

Tuberculosis Through Ages

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“Tuberculosis is Ebola with wings, can affect any tissue of the body, any where in the world.”

Tuberculosis has affected man kind from very ancient times. Man has continued to live in a state of uneasy equilibrium which can be easily disturbed in favor of the disease. Neither man nor the bacillus has shown sufficiently strong supremacy to win this battle. It is as old as mankind. Soma, the Moon God, suffered from “Tuberculosis”. It is mentioned in Yajurveda. Hymn in Rig Ved is there to cure Yakhma. Recent Data reveals that TB existed 40,000 years ago, which corresponds to the period subsequent to the expansion of Homo sapiens out of Africa. Its existence is evident in Neolithic manand, Mummies of 5000 BC. Sushrut (600 BC) described the disease and opined difficult to cure. Hippocrates (460-377 BC) opined, there is no cure for the disease. Raj yakhma (India), Phthisis (Greek), consumption (Latin) and the White Plague are all terms used to refer to Tuberculosis through out history. Treatments varied from good food, clean air, herbs, mantra, tantra to touching of the king's feet on Scrofula, (gland TB on the neck.)¹

The disease graduated from hereditary to infectious status after the discovery of its causative organism, to the bewilderment of the entire world when a dwarfish bespectacled stocky built scientist,. Robert Koch discovered the tubercle bacillus under the microscope and told to the whole world that it is not an hereditary disease but an infectious airborne respiratory disease, can affect every organ of the body except the hair and nails. After 50 years, the drugs followed in quick



Fig 1, Touching of kings' feet.

succession. Then a complete fullstop for nearly forty years. Who wants to develop a drug for poor countries, poor people, with tremendous cost than the ordinary drugs with low profit.

Till date Tuberculosis is considered as a major global health problem and an important cause of morbidity and mortality in high burden countries including India. WHO Report of 2018 is, there were 10 million estimated new cases with 1.5million deaths world wide making it the topmost infectious killer. About 4000 people die and 30,000 people fall ill every day. There were an estimated 2.7 million TB cases in India with .45 million deaths in 2018.²

India has the largest number of tuberculosis infected cases in the world. Still Tuberculosis is a Social taboo. People do not want to disclose that they are suffering

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Fig II. Robert Koch

from tuberculosis. Neither we give it a status in our conferences and seminars. I failed to secure an hour slot for the topic in 8 halls in 3 days program of the AICOG held in Bhubaneswar, I was the adviser to scientific committee of the conference.

WHO declared it as global health emergency in 1993. Many foundations like Bill Gates and Millinda foundations joined hands to work against tuberculosis. It was 'high time to sow new seeds now as all the low hanging fruits have been eaten' The initiative of setting up bodies like Global Alliance of TB drug development (2000) have started to discover new drugs in a vigorous way and several drugs came to treat the DS and DR patients, Bedaquiline came as a drug to treat MDR tuberculosis, Pa, a bactericidal drug which even kills the MDR bacteria in HIV positive patient, Linezolid and moxifloxacin and many others.

The progress so far

More than 100 years after its discovery, tuberculosis infection has attained the status of a notifiable infectious disease in India in 2012. ACMS activities

has been boosted up and a new logo of RNTCP has come in stead of the previous one. Govt. Decision and vision "TB Free India".

WHO adopted End TB strategy to end the global TB epidemic by 2035. zero deaths, diseases and suffering due to tuberculosis. WHO released the use of Gene Expert for pulmonary tuberculosis in 2011.

Tuberculosis is a bacterial infection usually caused by, *Mycobacterium tuberculosis*. and sometimes by *M. bovis*. They are also called the tubercle bacillus, because they cause lesions called tubercles. The mycobacteriums are obligate aerobes with a replicating cycle on the order of 17 –24 hours which is a prolonged period than the other bacteria's. and are characterized by their acid-fast staining. They look red under the microscope. Through out the body the microscopic picture is similar, the tubercles consists of granular inflammation, Langhans Giant cells, Epitheloid cells and central caseation associated with chronic inflammation.

Currently available new TB tests represent great advance but not yet replaced the older tests. Our gold standard of the diagnosis is still the same as before -Isolation of *Mycobacterium tuberculosis* by culture. -Histopathology, and by Laparoscopy's definitive signs.

