TUBERCULOSIS: STOP IT WITH EFFECTIVE TREATMENT

ABSTRACT –

AIM-Tuberculosis is one of the oldest human diseases, dating back over 17,000 years based totally on molecular proof. Despite modern diagnostic and treatment approaches, people continue to suffer from tuberculosis, and it tops the list of ten deadly infectious diseases in the world, second only to the Human Immunodeficiency Virus. TB is a worldwide pandemic, as per World Health Organization (WHO).It tops the causes of death among HIV-positive individuals. In this review we assess the challenges faced due to tuberculosis and its management and the strategies adopted to tackle it.Because of the dearth of number one health-care infrastructure in rural regions of several states which includes Health care provided privately not regulated nicely, which ends up in First- and second-line anti-TB drugs are widely used irrationally; infection with human immune deficiency virus; loss of political will; and, The most crucial, the corrupt management are all fundamental demanding situations in India's combat against tuberculosis. Another rising danger to TB eradication is multidrug-resistant tuberculosis (MDR-TB), which is the outcome ofa failing or deteriorating TB control programme. The World Health Organization's "STOP TB" policy aims to eradicate tuberculosis as a public health hazard by 2050.

KEYWORDS-
Tuberculosis; LTBI; Line Probe Assays; LAMP; COVID -19;RNTCP;Fusion Deposition Modelling.

INTRODUCTION:

Tuberculosis is an air-borne disease. It is caused by the Mycobacterium tuberculosis complex[Figure 1]. The causative agent of this disease was discovered by Robert Koch in 1882.

Latent tuberculosis infection (LTBI) and active tuberculosis disease are the two types of tuberculosis. LTBI refers to someone who has an M. tuberculosis infection in which the germs are still alive but not generating active TB disease. Active tuberculosis disease (also known as active TB) occurs when the TB bacteria multiply and the immune system of the individual is impaired, resulting in infection [1]

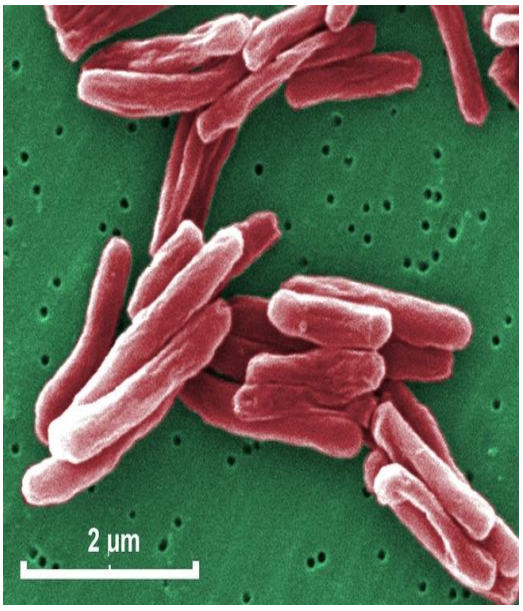

FIGURE 1: MYCOBACTERIUM TUBERCULOSIS
[REFERENCE Photo: CDC/Janice HaneCarr 2015 www.micrbiologyinpictures.com medically important- acid-fast bacteria -]

RISK FACTORS OF TUBERCULOSIS

You may be at a higher risk of contracting tuberculosis if:

1. *Lively tuberculosis is present in a chum, co-worker, or member of the family.*
2. *One belongs to a tribe where tuberculosis is extra probable to feast or you effort or stay with the people who have the disease. Vagrant humans, persons with HIV, persons residing in prison or in jail, and .those people are also included who insert narcotics into the veins are all included.*
3. *You are working in a hospital or else reside in a assisted living facility.*
4. *One is working as a health maintenance provider for people who are at greater risk of contracting tuberculosis.*
5. *You smoke cigarette. [2]*

TRANSMISSION OF TUBERCULOSIS

When someone with tuberculosis does coughing, sneezing, talking, laughing, or singing, minute particles containing the bacteria are released. One can catch it, if somebody breathes in these microorganisms. It's not simple to contract tuberculosis. You normally have to be surrounded by someone who contains bacteria that are abundant in their lungs for a long time. It is most likely that an individual gets sick from a co-worker, friend, or family member.

