

**AN OVERVIEW ON TUBERCULOSIS AND
WORLDWIDE STEPS TO COMBAT TB INCLUDING
AWARENESS PROGRAMME IN INDIA**

ABSTRACT

Objectives of current review is to collate history of Tuberculosis (TB), overview of the current literature on epidemiology, world health organisations (WHO) recent strategic plan to overcome and eliminate TB from the root, and to determine current knowledge gaps for control of TB. This study is a review, a descriptive approach of state-of-science for better treatment strategies for TB. The article finds that to reach to end TB goal, WHO, we have to follow the guideline of who about TB control, along with that the Indian government also maintained awareness program. Current findings on TB suggest that with the development of science and technology, researches being conducted to minimise the drug resistance tuberculosis, as well as WHO sets new strategy to fight against TB, which could potentially change the casual outlook of the people towards their health habits, health issues, and will help them in future to tackle from this deadly killer disease.

Keywords: Tuberculosis; Deadly Killer disease; Epidemiology; World health organization; Awareness programme in India.

Key Highlights

- A brief overlook on TB history including past, present and future challenges to combat TB
- TB epidemiology, diagnosis, treatment, and current scenario with various national and international schemes for supporting to the TB patients and their better livelihood
- Year wise themes of world TB day
- Risk of Developing TB over a Lifetime and WHO's and SDG's End TB strategies
- Worldwide drugs treatment of TB
- Awareness Program in India to eliminate TB

1. INTRODUCTION

Tuberculosis (TB) is an endemic infectious disease in many developing nations and it has resurged in the developed world associated with the HIV/AIDS epidemic [1] and in order to fully address the global TB burden, there is need to know through knowledge about its history, epidemiology, diagnosis, current drug treatment, and novel drug delivery strategies for the effective management of TB. The main thrust of this paper is a review of the present and through report on TB.

1.1. History

In Indian continent TB is oldest communicable, fatal contagious disease that is deeply rooted among Indian population. TB has a history of being together with mankind for very long and was first discovered by Hippocrates in 400 BC[2]. History has evidence that many emperors died and many empire demolished due to this fatal disease in India[3,4,5]. The first written documents describing TB, dating back to 3300 and 2300 years ago, were found in India and in China respectively [6].

1.2. Epidemiology

TB is a granulomatous airborne infection disease caused by bacterium mycobacterium tuberculosis (M.TB), considered among the leading causes of mortality in India, which transmitted by means of invisible droplet nuclei containing the organisms that have left the reservoir during breathing, sneezing or coughing, of which this organism may remain airborne up to 6 hours, disease [7,8]. TB disease commonly affects the lungs; referred to as pulmonary TB, and extrapulmonary TB is the TB affecting the organ other than lungs, including the larynx, the lymph node, the pleura, the brain, the kidney, or bones and joints[9,10]. Miliary TB, common in infants and children younger than 5 years of age, occurs when tubercle bacilli enter the bloodstream and disseminate to all parts of the body. TB meningitis is the TB in the tissue surroundings the brain or spinal cord [11].

1.3. Discovery

According to Dr. Richard Morton pulmonary TB was associated with 'tubercles' due to the variety of its symptoms[2]. In the Ancient Greece TB was well known and called Phtisis. The extreme anemic pallor of people affected by TB was at the origin of the new term "white plague", coined during the 18th century[6]. By the end of 1839, TB was defined and accepted as one single disease and was termed as TB by a German physician, J.L. Schonlein[2]. Dr. Koch on March 24, 1882, identified, described the bacillus M.TB, after that World Health Organization (WHO) and the International Union declared the first world TB day in 1982[10,12,13,14,15].

1.4. Transmission and Pathogenesis

Transmission and progression driven by social factors such as poor living conditions and poor nutrition[16], spread through inhalation of airborne M.TB cells, multiply in macrophages and within the large cystic tubercles, formed liquefied tissue surrounded by infected macrophage[12], also tubercle bacilli spread via lymphatic system and bloodstream to many different organs[17]. After the inhalation, establishes primary infection, may cure if human have a strong immune system[12]. The major sources of infection are human and bovin, of which human beings with M. bovis almost occurs

by inhalation of aerosols and consumption of milk containing bacillus [13]. There are complex factors including factors that determines the strength and infectivity of the source, the integrity of the host defence of the exposed individuals, intrinsic properties of the bacillus itself, including viability, vulnerability or resistance to environmental stressors, genetic mutations, drug resistance, and virulence for a particular host[18]. As can be seen in Fig 1, the sources of transmission of M.TB are environmental factor, microbial factor other such as through coughing.

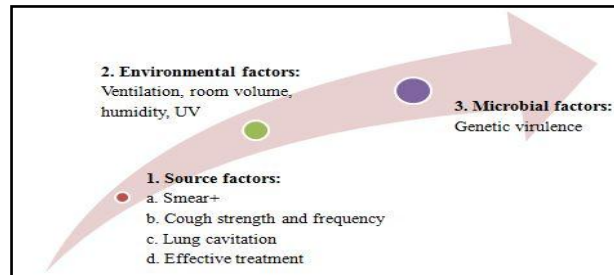


Fig 1: Source of TB infection [18]