Culture is the gold standard and it is done in various ways like LJ Culture, -BACTEC, MIGHT (Liquid culture) -PCR. Rapid detection and quantification, requires only 1-10 bacteria/ml. Sensitivity > 90%, Specificity> 98%, Result within 6 hrs. The newer one is Gene Xpert MTB/RIF System, A cartridge based nucleic acid amplification test (CBNATT), WHO approved it and recommended it for rapid diagnosis of DR and MDR pulmonary tuberculosis cases in 2011 and in EPTB in 2013. We are now using it to diagnose FG TB too. FG TB, results are not promising. Sensitivity-30 % Specificity almost 100 %, higher cost, negative report due to blood contamination.

Now Line probe Assay has also came into being.

Contact Tracing

A new method is introduced to detect tuberculosis in its earliest stage,, so that treatment is given early and elimination is easier. If a person or a relative is in contact with a tuberculosis patient, the Govt.

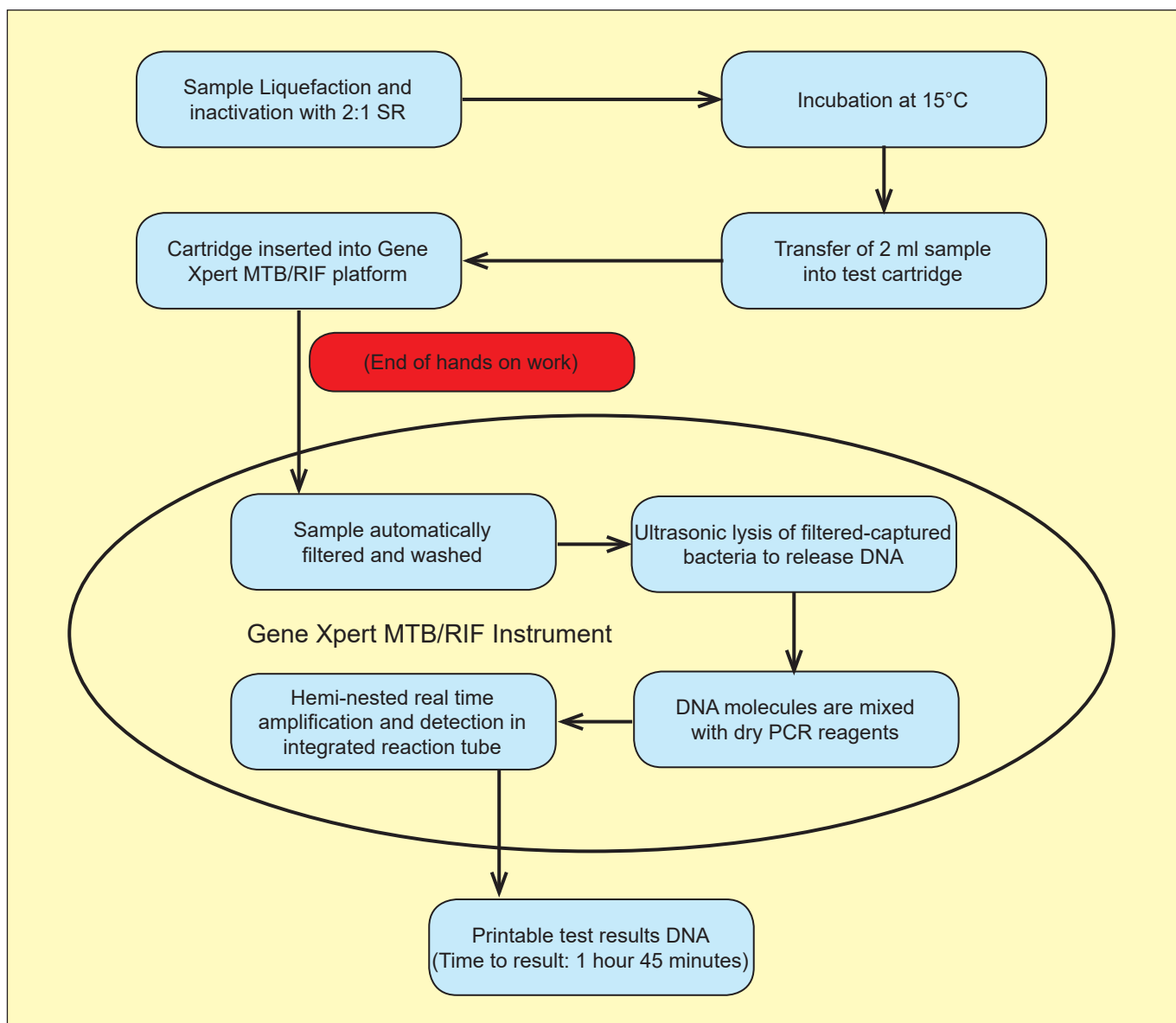


Fig III, GeneXpert MTB/ RIF instrument, How it works.

