REVIEW ARTICLE

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Tuberculosis - Review on Chemotherapy, Diagnostics, Vaccines, Herbal Remedies, Markets and Current Global Clinical Trials

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Abstract: Tuberculosis also known as Phthisis, Consumption, The Great white plague, The robber of youth, is highly infectious disease with an extended history of its occurrence among the Homo sapiens from ages, till now. Since ages it has consumed millions of life and continues to do so in the present times. After the discovery of the infectious agent, i.e., *Mycobacterium tuberculosis* by Robert Koch a German Bacteriologist, many advances in the medical science related to its pathogenesis, treatment options, prevention have taken into place. No doubt medical research have come long way ahead regarding the chemotherapy for the disease respectively, there still exists a huge challenge in the management of the disease and complete cure with a goal of complete eradication. The fact that the micro-organism rapidly adjusts against the chemotherapeutic agents administered to the infected body, as it multiplies rapidly and grows into an immune colonies against the existing chemotherapeutic agents known as resistant strains, it possess a high degree of challenge to cope with the infection taking in consideration of its high degree of transmissible nature. Therefore, it becomes pre-requisite to write on this review to develop an understanding of the management of tuberculosis which still haunts the medical science and health care practitioners. From normal strains of *Mycobacterium tuberculosis*, to (MDR) Multi-drug resistance strains, to XDR (Extended Drug Resistance) Tuberculosis and TDR (Total drug resistance) tuberculosis, the management of disease has come to a stage, Square one, i.e., right to an age where their used to exist no cure for the disease. The present review focuses on the history, description of TB, Chemotherapy, Diagnostics, Vaccines present and in trials, Herbal remedies and Current clinical trials happening across globe. India possess huge degree of morbidity and mortality related to the disease, topping the charts globally and acts as great burden on the population compared to other nations. The current review also focuses the clinical trials happening across India in our fight to completely eradicate the disease burden like it did for polio.

INTRODUCTION

If we look down the history of *Homo sapiens* and their fight against the Invading Diseases, no more lives have been taken by a single disease, then that, by Tuberculosis - The Fight is still on since Ages and we will surely win.

HISTORY

Deadly disease since ages, The Tuberculosis, had been the leading cause of deaths, than any other disease, in the history of mankind or homo-sapiens. It has history of affecting the humans since reported 15,000 to 20,000 years ago. Many developments were made in the history of tuberculosis, which even consumed the lives of many scientists who dedicated their study towards finding a cure for this deadly disease. The maximum damage to human kind had been, during the 18th and 19th century, when, around 70 % to 90 % of the population in Northern America and Europe were affected by the organism, the *Mycobacterium tuberculosis* and mostly died, giving endemic nature to it. During that age it consumed maximum lives and was the reason of focused study by the scientists to find the cure. Since the age of 2500 BCE to 460 BCE, till 17th, 18th and 19th century it has been known by many names, mainly, 1) Phthisis, 2) Consumption, 3) The great white plague, 4) White death, 5) The robber of the youth (Since it affected people in the age bracket of 18 to 35), 6) The captain of all these men of death, 7) The graveyard cough, 8) The King's Evil (As it was believed that mere touch of a King could cure the patients), 9) Scrofula and 10) The Wasting disease. All these names originated with an associated history attached to them. There is no doubt that tuberculosis had been infecting and affecting mankind since ages, as the, Paleopathological evidence dates back its existence since 8000 BCE and noted evidence in the Egyptian mummies, decayed spine bone damaged structures dating back to around 2400 BCE. The term "*Phthisis*", originated and was termed by Hippocrates (410 – 400 BCE) to describe the disease of weakness of lungs, as in Greek the term means (phthein = waste away) (Figure 1). In the year 1679 Sylvius de la Boè, An Amsterdam physician, in his work, *Opera medica*, used the term tubercles for the first time. The term "*Consumption*", was frequently used in 17th and 18th century till 19th century when the term tuberculosis originated in mid-19th century coined by Johann Lukas Schonlein, later was used by Hermann Brehmer, Jean Antoine Villemin and Robert Koch. The epidemic of tuberculosis was so much wide that during the year of 1851, that 1 out of 4 person used to die of TB. Many treatment methodologies were used to find cure of TB. The famous was Sanatorium drive, which during that age, people believed could cure TB. The method was to give fresh air, good food to the patient followed by keeping in sanitized location. The drive became very famous, followed by surgical procedures like Pneumothorax, procedure of lung collapse till the year 1882. In the year 1882, Robert Koch, The German bacteriologist, discovered the known pathogen that caused TB, The *Mycobacterium tuberculosis* (Figure 2). The discovery revolutionized the medical fraternity and gave drive to better research activities in pursuit to find appropriate cure. With the discovery of *Mycobacterium tuberculosis*, it became clear, that

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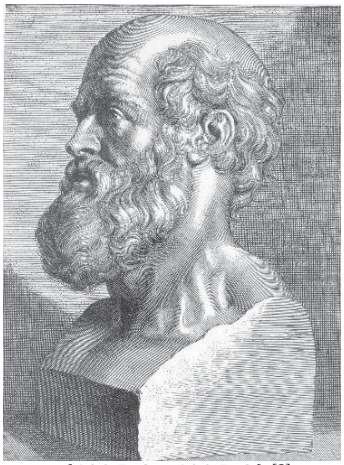

Figure 1: Hippocrates (430 B.C. - 400 B.C.) [2]

