treatment regimen allows drug-resistant mutants to become the dominant strain.

c. Non-completion of the entire course of the treatment regimen

d. Health care providers prescribe the wrong or inappropriate treatment regimen.

e. The wrong dose or wrong duration of the

course of treatment.

f. Failure to achieve necessary drug levels to deal with all populations of mycobacteria even with appropriately administered drugs.

g. Poor quality drug.

Various types of drug resistance have been defined based on the pattern of resistance to different drugs used for the treatment of TB.

Types of Drug-resistant Tuberculosis

a. Mono-resistant TB (MR TB). The infecting *Mycobacterium tuberculosis* strain is resistant to anyone first-line anti-TB drug.

b. Multidrug-resistant TB (MDR-TB). When the infecting *Mycobacterium tuberculosis* strain is resistant to both Isoniazid and Rifampicin with or without resistance to other first-line anti-TB drugs.

c. Rifampicin resistant TB (RR-TB). When the infecting *Mycobacterium tuberculosis* strain is resistant to Rifampicin with or without resistance to other anti-TB drugs.It includes any resistance to Rifampicin:

   i. mono-resistance: resistance only to Rifampicin.

   ii. poly-resistance: MDR or XDR.

d. Pre-extensively drug-resistant TB (Pre-XDR-TB). TB is caused by *Mycobacterium tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any of the fluoroquinolone used for TB (levofloxacin or moxifloxacin).

e. Extensively drug-resistant TB (XDR-TB). TB caused by *Mycobacterium tuberculosis* strains that fulfil the definition of Pre-XDR-TB and at least one additional Group A drug (presently to either Bedaquiline or linezolid or both)

Of all the above types of DRTB, as a first step,it is important to find out the status of resistance to rifampicin and isoniazid or, in other words,to find out the status of MDR in the patient. These two drugs are the main component of the first-line drugs. The treatment regimen will be different if the MTB strain is resistant to these drugs or MDR strain. So, when a patient is diagnosed for the first time, it is simultaneously essential to know the MDR status.

Detection Methods of Drug Resistance in MTB

There are many methods of detection of resistance. They can be subdivided into:

A) Phenotypic Methods: To perform phenotypic drug sensitivity testing (DST), mycobacteria are initially grown in culture media. Growth of the bacteria on the solid medium is identified by the colony character and on liquid media by fluorescence which is detected by the automated detection system of the instrument indicating a reduction in oxygen tension due to bacterial growth.

To determine the susceptibility of any drug, MTB is grown on the culture media in the presence of the drug and in the absence of the drug.

■ If there is no growth in the medium containing the drug, it is considered as sensitive

to the drug (MTB bacteria will get killed by the drug).

■ If MTB growth occurs in the presence of the drug, it is considered resistant to the drug.

Examples of Phenotypic Methods

a. BACTEC 460 TB SYSTEM Radiometric Method

b. Mycobacterial Growth Indicator Tube (MGIT) Method

c. Versa TREK Method

The main problem with the phenotypic method is that it involves handling live bacteria. Hence, a higher level of biosafety measures involves handling live bacteria, so higher biosafety measures are required. Also, as it needs the bacteria to grow and MTB is slow-growing, it takes several weeks to know the results.

B. Genotypic Methods: This is done by the detection of genetic mutations that are responsible for drug resistance. These are detected using molecular methods, which are highly sensitive and specific and take much less time than that of the phenotypic methods.

Detection of rifampicin resistance is the most important to be assessed first when diagnosed with TB. This is because rifampicin resistance acts as a surrogate marker for MDR TB, because>90% of rifampicin-resistant isolates are also resistant to isoniazid. So, the resistance result of rifampicin indicates the MDR status of the MTB strain. Various diagnostic systems can detect the MTB DNA and the rifampicin resistance.

WHO endorsed Methods

♦ **Xpert MTB/RIF** (Gene XPert, Cepheid) Cartridge based nucleic acid amplification test (CBNAAT)

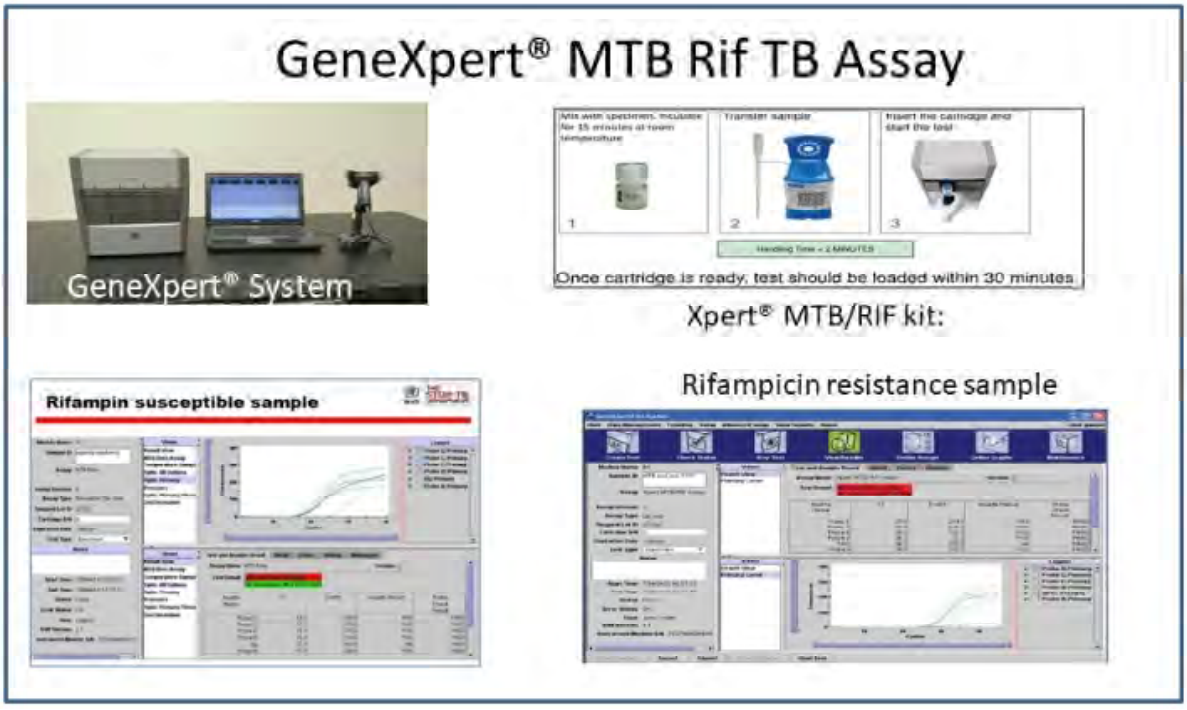

Figure 1:CBNAAT for MTB detection and resistance to rifampicin

Truenat system for MTB and Rifampicin resistance detection

Figure 2:TrueNat system for detection of MTB and resistance to rifampicin

- **Truenat** (Molbio diagnostics, India) is a similar chip-based system

Both these systems can detect MTB and rifampicin resistance within 2 hours.

WHO recommends that the CBNAAT (Cartridge based nucleic acid amplification test): Xpert MTB/RIF to be used as the initial diagnostic test for all adults and children with signs and symptoms of TB, rather than microscopy and culture.

LPAs (Line Probe Assay): This is a WHO endorsed molecular method for detecting rifampicin and isoniazid resistance and resistance against fluoroquinolones in smear–

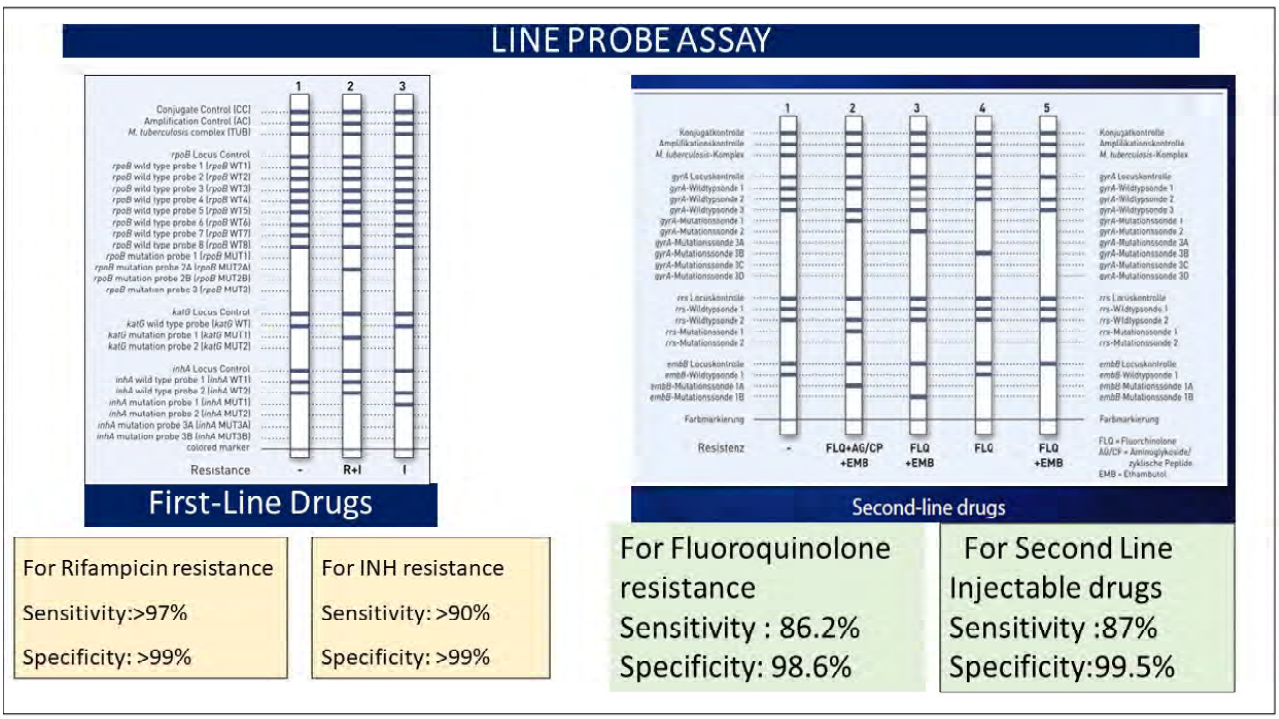

Figure 3: Line probe assay (LPA) for detection of resistance to drugs in MTB

positive clinical specimens (direct testing) in cultured isolates of MTB. The method is based on PCR and reverses hybridization.

Do We Have Treatment for DRTB

Treatment of DRTB is available, and when taken correctly, it is quite effective. However, the treatment usually is given for a more prolonged period and involves a combination of more than four drugs.Recently, oral drugs like Bedaquiline, Delamanid and Linezolid have been included in the MDR treatment regimen in place of injectable medications to make the treatment more compliant.

Patients with DRTB are managed with the help of a country-wide network of DRTB centres. The result of DST, history of previous drugs taken by the patient, and the adverse reactions are considered to select the appropriate treatment regimen.

Can DRTB Be Prevented?

To a great extent, development of drug resistance can be prevented.The Government of India has initiated several measures through its national Tuberculosis Elimination Programme (NTEP) :

- Selection of proper treatment regimen
- Development and implementation of a more effective and compliant treatment regimen
- Easy availabilityof drugs throughout the country
- Early case detection of TB as well as DRTB by rapid molecular methods
- Prevention of airborne transmission by proper biosafety measures, particularly in crowded hospital premises.

Key Points

- The bacteria *Mycobacterium tuberculosis* causes TB.
- Drug resistance to MTB develops due to the generation of mutation in the bacteria during the treatment
- Rapid molecular testing is available to diagnose MTB and detect rifampicin resistance throughout the country by NTEP.
- Most common cause of drug resistance development is non-compliance to drug
- DRTB can be prevented by early diagnosis and proper treatment with proper monitoring

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HIV AND TB

8

Prasanta Raghab Mohapatra

Acquired Immune Deficiency Syndrome (AIDS) is a progressive life-threatening disease caused by human immunodeficiency virus (HIV) by damaging the body immune (defence) system. Much before HIV infected humans, a similar virus called simian immunodeficiency virus (SIV), originated from naturally infected old wild-living chimpanzees and gorillas in west-central Africa. These SIVs were perhaps transmitted to humans when African meat-eaters hunted infected chimpanzees for meat and came in interaction and mucosal transmission with the infected blood. Over decades, this disease entity was unknown and slowly spread across Africa and later into other parts of the world. This was first recognized in the western world as a new disease during 1981 when rising numbers of young homosexual men developed unfamiliar opportunistic infections and uncommon cancers. Since then, HIV has become one of the most devastating infectious diseases and persistent killers in human history. HIV is a virus that weakens the immune system. If HIV is not treated, it leads to cause severe damage to the immune system and manifests with a syndrome which presents as varied symptoms called AIDS (acquired immunodeficiency syndrome).

Tuberculosis (TB) is caused by a bacteria called *Mycobacterium tuberculosis*, transmitted by aerosol (cough mediated through the air), and unlike AIDS, it is curable with proper treatment. In 1720, for the first time, the infectious basis of TB was inferred by Benjamin Marten. Robert Koch isolated the tubercle bacillus in Berlin on 24 March 1882.India was the first country to start a national TB program (NTP) in 1962. The world could not eliminate TB to date, it ultimately has been a significant killer over the centuries till date with the creation of drug-resistant TB. TB is (still) the leading cause of death among AIDS patients worldwide. Among the biggest treatment dilemmas is how to manage TB/HIV at the same time.

With time, HIV has spread worldwide. TB in HIV infected people has been common due to the ease of transmissibility, complex immunological response, chronic progression and the need for long-term treatment and drug resistance. HIV is the most important risk factor for the progression of latent *Mycobacterium tuberculosis* infection to active disease. The risk of latent TB infection (LTBI) progression into active TB disease is nearly twenty-fold. The most common cause

of death among people living with HIV (PLHIV) is tuberculosis. In HIV TB co-infection, poor immune defences lead to poor control of the TB infection, leading to widespread dissemination of various opportunistic infections.