has introduced a method of checking them for tuberculosis in their nearest chest clinics. The tests are Moutoux test, Chest X-Ray, T-SPOT- TB Test and QuantiFERON - TB Gold Test. This test is not affected by prior BCG vaccination. C - TB test, a skin test, which overcomes the limitations of TST and IGRA. It uses recombinant ESAT -6 and cFP-10 proteins. Low cost, high specificity. Other tests are on the pipeline.

Chemotherapy, the treatment of choice. Clinicians should refer to the current RNTCP guidelines, recently the name changed to NTEP. DOTs (Daily dosing regimens) are being introduced now in RNTCP, previously it was thrice weekly regimen. The whole country is covered, and electronically monitored.

- Drugs- 2EHRZ/4EHR
- Duration- 6 months
- Daily Dose Regimen.
- Fixed dose combinations (FDC) doses is preferable. FDCs are distinct from combination packs (Combi packs). Now Streptomycin is removed from the first line group of drugs.

MDR TB

It is much easier to prevent MDR TB than to treat it in sophisticated institute for longer period with costlier drugs with more toxicity, resulting in hardly 50% recovery. Method is simple i.e., adopting standardized, up-to-date, proven, evidence based 4 drug regimen for treating TB cases. And for that reason, the physicians, the patients, the pharmaceuticals and the Government

has to be aware of the problem A case with MDR TB having resistance to any one of the second line injectable (Kanamycin, Capreomycin and Amikacin) and any one of the fluoroquinolones (WHO 2006) is known as XDR –TB which is very difficult to treat.

Management:

The WHO 'End TB strategy' has set targets for eliminating TB with 80 % and 90 % reduction in incident rate and as well as 90 to 95 reduction in mortality rate by 2030 and 2035 respectively. The government of India intends to end TB by 2025 which is a well appreciated initiative. For that WHO had initiated the Universal Drug sensitivity testing by those two molecular tests, by CBNAAT for rifampicin resistant and LIPA to detect MDR and XDR Tuberculosis.

When WHO started the DOTs Regimen, the criteria was there should be National Tuberculosis Programme (NTP) in the country. India is the first to introduce the National Tuberculosis programme, from 1962 and it continued till 1997. On those days the main programmes were Tuberculin skin test and BCG vaccination and implementation of short course chemotherapy. In 1997 it was renamed Revised National Tuberculosis programme (RNTCP). During this period many new medicines came out. Thrice weekly DOT's Regimen was introduced. In 2020 January The India Government renamed it as National Tuberculosis Elimination programme. (NTEP).

Various trials are ongoing to design innovative shorter regimens containing newer and repurposed drugs that can serve the purpose to treat drug sensitive and drug resistant TB cases favoring an universal treatment approach. These trials are conducted by Research Excellence to stop Tuberculosis resistance (RESSIST – TB), an initiative adopted under End – TB strategy by WHO to promote and conduct research on therapy for rapid control of DR-TB. (2) Merits of Universal drug Regimens include shorter treatment duration as well as culture conversion time leading to decreased risk of transmission of infection among all forms of TB patients including HIV co infection and enhancement of streamlined care delivery. Pretomanid (Pa) is one of the promising newer drug that has shown to increase treatment success rates in MDR/XDR TB and can be considered as backbone of universal drug regimen. The Nix TB trial showed a cure rate of of 90 % after 5

to 7 months treatment with regimen containing Bdq, Pa, and Linezolid (Lzd) in XDR Tuberculosis cases. Current results of this greatly simplified and shortened all-oral regimen for drug resistant TB are encouraging in terms of both efficacy and safety. Patients with Extensively Drug Resistant (XDR) tuberculosis (TB) have had limited options for treatment and high mortality. Nix-TB is an ongoing open label study in South Africa of bedaquiline (400 mg qd for 2 weeks followed by 200 mg tiw), pretomanid (200 mg qd) and linezolid (1200 mg qd) given orally for 6 months and followed for two years. Given the significant burden of TB world wide coupled with unfavorable outcomes, it is vital to evaluate these universal regimens under programmatic conditions. It may be possible, they may help in eliminating tuberculosis from the surface of the earth.