1.5. Microbiology of Mycobacterium Tuberculosis

Mycobacterium genus covers more than 140 species, these species are divided into three major sets, M.tuberculosis complex, M. leprae, and mycobacteria other than tuberculosis(MOTT)[19]. The M.tuberculosis complex of organisms, which can cause human disease, consists of M Tuberculosis, Mycobacterium africanum, M. bovis, M. microti, and M. canetti. M. bovis was responsible for about 6 % of all human tuberculosis deaths in Europe before the introduction of milk pasteurisation; subsequent attenuation of a laboratory strain of M. bovis led to the development of BCG vaccine in 1921[13]. M. tuberculosis is an intracellular pathogen, aerobic, non-motile, non-encapsulated, non-spore forming, acid fast bacilli[9], grows most successfully in tissues with high oxygen content. The lipid rich cell wall of mycobacteria plays an essential role in growing the bacteria, made up of two segments, upper and lower, with core a mycoyl arabinogalactan-peptidoglycan complex. The upper segment made up of free lipids, some with longer fatty acids complementing the shorter alpha chain and vice versa, where proteins, phosphatidyl inositol mannosidase, the phthiocerol containing lipids, lipomannan, and lipoarabinomannan also can be found. Furthermore, the cell envelope of M. tuberculosis also contains an additional layer beyond peptidoglycan that rich in unusual lipids, glycolipids, and polysaccharides. M. tuberculosis is able to parasite human mononuclear phagocytes. M. tuberculosis will spend most of its life cycle in macrophages. M. tuberculosis has the ability to multiply inside the macrophage phagosome[19].

The size of the Mycobacterium is less than 5μ and the generation time of this bacterium is 18-24 hours[18], which is extremely slow compared with other bacteria (Escherichia coli divides every 20 minutes). This slow replication rate and ability to persist in a latent state result in the need for the long durations of drug therapy for the prevention TB infection. M. tuberculosis can remain dormant for a few years without the symptoms[12,13,20,21]

1.5.1. Types of TB

1. Childhood-type TB,
2. Adult-type TB.

1.6. Risk of Developing TB over a lifetime

Person's with latent TB infection is not infectious, however, about 10% of healthy individuals with latent TB infection, active TB may eventually develop over their lifetime[22], highest risk of progressing to active TB disease is in the first two years after initial infection, left untreated, a person will infect on average 10 to 15 persons a year. The most effective approach to TB control is the identification and cure of these infectious cases. Proper treatment of infectious cases makes them very quickly non-infectious so that they can no longer spread TB to others. Because effective treatment breaks the cycle of transmission, cure is the best prevention. Patients with active pulmonary TB may be asymptomatic, have mild or progressive dry cough or present with multiple symptoms, including fever, fatigue, weight loss, night sweats, and a cough that produces the bloody sputum. If

TB is detected early and treated fully, people with the disease quickly becomes non-infectious and eventually cure[23]. Multi drug resistance (MDR) are the TB where M. TB strain are resistant to all recommended therapies for people with latent infection who are not known contacts for a person with active MDR-TB disease. The priority population for testing and preventive therapy for latent infection is household contact of TB patients who are likely to be infected by their household members. However, in settings where the incidence of new is high, infections also frequently occurs outside the home[24,25].

1.7. Diagnosis [26, 27, 28, 29,30,31]

Following are the sign and symptoms of pulmonary tuberculosis

- Persistent cough for more than two weeks
- Sputum production which may or may not be blood stained.
- Weight loss
- Chest pain
- Shortness of breath
- Intermittent fever
- Loss of appetite, fatigue and malaise
- History of contact with a smear positive PTB cases

1.7.1. Laboratory diagnosis:

To understand the actual tuberculosis burden situation, the burden sometimes needs to be determined in terms of incidence per capita rather than by use of absolute number to enable comparisons with other regions[32]. Diagnosis of childhood tuberculosis is a challenge due to the pauci-bacillary nature of infection and the difficulty in obtaining appropriate sample[33]. The difference between diagnosing of TB infection and active TB disease is fully depends on the screening of tests [11,94] and it is included in Table 1.

TABLE 1: DIFFERENCE BETWEEN TUBERCULOSIS INFECTION AND TUBERCULOSIS ACTIVE DISEASE ON THE BASIS OF DIAGNOSING TEST

Characteristics	Tuberculosis infection	Tuberculosis Disease
Symptoms	None	Cough present, weight loss, fever, night sweat
Tuberculin skin test	Positive	Usually positive
Interferon gamma immune assay (IGRA)	Positive	Usually positive
Sputum bacteriology	Negative	Usually positive
Chest radiography	Normal	Usually abnormal
Infectiousness	No	Often infectious (before treatment)
Case of Tuberculosis	No	Yes
Preferred Treatment	Preventive treatment	Tuberculosis treatment

Adapted from source [73]

2. CURRENT SCENARIO OF TB

About 1/3rd of the world's population is infected with TB. Every year ~3 million people die from tuberculosis, mostly in developing countries where it kills 1 in 5 adults. India accounts for one quarter of the global TB burden. Primarily it affects the lungs, although it can affect other organs and systems. WHO reported that 10 million people fell ill with TB and there were 1.5 million TB deaths (including 251000 among people with HIV) in 2018, making it the top infectious killer worldwide[11,35,36,37,38]. The eight countries which contribute to 60 % of global epidemic burden of TB is depicted in Fig 2.

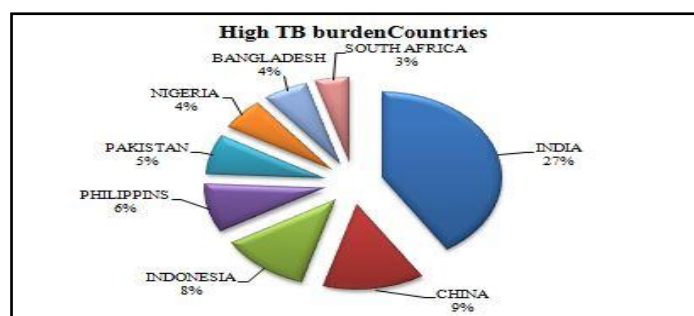


Fig 2: Current scenario of high TB burden countries [73].