Although the current TB-HIV epidemic is in a declining trend, it is still associated with a high social stigma. The difficulty in treating and preventing both has been a permanent challenge for the last few decades. As per the Global TB report 2021, with the emergence of the coronavirus virus disease 2019 (COVID-19) pandemic and the resulting lockdown, there has been a significant reduction of TB diagnosis and treatment, which has led to increased TB deaths, many unnoticed. The COVID-19 pandemic has reversed years of progress in providing essential TB control services. The most obvious impact is a significant global drop in the reporting of number of newly diagnosed cases with TB. India has contributed 41% of the worldwide decline during the first wave of COVID-19 (between 2019 and 2020). Similarly, it has also affected HIV detection and management adversely.

As per World TB report-2021, there were 1.3 million TB deaths among HIV-negative people and an additional 214 000 among HIV-positive people. About 34% of the total number of TB deaths in HIV-negative and HIV-positive people occurs in India.

As per the recent data from National AIDS Control Organisation (NACO), Ministry of Health and Family Welfare, Government of India, the predominant mode of transmission of HIV infection in India is through heterosexual contact (94%),and the next mode is by prenatal (parent to child) transmission. Prevalence among some crucial groups of populations, including female sex workers (FSW), men who have sex with men (MSM), transgender (TG), and people who inject drugs (PWID), are 1.56%, 2.6%, 3.14% and 6.26%,respectively.

Transmission and Clinical Manifestations of AIDS

The virus is usually transmitted through definite contact with infected blood, semen or vaginal fluids. If the virus cannot be eliminated, in a few weeks of getting HIV infection, the virus replicates in human cells. With the increased load of virus and decreased body immunity, flu-like symptoms such as low-grade fever, sore throat and fatigue usually

Estimates of TB Burden (WHO 2019) in India	Number	Rate per lakh Population
Incidence of TB cases (includes HIV + TB)	2.640 million	193
Incidence (HIV+TB only)	71,000	5.2
Incidence (MDR/RR-TB)	124,000	9.1
Mortality (deaths) (excludes HIV+TB)	436,000	32
Mortality (deaths) (HIV+TB only)	9,500	0.69

occur. The disease generally has few symptoms or is asymptomatic until it progresses to AIDS. The symptoms of AIDS include weight loss, fever, night sweats, fatigue, swollen lymph nodes, mouth or orifical ulcers and recurrent infections. No definite cure and freedom from HIV exist for AIDS patients. Still, strict adherence to antiretroviral treatment regimens (ARVs) can dramatically slow the disease progression and prevent secondary infections and complications. If a person is infected with HIV, the virus stays in the body for life as there is no effective cure for HIV. But with proper treatment and medical care, HIV can be brought under control. People with HIV who get effective HIV treatment can live long, healthy lives and protect their partners. With proper medical care and anti-HIV drugs, the progression can be controlled.

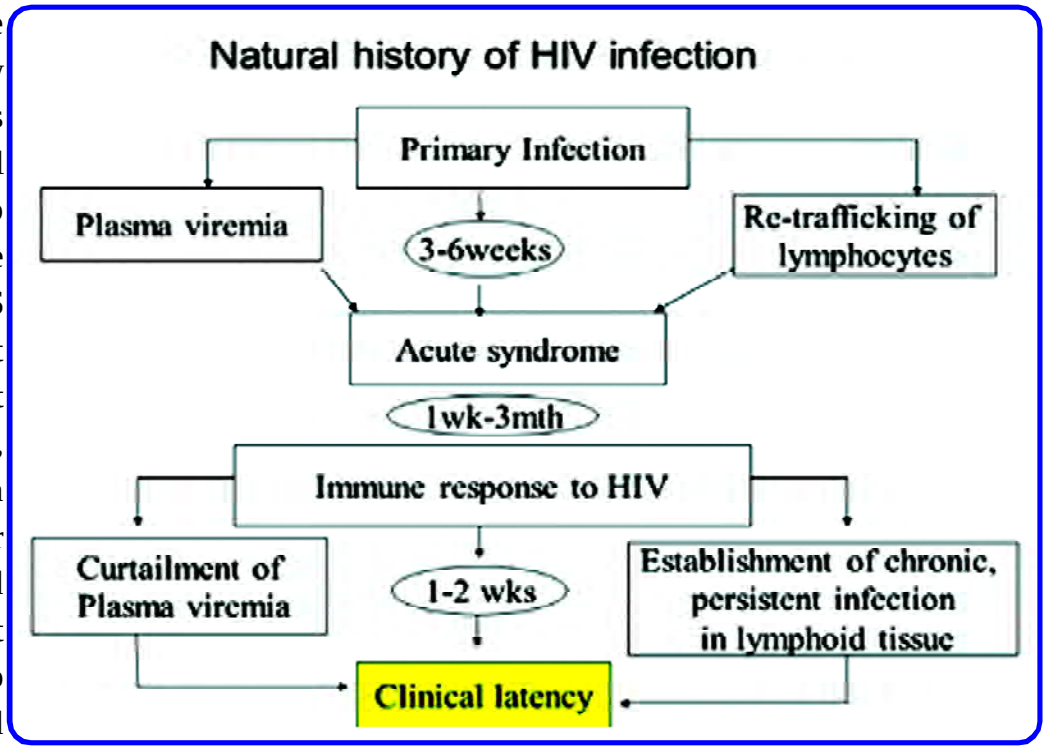

Figure 1: Natural history of HIV infection

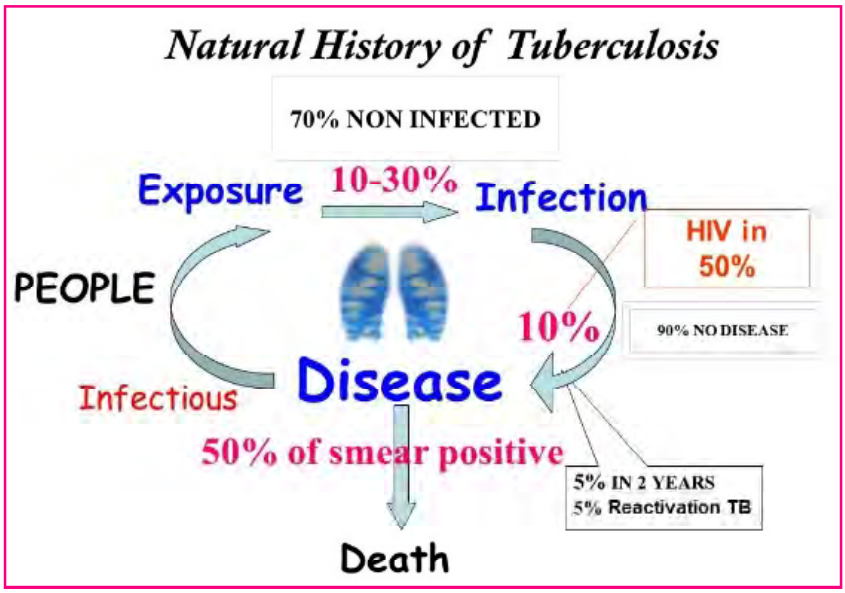

Figure 2: Natural history of tuberculosis

Pathogenesis of HIV and TB

Mycobacterium tuberculosis has been causing various opportunistic infections involving most organs, most commonly Pulmonary Tuberculosis. Tuberculosis lymphadenitis is also another common disease affecting cervical lymph nodes. Due to the complexity of the bacteria,

pathogenesis. Our immune system is regulated by lymphocytes, a type of white blood cell in our body. Based on the factor called Cluster Determinant (CD), lymphocytes are of two types such as CD4 (helper T cells) and CD8 (cytotoxic T cells). CD4 cells are responsible for body immunity (cell-mediated) and fight against infections. The CD 4+ T helper cells confer the Cell-Mediated Immunity (CMI). CD4+ T helper cells also provide the defence against TB infection. The hallmark of HIV infection is the depletion of CD4+ T helper cells. Once immune suppressed, the body cannot clear the virus and suffer from continuous viral replication. CD8+ lymphocytes have an essential role in the early control of viremia, but ultimately immune system becomes fatigued and dysfunctional with persistent viremia. HIV remains a chronic infection due to genomic integration of the virus in the human body, its cellular dormancy, and genetic changeability, tendency, and capability for immune escape. A persistent antigenic stimulation leads to dysfunction of T cells; therefore, with a decrease of T-helper cells, our body immunity decreases, resulting in reactivation of TB, or ease of re-infection by exogenous TB bacteria or development of progressive primary disease in HIV infection. A poor CMI leads to a weakened defence against TB and is probably the most potent known risk factor for the development of TB. The interaction between HIV and TB infections is bidirectional. Therefore, adequate CMI is required to create an immune response against *M. tuberculosis*. HIV infection causes CD4+ T-cell depletion and failure to impart immune response to *M. tuberculosis*. Hence, as the CD4+ cell counts decline, the rate of reactivation of TB is likely to increase. The chance of dissemination or spread of TB in the body also increases as the CD4+ T-cell counts fall below 200/microliter due to poor immune response. HIV infected persons are also at higher risk for progressive disease following primary TB infection and subsequent TB episodes from exogenous re-infection.

Impact of TB on HIV: There has been a significant increase in plasma HIV viremia during the acute phase of TB disease. There is evidence of accelerated HIV progression partly attributable to the increased systemic immune activation in HIV TB co-infection.

Several other mechanisms in the presence of tuberculosis infection may contribute to augmented virus replication. Even the local sites of active tuberculosis infection used to act as epifocal of HIV replication irrespective of systemic HIV-1 activity.

- Increased secretion of different pro-inflammatory cytokines, like tumour necrosis factor (TNFá), has been known to induce viral replication.
- Immune activation due to TB infection leads to increased expression of chemoreceptors (CXCR4 and CCR5) leads to increased viral entry into the immune cells and subsequent high replication and viremia.
- Lipoarabinomannan, a cell wall element of MTB, trigger virus replication in virus-carrying cells by inducing TNF–á and IL-6 production.

Clinical Presentation

The clinical presentation of HIV associated tuberculosis is varied and often atypical. Clinical presentation of TB in HIV infected patients largely depends on the level of immunosuppression. In patients with relatively preserved immune function (CD4+ count > 200 cells/mm3), pulmonary TB (PTB) is seen more frequently than extra pulmonary TB (EPTB). With progressive depletion of CD4 count, the clinical presentation of tuberculosis used tobe more atypical. TB frequently manifest with atypical feature like lower lobe pneumonia, similar to bacterial pneumonia rather than typical fibro-cavitary diseases of the upper lobes as seen in immunocompetent persons. As the immune suppression increases, the chest radiograph may show prominent mediastinal or para-tracheal lymphadenopathy or miliary form of tuberculosis. Extra pulmonary TB accounts for only 20 percent of cases in HIV negative persons, but it accounts for half of the cases in HIV positive persons. The disease also tends to be disseminated, involving two or more non-contiguous organs concomitantly. The most common sites of extrapulmonary disease are peripheral lymph nodes and pleura. In lymph nodes, there may be poor granuloma formation with increasing immunosuppression.

Other common extrapulmonary sites are pericardial, peritoneal, abdominal and neurological. The neurological manifestations of HIV TB co-infection are tuberculous meningitis (TBM), tuberculomas, and tuberculous brain abscess, meningeal TB being the most common of them. Progressive deterioration in the immune system may also lead to widespread dissemination of tuberculosis blood circulationleading tomultiple micro-abscesses, organ involvement and abdominal lymphadenopathy.

Diagnosis

*HIV testing:*The national programme uses fourth generation rapid tests which detect p24 antigen as well as antibodies to HIV. Voluntary counselling and testing (VCT) are the traditional approach towards HIV testing with emphasis on pre-test counselling, apart from provider-initiated testing and counselling. For TB patients, it is desirable that HIV testing be carried out as an essential (not mandatory) part of TB treatment registration, and it should be done before or at the point of TB diagnosis. In children below 18 months of age, the persistence of maternal antibodies may lead to false-positive antibody-based tests. In this age group, the diagnosis of HIV is made by tests that detect HIV nucleic acid (antigen) on a dried blood sample (DBS) from the infant.

As per HIV testing services (HTS) guidelines (2015), the offer of testing is made to all TB patients (confirmed and suspects), patients with sexually transmitted infections, pregnant women in addition to provider-initiated testing and counselling (PITC).

*Diagnosis of TB:*The diagnosis of pulmonary tuberculosis in HIV negative patients is relatively easy as patients are often sputum positive for Acid Fast Bacilli (AFB). World Health Organisation recommends TB screening at the time of diagnosis of HIV before ART is started and at regular intervals

during follow-up. The sputum microscopy can detect tuberculosis bacteria in HIV infected persons in 45 percent of cases. Cartridge-based nucleic acid amplification test (CBNAAT), e.g. Xpert MTB/RIF or TrueNat, has much higher efficacy in detecting TB cases and also can see rifampicin resistance. It provides diagnosis and rifampicin resistance results in about 2 hours.

Management

Principles for managing HIV TB co-infected patients: If a patient with TB is diagnosed to have HIV, the urgency is to start TB treatment as per the treatment guidelines. All HIV TB coinfected patients are to be initiated on antiretroviral treatment (ART) regardless of the CD4 count. ART reduces the incidence and recurrence of TB and death rates. Co-trimoxazole, used for prophylaxis to prevent pneumocystis infections, should be given to all HIV TB patients.

As a routine, all HIV persons need to be screened regularly for TB using the 4-symptom questionaries- new-onset cough, fever, weight loss and night sweats among adults during their visit to the ART centre.

The management of active TB disease in both HIV infected persons and HIV negative persons is essentially the same with a few additional considerations. In HIV infected person, ART must be started early during treatment to reduce the risk of death. Appropriate management requires combining anti-TB drugs, ART and co-trimoxazole (trimethoprim-sulphamethoxazole) preventive therapy (CPT) to prevent progression of the disease and other opportunistic infections (OI). ART reduces mortality by about 80% (range 64-95%) in patients with drug-susceptible TB, and CPT (co-trimoxazole preventive therapy) halves mortality risk. The addition of TB Preventive Therapy (TPT) among PLHIV, who do not have active TB, prevents activation of latent TB to active TB disease.

Deaths occurring in the earlier months (first month) of TB treatment are usually due to TB, but the late deaths are due to HIV progression. The national programme of India also recommends simultaneous initiation of anti-TB treatment and ART for all coinfected patients with a CD4+ count less than 50 cells/ mm^3 to reduce mortality among severely immune-compromised patients. Initiating ART during TB treatment was associated with reduced mortality, improved ART compliance and sustained patient retention.