Germs that cause tuberculosis do not survive on external surfaces. The bacteria can't get transmitted through shaking hands or exchanging food or drink with someone who has it. [3]

The figure given below shows the various modes of transmission of tuberculosis.[FIGURE 2]

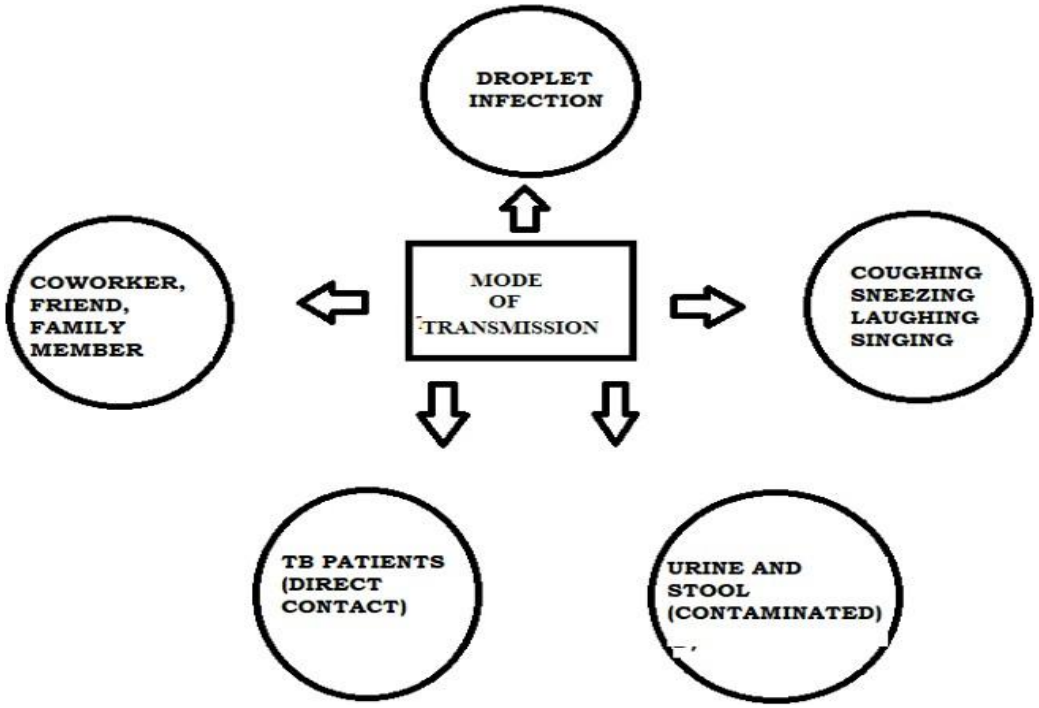

FIGURE 2: MODES OF TRANSMISSION OF TUBERCULOSIS

TB SCENARIO GLOBALLY

TB has been declared a worldwide pandemic and in 1993 it was declared as a 'global public health emergency' by the WHO. It is shown by molecular evidence that TB is over 17,000 years old. 24% of the worldwide prevalence, 23% of the worldwide incident instances and 21% of the worldwide deaths of TB is contributed through India.[4]

Of the people who are afresh diseased with tuberculosis bacilli, one in every ten people are getting infected with tuberculosis bacilli.

HIV impairs the system which regulates immunity, and people with concomitant infection have a weakened immune system. HIV and tuberculosis patients are much more prone to get tuberculosis. In between HIV-positive people, it is observed to be the primary cause of death.

Since 1990, HIV has been the most important factor which solely leads to the rise in the incidence of tuberculosis in Africa. According to the same information sheet, there were 9.37 million cases of tuberculosis worldwide which emerged in 2008, where the African and Southeast Asian regions (SEAR)

accounted for 30% and 34%, respectively. In Sub-Saharan Africa, however, the projected incidence rate is approximately twice as high as in the SEAR, with over 350 cases per 100,000 people. In the same year, 1.3 million individuals died of tuberculosis. The SEAR region had the most deaths, while the African region had the highest mortality per capita.