It is most ordinary opportunistic infection in Acquired-Immuno Deficiency Syndrome and is a very old scourge[39]. Amita Gupta et al mentioned that pregnant women, children < 15 years old and, HIV-infected persons contribute approximately 20% of the global TB burden[40]. TB treatment is challenging, requiring accurate and early diagnosis, drug-resistance screening and the administration of effective treatment regimens for at least 6 months through directly observed therapy (DOT) and follow-up support[41,42].

2.1. World Health Organization's (WHO) target

In 2014 WHO launched the End TB strategy within the framework of the United Nations (UN) Sustainable Development Goals (SDGs), include the core anti TB interventions (diagnosis, treatment and preventions), under Pillar I, and several socioeconomic and health interventions, (Health, economy, finance, interior and justice) under pillar II. Intensified research activities and innovation are covered by pillar III[43]. In the agenda UN, 2018, meeting on TB, “United to End TB: An Urgent Global Response to a Global Epidemic”, with the targets of reducing TB deaths and cases by 95% and 90% respectively between 2015 and 2035. India which contributes to one quarter of the global burden of TB has set in motion the National Strategic Plan (NSP) for TB elimination 2017-2025. As it can be seen in the Table 2, the year wise themes of world TB day which emphasis on what should be our action in future to be combat TB, for an example the theme of world TB day 2019 according to is “It’s time for action it’s time to end TB [44,45,46,47,48,49,50].

TABLE 2: Yearly Themes Of World TB Day

Year	Theme of world TB day
24 th March 2021	The clock is Ticking
24 th March 2020	It’s Time to end TB
24 th March 2019	<p>“It’s TIME” – put the accent on the urgency to act on the commitment made by global leaders to:</p> <ul style="list-style-type: none"> • Scale up access to prevention and treatment • Build accountability • Ensure sufficient and sustainable financing including for research • Promote an end TB stigma and discrimination and • Promote an equitable, rights-based and people centered TB response.
24 th March 2018	<p>“Wanted: Leaders for a TB-free world”</p> <p>It is focuses on building commitment to end TB, not only at the political level with hands of State Ministers of health, but at all levels from Mayors, Governors, Parliamentarians and with TB, Civil society advocates, health workers, doctors or nurses, NGOs and other partners. All can be leaders of efforts to end TB in their own work or terrain</p>
24 th March 2017	<p>“Unite to end tuberculosis: Leave no one behind”</p> <p>2017 is the second year of two-year “unite to end TB” campaign for world TB day. This year WHO will place special focus on uniting efforts to “Leave no one behind”, including actions to address stigma, discrimination, marginalization and overcome barriers to access care.</p>
22 th March 2016	“Unite to end tuberculosis”
17 th March 2015	“Gear up to end TB”
19 th March 2014	“Reach the 3 million” : TB is curable, but current efforts to find, treat and cure everyone who get ill with the disease are not sufficient of the 9 million people a year

Adapted from source [48]

3. WORLDWIDE TREATMENT OF TUBERCULOSIS

One of the challenges in treatment of latent and active TB is the lengthy duration of treatment regimens[51]. India is one of the first countries to invest in TB control after independence and the national TB programme is in place since 1962, which led to the establishment of district TB Centres (DTC) and TB Clinics across the country[52]. Sometimes, experts do talk about failures or shortcomings of NTP (National Tuberculosis Programme) and RNTCP (Revised National Tuberculosis Control Programme). It is important to review the strategies and evaluate the programme. In the recently developed NSP, all inputs have been taken from various stakeholders[53]. RNTCP is being implemented in-line with NSP[48], Action Plan (TAP) for the tribal patients[54], developed comprehensive guidelines for diagnosis and treatment of pulmonary tuberculosis and to monitor RNTCP effectively a web enabled and case based monitoring application called NIKSHAY has been developed by National Informatics Centre (NIC)[55].

There are three different regimens and each regimen is recommended for defined group[26]

- Directly Observed Therapy Short-course (DOTS) has been one of the major strategies to combat the epidemic of TB globally. In DOTS the patients are given the drugs under observation by the health workers. This direct supervision by health worker ensures patient adherence to the treatment.
- Long course chemotherapy (LCC), which is for 12 months.
- Retreatment regimen

3.1. Vaccination as part of treatment

Immunisation with the BCG vaccine is known to protect children from severe and disseminated forms of disease, decrease infection by 30%, and potentially offer some protection to adult populations[57]. A 2018 phase 2b study of a novel vaccine candidate known as M72/AS01E (GlaxoSmithKline, London, UK) was found to provide more than 50% protection from progression to active tuberculosis among adults with tuberculosis infection and could be a candidate to advance into larger studies[58]. Agger EM (2016) has reviewed and discussed the BCG vaccine, developed by an attenuation of the virulent *M. bovis*, further two different TB vaccination strategies are being pursued; replacing the current BCG with an improved BCG or an attenuated *M.TB*, or alternatively boosting BCG-immunity either shortly after BCG administration in infants or more predominantly as a booster in adolescence when there is an increase in TB incidence. Currently, there are sixteen novel vaccines in clinical development, of which the majority are BCG booster vaccines[59].

3.2. Drugs for the treatment of TB

For the treatment of TB first line oral anti-TB drugs, injectable anti-TB drugs, newer second line anti-TB drugs, oral second line anti-TB drugs and drugs with unclear function[39,60,61,62,63] are summarised in Table 3.