Another significant challenge is determining the optimum time to start ART for patients on TB treatment, as any delays in ART initiation are associated with a substantial risk of mortality. It has been recommended that in coinfected patients, TB treatment should be initiated immediately on diagnosis of TB, and ART should be initiated within the next eight weeks, irrespective of CD4+ cell count. Patients with CD4+ cell counts of less than 50 cells/ìlmustbe given ART within two weeks of initiation of TB treatment for a better outcome.

Antiretroviral Therapy

The virus hides in ‘immunological sanctuaries’ in the body; it is therefore too difficult to wipe it off. As antiretroviral drugs cannot eradicate the HIV infection, the goals

of ART are to achieve suppression of viral replication with the recovery of the immune system and eventual prolongation of life and improving quality of life. ART also prevents transmission of HIV by suppression of the viral multiplication.

Zidovudine was the first drug effective against HIV in 1985, but the virus developed resistance quickly with a single drug. The Discovery of non-nucleoside reverse transcriptase inhibitors (example: Nevirapine and later Efavirenz) made the therapy simpler and soon became standard of care along with two nucleoside reverse transcriptase inhibitors. The availability of different drugs in fixed-dose combination (FDC) by Indian pharmaceutical companies in generic forms made therapy simpler, reduced the number of tablets to be taken daily, thereby increasing adherence potential. India has contributed largely for global ART supply at a lower price,"a dollar a day" by an Indian pharmaceutical company, which has been the game-changer in increasing access to antiretroviral (ARV) drugs globally.

For the last two decades, the standard regimen for the treatment of HIV-1 infection has been "triple-drug therapy". In India, the National AIDS Control Organization (NACO) currently recommends a simple harmonized ART in the form of a single dose /tablet of fixed-dose drug combination including Tenofovir, Lamivudine and Dolutegravir to all newly diagnosed HIV-1 infection regardless of patients' CD4+ count or clinical stage. Efavirenz is now provided only for those women who do not want to take dolutegravir as it is considered safe to be administered during pregnancy.

Many times, HIV patients have intractable diarrhoea, and, in such cases, there is malabsorption of ARV and ATT drugs, which may lead to the emergence of drug resistance.

IRIS

The condition is commonly known as "immune reconstitution inflammatory syndrome" (IRIS). IRIS may present rapid clinical deterioration caused by the inflammatory response due to dysregulated immune response. IRIS is a clinical condition manifested in some cases of AIDS or immunosuppression due to recovering body immune response. It paradoxically makes the clinical symptoms of infection worse and, at times, very severe. *Mycobacterium tuberculosis* has been the commonest pathogen associated with IRIS.

HIV & MDR-TB

There were an estimated 484 000 incident cases of multi-drug resistance (MDR)/ rifampicin resistance (RR) TB worldwide in 2018, with India sharing 27% of the global burden. HIV and MDRTB co-infection are associated with much higher morbidity and mortality. During co-treatment of HIV TB, several factors like poor drug absorption, pill burden and overlapping toxicities leading to poor compliance, drug interactions leading to sub-therapeutic drug levels etc, may lead to emergence of drug resistance to anti-TB drugs as resistance to ARVs. Second-line anti-tubercular drugs are more toxic and often difficult to tolerate.

TB Preventive Therapy

TB Preventive Therapy (TPT) involves the administration of selective anti-TB drugs to TB negative people to prevent activation of latent TB. The effects of TPT have shown to augment the impact of ART on reducing the incidence of TB. Under the national programme, India is presently using Isoniazid (INH) for individuals with suspected latent TB infection so as to prevent progression to active TB disease.

National Framework for Joint HIV/ TB Collaborative Programs in India

Implementation of TB and HIV collaborative activities in India started in 2001 to present-day intensified case-finding (ICF), referral to NTEP designated microscopy centres (DMCs) and referral of TB patients with HIV risk for HIV testing and counselling.

The national policy framework for TB/ HIV Collaborative Activities between National Tuberculosis Elimination Programme (NTEP) and National AIDS Control Programme (NACP)guides establishing mechanisms for coordination between NACP and NTEP at national, sub-national and district levels. This framework also focused on the cascade of care for HIV-TB coinfected patients from initial suspicion to confirmation of TB and initiation of anti- tubercular treatment (ATT) and ART with monthly coordination meetings to review cross-referrals and track lost people at some stage of cascade.

HIV-TB Control

- Early diagnosis
- Effective TB treatment
- Control of infection transmission
- HIV prevention
- Inter-sectoral coordination for care for HIV-TB coinfected

Challenges

Some key challenges in HIV/TB have been a multi-fold burden of stigma, discrimination and economic loss suffered by people and families with the disease. As a result, there has been gaps between TB and HIV prevention, treatment and care services (e.g., increased access and coverage of HIV screening for TB patients, access to ART and other interventions) and coordination among NGOs working in TB and HIV projects including linkage of NGOs working for different high risk population like commercial sex workers (CSW), men who have sex with men (MSM), and intravenous drug users (IDU) to TB sites.

Some challenges in the management of HIV-TB infection include so many pill burdens, poor tolerance, poor drug absorption from the stomach, poor adherence, substance abuse, drug-drug interactions, overlapping toxicities, stigmatization and discrimination etc.

In addition to existing programmes, both NTEP and NACP must find better ways to prioritize service delivery that should focus on the wide-scale deployment of logistics, infrastructure, human resources and sustainability of uninterrupted services.

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9 TUBERCULOSIS PREVENTION: VACCINES & BEHAVIOURAL ASPECTS

[1]Abhinav Sinha
[2]Srikanta Kanungo

"Tuberculosis is a social disease, its understanding demands that the impact of social and economic factors on the individual be considered as much as the mechanisms by which tubercle bacilli cause damage to the human body"- Rene.J. Dubos

Introduction

Tuberculosis (TB) is an infectious disease usually caused by *Mycobacterium tuberculosis*, transmitted from one person to the other primarily through droplets while coughing, sneezing and spitting etc. It mainly affects lungs known as pulmonary tuberculosis but can also involve other body parts, commonly referred to as extra pulmonary tuberculosis. The most important risk factors for TB infection are Human Immunodeficiency Virus (HIV), diabetes mellitus, crowding, malnutrition, alcoholism and Hodgkin lymphoma. World Health Organization declared tuberculosis as a public health emergency in 1993 when it urged governments to scale up their efforts to prevent and control TB. Soon, directly observed treatment, short course (DOTS) was launched. Following the WHO's mission, India initiated its National Tuberculosis Programme (NTP) in 1962.Later, in 1997 the strategy was revised with implementation of DOTS under Revised National Tuberculosis Control Programme (RNTCP). A case based web platform 'Nikshay' was launched in 2012 to electronically report and keep a track of TB data. Recently IN 2020, National Tuberculosis Elimination Programme was launched with a vision to achieve 'TB free India'. Despite being preventable and 60 years of efforts, India still has the highest tuberculosis burden and mortality in the world.

Pillars for TB Prevention and Control

Tuberculosis can be prevented, treated and cured with emphasis on three priority areas:

1. Identify TB cases, complete their treatment and render their status as non-infectious.
2. Screen the contacts of active cases to determine if they are the active disease themselves; or whether they have been infected; or prophylaxis is required especially for children and other high risk persons.
3. Screening, testing and treating high risk populations such as immunosuppressive drug users, HIV patients, slum dwellers etc. for latent TB infection.

These three strategies not only focus on individual cases but also fulfill broader epidemiologic functions by reducing active case loads and hence, ceasing the transmission in the community. However India faces daunting challenges in TB control due to high latent TB infection in the community which may re-activate at any time. Additionally, delayed diagnosis and inadequate treatment also accentuate the issue. Furthermore, the situation becomes complex among multi-drug resistant (MDR-TB) and extensively drug resistant (XDR-TB) which remains undetected, or after detection have poor chances of treatment success with a high loss to follow up.

"Knowing is not enough; we must apply. Willing is not enough; we must do."- Goethe

Patient Centered TB Care

The End TB strategy recommends a patient centered approach for care and prevention of TB. This should be locally contextual, culturally tailored and consider equitable distribution. This can be achieved through accessible healthcare facilities; availability of human resources such as doctors, nurses, laboratory technicians and treatment supervisors; availability of material resources such as smear microscopy, x-ray and medicines; quality services; relevance of services in harmony with the needs of patients such as nutritional, financial and psychosocial support; timing and continuity of care, technical quality and social accountability.

Prevention Strategies

"Prevention is better than cure."

Targeting preventive therapy is the most effective intervention to control tuberculosis. It is the most comprehensive strategy as only appropriate social behavior can address the challenge of dealing with the large latent cases of TB. Hence, following steps should be taken to prevent TB:

Air Borne infection Control

It aims to minimize the risk of transmission broadly at two levels: community and institutional level. At community level, social habits such as spitting, sneezing without covering face, not following cough etiquettes, alcoholism, debilitating or mentally challenged patients and delay in presenting to the facility pose a significant challenge. Additionally, special groups such as migrant population; slum dwellers; backward and tribal pockets; institutional setups such as old age homes, destitute homes, children homes and jails; patients having multimorbidity and comorbidities such as HIV and diabetes are at a higher risk. Environmental pollution also contributes to challenges in spreading TB at community level.

At institutional level, patients with chest infection at outpatient settings and poor ventilation while at in patient facility cough screening, use of mask and counselling needs to be focused. Additionally, at institutional level certification for AIC compliance should be necessary, fast tracking of cases, provision of N95 masks for staff, separate facility for positive patients, infection control measures at ART clinics, personal protective equipment (PPE) for staff, periodic trainings is necessary.

Contact Tracing

Transmission from index case to the contact can happen anytime hence all contact should be identified with attention to symptomatic people, children below six years of age and other high risk groups.

Undernutrition

It is one of the most common risk factor for progression of TB in India. Previous evidence suggests TB incidence could decline by 14% with per unit increase in body mass index (BMI). Therefore, we should aim at reducing undernutrition especially among at risk population. Furthermore, undernutrition can also lead to severe disease, adverse effects and higher likelihood of relapse after cure. The NTEP recommends nutritious food and a daily micronutrient supplements. Additionally, TB patients are financially supported for taking good nutrition under 'NikshayPoshan Yojana'.

Preventive Therapy

Children below six years of age are more susceptible to TB infection and hence will be evaluated for active TB. Once active infection has been ruled out, a preventive therapy of isoniazid (INH) irrespective of their BCG vaccination or nutritional status is started. The advised dose for INH is 10mg/kg body weight for a minimum of six months.

Tuberculosis Vaccine

Sustainable Development Goals (SDG), WHO End TB Strategy, and the End TB Goals by Stop TB Partnership targets to end the global epidemic of TB by 2035 which remains a daunting target. Developing an intervention against tuberculosis is a crucial global health priority. Although, Bacille Calmette Guerin (BCG) vaccine has been successfully used to protect against childhood TB for almost a century still adult TB vaccines are in the development stage. BCG vaccine provides protection against TB during childhood up to 10 years of age but its efficacy wanes during adolescence with minimal protection against adult pulmonary TB. Currently, adult TB vaccine candidates are in pipeline for clinical trials which can be grouped into two broad categories: the first being mycobacterial whole cell-derived vaccines and subunit vaccines which are directed against some selected antigens. The various vaccine candidates and their current status is provided below:

Vaccine Candidate		Clinical Trial Phase				
		Phase 1	Phase 2	Phase 2a	Phase 3	Licensed
Mycobacterial whole cell-derived	Live			MTBVAC	VPM1002	BCG
	Killed		RUTI	DAR-901	MIP, Vaccae™	
Sub-unit	Adjuvant	Gam TBvac	ID93+GLA-SE	H56:IC31	M72+AS01E	
	Viral Vectored	Ad5Ag85A, ChAd0x185A		TB/Flu-04L		

Mycobacterial Whole Cell-derived Vaccines

These vaccines are derived from *Mycobacterium tuberculosis*, BCG or closely related strains of non-tuberculous mycobacteria. These can further be classified into live vaccines that are attenuated through genetic modification and killed or fractionated. These vaccines comprise of different antigenic components which offer a diverse immune response.

Subunit Vaccines

These vaccines target a small number of selected antigens (six or less). The main challenge in developing these vaccines is identifying the optimal antigen to be included. The current used antigens have been tested in animal models prior to developing vaccines candidates.

The significant protection rendered by M72/AS01E candidate during Phase 2b of clinical trials points towards feasibility and strongly encourages a brighter future and continued efforts in this direction. However, there is an urgent need to develop an effective vaccine which can be easily administered and cost-effective so that it is accessible for all and especially for marginalized communities such as slum dwellers who are at a higher risk of contracting TB. Additionally, strategies such as routes of administration and vaccine platforms need to be channelized. Lessons learnt on vaccine equity during COVID-19 pandemic should be applied for egalitarian distribution of TB vaccines especially among LMICs.

Conclusion

Given the magnitude of TB in India and its associated cost, it cannot be overlooked to achieve Universal Health Coverage. Persistent efforts are required to control and manage TB with increasing pace.Although, effectiveness of prevention has been long established still public health measures aim at active case finding and treatment. Hence, prevention should be at the core of all public health programmes aimed at controlling TB infection. Developing indigenous vaccine candidates should be targeted. Political commitment along with prioritization of resources can help in achieving goals. Additionally, at individual level people should be vigilant, take precautions, report to the health facilities at the earliest and complete treatment to end TB.

Key Messages for Achieving Tuberculosis Control in India

- Provision of cost-effective high quality rapid diagnostics and treatment for all everywhere.
- Inclusion of high risk populations including close contacts in care through active case finding.
- Invest in making tuberculosis patients financially stable to achieve full treatment.
- Increased efforts to accelerate tuberculosis research and development of diagnostics, therapeutics and vaccines.
- Accountability of stakeholders and key personnel in achieving targets.

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Conclusion

TB is already a leading cause of morbidity and mortality and remains a significant public health problem in the developing world. The present-day COVID-19 pandemic put the control program to a decade back. The HIV epidemic has caused a resurgence of TB. HIV TB co-infection has a major impact on human health and throws unprecedented challenges on the already strained health care system in most countries. The dual epidemic also pushes the victim to a spiral of poverty, stigma and discrimination.

Clinical management of HIV TB co-infection is challenging. There are significant issues like pill burden, drug interactions, toxicities, poor adherence, which may impact the treatment.