Figure 2: Robert Koch [3]

tuberculosis is infectious disease and can be infected from person to person through droplet infection and it's not hereditary disease as it was postulated earlier. The discovery of *Mycobacterium tuberculosis*, resulted in the discovery of *Actinomycin*in 1939 from actinomycetes and *Streptomycin* from *Streptomyces griseus* in the year1943. The BCG vaccine became popular but was soon realized that it didn't cured TB. [1]

TUBERCULOSIS

Tuberculosis is highly deadly disease caused by bacteria, *Mycobacterium tuberculosis*, it still haunts the mankind as it used to in history. Around 1/3rd of world's population is infected by tuberculosis bacteria, which consumes around 2 million people yearly. Tuberculosis spreads through air depicting its highly contagious nature. The infected person, can transmit the disease to the healthy person or immunocompromised patients, like HIV-positive patients. It may remain latent or become active in the infected persons body. People with Latent TB don't transmit the disease, as the Active TB person does. Most commonly tuberculosis affects the lungs and result in pathophysiological changes in the infected body. Tuberculosis of lungs is known as pulmonary tuberculosis and if TB infects the other organs of the body, it results into Extra-pulmonary tuberculosis. Examples of Extra-pulmonary tuberculosis are, TB of Brain, TB of meninges, TB of Kidney, etc. Immunocompromised patients are more prone to develop active TB and often is the major cause of mortality. Like, The HIV positive patients whose immunity is compromised, mostly die of TB. There are 50 percent chances of HIV^{+} patients developing this deadly disease, often resulting to be cause of their deaths.

The danger of tuberculosis also lies in the fact that few of the strains are immune to the presently available chemotherapeutic drugs and are known as, Multi-drug resistant tuberculosis (MDR-TB), Extended Drug Resistant tuberculosis (XDR-TB) and Total drug resistant tuberculosis (TDR-TB), depending upon the extent of immunity developed by the strains of *Mycobacterium tuberculosis*. The first outbreak of drug resistant tuberculosis, was, reported in US in the year 1970. Few years later, World health organization declared, tuberculosis as emergency disease globally in the year 1993. In the year 1995, WHO, initiated global drive to curb the menace caused by *Mycobacterium tuberculosis*, with DOTS strategy to deal with the growing cases of TB, Globally. In the same year, the first cases of Multi-drug resistance TB, was reported in London (UK). Sadly, in the year 2012, The Clinical infectious Diseases Journal reported cases of TDR-TB in India. TDR i.e. Total-drug-resistant TB is the deadliest of all the strains, for which no cure exists till date. Any person who comes in contact with TDR TB patient, is sure shot to develop the TDR TB in himself and is sure to succumb to the disease. Tuberculosis in pregnant women has been detected and is the leading cause of neonatal TB or tuberculosis in infants. TB in neonatal can be acquired in utero (Congenital TB), or through airborne transmission after delivery (Postnatal TB). Studies have ruled that, around 34 % of pregnant women in India suffer from latent tuberculosis infection (LTBI). As compared to developed nations, the TB in pregnant women is higher in endemic regions of Asia and Africa. The prevalence rate is as high as more than 60 new cases per 100000 inhabitants. India and china total account for more than 40 % of total TB cases globally. India alone contributes to 26 percent of Global TB burden. This signifies the major cause of concern for communities in India and China as well as globally. [4] To deal with growing nuisance of TB in India, there is need to develop common understanding of the disease among patients and the population shall sensitized regarding the activities to curb the spread and the menace. [5]

RISK FACTORS ASSOCIATED WITH TB

There are numerous risk factors associated with tuberculosis, the knowledge of which would help us in dealing with TB in a better way.

Genetic Factors

Research has proved that certain genes are more susceptible to TB or its nuisance as infection in the body of infected person. The genes having high degree of TB susceptibilities are, 1) Natural resistance-associated macrophage protein, 2) Interferon Gamma, 3) Nitric-oxide synthase 2A, 4) Mannan binding lectin, 5) Vitamin D receptor, 6) Toll like receptors. [6]