Table 3: Classification Of Anti-TB Drugs

First Line Oral anti-TB drugs	Injectable anti-TB drugs	Newer second line anti-TB drugs	Oral second line anti-TB drugs	Drugs with unclear function in the treatment of drug resistant TB
Isoniazid	Sterptomycin	Levofloxacin	Thioacetazone	Clofazimine
Pyrazinamide	Kanamycin	Ceprofloxacin	P-amino salicylic acid	Linezolid
Ethambutol	Amikacin	Oflaxacin	Ethionamid	Thioacetazone
Rifampicin	Capreomycin	Moxifloxacin	Cycloserine	Clarithromycin
Sterptomycin	Vincomycin	Gatifloxacin		

Adapted from source [39,60,61,62,63]

These days, researches focus on employing non-antibiotic drugs for the eradication of TB infection. Vitamin C, A, D singly as well as in combination with first line drugs are also used, which show that trace elements play an important role in the success of anti-TB drugs[62].

In 2006, a more resistant strains of M.TB, XDR-TB emerged which is resistant not only to isoniazid and rifampicin but also to fluoroquinolones and second line aminoglycosides. XDR-TB may be MDR-TB with additional resistance to any fluoroquinolone and at least one of the three second line injectable drugs. Treatment for XDR-TB requires the use of third line anti-TB drugs but these drugs have more side effects than first or second line TB drugs[42,64,65]. Treatment of MDR-TB is expensive, prolonged (18–24 months) and complex (with at least a combination of five drugs that include some injectable drugs), and is associated with a higher incidence of adverse effects[63,66].

3.2.1. Recently approved drug in TB treatment

Bedaquiline, approved by the Food and Drug Administration (FDA), targets both active and dormant bacilli and Delamanid, by the European Medicine Agency, is a metronidazole derivative with bactericidal and sterilising activity. Unlike bedaquiline and Delamanid does not show cross-resistance with other anti-TB drugs[22,67].

- **Phases of anti-TB Treatment**

There are two phases of treatment[26,30,56]

1. Initial phases, 2. Continuation phase

The dosage regimens for adults are as shown in Table 4 and the RNTCP daily treatment regimen is shown in Table 5.

Table 4: The Dosage Regimen For Adults

Patient Body Weight (Kg)	Initial phase			Continuation phase		
	2 months			4 months		6 months
	Daily	or Daily	or 3 times per week	Daily	or 3 times per week	Daily
	HRZE 75mg+150mg+400mg+275mg	HRZ 75mg+150mg+400mg	HRZ 150mg+150mg+500mg	HR 75mg+150mg	HR 150mg+150mg	EH 400mg+150mg
30-39	2	2	2	2	2	1.5
40-54	3	3	3	3	3	2
55-70	4	4	4	4	4	3
71 and more	5	5	5	5	5	3

Adapted from source [56].

Table 5: RNTCP Daily Treatment Regimen

Category	Type of Patient	Regimen	
		Initial phase	Continuation phase
I (RED)	New smear positive Seriously ill smear negative PTB Seriously ill extrapulmonary TB	2HRZE	4RH
II (BLUE)	Previously treated sputum smear positive: -relapse -treatment after interruption; -Treatment failure	2HRZES/1HRZE	5RHE
III (GREEN)	New smear negative PTB (older than category I) and less severe form of extrapulmonary TB	2HRZE	4RH

Adapted from source [56].

4. AN OVERLOOK AT TB AWARENESS PROGRAM IN INDIA

Improving quality of TB care in the private sector is crucial to end TB in highest TB burden. Modelling shows that optimism private sector engagement in India could avert 8 million deaths from TB between 2019 and 2045. In high drug resistance TB burden countries, access to rapid drug susceptibility testing (DST) and second-line drugs is essential to success[44,45,46]. Simulated patient studies among tuberculosis care providers in India, Kenya, China, and South Africa show that a wide spectrum exists in the quality of services offered to people with tuberculosis, with many receiving suboptimal services[68]. An awareness of atypical clinical manifestations of tuberculosis is important, especially in regions where TB continues to be a major public health problem, such as India[69]. Today, India awakes people by giving the advertisements on Television, newspapers, hoardings on the public place, posters on the walls, public transport and many other ways about TB. In DOTS there is a tagline saying "Pura Course, Pakka Ilaj" also on the television advertisement by the National Health Mission (NHM) saying "TB Harega Desh Jeetega". The NHM of India starts 'Nikshay Poshan Yojana' under Extended Gram Swaraj Abhiyaan for the nutritional support to TB patients and under this financial incentive of Rs. 500/- per month per each notified TB patient for the complete duration of treatment. The incentives are distributed via DBT (direct benefit transfer). According to this Yojana every state in India is giving financial support for the nutritional support to the TB patients. Table 6 information highlights the Nikshay Poshan Yojana in every state in India[48].