Although the HIV TB epidemic scale may look daunting, sustained efforts through awareness, preventive strategies, better diagnostic tools, newer and less toxic drugs, cutting-edge research, and knowledge sharing have been carrying a positive change. Committed leadership and an integrated approach are needed to defeat this scourge. We also need to be aware of the setback that the recent COVID-19 pandemic had on the sustainability of the collaborative activities at all levels of health care and how to reverse these setbacks.

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10 TUBERCULOSIS IN DIABETIC POPULATION

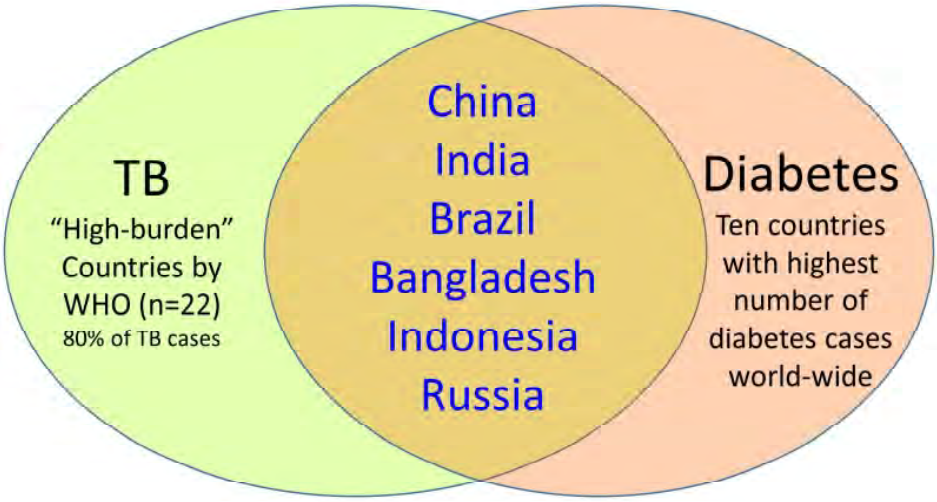
Tahziba Hussain

Introduction

Type 2 Diabetes Mellitus (T2DM) has become a pandemic and is in fact the bane of the modern times. At present, there are 300 million people affected with diabetes globally and the number is likely to rise two-fold in the future five years.

India has the highest burden of tuberculosis (TB) and second highest burden of diabetes in the world, with annual TB incidence of 2.2 million cases (range 2.0-2.5 million) and around 63 million people living with diabetes.

About 75% of people with diabetes live in low- and middle-income countries and about half of them are unaware of their diabetes status. The global increase in type 2 diabetes mellitus (DM) is recognized as a neglected, important and re-emerging risk and challenge to tuberculosis (TB) control. Individuals with DM have **three times** the risk of developing TB and there are now more individuals with TB-DM co-morbidity than TB-HIV co-infection. India has been dubbed the **Diabetic Capital of the world** with its huge diabetic population. India has the highest number of TB cases and also the highest number of dually infected individuals, in the world. The association and synergistic role between T2DM and TB in causing human disease has been recognised since long back. Globally, about 10% of TB cases are associated with diabetes. The linkage between T2DM and TB is a challenge for global tuberculosis control. Improved understanding of the bi-directional relationship of the two diseases is necessary for proper planning and collaboration to reduce the dual burden of diabetes and TB. In people with TB, it may be appropriate to actively screen for DM. Prevention, screening, and treatment of both diseases together is more effective. A model similar to the TB-HIV program may be the best approach. Recognizing the serious threat posed by Diabetes-TB, the National Tuberculosis Elimination Program (NTEP) calls for strengthening collaboration between TB and diabetes control programs for better management of diabetic patients with TB and TB patients with diabetes. The diabetes epidemic has a huge impact on the dynamics of epidemiology of TB and poses several challenges to control of TB in a resource-poor country like India. Diabetes/TB burden can be brought under control by timely diagnosis of TB among diabetics by intensified case finding, by adequate and effective treatment



of detected cases and preventive therapy. Diabetes epidemic poses a serious threat on control of TB, and the current gaps in knowledge related to diagnosis, prevention and treatment of TB among people with diabetes.

Convergence of countries with highest burden of TB and DM worldwide. Among the ten countries with the highest number of diabetes patients worldwide, six are also among the 22 high-burden countries that contribute 80% of the TB cases worldwide.

Bi-directional Relationship

Type 2 Diabetes mellitus and Tuberculosis (TB) often manifest together leading to complications at various levels.

Several studies have reported that diabetes, smoking and alcohol abuse are the risk factors which can actually raise the risk of developing active TB twice or thrice. It was observed from a mathematical modelling analysis of the effects of smoking on TB infection and mortality that smoking might lead to an excess of 18 million TB cases and 40 million deaths from TB between 2010 and 2050. In India, a major portion of the TB burden can be attributed to smoking (40%) and DM (15%).

There is a bi-directional relationship between TB and diabetes, and they both impact the presentation of each other. Diabetes is being increasingly recognized as a risk factor for TB and may affect its presentation, whilst TB may worsen glycemic control or lead to IGT (impaired glucose tolerance) among TB patients. This relationship demands adjustment in treatment and the need to employ insulin in the treatment of hyperglycemia during active TB infection when required. A review of the anti-glycemic agent(s) is also warranted once TB treatment is over.

The expected rise in diabetes cases in developing countries (driven mainly by type 2 diabetes) which also bear the brunt of tuberculosis would increase the influence of diabetes on TB in the coming future.

Many studies suggest that DM is associated with the clinical presentation of TB. Namely, TB-DM patients (versus TB-no DM) are more likely to present with pulmonary (versus extra-pulmonary), cavitary (versus

non-cavitary) and sputum smear-positive TB at diagnosis. During the course of TB treatment, TB-DM patients take longer to convert from sputum smear-positive to -negative. Some studies also find that DM patients are more likely to present with drug-resistant and multi-drug resistant TB, although this relationship is not seen in all studies.

A study using dynamic TB transmission models to analyze the potential effects of DM on TB epidemiology in 13 countries with high burden of TB concluded that stopping the rise of DM would avoid 6 million incident cases and 1.1 million. TB deaths in these countries in 20 years. Thus, every community worldwide needs to evaluate the prevalence of DM and its contribution to TB. This information is variable between regions and critical to guide for the most efficient use of limited resources for TB control programs.

Pulmonary Versus Extra-Pulmonary TB

Pulmonary TB accounts for 70-80% of the cases, and it is generally accepted that immune compromise facilitates hematogenous dissemination of *M. tuberculosis*, pre-disposing to extra-pulmonary TB. Such is the case of TB patients with HIV-AIDS or those taking TNF blockers. This contrasts with TB-DM patients who are less likely to present with extra-pulmonary TB.

This may be due to a hyper-reactive cell-mediated immune response to *M. tuberculosis* in DM patients that may be suboptimal for containing *M. tuberculosis* growth within the lung, but effective for preventing its dissemination and reactivation elsewhere.

Cavitary and Smear-positive TB

M. tuberculosis induces a strong cell-mediated immunity leading to the formation of pulmonary granulomas (tubercles) that are thought to be a double-edged sword for the host. Granulomas initially limit *M. tuberculosis* growth, but in hosts in whom *M. tuberculosis* continues to replicate, these structures undergo central caseation with rupturing and spilling of thousands of viable bacilli into the airways. This “cavitary TB” is associated with sputum smear-positivity. TB-DM patients are more likely than TB-no DM to present with cavitary TB that is accompanied by higher bacillary burden in sputa.

Together, the higher frequency of PTB vs extra-pulmonary TB, cavitary TB, and smear-positive TB at diagnosis and extending during treatment, would predict that TB-DM patients are more infectious than TB-no DM.

TB Treatment outcomes in TB-DM Patients

There is growing evidence from observational studies that TB-DM is associated with an increase in adverse TB treatment outcomes, specifically for delays in mycobacterial clearance, treatment failures, death, relapse and re-infection.

Delays in Sputum Smear Clearance and Treatment Failure

TB-DM versus TB-no DM patients are more likely to remain sputum smear-positive after completion of the intensive phase of treatment, and this outcome is an early predictor of treatment failure (sputum smear or culture positivity at five months or later

during treatment), which is also more likely in TB-DM versus TB-no DM.

Relapse and Re-infection

TB-DM patients also appear to have a higher risk of relapse. The review by Baker et al reported a nearly 4-fold risk of relapse in TB-DM versus TB-no DM. A prospective study in southern Mexico with 1262 TB patients characterized for *M. tuberculosis* genotypes further distinguished between relapses and re-infections, and found higher adjusted odds of both outcomes in DM vs no DM.

Should TB-DM patients be Managed Differently from TB-no DM?

The clinical findings and higher risk of adverse outcomes in TB-DM patients indicate the need for prospective cohort studies aimed at confirming these observations and identifying the underlying factors leading to treatment failures in DM.

Immunity

People with a weak immune system as a result of chronic diseases such as diabetes are at a higher risk of progressing from latent to active TB. People with diabetes have a two to three times higher risk of getting infected with TB, compared to people without diabetes.

Large proportions of people with diabetes as well as TB remain undiagnosed, or are diagnosed at a late stage. Due to lack of early detection and treatment, complications from TB-diabetes co-morbidity lead to high cost on treatment and out-of-pocket expenditure. Early detection can help improve care and control of both diseases.

Diabetes can lengthen the time for sputum culture conversion. Theoretically, this could lead to the development of drug resistance if a 4-drug regimen in the intensive phase of therapy is changed to a 2-drug regimen in the presence of culture-positive TB.

People with TB and co-existing diabetes have a four times higher risk of death during TB treatment and higher risk of TB relapse after treatment. The World Health Organization (WHO) recommended that TB treatments should be rigorously implemented for people with TB–diabetes co-morbidity.

Diabetes is complicated by the presence of infectious diseases, including TB. It is important that proper care for diabetes be provided to patients suffering from TB–diabetes co-morbidity.

TB is associated with worsening glycaemic control in people with diabetes. It has been argued that good glycemic control in TB patients can improve treatment outcomes.

The precise biological mechanisms that result in this interaction between diabetes and TB are still not clear. Epidemiological models have shown that diabetes accounts for 20% of smear-positive pulmonary TB and recent analyses have indicated that the increase in diabetes prevalence in India has been an important obstacle to reducing TB incidence in the country.

The Underlying Pathophysiological Mechanisms

The increased risk of TB among diabetes patients is multi-factorial and several putative mechanisms have been proposed. There is

decreased cellular immunity due to reduced T-lymphocyte count as well as function and a low neutrophil count. Diabetics show a reduced T-helper 1 (TH 1) cytokine response level, tumor necrosis factor (TNF-alpha and TNF-beta), interleukin-1, and interleukin-6 production compared to their non-diabetic counterparts. The susceptibility of diabetes patients to TB is mainly due to reduced numbers and function of T-lymphocytes. particularly TH1 cytokine inhibition of *Mycobacterium tuberculosis*. There is macrophage dysfunction in diabetes which results in impaired production of reactive oxygen species and phagocytic and chemotactic function. Chemotaxis of monocytes is also impaired in patients with diabetes, a defect which does not improve with insulin. Hyperglycemia is thought to also impair the force of respiratory burst in expelling pathogens. Whilst these proposed mechanisms are plausible, it is important that further mechanistic studies are done to confirm them or otherwise. The stress response to infection may also play a role in dysglycemia, a situation mediated by the effect of interleukin-1 (IL-1), interleukin-6 (IL-6), and TNF-alpha. This temporal relationship has been demonstrated in some studies where between 19 and 42.6% of active TB patients were discovered to have IGT or diabetes with a significant reduction or complete regression in the rates following treatment.

TB may cause TB pancreatitis as well as pancreatic endocrine hypofunction which may lead to IGT or new onset diabetes or worsen its control. TB pancreatitis may become obvious only after the person develops diabetes. Lastly, whilst malnutrition has been proposed as a risk factor for infections and dysglycemia, body mass index has not been associated with IGT or diabetes.

Understanding the Immune Dysfunction to Mtb in DM patients

Given that efficient Mtb killing by anti-mycobacterial antibiotics requires cooperation between innate and adaptive immune responses, the higher frequency of adverse outcomes in DM patients suggests that the hyper-reactive immune response to mycobacterial antigens in TB-DM patients is not effective for Mtb killing. There are several possible explanations for the contribution of dysfunctional immunity to these adverse treatment outcomes.

1) The higher Th1 and Th17 response is only present in the peripheral blood of TB-DM patients, while anti-inflammatory responses that facilitate Mtb growth only occur in the lungs.

2) There is a higher production of pro-inflammatory cytokines like IFN-ã in the lungs of humans (as observed in mice), but it is not effective for downstream activation of macrophages or cytotoxic T-cells that ultimately kill Mtb.

3) The hyper-reaction to Mtb antigens may be deleterious and contribute to lung tissue damage with more severe TB and the higher frequency of death in TB-DM patients.

Understanding this complex relationship between excessive immunity in TB-DM will

help improve the clinical management of TB patients, regardless of their DM status.

Bi-directional Screening

In India, the screening of TB patients for diabetes is relatively easy and a high rate of detection of DM, ranging from 10%-44% in TB patients has been observed in many studies in different states. However, screening for TB among diabetes patients is less easy, with several studies reporting challenges such as less registration of patients and reluctance to provide sputum specimens. The doctors and/ or technical staff, on the other hand, are reluctant for this additional work and do not record the screening systematically. Routine screening for dysglycemia should be done for all TB patients, especially at the time of diagnosis. Among patients with diabetes, there is a stronger case to be made for screening for TB routinely or at the least suspicion. Diagnosed patients should promptly be referred to a TB centre for treatment. Strategies for the prevention of TB must continually be emphasized. These include improvements in housing and nutrition, poverty reduction, treatment of HIV/AIDS, and above all the availability of diagnostic tools such as sputum smear microscopy, X-rays, and automated molecular tests

Odisha

Good geographical coverage of the TB control programme in Odisha with emphasis on universal access to active TB case finding in the community is probably the reason. Several studies have reported that Diabetes makes a substantial contribution to incidence of TB. TB control efforts might be benefited from active case finding and treatment of latent TB in people with diabetes and increased efforts to diagnose and treat diabetes in populations where diabetes affects the risk of TB to a larger extent. In India, the growing problem of diabetes in this high-risk group population could make prevention of tuberculosis, a priority area in the future. Further research is needed to determine this and ascertain the average timing of TB screening among diabetes patients. More research is warranted to investigate how the incidence of TB impacts diabetes control efforts in this state.