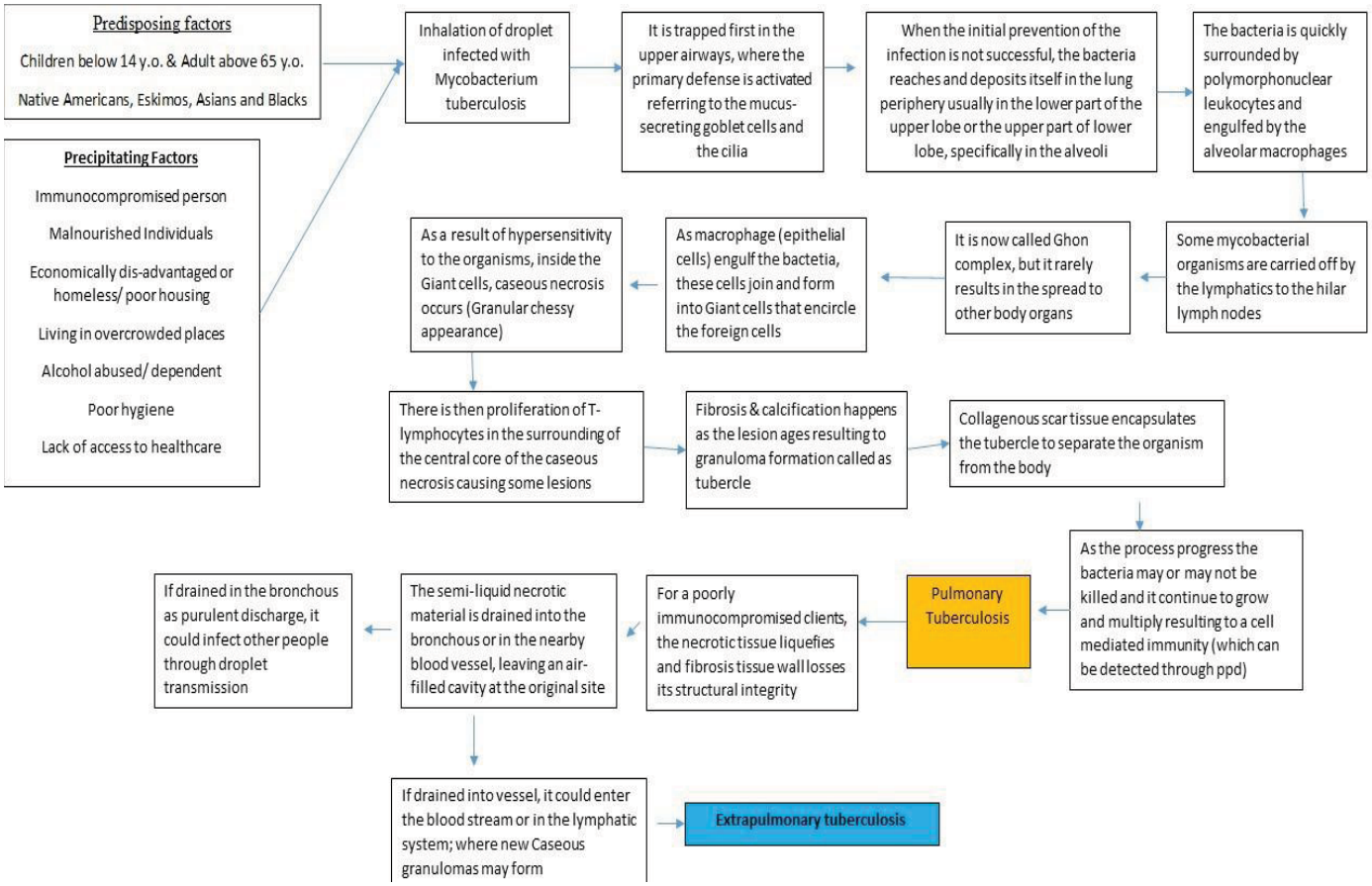

Figure 3: Pathophysiology flow chart

HIV-Infection

HIV+ve patients are more susceptible to TB and has proved to be greater challenge for the medical science in their efforts to eradicate TB from global map. [6]

Diabetes Mellitus

Diabetes mellitus has proved to increase the severity of TB and proven results contribute to the result that Diabetes mellitus makes TB more lethal. [6, 7]

Use of Immunomodulator Biologicals

There is growing evidence of Immunomodulators affecting the TB. [7]

Tobacco Smoking

Studies have proved that tobacco smoking is directly associated with increasing the severity of TB in patients. [7]

Cancer

Evidence of Cancer and TB is mostly postulated and there is growing understanding that Cancer may deteriorate the TB infection in the patient's body. [8]

PATHOPHYSIOLOGY OF TUBERCULOSIS

Mycobacterium tuberculosis

Mycobacterium tuberculosis is rod-shaped, non-spore forming, aerobic bacterium, typically measures 0.5 µm to 3 µm, classified as acid-fast bacilli and have unique cell wall structure important for their survival. The well developed cell wall contains a considerable amount of a fatty acid, mycolic acid, covalently attached to the underlying peptidoglycan bound polysaccharide arabinogalactan, providing an extraordinary lipid barrier. This barrier is responsible for many of the medically challenging physiological characteristics of tuberculosis, including resistance to antibiotics and host defense mechanisms. The composition and quantity of the cell wall components affect the bacteria's virulence and growth rate.

Pathophysiology

The pathophysiology of tuberculosis consists of initiation of droplet infection in the host body. The disease *Mycobacterium tuberculosis* infected in the droplets of diseased patients gets inhaled by the normal individual. The mucus secretion in the bronchioles area is able to ward off the invading pathogens by engulfing them in the mucus secretion followed by expiration. This is the first defense against the invading pathogen. However, few bacteria's are able to traverse through the first line of defense and reach alveoli. The second line of defense gets activated, by the activation of macrophages which engulfs the invading pathogen and make efforts to kill it there itself. If the invading pathogen or bacteria survives this second line of defense, the host comes in the stage of latent TB. When the increasing population of bacilli kills the macrophages and spreads across the lungs and to other parts of the body, it's in the stage of Active TB and can infect the other people in surrounding areas causing endemic. The pathophysiology

Table 1: Categorization of TB Patients [12]

Registration of Groups	Characteristics
New Cases of afb +/-	Previously never had treatment for TB or have taken Anti-TB drugs for less than 1 month
Previously Treated Cases	Have taken greater than or equal to 1 month treatment
Relapse	Patients whose treatment have been interrupted for more than 2 consequative months
Default	Sputum smear or culture is +ve for mycobacterium TB at 5 months or later during treatment / MDR strains detected at any point of time oftreatment,
Failures	whether smear positive or negative for AFB.