The WHO's Southeast Asian Region (SEAR) is vitally significant from a global standpoint. In addition to having 25% of the world's population, it also houses 30% of the world's poor, which makes it have high rates of infectious and non-infectious diseases, despite having relatively inadequate healthcare facilities. Without tangible success in this region, worldwide health advancement becomes impossible. Communicable diseases cause six million of the 14 million fatalities in this region, accounting for 42 percent of the Age-adjusted lifespan lost as a result of disability.[5][6]

INDIAN SCENARIO OF TB

TB is described in the Vedas and old Ayurvedic traditions of India. The battle against tuberculosis in the country India is divided into three periods: the first period, before the discovery of chemotherapy and X-ray; the period after the independence, when TB control programmes were established nationwide and executed; and the ongoing period, when the current WHO-assisted TB control programme is in place. [7]

TB IN CHILDREN

It has been suggested by models that active TB disease in children is extra common than official statements suggest, and that MDR-TB cases are far more innumerable than previous approximates[8][9]. In adults, active tuberculosis gives rise to pulmonary disease, but in the case of children, the spectrum of the disease is distinct, there is a wide variety of this condition, ranging from mild lymphadenitis to severe disseminated disease[10][11][12]. A child who has spent time with an adult who has active TB disease is more likely to contract M. tuberculosis and progress to full-blown active TB disease, hence LTBI testing and treatment are prioritised for them[13]. The same concepts that apply to adult LTBI treatment apply to youngsters.

Antituberculosis medications are generally well tolerated by youngsters, with little danger of toxicity. The dosage of the drug in children must be modified based on body weight and age due to developmental changes in pharmacokinetics and pharmacodynamics. Antimicrobial resistance in grown-up patients along with active TB disease who have had proximity with children may become useful in deciding on a regime. The essential concepts and conventional dosage regimens for treating active tuberculosis in children are identical to those used in adults. In the intensive phase, treatment should be provided at least thrice a day, and in severe cases of active disease, it may be extended for up to 9–12 months[14]. The WHO recommendations address how to manage HIV infection in children with active TB illness[15][16]. HIV-positive children having MDR-TB is treated using the same concept as MDR-TB in the children who are HIV-negative[17].

TUBERCULOSIS DETECTION FOR CHEST X-RAYS OF A HIGHLY TUBERCULOSIS ENVIRONMENTS FOR DETERMINING TREATMENT ORDER

The usage of artificial intelligence (AI) in the medical field for diagnostics purposes has boomed significantly over the last period, and an increasing number of medical images are being analyzed with neural networkspowered by AI, such as chest radiographs and roentgenograms.[18][19]

As of 2020, tuberculosis caused nearly as many deaths as COVID-19[20]. As a result, the World Health Organization recommends chest x-rays as part of tuberculosis screening and triage[20].

People who have tuberculosis symptoms or significant danger of tuberculosis undergo a triage test.[21]

The variability between readers as well as within readers is high, the specificity is moderate, and limited radiologist availability have all hampered the use of Screening and triaging with chest x-rays, It is particularly relevant to tuberculosis-endemic countries. Bangladesh is one of these countries, having a tuberculosis prevalence of 260 cases per 100,000 people in urban regions and a higher prevalence in rural areas.[22]

Artificial intelligence (AI) has the potential to dramatically improve visual reading capabilities in a range of situations. To recognize TB-related anomalies in Chest radiographs is employed as this system employs neural networks and deep learning.[23] Neural networks are interconnected functions that are drawing inspiration from the human nervous system. The weight and bias coefficients of each function are different[24].Based on AI algorithms, an irregularity score (ranging from zero to hundred or 0-1) is generated that indicates the risk of TB-related irregularities.