UNDER PEER REVIEW

Table 6: Nikshay Poshan Yojana In Every State In India

Sr. No	State	Economic assistance	Nutritional support	Psycho-social support
1	Arunachal Pradesh	-	TB patients receive food support and are counseled on treatment adherence.	
2	Assam	-	MDR-TB patients receive wheat, rice, green gram, pulses, chickpeas, jaggery, soy bean and peanuts every months for 6 months	Cured TB patients become champions for treatment completion and are invited to speak about their challenges and experiences to motivate TB patients to adhere to treatment
3	Bihar	-	TB patients receive monthly ration pack for a period of 6 months. Ration pack includes rice, wheat and a variety of pulses. The food based support is complemented by monthly checkups to track improvements in the patients weight	
4	Chhattisgarh	MDR-TB patients receive a benefits package of Rs. 50,000 per family per annual income under state insurance scheme to cover the cost of in patients care. The benefit package includes pretreatment evaluation covering all costs of hospitalization, clinical and laboratory tests follow up evaluation and medicines for side effects managements.	Chhattisgarh provides monthly food baskets containing milk powder, ground nut and soy bean oil. At the time of distribution of first basket patients are counselled on treatment adherence and the importance of nutrition.	Patients receive counseling for the side effects managements, treatment adherence and microbiological and clinical examinations. Cured TB patients called as ' Axshya Saathis ' share their stories at time of food disbursement to motivate current patients to adhere to treatment.
5	Delhi	Cash benefits given to patients for treatment and diagnostic service required. Patients received educational training, livelihood training in-kind support such as treatment incentives and blankets	Monthly ration in the form of dry ration or consisting of wheat flour, rice green gram, soy beans and groundnuts. MDR-TB patients receive additional supplements of protein powder with milk, biscuit, and pulses,	Patient are counselled on how best to use the monetary assistance towards their recovery and betterment
6	Goa	Patients receive Rs. 600 incentives as a financial assistance till full DOTS completion. DR-TB patients receive financial assistance till full treatment completion	-	-
7	Gujarat	TB patients below poverty line receive Rs. 500 per month on a quarterly basis through DBT or RTGS. Beneficiaries includes nomadic tribes, Scheduled caste (SC), Scheduled tribes (ST), and socially as	District TB office provides raw food materials to TB patients with special focus on drug resistant TB patients (DR-TB)	-

		well as educationally backward classes		
8	Himachal Pradesh		DR-TB patients receive a packaged 'Nutrimix' (food supplement) containing roasted wheat, sugar, soy bean, black gram, refined oil, whole milk powder, and groundnut, for the entire duration of treatment. Ten packets of Nutrimix 100gm each are distributed to patients every month.	
9	Jharkhand	TB patients belonging to Scheduled caste (SC), Scheduled tribes (ST), and Other Backward Class (OBC) receive monetary support up to Rs. 10,000 via bank transfer	TB patients admitted in missionary hospitals in remote tribal areas receive nutritional support for 2-3 months in addition to indoor care. MDR-TB patients in Bokaro district receive supplementary food packages containing rice, pulses, grams and soy bean on a monthly basis.	
10	Kerala	Patients with annual family income below Rs. 1,00,000 receives Rs. 1,000 per month through the TB pension plan.	Patients with annual family income below Rs. 1,00,000 receives food baskets comprising of oats, toor dal, soy beans, peanuts, milk powder, and ragi powder every month	Treatment support group (TSGs) encourage patients struggling with treatment adherence through counseling, food kit provision, travel support, and pension assistance among other services
11	Madhya Pradesh		MDR-TB patients receive supplementary nutrition support in the form of dry ration on a monthly basis	
12	Maharashtra	TB patients travelling in Maharashtra State Road transport Corporation (MSRTC) buses can now travel for free by showing an RNTCP issued ID	TB patients in Mumbai receive support in the form of pulses, rice, peanuts, jiggery and wheat for a period of two months as part of a new initiative by Brihanmumbai Municipal Corporation (BMC)	
13	Meghalaya		Meghalaya provides economically weaker TB patients with food baskets which comprises Bengal gram, Horlicks and 2.5 dozen eggs every months	
14	Punjab		Community based organization provides nutrition support and supplementary medicine to drug resistant TB patient. Under Antodaya Ann Yojana, the state also provides nutrition support to drug resistant TB patients at subsidized rates.	
15	Tamil Nadu	Small and Marginal farmer, Inland fisherman, and plantation labourers suffering from TB are given a monthly pension of Rs.1000 for the entire duration of treatment. Patients receive water filters, water cans, bed sheets and pillows. Livelihood training like tailoring and craft-making is organized for	DR-TB patients receives monthly support in the form of ration such as peanuts, groundnuts, dates, green peas, chick peas, soy milk and protein powder for 6 months. In patients nutrition care includes proteins and vitamins supplements. Patients also taught food preparations and are counselled on the importance of nutrition	Sensitization meeting are organized to inform patients about their right and responsibilities and to motivate them to adhere to treatment

		patients to generate income		
16	Telangana	Patients receive the financial assistance in the form of vocational training, livestock and payment of school tuitions, among other upon treatment completion	The state provides raw materials like rice, groundnuts, edible oil, jiggery and milk to Below Poverty Line (BPL) and DR-TB patients. Children under 6 years suffering from TB are provided double the ration through ICDS' Anganwadi system	Home based counseling is provided to MDR-TB patients, on social stigma, depression, side-effects management and treatment adherence. Field staff sensitizes households on their entitlements and linkages to applicable social welfare schemes

Adapted from source [48].