There is no doubt that tremendous progress has occurred in the field of tuberculosis starting from screening, to prevention to diagnostic techniques to newer drug developments. Let us see, what progress has occurred in our branch.

Though late, the scientific community has realized that if EPTB and pregnancy is not handled properly TB can't be eliminated. EPTB constitute about 15-20 % of all TB cases, in immune competent patients and 50 % in immune suppressed patients. There is no uniformity in diagnosis and treatment of EPTB and it is raising problems for the control of TB. Hence Guidelines on extra-pulmonary tuberculosis for India was formulated for each EPTB, including Genital tuberculosis and that is released in 2016. The recommendations were made during a meeting of the INDEX-TB guidelines group in July 2015 at AIIMS, New Delhi. The Methodology Support Team apprised the guidelines panel of the methods used in conducting the systematic reviews, and advised on the interpretation of the evidence. WHO policy document 2013 adopted a GRADE system approach to arrive at recommendations for TB in Extra-Pulmonary sites (EPTB). The Genital Tuberculosis group suggested many investigations like HSG in infertility, FNAC etc, and concluded that the diagnosis of FG TB should be made based on any one of: Laparoscopic appearance typical for FG TB. Any gynaecological specimen positive for AFBs on microscopy or positive for Mtb on culture. Any gynaecological specimen with findings consistent with FG TB on histopathological

