Medicon Medical Sciences
Volume 7 Issue 3 September 2024
Article Type: Review Article
ISSN: 2972-2721

Pertinent Issues in Tuberculosis

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Received: July 22, 2024; **Published:** September 04, 2024

DOI: 10.55162/MCMS.07.235

Abstract

The article traverses through the issues that have emerged regarding TB in India & at global level. The issues revolve around socio economic, pharmacology in modern system, role of AYUSH & other stakeholders.

The article concludes that nutrition is a big factor in dealing with TB. Immunity is another factor. Life style & health promotion activities are cross cutting. Hence, all these factors should be the part of the entire TB intervention in which pharmacology is just one part.

Keywords: TB; RCT; BCG; Chemotherapy; ATP; AYUSH

Introduction

This section includes the successful trial of Streptomycin in TB & the efforts regarding the BCG vaccination.

The British Medical Research Council used the first available supplies in 1946 to conduct a pioneering Randomized Control Trial (RCT) of the efficacy of the drug Streptomycin [1-6].

In the RCT, 55 treated patients were compared with 52 control patients. Improvement was noted in 31 treated & only 16 untreated patients. Deaths occurred in 12 of those treated & 24 of those not given the drug. In 1950, the first report of Streptomycin treatment appeared in the British Journal of Tuberculosis & Diseases of the Chest (BJTDC) [1-6].

The concept of vaccination in TB was initiated when Albert Calmette & his associate Camile Guerin took the challenge of developing a vaccination. They started to work on a vaccine for TB. Calmette was the founding director of the Pasteur Institute of Lille & here a herculean effort was taken to attenuate Mycobacterium Bovis for use as a vaccine. Calmette who survived the disruptions of World War I tried the Bacille Calmette Guerin (BCG) vaccine in Paris in 1921 [1-6, 49-52].

The first recipient of the vaccine was an infant born of a mother dying of pulmonary TB & placed in the care of a tuberculous grandmother. The infant survived & did not have TB. From 1921 to 1928, more than 100,000 children were immunized that included Calmette's children also. Subsequently, the vaccine was accepted in Europe but not widely used in Britain. In 1928, Calmette published a paper in the British Journal of Tuberculosis advocating for the wider use of the vaccine [1-6, 49-52].

Literature Review

Here in this section, the first & foremost issue discussed is the development of chemotherapy for TB treatment.

The discovery of Para Amino Salicylic Acid (PAS) by Jogen Lehmannn in 1943 & Thiosemicarbazone by Gerhard Domagk during war time Germany that culminated in 1945 yielded the first therapeutic agents with efficacy in TB. Unfortunately, both were only bacteriostatic. In 1944, Albert Schatz, Elizabeth Bugie & Selman Waksman isolated 'Streptomycin'. This was the first antibiotic & first bactericidal agent effective against Mycobcterium TB. Subsequently, in next few months, on 20th November, 1944, a young woman with TB was treated successfully with Streptomycin [7-9].

Subsequently, the first oral mycobactericidal drug 'Isoniazid' was developed in 1952. Streptomycin was an injectable drug. In 1949, P- Amino Salicyclic Acid was developed. Pyrazinamide came in 1954. Cycloserine came in 1955. Rifamycin came in 1957. Etambutol in 1962 followed Rifamycin. Rifampicin came in 1963 [10].

Following that, Aminoglycosides like Capreomycin, Viomycin, Kanamycin, Amikacin were developed. Quinolones came next as moxifloxacin, Levofloxin, Ofloxacin, Ciprofloxacin. However, the Aminoglycosides & the Quinolones are used in Drug Resistant (DR) TB cases [10].

Clinical Features

The disease is called 'Kshay' (Consumption) as there is severe wastage of muscles. There is rise of body temperature in the evening, weight loss, cough & weakness. This is typical in case of pulmonary tuberculosis. TB can be extra pulmonary also. It can affect bronchus, skin, brain, intestine, bone, kidney as well [11-16].

Challenges

Today, our names for TB tell us where TB is located (pulmonary, extrapulmonary) and how to treat it (drug-susceptible, drug-resistant, multidrug resistant, and extensively drug-resistant) [11-19].

CDC and many organizations around the world are working towards a future where we call TB "history." Until TB is eliminated, World TB Day won't be a celebration. But it is a valuable opportunity to educate the public about the devastation caused by TB and how it can be stopped.