Table 2: Chemotherapy Drug Classification [13]

Drug Classification	Drugs
First Line Drugs	Isoniazid (H), Rifampin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S)
Second Line Drugs	Ethionamide (ETo), Prothionamide (Pto), Cycloserine (Cs), Terizidone (Trd), Para-aminosalicylic acid (PAS), Rifabutin, Thiacetazone (Thz) Fluoroquinolones: Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin Injectables: Kanamycin (Km), Amikacin (Am), Capreomycin (Cm)

Table 3: MDR TB Drug Treatment [12]

Groups	Drugs
Group 1: First Line Oral Agents	Pyrazinamide (Z), Ethambutol (E), Rifabutin (Rfb)
Group 2: Injectable Agents	Amikacin (Am), Kanamycin (Km), Capreomycin (Cm), Streptomycin (S)
Group 3	Levofloxacin (Lfx), Moxifloxacin (Mfx), Ofloxacin (Ofx)
Group 4: Oral Bacteriostatic Second Line Agents	Cycloserine (Cs), Terizidone (Trd), Ethionamide (Eto), Protionamide (Pto)
Group 5: Agents With Unclear Role in Treatment of Drug Resistant Tb	Linezolid, Amoxicillin/ Clavulanate, Thioacetazone, Imipenem / Cilastatin,High dose Isoniazid, Clarithromycin

is detailed in the flow chart in Figure 3. [9] Thus, the flow chart clearly signifies the way tuberculosis develops and spreads. [10]

Clinical Manifestation

Easy fatigability , Anorexia or loss of appetite, weight loss and body wasting, Persistent long term low grade fever, chills and night sweat, Persistent long term nonproductive cough but may produce purulent sputum in long term (2 weeks or long), non-resolving bronchopneumonia, dull or pleuritic chest pain, dyspnea, hemoptysis, Anemia in Some.

CHEMOTHERAPY OF TUBERCULOSIS

Chemotherapy is known as therapy using drugs or chemical agents against the invading bacteria's, viruses, pathogens or any foreign body which deteriorates the normal condition of the body. With characteristics matching that of Cancerous cells, Chemotherapy is also used as term for non-cancer forming cells which result in downgrading the normal condition or homeostasis. Antibiotics have been the greatest revolution in the 20th century. Their advent gave major tools in the hands of medical practitioners to deal with the diseases invading *Homo sapiens*. Out of the problems associated with the use of Antimicrobials, have been, Toxicity, Hypersensitive reactions, Drug resistance. Looking at the nature of *Mycobacterium tuberculosis*, the major problem is development of drug resistance, that too due to mutations. A mutation is defined as a stable and heritable genetic change that occurs spontaneously and randomly among the micro-organisms. Any sensitive population of a microbe contains a few mutant cells which require higher concentration of Antimicrobials for inhibition. When a sensitive strain has been replaced a resistant one, it is called, vertical transfer of resistance and it is this type of mutation which is generally seen in the use of single antimicrobial to restrict the progress of tuberculi bacteria. [11] Over the ages, chemotherapy for Tuberculosis has evolved to a more effective and efficient treatment regimes. Patients have been divided as Pre-treatment groups and new cases, depending on the fact that either they were previously treated for TB or not (Table 1).

Chemotherapy classification for tuberculosis has been divided into two main categories, i.e. first line and second Line drugs (Table 2).

Treatment for MDR-TB cases shall be followed as per the guidelines by WHO (Table 3). [12]

Many treatment guidelines have been put into place to deal with tuberculosis, out of which DOTS treatment had been widely used in the developing nation and included in the national health policies of the countries of these origins, like India, Bangladesh, Pakistan, etc. DOTS means, Directly Observed Therapy, Short-course. DOTS therapy includes prescribing and monitoring the effects of anti-tubercular drugs by the health care practitioner and the patient is in complete observation of the assigned medical practitioner. There are five basic elements of DOTS therapy, which includes, 1) Political commitment and appropriate financing, 2) Case detection through quality assured bacteriology, 3) Standardized treatment, with supervision

Table 4: TB Diagnosis Tests [15]

Test	Type Available	Strengths	Weaknesses
Microscopy	LED/ Fluorescent microscopy	High specificity, Short TAT (TURN-AROUND TIME)	Low sensitivity in people with low bacillary load
Culture	Liquid (MGITT) Solid	High Sensitivity	Long TAT High contamination rates (Liquid Culture)
PCR Based Assay	Line probe Assay	Short TAT, Detects Rif and INH resistance, High sensitivity for MDR-TB	Reduced sensitivity in smear negative
	Xpert MTB/RIF	Short TAT, Detects RIF resistance , High sensitivity for RIF resistance	Does not detect INH resistance Reduced sensitivity in smear negative

and patient support, 4) An effective drug supply and management system and 5) Monitoring and evaluation system and impact measurement. [14]

DIAGNOSIS OF TUBERCULOSIS

There have been many procedures which can confirm the presence of TB in the patients, they have been mentioned in Table 4.