ADVANCEMENTS IN THE MOLECULAR DETECTION OF TUBERCULOSIS

Due to under diagnosis and underreporting to national TB programmes, roughly 3 million patients with tuberculosis were termed "missing". The End tuberculosis Strategy of the WHO asks for the recovery of these millions of people to attain the 2030 maintainable growth objective of eliminating tuberculosis. This goal will necessitate the development of new analytic examinations and the optimization of examination deployment methodologies. Because symptoms and testing technologies overlap for TB and In the context of the ongoing COVID-19 pandemic, SARS-CoV-2 appears to be circulating, it is also necessaryto explore merging TB and SARS-CoV-2 testing. [25]

DEVELOPMENTS OF TESTS AND PLATFORMS WITH THE SUPPORT OF WHO

1. ***LINE PROBE ASSAYS***

   For more than a decade, WHO has authorised LPA for first-line tuberculosis medicines (Isoniazid,Rifampicin) for the identification of multidrug-resistant tuberculosis.(26). Hain Lifesciences-Bruker's MTBDRplus and Nipro's NTM+MDRTB 2 are two of these tests (Osaka, Japan).

2. ***LAMP***

   It is an isothermal Polymerase Chain Reaction amplification technology called Loop-mediated isothermal amplification that could be used in a variety of situations, including peripheral health care. Because of its higher diagnostic performance, WHO has recommended Assay using A TB-LAMP based on LAMP as a viable substitute for smear microscopy since 2016. It also doesn't

necessitate a lot of expensive laboratory equipment. TB-LAMP is underutilised despite this, but several nations are developing to improve adoption of LAMP, countries may develop their own versions for use within their borders.

HURDLES IN DEVELOPMENT OF TB VACCINE

Drug-resistant tuberculosis (DRTB) has emerged and spread in most of the countries with a high tuberculosis (TB) burden. Because injection aims are anticipated to be Drug targets are completely independent, Mycobacterium tuberculosis vaccines should be capable of combating both drug-sensitive and drug-resistant strains. As a result, novel tuberculosis preserves the efficacy of tuberculosis drugs while also addressing the critical problem of drug resistance. Due to scientific and economic hurdles, private sector biopharmaceutical companies are only partially supporting the development of TB vaccines.

One of the most significant scientific issues is the absence of a verified, prognostic physical model or a protective correlation. So far, inoculation efficacy trials, which are expensive and time-consuming, can only be performed late in the research process; have been the first chance to recognize vaccine candidates that show promise. Without an effective means to triage candidates early in the research process, TB vaccine development has proven inefficient. Researchers are working on expanding medical efficacy by

implementing pre-proof-of-concept trials that determine whether treatments have a expressive organic result, Preventing infection and preventing recurrence in high-risk populations, as well as optimizing or validating the use of a non-human primate model or other animals as a test device, accurate, Models of human disease and their prediction[27][28]. Sample collection should be included in all vaccination efficacy trials to aid in the Correspondence of protection discovered and validated[29].

One more problem is that any proposed vaccination for newborns should be evaluated in comparison to the approved vaccine (In addition to protecting infants from tuberculosis and leprosy, Bacillus Calmette-Guérin also protects them against leprosy[30].

This raises the bar for any vaccination which aims to displace the BCG immunisation in babies.

Although tuberculosis is the largest reason of death worldwide owing to a solitary infection, themarket for TB vaccines is limited[31]. The problem persists even in countries with high incomes, the deprived with limited financial resources account for the majority of active tuberculosis cases. As a result of this reality, the for-profit sector has been limited in its investment in developing TB vaccines. [32]

DISABILITIES RELATED TO TUBERCULOSIS

Physical limitations caused by tuberculosis differ depending on whatever part of the body is afflicted. Human beings with a record of pulmonary TB, for instance, may expand continual obstructive pulmonary sickness (COPD), bronchiectasis, aspergillosis, pulmonary high blood pressure, or pulmonary fibrosis, as well as a spread of lengthy-time period respiration-related sequelae which include impaired lung feature (obstructive, restrictive, reduced diffusing capability, or decreased lung volumes)[33][34][35][36]. COPD because of tuberculosis is projected to reason 5.9 million incapacity-adjusted lifestyles years (DALYs) international[37].

Apprehensive gadget tuberculosis, which influences the meninges, mind, spinal twine, or cranial and peripheral nerves, can bring about intense, irreversible incapacity[38]. Due to spinal curvature and injury to neurological structures, spinal TB can reason paraparesis and quadriparesis, which can lead to chronic physical impairments[39]. Some limitations are caused by the host's organ or tissue deterioration caused by tuberculosis, while others are caused by treatment side effects. Treatment for tuberculosis is efficient in preventing mortality and limiting impairment, but certain drugs have adverse effects that might cause temporary or permanent incapacity. Previous research has found that persons who have been treated for DR-TB had a higher prevalence of visual disturbance and hearing loss[40][41]. However, the World Health Organization no longer recommends some of the drugs used in these researches, such as kanamycin and capreomycin[42].