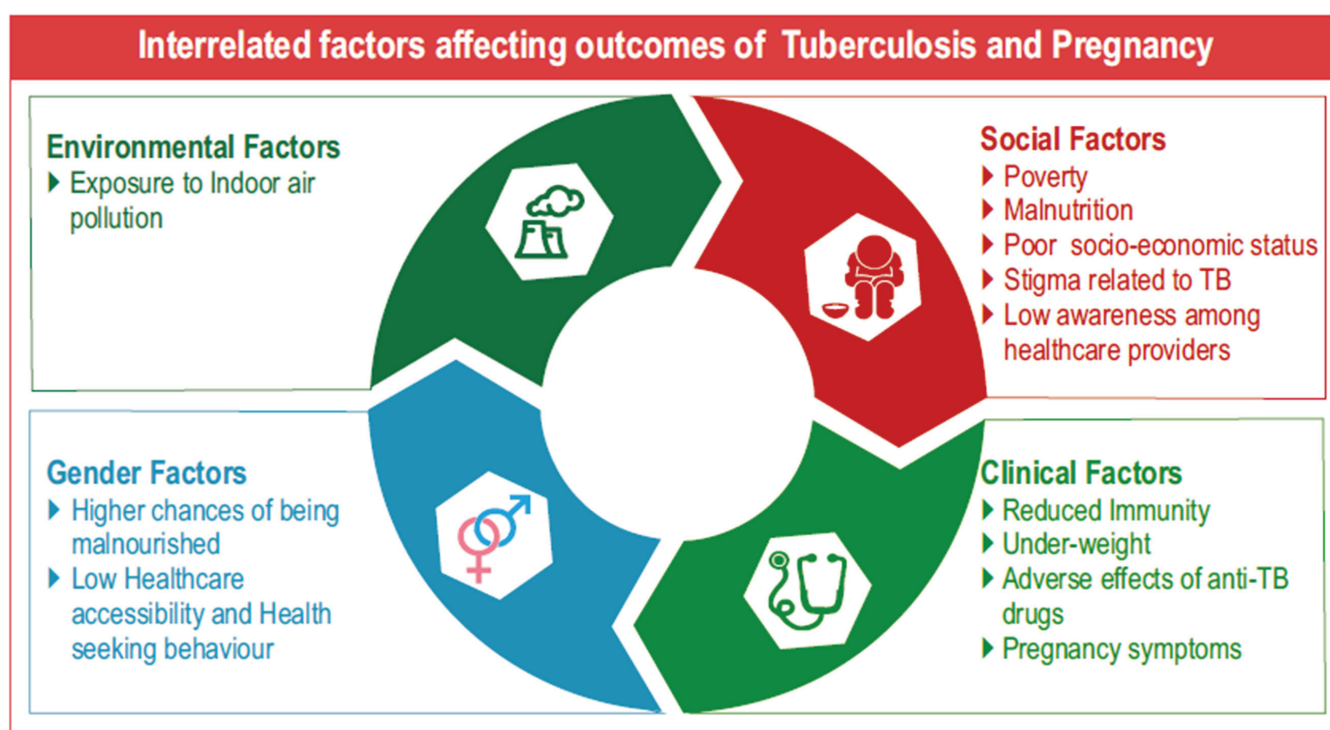


Fig IV

examination. PCR-based tests are increasingly used to diagnose FGTB. A literature review prepared for this guideline found that estimates of sensitivity and specificity varied widely across reports in the literature. The Technical Advisory Subcommittee for FGTB raised concerns about their experience of high rates of false positives when these tests are applied to peritoneal/gynaecological specimens. The committee has suggested, treatment neither should be started nor should be stopped only on the positivity or negativity of PCR. But nothing is a last word in science.

In a study done by J.B. Sharma et al, out of 177 cases of GT, gene Xpert was positive in 18.56% cases Gene Xpert had sensitivity of 35.63%, specificity of 100%, positive predictive value of 100% and negative predictive value of 58.82% and diagnostic accuracy of 66.47% in the present study. Gene Xpert is a very useful test to rule in tuberculosis whereas when it is negative it is not a good test to rule out tuberculosis.³

To find out the magnitude of the problem in pregnant women and how to manage the issues, Collaborative Framework for Management of Tuberculosis in Pregnant Women, Feb 2021 was produced jointly by the Central TB Division (CTD) and Maternal Health

(MH) Division of Government of India Ministry of Health and Family Welfare.

Early diagnosis and treatment of TB in pregnancy would not only reduce the adverse effects of maternal TB, but also reduce overall burden of childhood TB in India. For this the national guideline has been developed. As tuberculosis has many factors to its management the collaborative group considered the inter related factors which affects its outcome like, Social, Environmental, Gender and clinical factors. (FIG IV). They have integrated TB and MH services in primary, secondary and Tertiary services. (FIG IV). They have also formulated guidelines how to manage DR pregnancy cases. (FIG VI).

Another major decision they have taken is Universal Screening for tuberculosis in pregnancy. The collaborative group recommended it on 21st April 2022, The screening test will not be Moux test but C- TB skin Test.

Tuberculosis and Covid-19

Covid 19 is the largest pandemic witnessed by the world in more than a century, but one should not forget tuberculosis which is an already existing pandemic for hundreds of years. From 2015 to 2019, The health