Conclusion

Screening for TB among T2DM patients in diabetes clinics would lead to earlier detection of TB, which in turn, would help in early treatment while decreasing the risk of nosocomial transmission. It will further lead to better TB-specific treatment outcomes and prevention of diabetes complications. We, therefore, feel that screening T2DM patients, irrespective of their complaints and symptoms, at regular intervals, for signs and symptoms of TB would go a long way in early detection of the Tuberculosis.

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11

COVID-19 AND TUBERCULOSIS: TACKLING THE DUAL PROBLEM IN FUTURE

Sampat Dash

A Merger of an Age-old Pandemic with a New One

December 2019 will always be remembered in history as the date that changed the world and Wuhan, the place from which it all started. However, before the Coronavirus Disease 2019 (COVID-19) pandemic, we in India were struggling with many other communicable disease pandemics of which tuberculosis (TB) is the most aged one. Description about this is also present in our Vedas as "Rajyakshama" which means to decay. Prior to the discovery of TB bacilli by Robert Koch,the disease was considered to be due to bad air and poor hygiene of the surrounding environment.However, on 24 March 1882, after the bacilli was discovered, our understanding of this disease became clearer. So, this day is celebrated every year as "World tuberculosis day" to create awareness and continue our effort to fight this pandemic. India and China are the two most populous countries in the world and both are developing countries with population density being much more than the western world. Hence, the number of TB cases are way more than any part of the world and one out of four TB cases are found in India. This is not limited to drug sensitive TB cases but also drug resistant ones. So,a huge amount of health care resources in both these countries are mobilised to fight this pandemic even before the COVID-19 pandemic. But with COVID-19 coming to this part of world, it further strained the health care system leading to opening of many dimensions about management of tuberculosis pandemic.

What COVID-19 Has Done to The World

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which causes COVID-19, is considered to be a zoonotic virus that has transferred from the bats to the humans and was first detected in Wuhan province of China. Initially, the World Health Organization (WHO) never thought about the severity of this disease,however with its rapid spread all throughout the world, it was declared as a pandemic on "11 March 2020". Initially it was considered to spread only by fomites, but with time our understanding of this disease, it was found to be spreading by fomites and aerosols also. The spread started fromChinato Europe,and then to America, and finally the south east Asiasubcontinent. And obviously with a population of millions, this disease caused

havoc in all possible dimension including lock down to diverting all resources and manpower for this disease hence creating a deficit in all other disease management that has been previously being taken care of. This caused a gross mismatch between the COVID-19 disease and all other disease of public significance.

Similarities of this DUO (COVID-19 and Tuberculosis)

Both of these diseases primarily affect the respiratory tract to start with fever, cough and both can present with breathlessness to blood in sputum (Figure 1). TB and COVID-19severity mainly depend on the ability of the body's immunity to fight any infectious diseases. So, patients with multiple comorbidities like diabetes mellitus (DM), cardiac issues and people having any chronic disease of kidney, liver, brain are the ones who suffer more and land up in a serious state to the hospital. Hence, even though these diseases affect people of all age groups, those with poor immunological status are the ones that become sick enough to cause hospitalization and death. One more factor that also play an important role in India is the huge number of chronic respiratory disease patients like chronic obstructive pulmonary disease (COPD), uncontrolled asthma, people working in many industrial areas with poor air quality, as all these factors makes the local immunity of the lungs to work in a poor state making them prone to all types of respiratory disease including both COVID-19 and tuberculosis (Figure 2). COVID-19 also causes a more serious state in people who are already suffering from tuberculosis as their lungs are already in a bad shape. So, for countries like India, this Duo of COVID-19 and TB appears to be more stressful than other parts of world where they don't have TB.

The Adverse Effects of This Duo (TB and COVID-19)

The fright of COVID-19 made the world to put many restrictions, to start from stopping international flights to locking down the whole countries. This created a stigma for patients with respiratory complaints to come for consultation and treatment of their diseases including tuberculosis. The fear of COVID-19 also caused many institutions to shut down regular OPD services and divert all their resources for COVID-19 management. All these events hampered not only the new cases of tuberculosis from getting diagnosed but also the previously diagnosed cases from getting treated properly. Hence the pandemic of COVID-19 actually increased the severity of tuberculosis pandemic because of poor case findings and patients not getting proper treatment.

There is Always a Ray of Hope

The advice of "physical distancing, use of masks, and hand hygiene" has become a norm in this COVID-19 era. This has definitely caused a sense of awareness among the public about respiratory hygiene and avoiding any type of activities that cause crowding where there is a high chance of spreading any respiratory disease, hence tuberculosis prevention got a direct benefit. Not only these measures but also shutting down all type of locomotives, factories and other industries

for a significant time cause the air quality to improve significantly and hence disease which deteriorate due to of air pollution like COPD and Asthma exacerbation has definitely come down leading to significant amount of improvement of the health condition of these patients.This led to less hospital visit and exposure to COVID-19 environment. COVID-19 pandemic has made the authorities of all countries to understand the importance of health care system and the need of hour is to prepare the health system not only on the basis of manpower but also with infrastructure to be always ready for any such pandemic in coming days. Medical personnel have also understood the importance of personal protective measures while taking care of seriously ill respiratory cases like ARDS to prevent all aerosols generating procedures. The coordination between different health systems with lab networking including transporting seriously ill patients from one place to another improved a lot. ECMO understanding has also improved among the medical fraternity and this will definitely be of help in coming days to be used in deserving patients not limited to COVID-19. People also understood the importance of good health and the need of hour is to maintain good health and taking care of their comorbidities. All these will definitely improve in coming days the health care system and the health of the public leading to better control of not only COVID-19 but also other pandemic including tuberculosis both in outpatient management as well as taking care of those getting admitted with respiratory complications.

Where We are Now

We also need to look into the gain we achieved in this pandemic. Even though the loss is huge both in form of life and livelihood, but this pandemic also opened our eyes for a new tomorrow. We came to know about the gaps in health care system in terms of infrastructure, manpower, coordination between different departments involved in health care management, the need of public private relationship in managingCOVID-19 pandemic. Hence, it is the need of the hour to use the knowledge we gained during thisCOVID-19 pandemic to counter the age-oldtuberculosisfight to make a better tomorrow.

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In the article: NOBEL LAUREATE SIR C.V. RAMAN AND HIS DISCOVERY published in February 2022 issue of the magazine, there was a typographical error in the year of birth of Sir C.V. Raman. It should be 1888. The error is regretted.

STIGMA RELATED TO TUBERCULOSIS (TB) IN INDIA

12

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[2]Pranab Mahapatra

Stigma is a negative response that may manifest in disparities in behaviour towards stigmatised individuals (Abbey et al., 2011). It occurs when these individuals with a distinct attribute or personal trait are treated differently. When these stigmatising behaviours or attitudes are associated with a specific health condition, we refer to this as health-related stigma (Stuber et al., 2008).Sometimes, people have preconceptions or ideas about what a person should be like, based on their perception and belief. This is especially true for people who have contagious diseases. People prefer to distance themselves from these patients and their family members physically and socially, often leading to stigma and discrimination. This can come in a very subtle way, especially in the early stages, when people start to ask about a person's health, look suspiciously at them, or say things that don't make sense. On the other hand, there is overtly hostile behaviour or discrimination. A lack of understanding of these illnesses or fear often causes stigma. These problems get worse when people give out incorrect or misleading information. Stigma hurts the stigmatised person and their family members (Eicher and Bangerter, 2015).

Tuberculosis is a disease that can spread from person to person. It is a significant cause of ill health and one of the top causes of death in the world. It is caused by the bacterium *Mycobacterium tuberculosis*, which is spread from one person to another through droplets of cough. The disease usually affects the lungs (pulmonary TB), occasionally spreading to other parts. About a quarter of the world's people have *M. tuberculosis*infection. TB is a big problem in many low- and middle-income countries (LMICs). India has the highest number of people who have tuberculosis in the world, and tuberculosis control has been the focus of the Government of India's revised national tuberculosis control programme (RNTCP). TB can be prevented, as well as cured with appropriate treatment. About 90% of people who get tuberculosis disease can be treated with a 6-month drug regimen (WHO, 2021). Tuberculosis spreads more easily when people do not seek help or get a diagnosis quickly because of stigma. This increases the size of the tuberculosis pool, which makes it more likely that people who live with them and in the community will spread the disease. However, one of the major programmatic

challenges is stigma related to tuberculosis (Chakrabartty et al. 2018; Thomas and Stephen, 2021).

Stigma is often a roadblock in the path of appropriate health care for tuberculosis, delaying diagnosis and making it more challenging to manage and treat illnesses. People's perceptions and beliefs about tuberculosis influence how patients seek health care. The stigma around tuberculosis was caused by people being afraid of the disease itself, but it was also based on people's beliefs. More than half of people with tuberculosis experience stigma after being diagnosed, which causes them to stop taking their medication (Thomas and Stephen, 2021). Moreover, patients with TB are afraid of the spread of disease, so they don't prefer to go to a public place to avoid verbal abuse.

In India, both men and women face different problems because of the stigma. Tuberculosis-related stigma was highest in unmarried, economically inactive women with low socioeconomic status who were more likely to be stigmatised. Women had more tuberculosis stigma than men. Unmarried women with TB feel that they will face a challenge in getting a partner for their marriage. Those who are married at the time of TB diagnosis, were afraid of separation, divorce, isolation, and rejection from their families, especially their in-laws. Men were stigmatised and feared losing their jobs (Somma et al., 2008; Thomas and Stephen, 2021). The married women put off getting checked out and getting treatment because they don't want their husbands to find out about the disease and leave them. For men, stigma caused them to lose their jobs.

It's essential to look at the gender aspect of the illness it has a significant influence on careseeking all along the course of the disease. The social meanings associated with the gender can affect the response to illness and continued treatment. A careful look at the things that keep or break down stigma could help guide efforts to reduce its adverse effects and turn stigma into support.

Stigma and discrimination can worsen symptoms and make it more difficult to get treatment. Patients lost hope and had lower self-esteem because of stigma, which led to more psychiatric symptoms, problems with social relationships, and less likelihood to stay with treatment. Other adverse effects of stigma are unwillingness for treatment, staying away from family, friends, or co-workers, thus getting deprived of the support for treatment. It also makes it more difficult to find work, school, or social activities, and find a place to live where they can be protected from harassment. There are a lot of issues that aren't taken into account in the tuberculosis control program in India. There needs to be a participatory community approach where communities are involved at every stage for sensitisation and prevention of stigma.There are still problems in all tuberculosis control efforts because of the stigma around TB. This needs to be dealt with across multi-layers in the tuberculosis care cascade and requires psychosocial interventions that are patient-centred and health provider-centred. We need human-friendly, stigma-free, need-based

psychosocial interventions in addition to clinical interventions because tuberculosis is not just a medical disease but also a social disease, and we need to treat both the aspects at the same time.

People should learn how to deal with tuberculosis patients. Tuberculosis related stigma can hurt the patient and their family, and it may cause them to stay away from society because of shame and fear. There is a need for education to provide practical advice to people and families and teach communities to support people with tuberculosis.

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NTM:THE HIDDEN MENACE

13

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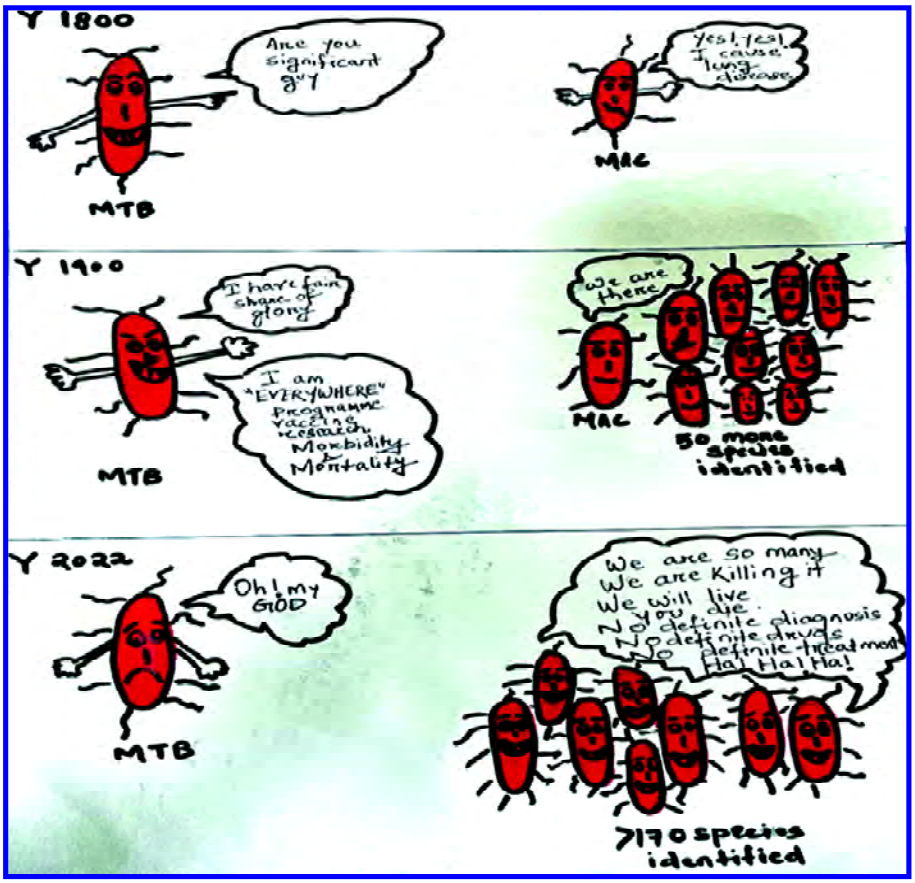
History

NTM, also known as non -tuberculous mycobacteria,has been known to exist as saprophytes and are known to cause disease in humans since 1800 A.D. It was earlier also known as MOTT (Mycobacteria other than tuberculosis), atypical mycobacteria, environmental mycobacteria, opportunistic mycobacteria, anonymous mycobacteria. The term non tuberculous mycobacteria (NTM) was unanimously coined by the American Thoracic society in 1997 and has been used since then(1). NTM was first isolated in 1890from a chicken. Hence it was known as *M. avium*. *M avium* was established as pathogenic mycobacteria causing disease when it was isolated from a man with silicosis in the year 1943(2).