TB survivors may also be more likely than the general population to suffer from mental health issues[43][44].

Mood problems such as anxiety and sadness may be linked to tuberculosis (TB) disease, TB therapy, or circumstances unrelated to TB.

TB patients may face stigma and discrimination as a result of cultural norms or beliefs connected with TB, which can induce or exacerbate mental health difficulties. The protracted treatment duration of 9–20 months for DR-TB causes disruptions to typical job, family, and social activities. Although not thoroughly investigated, the impact of tuberculosis treatment on children's and teenagers' cognitive development as a result of school disruption may be significant[45] .

Notwithstanding extended hobby inside the lengthy-time period outcomes of tuberculosis, the global incidence of TB-related disability is unknown right now.We desired to estimate the worldwide prevalence and forms of TB-associated impairments in this systematic review. [46]

TB AND DIABETES

Type II diabetes triples the likelihood of advancing tuberculosis (TB) disease and pairs the danger of demise during Tuberculosis treatment, Additionally, negative outcomes from Tuberculosis treatment. Diabetes may raise the incidence of Mycobacterium tuberculosis (MTBI) latent infection; however the size of this effect is unclear. Although this syndemic has gotten a lot of attention, In the majority of published studies, diabetes screening in Tuberculosis patients or observational follow-up of Tuberculosis treatment outcomesbased on diabetes diagnosis has been the focus of research. Targeted vaccination programmes, LTBI screening, and preventative therapy among diabetic patients, or, perhaps most importantly, improved diabetes management and prevention, are all possible techniques to avoid the development of tuberculosis disease[47].

TUBERCULOSIS IN INDIA DURING COVID-19

Pandemic SARS-CoV-2 that was caused by the COVID-19 virus is mostly a breathing ailment A typical cold or pneumonia can be as severe as the typical cold[48][49]. Infection spreads from person to person through droplets that are breathed in or transmitted to the body through contact with infected surfaces.

Supportive care is now the most common action option, while major illnesses may necessitate the use of a ventilator, a vaccine is being developed and efforts are being made to develop it.

More over a quarter of the domain's tuberculosis cases are in India. On a global scale, this equates to around 2.6 million instances out of a total of 10 million. Nearly 0.44 million persons in India have died as a result of the disease. According to the WHO, India accounts for one-third of all drug-resistant tuberculosis cases worldwide[50].

The COVID-19 epidemic has created a global health emergency. National TB programmes, on the other hand, must be actively involved to provide an efficient, timely reaction to COVID-virus while preserving Tuberculosis facilities[51].

Because of nationwide lockdown and control of infection efforts, the COVID-19 epidemic has imposed considerable Assessments conducted face-to-face that are limited and mobility of persons[52][53].

TESTING OF COVID 19 AND TB

The testing of patients with tuberculosis for COVID-19 and vice versa has become a hot topic in recent years. COVID-19 and tuberculosis share clinical symptoms and presentations, such as fever, Breathlessness, and coughing. Although the two diseases have subtle differences, COVID-19 infection develops faster than tuberculosis.

In a Tuberculosis-endemic nation like India, Tuberculosis may have been contracted simultaneously with the COVID-19 infection.

The European Laboratory Initiative has suggested that GeneXpert machines be used for COVID-19 testing without jeopardising their ability to screen for tuberculosis [54]. The Indian Council of Medical Research recently accepted the use of the Testing TruelabTM's beta CoV on TrueenatTM workspace for screening COVID-19 as a screening test for drug-resistant tuberculosis [55].

RELATIONSHIP BETWEEN COVID-19 AND TB

As more information and research about COVID-19 and TB become available, People with latent TB and existing disease may be more vulnerable to contracting SARS-CoV-2 and developing severe COVID-19 pneumonia, according to preliminary data[56][57]. New Delhi, India-based mathematical model-based forecasting studies underline the need for primary prevention strategies, particularly in TB patients, as wellas the need for TB centres to be prepared for concurrent infections [58].