The other characteristics of different diagnostic tests are, Smear microscopy requires ~10, 000 TB bacilli per ml of sputum to be detected positive. Culture can be positive with only ~10-100 TB bacilli per ml of sputum. And GeneXpert requires ~130 TB Bacilli per ml of sputum for positive results. [15]

GeneXpert is highly reliable test, which has been widely used by diagnostic companies across the globe. The advantage of this test includes, 1) It detects MTB and Rifampicin resistance from one specimen at time, 2) Processing time for the test is approx. 2 hours, 3) It is specific for MTB complex; it can differentiate MTB from other mycobacteria's, 4) The samples can be CSF (Cerebrospinal fluid), aspirates (Gastric or lymph node), or tissue (i.e. pleural biopsy), 5) The test is conducted in closed compartment i.e. cartridge, so chances of cross – contamination or human error is less. However, still, Culture method is required, in cases such as, HIV positive TB suspects who have a negative GeneXpert test, TB cases diagnosed as Rifampicin resistant on GeneXpert for susceptibility testing of other drugs, In unusual cases where despite a Rifampicin susceptible result the patient is failing treatment and treatment adherence is good and thus resistance to drugs other than Rifampicin is suspected. [16]

NEWER TB CHEMOTHERAPEUTIC DRUGS

With the immergence of MDR-TB, XDR-TB, there is increase focus on development of newer Anti-TB dugs. To be brief, MDR-TB means *in-vitro* resistance development by *Nycobacterium tuberculosis* against Isoniazid and rifampicin, while XDR-TB is defined as resitant strains development against at least one fluoroquinolones and one injectable second line anti TB drug in addition to isoniazid and rifampicin. WHO estimates the development of around 480,000 cases of MDR-TB globally. Apart from this, the management of TB becomes complex and challenge for healthcare practitioners due to occurrence of adverse events where pharmacovigilance comes into place, problems in patient's adherence, lack of clinical experience and adequate availability of appropriate diagnostic tests and second line anti-TB drugs depending upon country by country basis. Keeping in view of this, US FDA has approved newer Anti-TB drugs, which are mainly, Bedaquiline, Delamanid, Pretomanid, Sutezolid, SQ109 and Benzothiazinones. These drugs are still in Clinical trials, most of whom are in Phase II clinical trials and hopefully these drugs would be available for people if the results are beneficiary proving their effectiveness. [17]

Currently trials are happening across globe in the field of fluoroquinolones to restrict the treatment regimens to 4 months' time. These are OFLOTUB trial (NCT00216385) comparing with Gatifloxacin substituting Ethambutol, followed by a 2 month maintenance phase of gatifloxacin, isoniazid and rifampicin. Another trial is REMox TB (NCT00864383) is comparing standard 6-month therapy with two study regimens (2 months of moxifloxacin, isoniazid, rifampicin and pyrazinamide followed by 2 months of moxifloxacin, isoniazid and rifampicin (2MHRZ/2MHR) or 2 months of ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by 2 months of moxifloxacin and rifampicin (2EMRZ/2MR)). RIFAQUIN trial (ISRCTN44153044) is comparing the standard 6-month regimen with two study regimens (2 months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by 2 months of twice-weekly moxifloxacin and rifapentine (2EMRZ/2PM2) or 4 months of once-weekly moxifloxacin and rifapentine (2EMRZ/4PM1) in a maintenance phase). The very recent studyopens new perspectives on what regimens can be designed with the newly available anti-TB drugs. This new phase IIb trial compared the bactericidal activity of 8-week regimens including moxifloxacin and pretomanid (100 or 200 mg, according to the arm) plus pyrazinamide against the standard anti-TB regimen to treat sputum smear positive patients with both drug-susceptible and drug-resistant TB. The bactericidal activity of the of the 8-week regimens was higher than that of the current WHO-recommended regimen in both drug-susceptible and drug-resistant TB after 2 months of treatment. The experimental treatment was well tolerated and no episode of QT interval exceeding 500 ms was identified. The study showed that rifampicin-sparing regimen might work (allowing easier and safer

Table 5: Vaccine Under Development [22]

Vaccine	Description	Indication	Clinical Trials	Comments
Recombinant BCG	BCG, Essential genes (e.g. ESAT-6) restored	BCG replacement	None	Early preclinical studies
VPM1002	BCG, *listeriolysin* O gene added, urease c gene deleted	BCG replacement; disease prevention in BCG vaccinated adults	Phase 1 and 1b completed Phase 2 in neonates is ongoing	Phase 3 in HIV +/- in planning
MTBVAC	*M.tuberculosis*, live, attenuated via deletions in *phoP* and *fadD26*	BC replacement	Phase 1 in progress	Phase 2 in neonates is planned for 2015
DAR-901	*Mycobacterium obuense*, heat inactivated, sonicated	Disease prevention in BCG vaccinated adults especially HIV+	Phase 1, 2, 3 studies with agar grown SLR-172 precursor to DAR-901 completed. Phase 1 with reformulated, broth-grown DAR-901 in progress	Phase 3 planned in HIV +/- adults; inactivated vaccine, safe for HIV+ patients
RUTI	*M.tuberculosis*, fragmented, Triton cleaned, liposomal grown under anoxic stress	Immunotherapy to support and reduce TB and LTBI chemotherapy	Phase 1 and Phase 2 completed	Two Phase 3 trials are planned, inactivated, safe for HIV+
BCG ▲*zmp1*	BCG, zinc metallo-protease 1 deletion (zmp1)	BCG replacement	None	Late preclinical development
Adjuvanted, non-replicating BCG	BCG, ▲panCD, auxotrophic for pantothenate	Boost after BCG prime in adolescents, adults and HIV+	None	Potentially more reactogenic than BCG

treatment of HIV-positive cases with protease inhibitors) while achieving rapid sputum culture conversion and reduced transmission M. tuberculosis with the community. Given the potential to shorten treatment duration, hopes exist to improve patient adherence. [18]