UNDER PEER REVIEW

5. CONCLUSION

TB has been called the perfect expression of an imperfect civilisation[16]. TB is now found in every corner of globe and is one of the killer communicable disease caused by M. TB, transmitted by means of invisible droplet nuclei containing the organisms that have left the reservoir during breathing, sneezing or coughing sneezing. Infection and disease caused by M.TB strongly stimulates human moral immunity in humans[70]. In order to fully address the global TB burden, there is need improved diagnostic tests for active TB, seek to address the unmet needs for this patient group[71,72]. RNTCP is an on-going centrally sponsored scheme, being implemented under the umbrella of NHM[48]. The NHM of India starts 'Nikshay Poshan Yojana' under Extended Gram Swaraj Abhiyaan for the nutritional and financial support to TB patients[48]. So, to eliminate the TB from its grass root the awareness among the society about this deadly communicable disease, its transmission, prevention, treatment and WHO strategies, as well as governments initiatives and the fact related to this is a current and important need of today's era. As of now various preventive and treatment strategies has been developed, and along with that the various drug delivery system as well as mode of administration has been changed depending on the severity of the disease. One of the major challenges with this disease is its lengthy duration of treatment, so there is a need of the new drug delivery than the conventional, which is able to target the site of infection where mycobacterium resides. Inhalable drug delivery design could potentially solve this problem and many researchers are working on such a platform by preparing microparticulate and nanoparticulate systems to reduce the frequency of dosing and duration of drug treatment by sustaining it as well as to target pulmonary alveoli, the site of infection. There are a lot to do in this field of TB, it would be formulation aspects, new drug synthesis, patient compliance aspects, socioeconomic aspects and many more, to live healthy and respectful life for TB patient.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

REFERENCES

1. Andrade F, Videira M, Ferreira D, Sosnik A, Sarmiento B. Nanotechnology and pulmonary delivery to overcome resistance in infectious diseases. *Adv. Drug Deliv. Rev* 2013; 65(13-14):1816-1827. doi: 10.1016/j.addr.2013.07.020.
2. Mishra A, and Surolia A. Mycobacterium tuberculosis: Surviving and Indulging in an Unwelcoming Host. *IUBMB Life* 2018;70(9):917-925. doi: 10.1002/iub.1882.
3. Herzog, B.H. "History of tuberculosis". *Respiration* 1998;65:5-15.
4. Daniel T, History and Epidemiology of Tuberculosis, Section 1, Chapter 1 The History of Tuberculosis Past, Present, and challenges for the future, In: Schaaf S, Zumla A, eds. *Tuberculosis: a comprehensive clinical reference*. Philadelphia, PA: Saunders, 2009: 1–7.
5. Bhat ZS, Rather MA, Maqbool M, and Ahmad Z. Drug targets exploited in mycobacterium tuberculosis: Pitfalls and promises on the horizon. 2018;103:1733-1747. <https://doi.org/10.1016/j.biopha.2018.04.176>
6. I. Barberis, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. *J Prev Med Hyg* 2017; 58: E9-E12.

7. Dubey, N. & Goyal A. The role of nutritional value in causing tuberculosis and growth of tuberculosis microbes in the presence of some herbal plant extract, *WJPPS*, 2017;6(6):796-804.
8. <http://www.who.int/tb/strategy>
9. Swain SK, Behera IC, Sahu MC. Primary sinonasal tuberculosis: our experience in tertiary care hospital of eastern india. *Egyptian Journal of Ear, Nose, Throat and Allied Sciences* 2017;18:237–240
10. Burke SDA. Tuberculosis: Past And Present, *Rev In Anthropology*, 2011;40:27-52. Doi: 10.1080/00938157.2011.547754
11. <http://www.cdc.gov/tb/education/corecurr/pdf/chapter2.pdf>
12. Vasava MS, Bhoi MN, Rathwa SK, Borad MA, Nair SG, Patel HD. Drug development against tuberculosis: Past, present and future, *Indian journal of tuberculosis* 2017;6(4):252-275.
13. Lawn SD, Zumla A. Seminar, Tuberculosis. *Lancet* 2011: 378. www.thelancet.com
14. Jindal S. Koch's postulates- Pitfalls and relevance in the 21st century. *IJTB* 2018;1:1-2. <https://doi.org/10.1016/ijtb.2017.12.003>
15. Saxena N, Srivastava N, Shukla P, Tripathi GK. The Drug Discovery Development for Treatment of Tuberculosis. *Journal of Drug Delivery and Therapeutics* 2019;9(3): 802-819. <http://dx.doi.org/10.22270/jddt.v9i3-s.2777>
16. Ortblad KF, Salomon JA. Till Barnighuasen, Rifat Atun. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015;1-10. [http://dx.doi.org/10.1016/S0140-6736\(15\)00324-4](http://dx.doi.org/10.1016/S0140-6736(15)00324-4)
17. Bonfioli AA, Miranda SS, Campos WR, Fernando O. Tuberculosis, *Seminars in Ophthalmology* 2005;20:169-175. DOI: 10.1080/08820530500231912
18. Ashwin S Dharmadhikari and Edward A Nardell, Tuberculosis, chapter 2 transmission of mycobacterium tuberculosis, *A comprehensive clinical research*, 2009,8-16. <https://doi.org/10.1016/B978-1-4160-3988-4.00002-0>
19. Jabbar.A, Diagnosis and Management of Tuberculosis, Chapter 5 Tuberculosis and its Diagnosis: A Review, 1-20. <https://openaccessebooks.com/diagnosis-management-tuberculosis/tuberculosis-and-its-diagnosis-a-review.pdf> Accessed on 03/05/2020
20. Brennan PJ. Structure, function, and biogenesis of the cell wall of Mycobacterium tuberculosis. *Tuberculosis* 2003;83:91-97. doi:10.1016/S1472-9792(02)00089-6
21. Earnst JD. The immunological life cycle of tuberculosis. *Nat Rev Immunol* 2012;12:581-591. doi:10.1038/nri3259
22. Rojano B, Caminero JA, and Hayek M. Curving Tuberculosis: Current Trends and Future Needs. *Ann Glob Health* 2019;85(1):5:1-7. <https://doi.org/10.5334/aogh.2415>
23. Jheong YZ, Lee KS. Pulmonary tuberculosis: up-to-date imaging and management. *AJR* 2008;191:834-844.
24. Knight GM, McQuaid FC, Dodd P, Rein M G J H. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modeling. *Lancet Infect Dis* 2019:1-10. Doi: [http://dx.doi.org/10.1016/S1473-3099\(19\)30307-X](http://dx.doi.org/10.1016/S1473-3099(19)30307-X)
25. Garg RK, Rizvi I, Malhotra HS, Uniyal R, Kumar N. Management of complex tuberculosis cases: a focus on drug-resistant Tuberculous meningitis. *Expert Rev Anti-Infe* 2018:1-72. Doi: 10.1080/14787210.2018.1540930
26. Demena M, Baraki N, Kifle Y, Seyoum B, Abdosh T, Galmesa A. Module Pulmonary Tuberculosis for the Ethiopian health center team. *Ethiopin public health training initiative*, Haryana University 2004: 1-64.
27. Anand N, Upadhyaya K, Tripathi RP. Drug development pipeline for the treatment of tuberculosis: Needs, Challenges, success and opportunity for future. *Chemistry and Biology interface* 2015;5(2):84-127
28. Halliday A, Masonou T, Tolosa-Wright M, Mandagare V, Lalvani A. Immunodiagnosis of active tuberculosis. *Expert Rev Respir Med* 2019;13:521-532. <https://doi.org/10.1080/17476348.2019.1615888>
29. Saxena N, Srivastava N, Shukla P, Tripathi G K, The Drug Discovery Development for Treatment of Tuberculosis. *JDDT* 2019;9(3): 802-819. <http://dx.doi.org/10.22270/jddt.v9i3-s.2777>
30. Leung CC, Lange C and Zhang Y. Tuberculosis: Current state of knowledge An epilogue, *Respirology* 2013;18:1047–1055. doi: 10.1111/resp.12156
31. Chopra M, Bhattacharyya D, Barthwal MS, Madan GD, Chakrabarthy B, Pandey IM, Chopra M, Cough of more than two weeks–Time to think beyond pulmonary TB, , *Indian J Tuberc* 2019;66:44-48. <http://dx.doi.org/10.1016/j.ijtb.2017.05.007>