IMPLICATION OF TB AND SARS-COV-2

During the current COVID-19 pandemic, Mycobacterium tuberculosis (TB) and SARS-CoV-2 may be concomitantly infected[59]. The damage induced by tuberculosis can make a patient more susceptible to COVID-19. When COVID -19 is taken by patients at the same time as TB, the prognosis is worse, which is likely caused by preexisting lung damage from Tuberculosis. If there is clinical worsening, individuals should be examined for either illness, even if the clinical presentation is uncharacteristic [60]. Tuberculosis patients can receive COVID -19 testing both at home and in the hospital, including those considered high risk, such as Human immunodeficiency virus-positive patients [61]. Tuberculosis has been listed by the Nigerian Ministry of Health as one of the risk factors for severe COVID-19 infection and death [62]. Nigeria, like India, has an endemic presence of tuberculosis.

EFFECT OF COVID-19 ON TB DISEASE CARE

According to some reports, COVID-19 may be slowing down the current gains in TB control [63]. The COVID-19 epidemic has had a profound influence on Tuberculosis therapy.

A comparison of the current situation in Nigeria with last year's pandemic can be made.COVID-19 preventive and lockdown techniques have limited the spread of the virus. In Nigeria, analysis, access to tests, and treatment centres are all similar.

Since the Lockdown, there has been a significant decline in traffic on the TB, Nikshay portal of the government of India [64].

SARS-CoV-2 is expected to spread since certain populations are latently infected. An

infection could trigger the onset of active tuberculosis in the ensuing months[65].

COMPLICATIONS OF CONCOMITANT TB AND INFECTIONS CAUSED BY COVID-19

COVID-19 immunity is not provided by anti-TB medication [66]. As a result, if a patient exhibits uncharacteristic symptoms that do not meet the standard clinical signs of either illness, they must theybe both TB and COVID-19 are detected, or vice versa. Motta et al. [67] stress the significance of being aware of the risk of collateral COVID-19 and Tuberculosis infection, which can have a catastrophic course

and result in death. In their two-unit studies on refugees with simultaneous Tuberculosis and COVID-19 infection, the case-fatality rate was significant (overall 10.8%), Co-morbidities are common in elderly patients.

There is a possibility that these patients contracted infections through nosocomial spread during previous stages of the COVID-19 pandemic.

They stress the significance of strict infection control for all the patients in the hospital, particularly those at higher risk, such as ageing patients with co-morbidities.

HOW COVID-19 AFFECTED THE TUBERCULOSIS IMMUNIZATION PROGRAM

The Bacille Calmette-Guerin vaccination protects from tuberculosis. Immunization services have been suspended due to the COVID-19 pandemic lockdown, which may lead to vaccine-preventable disease-related mortality and an extended load on health systems. Recently, World Health Organisation recommended that mandatory newborn BCG vaccination be continued amidst the COVID-19 pandemic in countries or settings with a greater incidence of tuberculosis, such as India, China, Turkey, Indonesia, Indonesia, and others[68]. The job of BCG in lowering the effect of COVID-19 has been a point of contention. [69]

TREATMENT OF TUBERCULOSIS

DUAL CONTROLLED DRUG RELEASE 3D PRINTED BILAYER TABLET

For the treatment of tuberculosis, an isoniazid (INZ) and rifampicin (RFC) bilayer tablet was designed using Fusion Deposition Modelling (FDM). This medication was formulated in an acidic matrix of hydroxypropyl cellulose (HPC) to make the stomach more conducive to drug release, The RFC formulation was developed to allow the release of the drug in the upper intestine (acidic conditions) (alkaline conditions). By limiting RFC degradation in acidic conditions and potentially avoiding drug-drug interactions, this design may provide superior clinical efficacy. The bilayer tablet was created by combining hot melt extrusion with 3D printing to create drug-containing filaments.Several HME and 3D printing procedures have been optimized to prevent drug degradation and to ensure consistent drug layer deposition in tablets. Variations in drug loading, infilling density, and covering layers were used to optimise the in-vitro drug release rate. At pH 1.2,more than 80% of INZ was released in 45 minutes, while around 76% of RFC was released in 45 minutes when the dissolution media was increased to pH 7.4. The study demonstrated how FDM technology mightbe used to produce oral fixed-dose combinations for individualised treatment. [70]