VACCINES

Keeping in view those current chemotherapeutic agents available to deal with widely spreading tuberculosis cases as it is estimated that the current available treatment regimens would be ineffective in dealing with the menace, an effective vaccine would be looked upon as better strategy. With the global cases of TB which accounts for one third of global population and increasing cases of MDR-TB, XDR-TB and TDR-TB, vaccines are considered as better tool in the hands of healthcare practitioners. BCG vaccine had been developed as whole cell vaccine for TB by Albert Calmette and Camile Guerin. Since then it has been widely given to people with an estimated 4 billion administration worldwide, still its effectiveness against TB is highly debatable with no sure short eradication data available. Sixteen different TB vaccine candidates are currently in clinical trials, with more in the preclinical pipeline. Most of these vaccine candidates are subunit vaccines, where selected MTB antigens are expressed in recombinant viral vectors or are administered as protein/adjuvant combinations. Approximately 12 different antigens are expressed in the subunit vaccines currently in clinical trials. A major challenge to TB vaccine development, however, is the lack of an immune correlate of protection against MTB infection or TB disease. Accordingly, there is little certainty about the actual protective effect that may be provided by at least some of the anti-gens currently under investigation in subunit vaccine candidates. [19-21] The current status of vaccines under clinical trials are mentioned in Table 5.

HERBAL REMEDIES

With the growing cases of new TB cases across globe, it's a big challenge to come up with effective treatment strategies for dealing with it. Traditional medicines are considered solution for it as neither has it caused side effects nor resistance development has been reported against them. Therefore, it gives better strategies to deal with this growing cause of concern for the medical fraternity.

Anti-TB medicinal plants have been researched upon and many plants have been found to have effective effects on the growth and spread of *Mycobacterium tuberculosis*. The plants researched to possess Anti-tubercular effects were *Taxus baccata, Senna alata, Andrographis paniculata, Adhatoda vassica nees, Acalypha indica L., Aloe vera*. All these plants possessed anti-tubercular activity against *M.tuberculosis* H_{37}Rv multi-drug resistant isolates. [23] Anti-tubercular effects were reported in the aqueous extract of *Withania somnifera* against *Mycobacterium tuberculosis*. [24] Anti-tubercular effects were reported in Adulsa (*Justica adhatoda*), Garlic (*Allium sativum*), Barberry (*Berberis vulgaris*), Liquorice (*Glycyrrhiza glabra*), Horsetail, Eucalyptus, Elecampane (*Inula helenium*), Honey. [25]Anti-TB effects were reported in medicinal plants in African continent, mainly plants having Anti TB effects are, *Carica papaya, Allium sativum, Citrus aurantifolia, Kohunkoho,*

Table 6: Clinical Trial Active Globally and in India [36]

S. No.	Clinical Trial	Current Status
1	Predictive value of Next Generation Interferon Gamma release assays for latent tuberculosis infection	Active, Recruiting, in UK
2	The HALT latent tuberculosis study	Active, recruiting, UK
3	MVA85A Aerosol v/s Intramuscular vaccination in adults with latent Mycobacterium Tuberculosis Infection	Active, recruiting, UK
4	Genome sequencing of Multi-drug resistant tuberculosis (MDR-TB) in sputum	Active, recruiting, UK
5	Development of Human Nasal challenge models with microbial constituents and Grass pollen	Active, recruiting, UK
6	Heterologous effects of BCG in Healthy UK Adults	Recruiting, UK
7	A BCG challenge model study to assess anti-mycobacterial immunity induced by BCG and candidate TB vaccine, MVA85A	Active, Not Recruiting, UK
8	Improving the detection of active tuberculosis in accident and emergency departments	Active, Not recruiting, UK
9	Study evaluating Aerosol and Intradermal administration of a candidate tuberculosis (TB) vaccine, MVA85A, as a way to increase immune response and avoid Anti-vector immunity	Not recruiting, UK
10	Safety study of ChAdOx185A vaccination with and without MVA85A boost in Healthy adults	Not recruiting, UK
11	A clinical trial to study the effect of anti-tubercular treatment for period of 6 months verses 9 months in female genital tuberculosis	Active, recruiting, INDIA
12	Intestinal tuberculosis diagnostics and differentiation from Chron's disease	Active, Recruiting, INDIA
13	Efficacy and Safety of Modified Anti-tubercular regimens in treatment of tuberculosis in patients with Underlying compensated and decompensated Chronic liver disease	Active, Recruiting, INDIA
14	Latency in Pulmonary tuberculosis	Active, Recruiting, INDIA
15	A clinical trial intended to compare the treatment effect of two anti-tuberculosis regimens, daily and intermittent regimens in HIV patients with Pulmonary TB	Active, Recruiting, INDIA
16	A Clinical Trial to study the effect of N-acetyl cysteine in patients with Pulmonary tuberculosis	Active, Recruiting, INDIA
17	Intensive smoking cessation versus Basic-smoking cessation advice in Smear-postive patients with Pulmonary tuberculosis	Active, recruiting, INDIA
18	To study the immunomodulatory effects of *Withania somnifera* in patients with Pulmonary tuberculosis	Active, Recruiting, INDIA
19	Vicente Ferrer HIV Cohort study	Active, Recruiting, INDIA
20	To assess the efficacy, safety and tolerability of 4 month regimen containing Ofloxacin compared to the Standard 6-month regimen in the treatment of patients with superficial tuberculosis lymph node	Active, Recruiting, INDIA