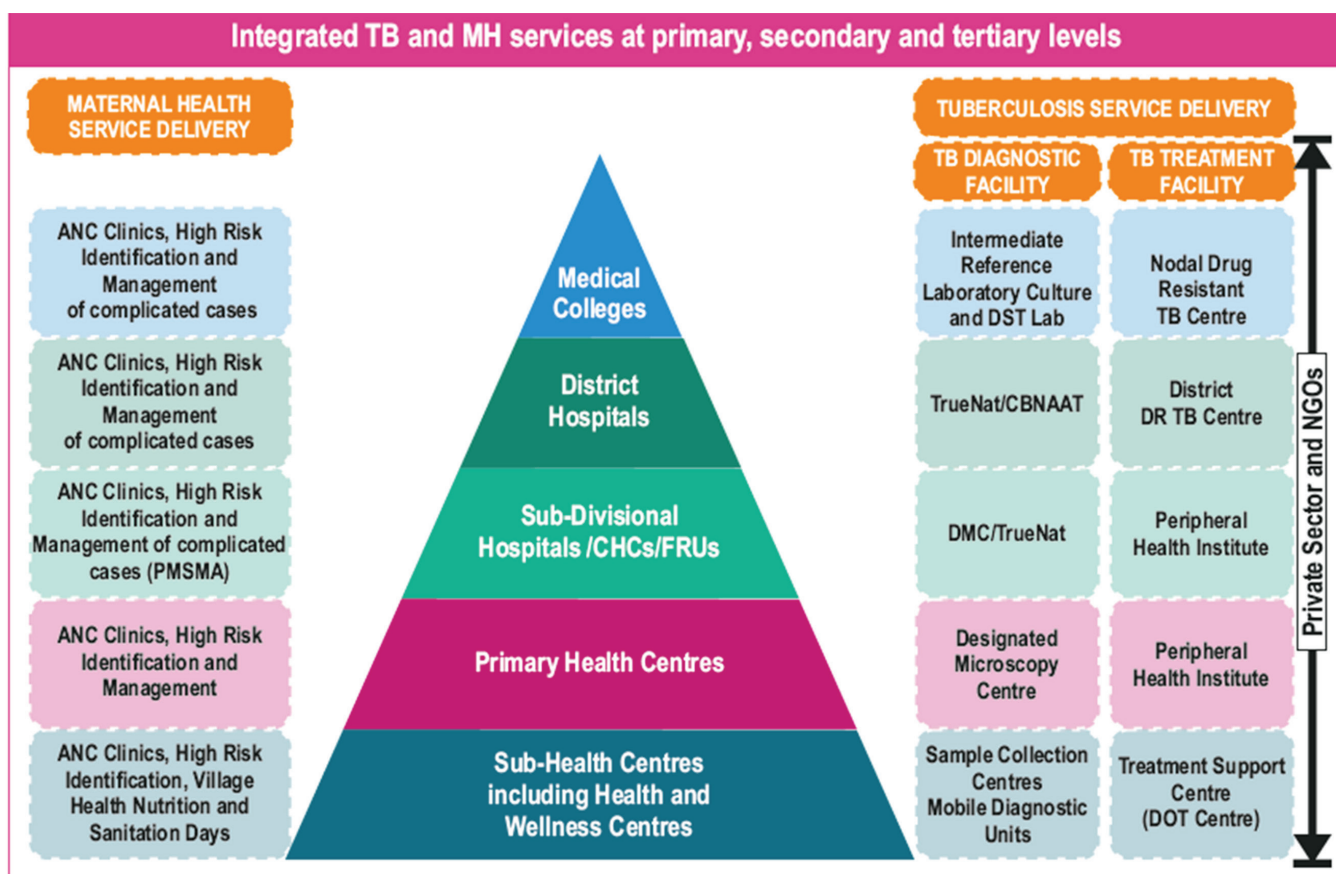
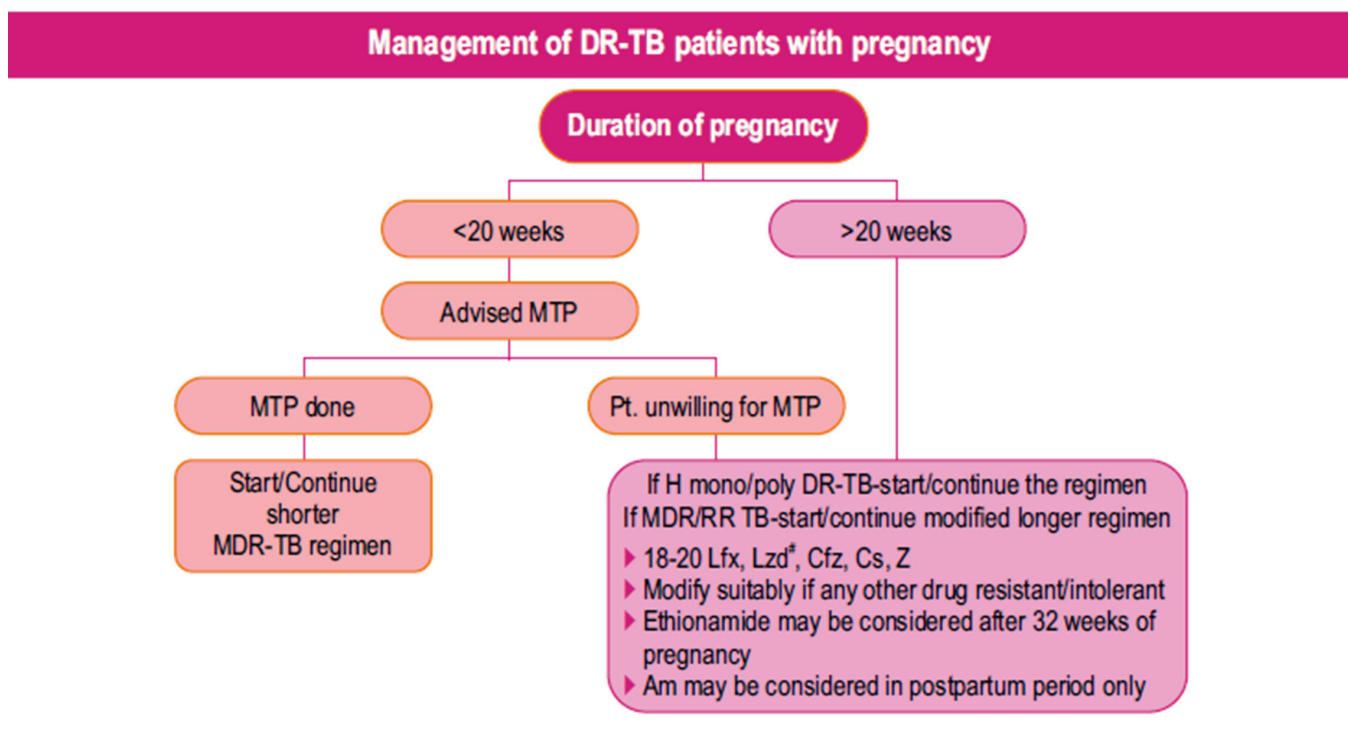