NATIONAL TUBERCULOSIS CONTROL PROGRAMME[71]

As part of the National Tuberculosis Control Program, launched by the Indian government in 1962, the United States and other countries provided effective treatment, established district tuberculosis centres, and aimed at finding as many tuberculosis cases as possible, We have established district tuberculosis centres in 454 of India's 496 districts, and we currently operate 330 tuberculosis clinics. We will strengthen

the existing tuberculosis demonstration and training centres in the state. By 1993, tuberculosis mortality rates had fallen to 53 per 100 000 people, the lowest level since 1970. A 1992 study of the national program, however, revealed inadequate budgetary investments and drug shortages, as well as an overemphasis on clinical and radiologic diagnosis techniques. An overemphasis was placed on clinical and radiologic diagnosis, and patient availability was lacking. There is a lack of widely accepted treatment regimens, insufficient use of sputum microscopy facilities, and a focus on identifying cases rather than addressing them. With the findings, the national plan is changing to achieve an 85 percent open rate with short-course (6-8 months) treatments and detect 70 percent of projected cases. The primary diagnostic method for self-referral is sputum testing, Health system standardization, uninterrupted drug supply at all levels, and

increased budget expenditures. A sub-district supervisory unit should be established to accomplish these goals, and training and operations research should be emphasized.

REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAMME

Based on the internationally recognised Straight Experiential Treatment Short-course method, the Revised National Tuberculosis Control Programme was begun in the year 1997 where it gradually expanded across the country with backing from the World Bank and other development partners. In March 2006, the entire country was covered. RNTCP has been acknowledged as the world's largest and rapidly-growing Tuberculosis control programme in terms of patient treatment. RNTCP is now being adopted across the United States.

All TB patients are provided with free diagnosis and treatment as part of the programme. For every 1 lac people in the general areas, there are microscopes, and for every 50,000 tribal residents, there are microscopes, mountainous, and tough parts to ensure excellent diagnosis. In the country, about 13000 microscopy centres have been built. Hospitals owned and operated by the government, Community Health Centres, and Primary Health Centres offer free TB treatment (PHCs). To the extent practicable, DOT facilities have been created near patients' homes. A DOT provider/DOT centre includes all public health facilities, subs centres, volunteers from the community, the American Society of Health-System Administrators, and self-help groups for women. [72][73]

CONCLUSION

As the preceding discussion shows, we have arrived a great way in our battle against this deadly disease, but, as the legendary poet named R. Frost famously observed, "...miles to go before I sleep," there is still a long way to progress before we can declare the world free of this disease. The World Health Organization's "STOP TB" policy aims to eradicate tuberculosis as a public health hazard by 2050. We need to strengthen our supervision efforts to assess the load of all types of tuberculosis (childhood, HIV-TB, MDR-TB) to increase our fight against this devastating illness. The sensible usage of first- and second-line anti-TB medications must be regulated urgently. They should never be sold in the form of over-the-counter medications. Local governments in the country India and other nations which aredeveloping should invest and encourage wholehearted efforts to localise anti-TB medicine manufacturing, resulting in more effective monitoring of their manufacturing and quality control standards. Identification ofthe products that are defective due to faulty manufacturing processes, worsened due to improper distribution and storage, and degraded, damaged, or spurious due to beneficial interests should all be part of the product quality surveillance offered in the marketplace. To make this disease more easily detectable, better diagnostic tests should be developed and made available on a grass-roots level. The links between primary health centres and DOTS centres should be strengthened, with more attention paid to prioritising the groups that must be followed first; utilising human resources from related public health programmes, such as HIV-malaria programmes; which promotes the expansion of new TB vaccines and drugs; and hindering the usage of homoeopathy medicines for the treatment of HIV and TB.

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AUTHOR'S CONTRIBUTIONS

Both the authors contributed in the equally for bringing this manuscript.

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