Background

NTM are diverse and ubiquitous in the environment and about more than 170 species(3) have been identified till date of which 30 species are known to cause opportunistic infections in humans. (3) The incidence and prevalence of different species of NTM causing pulmonary as well as non-pulmonary diseases is rising globally. The symptoms due to NTM infection is vague and cannot be grouped into a single entity.

Therefore, any bacteria causing tuberculosis like illness other than MTB was grouped as bacteria causing Mycobacteriosis. Mycobacteriosis was used to exclude tuberculosis disease from any other illnesses.

NTM causes opportunistic infection in immune compromised individuals and was most commonly isolated from HIV patients. Nearly about 30 species of NTM have been confirmed to cause human disease but human-human transmission is not commonly seen in NTM infection. They are also emerging as mycobacterium causing fatal illness as most of the species are difficult to treat due to their intrinsic resistance to common antibiotics available as well as non-availability of a common drug regimen for their treatment.

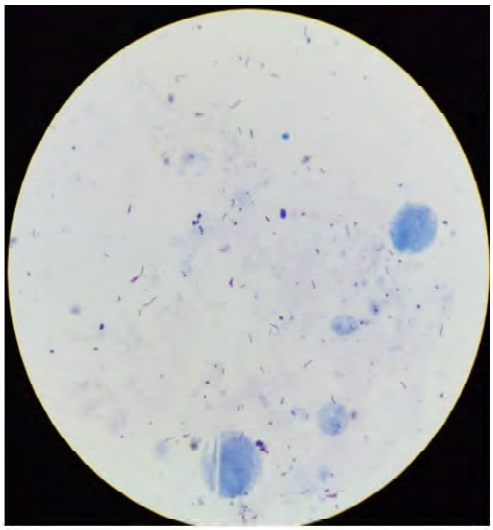
NTM is widely distributed in the environment, including soil, tap water, mud, food stuff. NTM has been isolated from many natural sources. Therefore, the man-made changes will greatly affect the biology of the organism and may increase the risk for causation of disease.

Microscopy

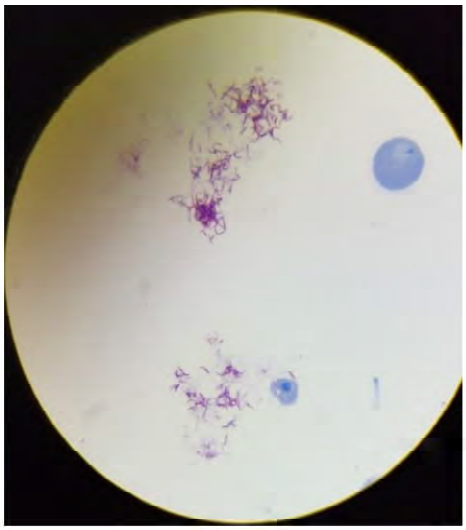
NTM are acid fast bacilli(pink in colour).The microscopic picture of NTM shows that they do not have the typical morphology(i.e. bacilli which are long slender with nodules) as of that of *Mycobacterium tuberculosis* (MTB), and can vary from being short AFB to filamentous in nature.

Culture

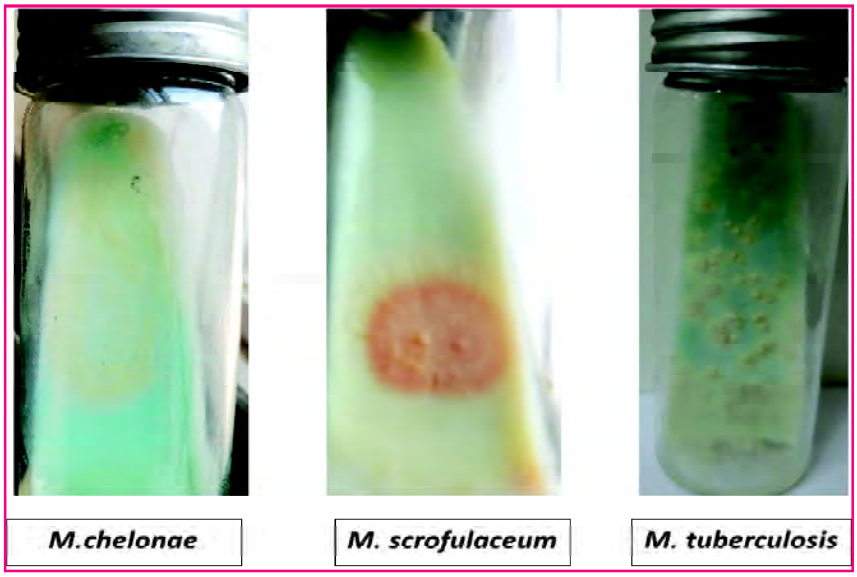
Most of the NTM are easy to culture and can be grown in media like Lowenstein Jensen (LJ), Middlebrook and Dubos broth/agar. Some NTM may require special ingredients like blood or supplements like ferric ammonium sulphate. Most of the NTM grow in temperature between 25°C and 37°C but some like *Mycobacterium xenopi* may require



Mycobacterium tuberculosis
(ZN stain)



Non Tuberculous Mycobacteria
(ZN stain)



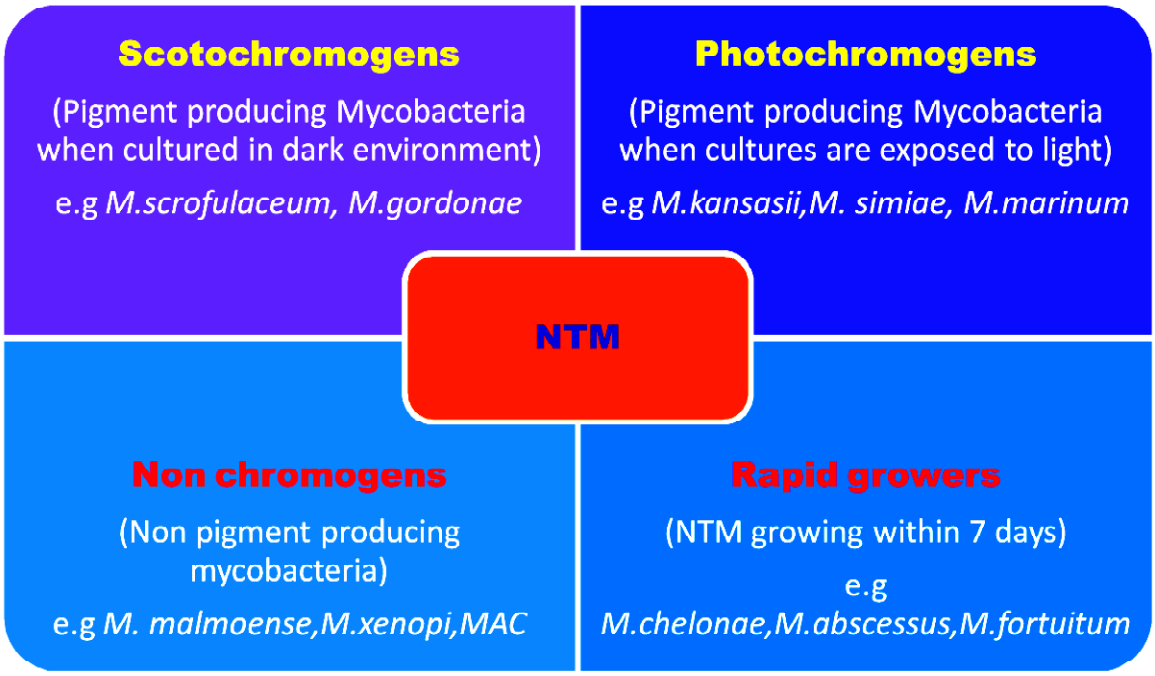
higher temperature like 45°C for its growth. The NTM can be identified by their characteristic growth pattern, pigmentation and rate of growth.

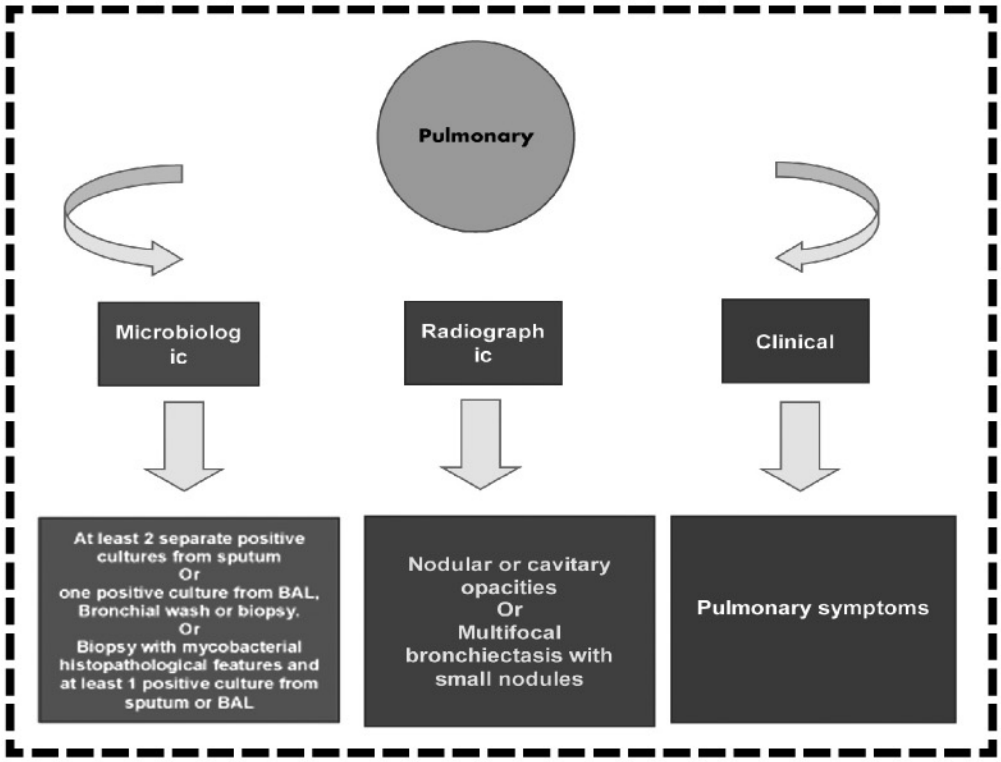
They have been classified into 4 types depending on the culture characteristics as per the Runyonclassification.

Identification to the Species Level

Identification of NTM up to its species level can be done by using different techniques:

1. Biochemical tests
2. HPLC (High performance liquid chromatography)
3. Isoenzyme and protein electrophoregrams
4. Gene probes
5. Gene amplification methods
6. DNA fingerprinting
7. Commercial kits using line probe assay (LPA)





(Note: details are beyond the scope of this article)

Species identification by LPA (line probe assay) method

Diagnosis of Non-Tuberculous Mycobacteria

Diagnosis of non-tuberculous mycobacteria is as per the guidelines laid by ATS/IDSA.

Disease Spectrum

NTM causes wide spectrum of diseases involving body sites such as lungs, skin, lymph nodes and soft tissue primarily. It also can cause infection involving body cavities, ear and eye. Symptoms due to non-tuberculous mycobacteria can be definite or vague with nonspecific symptoms like fever, weight loss, night sweats, anorexia and lethargy. Presenting symptoms varies with the organ affected. For e.g., if lungs are affected, the patients present with cough and respiratory symptoms. Similarly, if skin tissue and muscles are affected, it will present with abscess. Therefore, NTM should be suspected in any chronic infection, fever of unknown origin, and localised disease such as abscesses, ulcers, nodules not responding to antibiotics or anti-tubercular drugs.

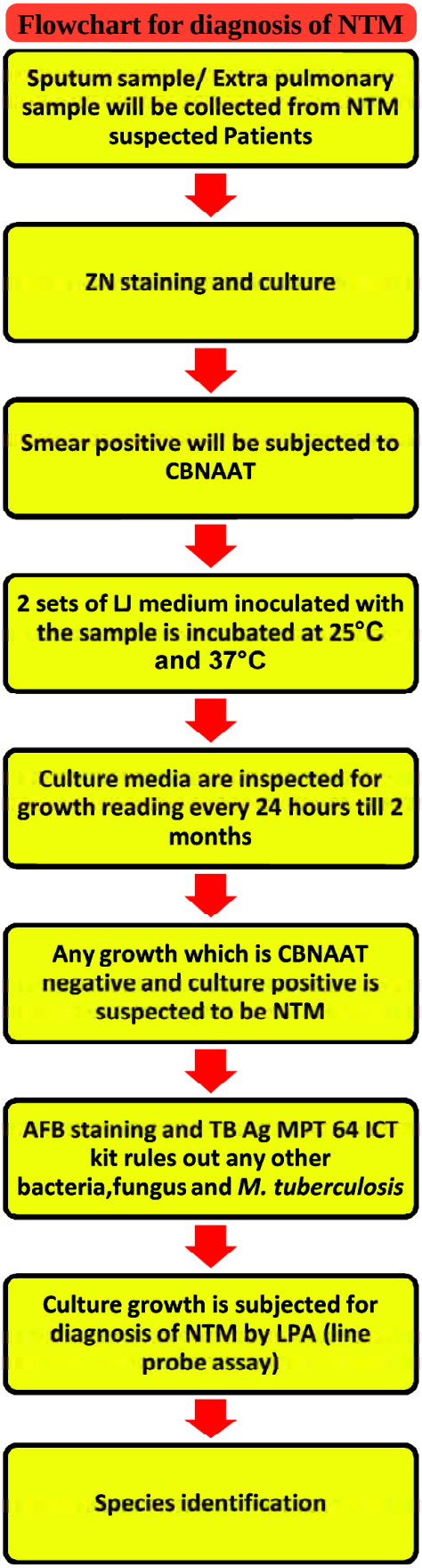
Management

Four aspects are important while treating NTM infection:

1.Prophylaxis:Some NTM can be treated with antimycobacterial drugs such as rifabutin.

2.Surgical:Surgical debridement is a necessity for the management of wound infections caused due to NTM followed by antimycobacterial drugs.

3.Medical treatment: It is based on the Mycobacteria species identified and the drugs that are sensitive for that particular species



which can be known by performing the drug sensitivity testing.