ajagi, Calliandra haematocephala, Citrus sinensis, Citrus paradise. [26] Anti-TB effects have been reported in *Sterculia setigera* Leaves, the study from Nigeria shows effectiveness of *S. setigera leaves* in healing TB cases. [27] Studies in Iran, have shown that Anti-microbial activity have been proven in plants showing effective Anti-TB activity, these plants are, Citrus limon, *Peganum harmala, Punica granatum, Rosa canina, Digitaria sativa*. [28] Study in Ethiopia have confirmed Anti-TB activity in *Allium ursinum, Dodonaea anguistifolia* and *Pterolobium stellatum*. [29] Anti-microbial activity has been found in *Trichosanthes dioica* (Roxb.) leaves extracts. [30] Anti-TB activity was explored in butanolic extracts of *Alstonia scholaris* flower and bark. [31] *Renu Gupta et al*., [32] found anti-tubercular activity in extracts of all five medicinal plants *viz*., *Acalypha indica, Adhatoda vasica, Allium cepa*, *Allium sativum* and *Aloe vera*. Anti tubercular activity have been reported in *Morinda citrifolia* (Canary wood), Camara vulgaris (*Lantana camara)* L, *Acacia senegal*. [33] A study in Indonesia, found that the aqueous extract of *Andrographis paniculata, Annona muricata, Centella asiatica, Pluchea indica* and *Rhoeo spathacea,* showed anti-TB effects against *Mycobacterium tuberculosis* $H_{37}Rv$ strain. *Pluchea indica* and *Rhoeo spathacea* showed good anti-mycobacterial activity against MDR strains and could be useful as complementary alternative therapy in combating the emergence of MDR strains of *Mycobacterium tuberculosis*. [34]Study in Uganda found that highest anti-tubercular effects were seen in the extracts of plants, namely, *Lantana camara, Erythrina abyssinica, Cryptolepis sanguinolenta, Warburgia ugandensis, Mangifera indica*. [35]

GLOBAL TB MARKET

With estimated 9 million cases of TB existing globally and 2 million cases developing yearly, keeping in view the treatment cost which is more than € 50, 000, it's estimated that global Anti-TB drug market exceeds € 650 billion euros. This comes to around Global market which exceeds

Rs 47,433.83 billion market. With estimated 480, 000 cases of XDR TB and treatment costs which exceeds € 160,000 it is estimated that global XDR-TB market exceeds, € 76.8 billion euros, which is roughly more than, Rs. 5604.489 billion rupees market. [17]

CURRENT CLINICAL TRIALS HAPPENING ACROSS GLOBE

Clinical trials are clinical investigations conducted on humans. It's a part of process of drug development which starts with the identification of leads and then experimenting it on animals, only after effective conclusions for safety on humans is confirmed, the clinical trials are conducted. Clinical trials are conducted in phase 1, phase 2, phase 3, phase 4 and phase 5. Each phases of clinical trials have specific goals and guidelines which are conducted in accordance to the global harmonization practices.

Few of the Clinical trials being conducted across globe and India are described in Table 6.

CONCLUSION

Tuberculosis is highly dreadful disease which has spread across globe and proved to be a major cause of concern globally and specially in India. India is one the center of TB cases and dominates globally in occurrence and spread of disease. Many strategies have been put forward and researched upon to eradicate the disease. With WHO reporting the TDR-TB cases in India, it's a national cause of concern to curb the disease. Out of the many treatment strategies it was found that vaccination and herbal remedies shall be looked upon as major area of research. No doubt, Chemotherapy has evolved to curb the disease in advance stages, the propensity of developing resistance to these agents pose threat to medical fraternity. With most of clinical trials happening across globe and in India, the day is not far, that, research would bring and effective and efficient treatment strategies to Stop TB which is one of the Goals established by WHO.