32. Martin PG, and Nathan K, Global burden of tuberculosis: where we are and what to do, *Lancet Infect Dis*, 2019;18:1291-1292
33. Singh V & Kabra S, Advances in Tuberculosis: Diagnostics, *Indian J Pediatr* 2019;1-2. <https://doi.org/10.1007/s12098-019-02942-3>
34. Al-Jahdali H, Memish ZA, Menzies D. Tuberculosis in association with travel. *Int J Antimicrob Agents* 2003;21(2):125-30.
35. Campanico A, Moreira R, and Lopes F. Drug discovery in tuberculosis. New drug targets and antibacterial agents. *Eur J Med Chem* 2018;150:525-545. Doi: [10.1016/j.ejmech.2018.03.020](https://doi.org/10.1016/j.ejmech.2018.03.020)
36. Bhat ZS, Rather MA, Maqbool M, and Ahmad Z. Drug targets exploited in mycobacterium tuberculosis: Pitfalls and promises on the horizon. *Biomed Pharmacother* 2018;103:1733-1747. <https://doi.org/10.1016/j.biopha.2018.04.176>
37. Kumar R. Empirical use of antituberculosis drugs should not be equated to their inappropriate and indiscriminate use. *Indian J Pharmacol* 2011;43(3):363–364. DOI: 10.4103/0253-7613.81494
38. <https://www.who.int/news-room/fact-sheets/detail/tuberculosis> accessed on 19/11/2019
39. Kaur M, Garg T, Narang R. A review of emerging trends in the treatments of tuberculosis. *Artif Cells Nanomed Biotechnol* 2016;44(2):478-84. DOI:10.3109/21691401.2014.962745
40. Gupta A, Hughes MD, Garcia-Prats AJ, McIntire K, Hesselring AC. Inclusion of key populations in clinical trials of new antituberculosis treatments: Current barriers and recommendations for pregnant and lactating women, children, and HIV infected persons. *PLoS Med* 2019;16(8):1-26. <https://doi.org/10.1371/journal.pmed.1002882>.
41. Zumla A, Nahid P, and Cole ST. Advances in the development of new tuberculosis drugs and treatment regimens. *Nat Rev Drug Discov* 2013;12:388-404. Doi: 10.1038/nrd4001
42. Vjecha MJ, Tiberi S, and Zumla A. Accelerating the development of therapeutic strategies for drug-resistant tuberculosis. *Nat Rev Drug Discov* 2018;17(9):607-608. doi: 10.1038/nrd2018.28
43. Gilpin C, Korobitsyn A, Migliori GB, Raviglione MC, Weyer K. The world health organization standards for tuberculosis care and management, *Eur. Respir J* 2018;51(3):1-14. doi: 10.1183/13993003.00098-2018.
44. Sharma N, Basu S, Chopra KK. Achieving TB elimination in India: The role of latent TB management. *Indian J Tuberc* 2019;66(1):30-33.
45. Herbert N, Masham BS, Suttie BA, Sharma V, Albani S, Domeneti O, Flurry R, Oliver M, Zumla A. Advancing political will to end the tuberculosis epidemic. *Lancet Infect Dis* 2017;18(7):711-712. [http://dx.doi.org/10.1016/s1473-3099\(17\)30679-5](http://dx.doi.org/10.1016/s1473-3099(17)30679-5)
46. Reid MJ, Arinaminpathy N, Bloom A, Bloom BR, Boehme C, Chaisson R, Chin DP, Building a tuberculosis-free world: The *Lancet* Commission on tuberculosis. *Lancet* 2019. [http://dx.doi.org/10.1016/S0140-6736\(19\)30024-8](http://dx.doi.org/10.1016/S0140-6736(19)30024-8)
47. Kanchar A and Swaminathan S. Tuberculosis Control: WHO Perspective and Guidelines. *Indian J Pediatr* 2019;86(8):703-708. <https://doi.org/10.1007/s12098-019-02989-2>
48. <https://tbcindia.gov.in>
49. Fogel N. Tuberculosis: A disease without boundaries. *Tuberculosis* 2015;95:527-531.
50. <http://www.int/en/news-room/22-03-2016>
51. Moran M. Background paper 6.8 Tuberculosis. Priority medicines for Europe and the world: A public health approach to innovation 2013:1-32.
52. Gupta D. Administrative challenges in implementation of RNTCP. *Indian J Tuberc* 2018; 65:187-189. <http://doi.org/10.1016/j.ijtb.2018.06.001>
53. Gupta D. Strategy and way forward for TB elimination. *Indian J Tuberc* 2018;65(1):4-5. <http://doi.org/10.1016/j.ijtb.2017.12.2013>
54. Mallick G, Nagaraja S, Sagili K, Khaparde K, Satyanarayana S, Chandha S, Revised National Tuberculosis Control Programme (RNTCP) Tribal Action Plan Fund Utilisation: How Does Chhattisgarh State in India Fare? *J. Tuberc. Res* 2019;7:1-10. <http://doi.org/10.4236/jtr.2019.71001>
55. <http://nikshay.gov.in>
56. WHO, (2002), Operational guide for National tuberculosis control programme on the introduction and use of fixed-dose combination drugs, WHO/CDC/TB/2002.308, WHO/EDM/PAR/ 2002:6. <http://www.who.int/tb/publications/fixed-dosecombination-report/en>
57. Peter Daley and Marek Smieja, Chapter 8 Tuberculosis, Evidence-Based Infectious Diseases, Third Edition. Edited by Dominik Mertz, Fiona Smail, and Nick Daneman 2018 John Wiley & Sons Ltd. Published 2018 by John Wiley & Sons Ltd., page no.87-97