4.Toxicity monitoring of drugs: Many drugs prescribed for treatment of NTM infection have considerable toxicity. Therefore, it is advisable to look after side effects like visual impairedness, kidney function test, liver function test, ototoxicity, any skin reactions.

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TUBERCULOSIS AND ENVIRONMENT

Jaya Krushna Panigrahi

Introduction

A disease is considered as any harmful deviation from the normal structural or functional state of an organism, generally associated with certain signs and symptoms, and differing in nature from external physical injury. A disease is indicative of the abnormal state of an organism commonly exhibiting specific symptoms. In a diseased condition, the normal functioning of the cells, tissues, and organs of a person deteriorates. Non-infectious or non-communicable diseases (NCDs), sometimes also referred to as chronic diseases, remain confined to the persons who have contracted them and don'tget transmitted to others. These are caused by a variety of circumstantial factors including infection by pathogens, nutritional deficiencies, genetic defects, environmental causes,lifestyle, gender and age-related problems of the individuals. Four major types of non-communicable diseases have been identified by the World Health Organization (WHO): cancer, cardiovasculardisease (e.g., heart attack, stroke), chronic respiratory disease (e.g., asthma), and diabetes mellitus. As per the WHO estimation, combined together, these four groups of conditions,resulting in non-communicable diseases, account for about 82 percent of all deaths.These can also arise from environmental exposures or from genetically determined abnormalities, which may be evident at birth or which may become apparent later in life. Diseases like diabetes, high-blood pressure, hemophilia, anemia, goiter, Down syndrome and cardio-vascular disorders come under this category.

On the contrary, the infectious or communicable or transmissible diseases (IDs) are transmitted from person-to-person, i.e. from infected persons or hosts to healthy persons through the transfer of various pathogenic agents such as viruses, bacteria, fungi or animal parasites, directly or indirectly. Transmission or dissemination of such infection happens either by direct contactor through any medium. Such spread is an ecological phenomenon, the host serving as the environment in which the parasite lives; complexity arises when the parasite occurs in more than one host species (Burrows, 2022). Tuberculosis, malaria, chickenpox, cholera, colds, influenza, herpes, measles and COVID-19are examples of common infectious diseases.The burden of infectious diseases

(IDs), especially of tuberculosis (TB), remains high in low and middle income countries (LMIC). Although the true dimensions of this co-morbidity have not yet been fully understood, there is a growing amount of data, over the last 10 years that suggest a clear association between NCDs and TB (Puchner et al., 2019).

Tuberculosis as a Communicable Disease

Tuberculosis, caused by a bacterium called *Mycobacterium tuberculosis*,is one of the deadliest, chronic communicable diseases of humans, which is also prevalent in livestock and wildlife. It is still considered a serious public health concern, in addition to its economic and social significance. Though the TB bacterium primarily attacks the human lungs, but it can also infect any other part of the body such as the kidney, brain and spine. The historical importance of this lethal infection is that it has been discovered to be existent in our immediate ancestor, *Homo erectus, as has been recorded from the fossil* skeleton of half a million years old.

As the WHO estimates, a total of 1.5 million people died from TB in 2020 (including 2,14,000 people with HIV infection). Thus, this makes TB the 13th leading cause of death and the second leading infectious killer disease after the COVID-19 (above HIV/AIDS) worldwide.It spreads through microscopic droplets,containing the pathogen, released into the air when someone with untreated, active form of tuberculosis of the lungs or throat coughs, speaks or sings and people nearby breathe in these bacteria and become infected. It is also a fact that although tuberculosis is contagious, it's not easy to diagnose.

Risk Factors Involved

For intervening and reducing the infection transmission of this chronic human disease, we need to understand the risk factors associated with it.Narasimhan et al. (2013) state that the risk of progression from exposure to the tuberculosis bacilli to the development of active disease is a two-stage process governed by both exogenous and endogenous risk factors. Exogenous factors play a key role in accentuating the progression from exposure to infection, among which the bacillary load in the sputum and the proximity of an individual to an infectious TB case are key factors. Similarly, endogenous factors lead to the progression from infection to active TB disease. They further opine that along with well-established risk factors (such as human immunodeficiency virus (HIV), malnutrition, and young age), emerging variables such as diabetes, indoor air pollution, alcohol, use of immunosuppressive drugs, and tobacco smoke play a significant role at both the individual and the population levels. Further, socioeconomic and behavioral factors as well as specific groups such as health care workers and certain indigenous population are also shown to have increased susceptibility to TB infection and disease. The following illustration explains the various aspects and links of the risk factors involved.

Environmental Factors

Tuberculosis as a contagious disease spreads from person to person. It has been

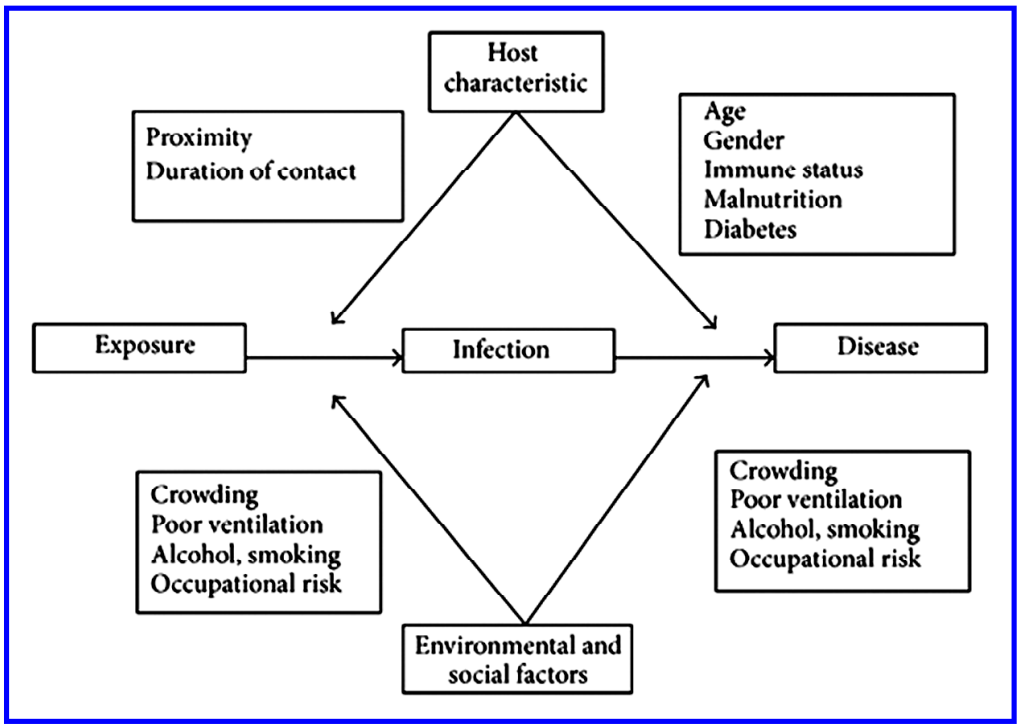

Fig 1: Risk factors for tuberculosis infection and disease (Narasimhan et al., 2013)

noted over the years that increased risk of TB is linked with certain environmental risk factors.However, poverty has a good connection with the increased incidence of TB as more and more poverty-ridden people, mostly from the developing world, have been historically the worst sufferers of the disease. Schmidt (2008) has opined that for centuries, TB has been linked anecdotally with environmental risk factors that go hand-in-hand with poverty, such as indoor air pollution, tobacco smoke, malnutrition, overcrowded living conditions and excessive alcohol use.The WHO report that the low- and middle-income countries (LMICs) of the world account for about 98% of the reported TB cases entirely corroborates such propositions.Hence, experts in the field of tuberculosis are aptly focusing their attention atpresent to confront these underlying risk factors through the TB eradication programmes so as to limit the spreading of the disease.

For the prevailing better environmental conditions in the developed or rich nations of the globe, the prevalence of TB is of much less proportion that remains confined there to the poor, mostly in urban neighbourhoods. Demographic, socio-economic and environmental factors, to which people are exposed, together play a significant role in the incidence of the disease. According to the analyses made by Dye and colleagues working at the WHO Stop TB Department, malnutrition, indoor air pollution from used solid fuels, and active smoking constitute the three top population-attributable TB risks globally, followed by HIV infection, diabetes, and excessive drinking. The WHO agrees to the proposition that poverty and urbanization create the perfect conditions for the transmission of tuberculosis.Some top most environmental risk factors are discussed here with additional focus.

a. Household Environment: One significant reason behind India carrying the biggest burden of this disease is the significant influence of the physical household environment where the

people reside. The socio-economic conditions of the people of lower and lower-middle income groups being below the desired level, they mostly live in unhygienic environments with inadequate sanitary system where indoor air pollution is of common occurrence. In a study conducted by Singh et al. (2018), prevalence of TB was found to be the highest among elderly people (0.9%), people with no education (0.4%) and people belonging to the poorest wealth quintile (0.53%). Crowding or higher population density has been considered as a crucial infection threat in both industrialized and non-industrialized countries. It includes overcrowded houses or congested rooms where enough space is not available to the people residing in such places. Such overcrowding scenarios are of common occurrence in slum areas of cities in developing nations, where the living conditions of the inhabitants are very much cramped. In case of prevalence of TB in such communities, the risk of disease transmission from infected patients to others is of higher degree.

Fig 2: Crowded slum housing in cities

Further, hospital admissions in colder months are significantly higher than in warmer months. As access to healthcare facilities as well as label of awareness is of low magnitude, the chance of early cure of this infectious disease remains low. It has been reported that in India, TB prevalence rates are consistently higher among urban children in comparison to the same group of the rural areas.Migrant people with increased mobility and seeking temporary works in different places fall victim to the disease very often as they spend their time in crowded, unhygienic living conditions. In many cases, the DOTS (Directly Observed Treatment, Short-course) protocol for TB detection and treatment are not adhered to that makes the bacterium more resistant and helps in progression of the disease.

b. Smoking: Many observations have led to the conclusion that smoking has the capacity to trigger more cases of the onset of tuberculosis. Though such cases of occurrence are certainly less than the cases caused by the HIV/AIDS, but considering the high number of persons addicted to smoking in a population, its impact on the magnitude of TB infection is certainly higher than that of the HIV. This is corroborated by Donald Enarson, senior advisor to the International Union Against Tuberculosis and Lung Disease, Paris, who hence suggests for cessation of smoking. Schmidt (2008) quotes him stating that although smoking's capacity to trigger TB infection among individuals is surely less than that of HIV/AIDS, it might actually engender more TB cases on a population basis because people who smoke far outnumber those

infected with HIV.Smoking of cigarettes, bidis, hookah and other tobacco materials has a good link with the occurrence of TB, which remains well documented. Singh et al. (2018) noted from their observation that the family members who were regularly (daily) exposed to smoke (second-hand smoke) inside the house were more prone to getting tuberculosis as compared to the households where people do not smoke inside the house.

Fig 3: Smoking substantially increases the risk of TB

Another important aspect is that almost half the world's population and 90% of rural households, as WHO estimates, depend on traditional stoves or open fires for cooking and heating, being fueled by low-cost, easily available kerosene; biomass such as animal dung, crop residues, wood and charcoal;and coal. These fuels release smoke for inefficient burning that is laden with health-damaging pollutants such as respirable particulate matters and carbon dioxide,causing indoor air pollution in poorly ventilated spaces. The women in the developing world being mostly involved in the cooking process, such pollution greatly affects their health. Thus, while tobacco smoking has adverse impacts mostly on the men, the indoor air pollution caused by smoke pollution from solid fuels exerts detrimental impacts on the women's health. Both these types of smokes, including second hand tobacco smoke, act as the TB risk factors affecting both the sexes. This happens as smoke impairs the ability of the lung ciliato clear the bacteria from the respiratory tract, thus resulting in infection. The medical practitioners hence advise simultaneous DOTS treatment and smoking cessation, as these might complement each other.

c. Alcohol Consumption: Another significant factor that induces TB incidence and enhances its progression is excessive consumption of alcohol. The immune response of the body declines in the diseased condition, while alcoholism in the scenario of risky social interactions with infected persons paves the way for increased transmission of the disease. When smoking tobacco and drinking alcohol tend to go hand-in-hand, the combined impacts of both make the person highly vulnerable to the disease as both act as strong risk factors. Concerning the alcohol dosage, Imtiaz et al. (2017) observed that tuberculosis risk rose as ethanol intake increased, with evidence of a threshold effect. Alcohol consumption caused 22.02 incident cases and 2.35 deaths per 1,00,000 people from tuberculosis in 2014. They also recorded that alcohol-attributable tuberculosis incidence increased between 2000 and 2014 in most high tuberculosis burden countries, whereas mortality decreased. A study has indicated that consumption of heavy amount of alcohol on regular basis (more than 40 g of ethanol per day or diagnosis of an alcohol use disorder) resulted in a nearly three-

Fig 4: Alcoholism behind the rise of TB

fold increase in the risk of tuberculosis.Thus, researchers consider alcohol use, alcohol dosage,and alcohol-related problems as risk factors for tuberculosis.

d. Malnutrition: The bidirectional association between malnutrition and tuberculosis incidence is a well-established fact. This has been evidently established in populations affected by poverty, famine, war, natural disasters, mass migration, and confinement in prisons or ghettos. Schmidt (2008) opines that given that it's usually impossible to retrospectively discern nutritional status in patients before their TB disease, it is hard to determine whether malnutrition led to TB or vice versa. This can only be done reliably through cohort studies that follow healthy subjects over time after determining nutrition status at baseline. Thus, it is a vicious cycle between malnutrition and occurrence of tuberculosis. Undernutrition can lead to progression of the latent infection to tuberculosis and TB worsens undernutrition, which in turn increases the severity of the TB disease. Thus, the need is to improve the nutritional status of the patient greatly so as to reduce the impacts of tuberculosis.Focus has to be given on the supply of adequate amounts of micro- and macronutrients, such as proteins and vitamins, so that natural immunity against the disease can be boosted. The role of proteins is illustrated by the fact that they not only fortify the immune function, but also strengthen the lung tissues by collagen proteins. To cite a case of vitamins, vitamin D helps with macrophage function, and macrophages help to clear TB bacteria. Many authors suggest that enhanced nutritional support of the undernourished populations at high risk of TB may reduce the incidence of the disease in such groups.