REFERENCES

1. Frith Jhon. History of Tuberculosis Part 1- Phthisis, consumption and the white plague [Online]. 2014 June [Cited 2016 January 22]; Available from: URL: http://jmvh.org/article/history-of-tuberculosis-part-1-phthisis-consumption-and-the-white-plague/.
2. Hippocrates [Online]. 2016 [Cited 2016 January 22]; Available from: URL: https://upload.wikimedia.org/wikipedia/commons/d/d2/Hippocrates_Light.JPG.
3. Robert Koch [Online]. 2016 [Cited 2016 January 22]; Available from: URL: http://media-2.web.britannica.com/eb-media/45/21045-004-76C50D15.jpg.
4. Artigao F B. Spanish society for pediatric infectious diseases guidelines on tuberculosis in pregnant women and neonates (I): Epidemiology and Diagnosis. Congenital tuberculosis. An Pediatr (Barc.), 83(4):285.e1-285.e8, 2015.
5. Shukla A A. Study of knowledge and practice of sputum disposal among TB Patients of Ahmedabad City. NHL Journal of Medical Sciences, 2(2):22-25, 2013.
6. Najmi N, Kaur G, Sharma S K, Mehra N K. Human Toll-like 59. Receptor 4 polymorphisms TLR4 Asp299Gly and Thr399Ile influence susceptibility and severity of pulmonary tuberculosis in the Asian Indian population. Tissue Antigens, 760:102-9, 2010.
7. Sharma S K, Mohan Alladi. Tuberculosis: From an incurable scourge to a curable disease-journey over a millennium. Indian J Med Res, 137:455-493, 2013.
8. Asnaashri A M H. The study of *Mycobacterium tuberculosis* in Iranian patients with lung cancer. Jundishapur J Microbio, 6(3):237- 241, 2013.
9. Nancy A, Knechel R N. Tuberculosis: pathophysiology, clinical features and diagnosis. Crit Care Nurse, 29(2):34-43, 2009.
10. Tuberculosis [Online]. 2016 [Cited 2016 January 22]; Available from: URL: http://www.rnpedia.com/nursing-notes/communicable-diseases-notes/tuberculosis-tb/.
11. Tripathy K D. Antimicrobial drugs General consideration, Essentials of Medical Pharmacology. Jaypee Brothers Medical Publishers (P) Ltd Reprint, 688-703, 2014.
12. Mohapatra B N, Mohanty C B K. Treatment of TB WHO Guidelines [Online]. 2010 [Cited 2016 January 22]; Available from: URL: http://www.apiindia.org/pdf/medicine_update_2011/81_treatment_of_tuberculosis.pdf.
13. Tripathi K D. Antitubercular drugs. Essentials of medical pharmacology. Jaypee Brothers Medical Publishers, Delhi, 17th Edition, 765-779, 2014.
14. Five elements of DOTS [Online]. 2016 [Cited 2016 January 22]; Available from: URL: http://www.who.int/tb/dots/whatisdots/en/.
15. WHO guidelines 2014[Online]. 2014 [Cited 2016 January 22]; Available from: URL: http://www.sahivsoc.org/upload/documents/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf.
16. GeneXpert TB Test – TB diagnosis and Resistance testing [Online]. 2016 [Cited 2016 January 23]; Available from: URL: http://www.tbfacts.org/xpert-tb-test/.
17. Ambrosio L D, Centis R. New Anti- tubercular drugs and regimens: 2015 update. European Respiratory Journal, 1-15, 2015.
18. Smythe W, Merle C S, Rustomjee R. Evaluation of initial and steady-state gatifloxacin pharmacokinetics and dose in pulmonary tuberculosis patients by using Monte Carlo simulations. Antimicrob Agents Chemother, 57:4164–4171, 2013.
19. Anderson S T, Kaforou M, Brent A J, Wright V J, Banwell C M, Chagaluka G. Diagnosis of childhood tuberculosis and host RNA expression in Africa. N Engl J Med, 370:1712–23, 2014.
20. Weiner J, Kaufmann S. Recent advances towards tuberculosis control: vaccines and biomarkers. J Intern Med, 275:467–80, 2014.
21. Comas I, Chakravartti J, Small P M, Galagan J, Niemann S, Kremer K. Human T cell epitopes of Mycobacterium tuberculosis are evolutionarily hyper-conserved. Nat Genet, 42:498–503, 2010.
22. Developing whole mycobacteria cell vaccines for tuberculosis: Workshop proceedings, Max Planck Institute for Infection Biology, Berlin, Germany [Online]. 2014 July 9 [Cited 2016 January 23]; Available from: URL: http://www.ncbi.nlm.nih.gov/pubmed/25882170.
23. Bernaitis L, Shenoy V P. Effects of selective Medicinal plants against multi-drug resistant *Mycobacterium tuberculosis* strains. RJPBCS,4(3):812-817, 2013.
24. Adaikkappan P, Kannapiran M, Anthonisamy A. Anti-microbial activity of *Withania somnifera* and *Pueraria tuberosa* against *Mycobacterium tuberculosis* H37 Rv. J Acad Indus Res, 1(4):153-156, 2012.

25. Mandhare P M, Garje B H, Khade A A. Importance of herbal remedies in the treatment of HIV and TB infection. Int J Sci and Res Mth, 1(2):1-17, 2015.
26. Borokini T I, Ighere D A. Ethnobiological survey of traditional medicine practices in Oyo state. J Med Plant studies, 1(5):1-16, 2013.
27. Babalola I T, Adelakun E A. Anti TB activity of *Sterculia setigera* Del., leaves (Sterculiaceae). J Pharmacognosy and Phytochemistry, 1(3):17-23, 2012.
28. Ghaemi E A, Mazandarani M. Antimicrobial activity of some medicinal plants used in traditional medicine in North Iran. Int Conf Life Sci and Tech, 3, 2011.
29. Balcha E, Mengiste B. Evaluation of *in-vitro* Anti-microbial activity of selected medicinal plants in Mekelle, Ethiopia. World Applied Sciences Journal, 31(6):1217-1220, 2014.
30. Rai P K. A novel Anti-microbial agents *Trichosanthes dioica*. Int J Pharm Bio Sci, 1(3):1-9, 2010.
31. Antony M, James J. Antimicrobial activity of plant extracts of *Alstonia scholaris*. Int J Curr Pharm Res, 4(1):40-42, 2012.
32. Gupta R, Thakur B. Anti-tuberculosis activity of selected medicinal plants against multi-drug resistant *Mycobacterium tuberculosis* isolates. Indian J Med Res, 131:809-813, 2010.
33. Gautam A H, Sharma R, Rana A C. Review on herbal plants useful in tuberculosis. Int Res J Pharm, 3(7):64-67, 2012.
34. Radji M, Kurniati M, Kiranasari A. Comparative antimycobacterial activity of some Indonesian medicinal plants against multi-drug resistant *Mycobacterium tuberculosis*. J applied Pharm Sci, 5(1):19-22, 2015.
35. Claude K, Lydia B. The *in-vitro* efficacy on rifampicin-resistant tuberculosis of extracts from medicinal plants used by traditional medicinal practitioners to treat tuberculosis in Uganda. Nat Prod Chem Res, 2:5, 2014.
36. Tuberculosis-Clinical trials [Online]. 2016 [Cited 2016 January 23]. Available from: URL: http://www.nhs.uk/Conditions/Tuberculosis/Pages/clinical-trial.aspx.

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