Fig V



Note: Please refer to PMDT Guidelines 2021 for management of DRTB in Pregnancy

Fig VI

and family welfare department of Government of India has worked too hard and achieved 10 % reduction in infection rate and mortality rate due to tuberculosis. The impact of pandemic COVID-19 on tuberculosis has been estimated by scientists and they have told that there is an 13 % increase in death rate due to tuberculosis in 2020. This may be due to 25 % reduction on notification rate, due to Shot down, Lock down, DOTS also suffered, the doctors of this sector are diverted to COVID hospitals and DR centers are converted to COVID hospitals. Tuberculosis is the top most infecticious killer of the world, corona just behind. Both are respiratory diseases having same symptoms, same risk factors and similar social predispositions. A metaanalysis showed that chronic respiratory disease cases can get two times infected with Corona -19. (Odd's Ratio- 2.46) Few studies showed, If a tuberculosis case is affected by Corona, the death rate is more. It also reactivates latent tuberculosis. The immunosuppressive drugs used in Covid-19 also reactivates tuberculosis cases. There are certain studies which shows that BCG vaccination gives certain protection to COVID-19 infected cases. The Ministry of health and family welfare, India have released an advisory on 26th August 2020 stating that prevalence of tuberculosis among COVID-19 patients is .37 % to 4.47 % and recommends bidirectional screening.

To conclude what one can write about the future of this type of a disease where everything is known, the causative organism is known, how it infects and spreads to other is known, the preventive measures are known, the drugs for treatment is available. Scientific knowledge is a continuously evolving process and recognizing how today's paradigms have been arrived at, is critical to understand how advances may be made in future. Mycobacterium tuberculosis bacteria is a tenacious organism. It has survived thousands of years and know how to avert its destruction. The only way it affects is through the air which is it's greatest asset. The world is no more indolent to the disease, every country has woken up to eradicate it, India has declared 'TB free India.' We all dream of a day, when the diagnosis becomes as easy as pregnancy wherever it is located, ultrashort course therapy so that it will increase the compliance and prevention becomes a reality.

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REFERENCE

1. Tuberculosis Manual for Obstetricians, and Gynaecologist, S.N. Tripathy and (Mrs) S.N. Tripathy, 2015, Jaypee Brothers Medical Publishers (P) Ltd.
2. Prasad R, Singh A, Gupta N, Are we moving towards development of Universal Drug Regimen for treatment of Tuberculosis. 2020, The Indian J. of Chest diseases and Allied Sciences. Vol. 2, No. I
3. Evaluation of Gene Xpert as compared to conventional methods in diagnosis of Female Genital Tuberculosis, Jai B Sharma 1, Sona Dharmendra 2, Shefali Jain 2, S K Sharma 3, Urvashi B Singh 4, Manish Soneja 3, SanjeevSinha 3, P Vanamail 2ur J ObstetGynecolReprodBiol, 2020 Dec;255:247-252

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