The Way Forward

Fig 5: Malnutrition often induces TB incidence

In the context of the global burden of disease (GBD), The Lancet journal states that the latest global disease estimates reveal a perfect storm of rising chronic diseases and public health failures.This has been fuelling the COVID-19 pandemic to acquire greater proportion.The most comprehensive global study - analyzing 286 causes of death, 369

diseases and injuries, and 87 risk factors in 204 countries and territories - reveals how well the world's population were prepared in terms of underlying health for the impact of the COVID-19 pandemic. In such a situation, the health systems across the globe, most importantly in the developing world, need to be improved and disparities are eliminated. Though a good progress has been made in the arena of prevention and treatment of infectious diseases worldwide to reduce mortality, there is still a huge unfinished agenda to contain diseases like tuberculosis. The need of the hour is much greater synergies among population health, prevention, treatment and care, and development efforts, besides political commitment and funding for the cause. As Tracey Burton states, vulnerable people around the world affected by TB cannot wait any longer for quality testing, treatment and care. Though many organizations, including WHO; Global Fund to Fight AIDS, TB and Malaria; Stop TB Partnership and UNDP, are working to address the urgent threat of TB menace, we need to undertake further stringent actions in this direction. Policy planners and decision makers need to focus additional attention towards the prevention and treatment interventions. Environmental factors boosting the TB incidences must be tackled with added attention. Our concerted efforts will translate into reality the targets of achieving the Global Plan to End TB 2018-2022, and the Sustainable Development Goal target to end TB by 2030.

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Odisha Environmental Society,
Bhubaneswar

8 ROLE OF ICMR- REGIONAL MEDICAL RESEARCH CENTRE (RMRC), BHUBANESWAR IN TUBERCULOSIS CONTROL AND PREVENTION

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The Indian Council of Medical Research (ICMR) is the supreme body for the formulation, coordination and promotion of medical research in India. At the same time, it is considered to be one of the oldest and largest medical research bodies in the world. The ICMR is funded by the Government of India through the Department of Health Research (DHR), Ministry of Health and Family Welfare (MoHFW).

ICMR has a network of 26 institutes, the headquarter being located in New Delhi. ICMR has made outstanding contribution as a knowledge generating agency and contributed in understanding various diseases of national importance such as malaria, Japanese encephalitis, tuberculosis, AIDS, Kala-azar, Filariasis, Leprosy and Poliomyelitis. Additionally, ICMR has made extensive contributions in the areas of nutrition, reproduction and maternal and child health, occupational and environmental health and research complimenting health systems. ICMR regional medical research institutes/ centres have been contributing in tackling regional health problems. Training and capacity building of young investigators, medical and allied health professionals and providing funding support for research projects to investigators all over the country are other very unique and significant contributions of ICMR. ICMR continues to provide extramural funding to strengthen research capabilities within the institutes of the council as well as other research institutes, medical colleges and non-Governmental organizations for various research projects.

ICMR- Regional Medical Research Centre (RMRC), Bhubaneswar

Out of the total 26 institutes, ICMR-RMRC Bhubaneswar is one of the renowned and well developed research institute in eastern India which is focussed on communicable and non-communicable diseases, human resource development, other basic , applied and translational research and has collaborated with other ICMR and non-ICMR institutionsincluding the State Government of Odisha, NVBDCP, Delhi, Gates Foundation, DBT, AIIMS New Delhi, IVI, DST, for enhanced research, skill improvement and mutual exchange of scientific viewpoints.From the beginning, the institute has various facilities such as insectariums, animal house, library and information, biomedical informatics

centre, national reference laboratory for TB and virology network laboratory.

National Reference Laboratory for Tuberculosis at ICMR-RMRC, Bhubaneswar

In 1997, India launched the Revised National TB Control Programme (RNTCP), based on the internationally recommended Directly Observed Treatment Short-course (DOTS) strategy. RNTCP expanded across the country in a phased manner with support from World Bank and other development partners. In March 2006, full nation-wide coverage was achieved, covering over a billion population. The main strategy in detection of TB cases is quality assured diagnosis. The RNTCP network of laboratories for TB is composed of National Reference Laboratories (NRLs), state level Intermediate reference laboratories (IRLs) and Culture & Drug Susceptibility Testing (C & DST) laboratories and peripheral level laboratories as designated microscopy centres (DMCs). Effective implementation of DOTS and DOTS Plus strategy is the key component of RNTCP under Central TB Division of the Ministry of Health and Family Welfare, Government of India. For ease of supervision and monitoring work, ICMR-RMRC, Bhubaneswar was designated as a National Reference Laboratory (NRL) for tuberculosis in 2013.

Figure 1: National Reference Laboratory (NRL) for tuberculosis at ICMR-RMRC, Bhubaneswar

In India, there are six designated NRLs namely National Institute for Research in Tuberculosis (NIRT), Chennai; National Tuberculosis Institute (NTI) Bangalore; National Institute of TB & Respiratory Diseases (NIRTD) New Delhi; Central JALMA Institute of Leprosy other Mycobacterial diseases, Agra; Regional Medical Research Centre (RMRC), Bhubaneswar; and Bhopal Memorial Hospital and Research Centre, (BMHRC) Bhopal.

The NRL for TB at RMRC, Bhubaneswar was assigned 10 states namely Odisha, West Bengal, Assam, Meghalaya, Mizoram, Manipur, Nagaland, Sikkim, Tripura and Arunachal Pradesh.

The main focus of the activities of the NRL includes:

- Quality assessment of smear microscopy (EQA)
- Quality assurance of culture and drug susceptibility testing of laboratories under it
- Providing support to laboratories for capacity building
- Impart training to state laboratories on technologies used for TB diagnosis
- Providing support to DOTS plus centers with laboratory support

Figure 2: Studies on tuberculosis in tribal populations

Projects on Tuberculosis Conducted by ICMR-RMRC, Bhubaneswar

During 2009 to 2011, ICMR RMRC Bhubaneswar carried out a project on diagnosis of pulmonary TB using culture in solid media (LJ) and carry out drug sensitivity pattern of the isolates. The diagnosis of pulmonary tuberculosis under Directly Observed Treatment Short-course (DOTS) programme was based on clinical symptoms, radiological findings and sputum microscopy. However, the sputum microscopy fails to detect the low or paucibacillary infections and an estimated 5000 to 10000 bacilli per ml is required for diagnosis of TB using AFB staining. The AFB staining also can not differentiate between *Mycobacterium tuberculosis* and other mycobacterium. Though the culture of *Mycobacterium tuberculosis* in solid LJ media takes 6-8 weeks to grow, it provides definitive diagnosis and study of its drug sensitivity further helps in the control of the disease more effectively. The study was carried out in collaboration with Capital Hospital, Bhubaneswar.

RMRC Bhubaneswar conducted a study on drug resistance among sputum positive tuberculosis patients in Rayagada district from 2011 to 2013. The study estimated the prevalence of drug resistance among tuberculosis patients in a tribal district of Odisha inhabited by 57% tribal population. This study provided the much-needed drug resistance information during the start of programmatic management of drug-resistant TB (PMDT) services at Odisha after a gap of 10 years from the first study in Mayurbhanj district in 2000-2001. The prevalence of multi-drug resistant TB (MDR TB) was 0% and 7.0% among new and previously treated patients in this study. The low prevalence of drug resistance observed in this area was a

good indicator of RNTCP programme being implemented in the Rayagada district.

In September 2013, RMRC initiated a project on performance of Light Emitting Diode microscope in different settings for a TB diagnosis. As microscopic examination of sputum smears is the main tool for the diagnosis of pulmonary tuberculosis in TB control programmes, newer microscopic methods were compared with the conventional ZN microscopy. The project was conducted in collaboration with Capital Hospital, Bhubaneswar, in which sputum specimens, along with consent form and patient information form, were collected from suspected pulmonary TB patients and processed for ZN, FM, LED microscopy (3 different methods) and solid culture with LJ medium.The results of the study showed that compared to ZN microscopy, LED FM was more sensitive in detecting TB bacilli.

During 2013 to 2016, RMRC Bhubaneswar conducted a prospective study to determine the incidence of tuberculosis among patients with Type 2 Diabetes Mellitus. In this study, 1200 patients with Type 2 Diabetes mellitus were screened for signs & symptoms of TB. Blood samples from these patients were analyzed for various biochemical parameters and HbA1C. Socio-demographic and clinical data were collected from all diabetes patients using standardized forms. Clinical evaluation of each patient included a detailed history of duration and chronology of chest symptoms like cough, dyspnoea, fever, chest pain, and haemoptysis. Out of 1200 patients, only 13 (1.08%) patients had TB active disease. The results showed that the incidence of TB among patients with diabetes was less than that reported from other regions.

During 2015 to 2017, RMRC Bhubaneswar was involved in a multi-centric study to estimate the burden of TB among the tribal population and develop an innovative health system model to strengthen TB control in the tribal areas. Odisha has 62 distinct tribal groups, making it the largest collection of tribal people in a single state in the country. Each of these tribal groups has its own indigenous customs and continues to practice them even today. More than half of their population is concentrated in four districts of Balangir, Dhenkanal, Kandhamal and Mayurbhanj. RMRC Bhubaneswar conducted another study on targeted Intervention to expand and strengthen TB Control in tribal populations under the Revised National Tuberculosis Control Programme (RNTCP), India, during 2016 to 2018.

Undernutrition is both an important risk factor for, and a common consequence of, TB. It is therefore a common comorbid condition for people with active TB and is associated with increased risk of mortality and poor treatment outcome. Most individuals with active TB are in a catabolic state and experience weight loss and some show signs of vitamin and mineral deficiencies at diagnosis. Weight loss among those with TB can be caused by several factors, including reduced food intake due to loss of appetite, nausea and abdominal pain; nutrient losses from vomiting and metabolic alterations caused by the disease. During 2016 to 2018, RMRC Bhubaneswar

conducted a study on the effectiveness of food supplementation on treatment outcomes and nutritional status of adults with pulmonary tuberculosis in Odisha.

From 2019 to 2021, RMRC Bhubaneswar was involved in a national survey for state-wise prevalence of microbiologically confirmed pulmonary tuberculosis in India, where RMRC was responsible for Chhattisgarh state. This ambitious study was planned to estimate the point prevalence of microbiologically confirmed pulmonary TB among persons aged e"15 years in India for 20 states / state groups.To estimate the burden of human pulmonary paragonimiasis in crab eating communities and smear negative suspected TB cases from some states of India, RMRC Bhubaneswar conducted a pilot study in two districts of Odisha, Nayagarh and Mayurbhanj. These districts were selected based on number of TB cases, geography and crab eating behaviour.

In a recently initiated study, RMRC Bhubaneswar will map hotspots of MDR-TB in Assam, Tripura and Sikkim using genomics approaches. The main objective of the project is to employ whole genome sequencing and traditional genotyping for mapping hotspots of primary MDR-TB in Assam, Tripura and Sikkim and to identify transmission patterns and source/s of MDR-TB using molecular epidemiology and clinical epidemiology.

In another study, RMRC Bhubaneswar, evaluated the burden of Atypical Mycobacteria or non-tuberculous mycobacteria (NTM) in causing respiratory infections. When evaluated clinically, it was found that the most of the patients had symptoms and signs as that of tuberculosis. The chest X-Ray images mimicked pulmonary tuberculosis but the patients did not respond to the common drug regimen for *M. tuberculosis*. As the diagnosis of NTM are important for therapeutic purpose, the project for diagnosis of non - tuberculous mycobacteria was undertaken in March 2018 considering only the pulmonary samples. Gradually extra pulmonary samples were also tested for presence of NTM. In this project, NTM has been isolated from 42 clinical samples (both pulmonary and extra

Figure 3: Studies on human pulmonary paragonimiasis by RMRC, BBSR

pulmonary). *M. chelonae, M. fortuitum, M. gordonae, M. abscessus, M. mageritense*are among the different isolates from the clinical samples.

Figure 4:Studies on tuberculosis vaccines by RMRC, BBSR

In the recent years, RMRC Bhubaneswar has been part of several multi-centric trials on TB diagnosis, therapy, and prevention. In a multicentre trial to assess the performance of centralized assay solutions for detection of MTB and resistance to Rifampin and Isoniazid, the institute will estimate the diagnostic accuracy of centralized assay solutions for MTB detection for smear-positive and smear-negative TB, including Xpert MTB/RIF (or Ultra) as a comparator and culture as the reference standard. The institute is part of an open-label, non-randomized, two-stage, dose-finding study of verapamil tablet formulation in adult tuberculosis patients in continuation phase of anti-tuberculosis treatment. The project aims to determine the compensatory increase in verapamil dose that can offset the increased metabolism of verapamil when it is co-administered with rifampicin to TB patients at their sixth month of treatment. The study also aims to confirm the safety and tolerability of verapamil in patients with TB without underlying cardiac disease. The study is being conducted as a collaborative project between RMRC, Bhubaneswar and SCB medical college, Cuttack. RMRC Bhubaneswar is also part of a phase III, randomized, double-blind, placebo controlled trial to evaluate the efficacy and safety of VPM1002 and Immunovac Vaccines in preventing TB in healthy household contacts of newly diagnosed sputum positive pulmonary TB patients.

To conclude, ICMR-RMRC Bhubaneswar has conducted studies on several aspects of tuberculosis during the last two decades. This includes evaluating the burden of tuberculosis, including MDR TB, in Odisha and other states. Special focus has been given to understand the burden of TB in specific populations such as tribal groups, malnourished, and people with diabetes mellitus. Several trials have also been conducted by RMRC Bhubaneswar to study the effects of anti-tubercular drugs and vaccines.

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1 "SCIENCE HORIZON" aims at developing the scientific outlook of students as well as the general people and seeks to give them information on scientific developments. It is published as a monthly magazine.

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14. There should not be repetition of specific words. While ensuring the contemporary spirit of the writing, it should reflect some valuable lesson for the society. It is also necessary to avoid mistakes in spelling, language use and factual details.

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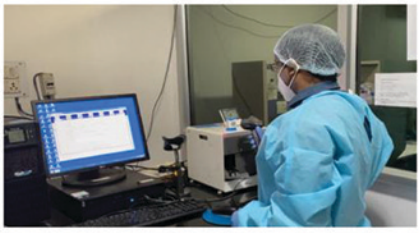


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