58. Seminar, Tuberculosis Jennifer Furin, Helen Cox, Madhukar Pai, Lancet, 2019: 1-15. Doi: [http://dx.doi.org/10.1016/S0140-6736\(19\)30308-3](http://dx.doi.org/10.1016/S0140-6736(19)30308-3)
59. Agger EM. Novel adjuvant formulations for delivery of anti-tuberculosis vaccine candidates. *Adv Drug Deliv Rev* 2016;102:73–82. http://www.who.int/selection_medicines/list/en.
60. http://www.who.int/selection_medicines/list/en.
61. Hari BN, Chitra KP, Bhimavarapu R, Karunakaran P, Muthukrishnan N, Samyuktha RS. Novel Technologies: A weapon against tuberculosis. *Indian J Pharmacol* 2010;42(6):338-344. DOI: 10.4103/0253-7613.71887
62. Khameneh B, Milad Iranshahy, Vahdati-Mashhadian N, Sahebkar A, Fazly Bazzaz BS. Non-antibiotic adjunctive therapy: A promising approach to fight against tuberculosis. *Pharmacol Res* 2019;1-40. <https://doi.org/10.1016/j.phrs.2019.104289>
63. Bahuguna A, Rawat DS. An overview of new antitubercular drugs, drug candidates, and their targets. *Med Res Rev* 2020;40(1):263-292. doi: 10.1002/med.21602.2019.
64. McHugh TD, Honeyborne I, Lipman M, Zumla A. Revolutionary new treatment regimens for multidrug-resistant tuberculosis. *Lancet* 2019;19:233-234.
65. Joana Costa-Gouveia, Jose A. Ainsa, Priscille Brodin and Ainhoa Lucia, How can nanoparticles contribute to antituberculosis therapy? *Drug Discov. Today* 2017;22 (3):600-607. doi: 10.1016/j.drudis.2017.01.011.
66. Sankhe K, Khan T, Bhavsar C, Morin M, Omri A. Selective drug deposition in lungs through pulmonary drug delivery system for effective management of drug-resistant TB. *Expert Opin Drug Deliv* 2019;16(5):525-538. <https://doi.org/10.1080/17425247.2019.160993>
67. Gualano G, Capone S, Matteelli A, Palmieri F. New antituberculosis drugs: from clinical trial to programmatic use, *Infectious Disease Reports* 2016;8:43-46
68. Furin J, Cox H, Pai M. Seminar, Tuberculosis Lancet 2019: 1-15. Doi: [http://dx.doi.org/10.1016/S0140-6736\(19\)30308-3](http://dx.doi.org/10.1016/S0140-6736(19)30308-3)
69. Jetley S, Jairajpuri Z, Pujani M, Khan S, Rana R. Tuberculosis 'The Great Imitator': A usual disease with unusual presentations. *Indian J Tuberc* 2017;64(1):54-59. <http://dx.doi.org/10.1016/j.ijtb.2016.01.001>
70. Jacob A, Mongkolsapaya J, Screatton G, Mcshane H, Wilkinson R. Antibodies and tuberculosis. *Tuberculosis* 2016;101:103-113. <https://dx.doi.org/10.1016/j.tube.2016.08.001>
71. Halliday A, Masonou T, Wright MT, Mandagere V, Lalvani A. Immunodiagnosis of active tuberculosis. *Expert Rev. Respir. Med* 2019;13(6):521–532. <https://doi.org/10.1080/17476348.2019.1615888>
72. <https://www.who.int/tb> Accessed on 19/11/2019
73. www.theunion.com Accessed on dated 14/05/2020