In 2018, as part of the "We Can Make History: End TB" World TB Day theme, CDC honored TB elimination leaders and history-makers through the TB Chronicles. The TB Chronicles depicted TB milestones that highlight both how far we have come and how far we must go towards ending TB [11-13].

World Health Organization (WHO) has committed to eradicate TB by the year 2050 as per the Global Tuberculosis Report, 2016 [20].

Link to HIV/AIDS

In Sub Saharan Africa, TB is fuelled by AIDS & the TB continues to be unabated. TB is responsible for 1.4 million TB deaths among infectious diseases after HIV. The current TB-HIV epidemic associated with its severe social implications, treating & preventing TB have represented a permanent challenge over the course of human history [12, 13, 17-22, 63].

In 2009, the national frame wok for joint TB/HIV collaboration was initiated. Prevalence of HIV in TB patients ranged from 1% to 14%. It was 30% higher in smear negative & extra pulmonary than in smear positive TB patients. TB/HIV collaboration started in 2001 in six states & eight additional states in 2004 [23, 63].

Current Situation in India

As per the India TB report, 2024, as on March 2024, the Ni-Kshay Mitra (TB patient friendly portal) data informs that there are 13.46 lakhs patients in India & out of these, 9.57 lakhs receive Ni-Kshaya support. The portal further informs that average weight gain is 4.2 Kilograms in beneficiaries in comparison to non-beneficiaries. The total number of Ni-Kshaya Mitra registered are 1.57 lakhs & the number of Mitras agrred upon is 1.23 lakhs. The total number of TB patients supported by Ni-Kshaya Mitra is 9.49 lakhs. Finally, the portal informs that the total number of food baskets distributed is 14.80 lakhs [24, 25].

Nutrition- the key issue

On that line of nutrition, the Indian Council of Medical Research (ICMR) supported Reducing Activation of Tuberculosis by Improvement of Nutritional Status (RATIONS) trail published in 2021 found a 10 kilogram of food basket really helped as risk of TB death reduced by 60% with a weight gain of 5%. The study mentions that body weight at diagnosis is predictive of higher risk of death while weight gain in the first two months was protective against TB deaths. It is inferred that food based nutritional support is to be considered an essential part of care with anti TB therapy rather than optional component which is dependent on availability of donor support. The two year study found that there was nearly 40% reduction in the rate of all types of TB & nearly 50% reduction of lung TB. Thus the study reaffirmed that nutritional improvement can provide significant protection against lung TB gives a new tool for prevention that has added benefits towards positive health & productivity [26].

As nutrition is critical to the fight against TB, it is here that the concept of Satwik, Rajasik & Tamasik type of foods as per India's ancient tradition of Ayurveda of AYUSH will come in handy. However, the concept has to be applied at each house hold keeping in mind the Socio-Economic status of each house hold [27].

Ever Greening of Patents related to TB

Strong Intellectual Property laws prevented the so-called 'Ever Greening of Patents' to enhance access to TB drugs in India. 'Bedaquilline' marketed under the name 'Sirthro' is considered the back bone of shorter treatment regimen for Multi Drug Resistant (MDR) TB which when approved it in 2012 was the new drug for the disease in 40 years. Bedaquilline compounds have been protected by patents in India & many parts of the world until 2023 [28].

The originator Johnson & Johnson (J&J) filed a secondary set of patent applications globally in 2022 seeking to obtain patent protection over modified Bedaquilline compounds which was the Fumarate salt of Bedaquilline. Such patents could have delayed the availability of afforadable generic versions of Bedaquilline beyond the 20 years primary patent protection period foreseen to end in 2023 [28].

The decision was in line with the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement that grants countries the flexibility to complement measures that protect public health including freedom to chose & apply the above-mentioned concepts. Using such concepts & provisions, the Indian Patent Office (IPO) rejected the secondary patent application of J&J [28].

Economic Burden of TB at Global level & in India

Regarding the epidemiology of TB in India, the prevalence of all forms of TB decreased from 506 per100,000 population in 1995 to 2007at a rate of about 6% per year. New smear positive TB decreased from 190 cases per 100,000 in 1995 to 100 in 2007 at the same rate of 6% per year [29].

Analysing the TB related mortality, currently 299 per 100,000 or 3.4 millions die in each year. Each year 2 million develop TB & 331000 die due to TB. TB mortality rate decreased from 44 per 100,000 population in 1995 to 29 in 2007 @ 4% decline per year. Case fatality in new cases has remained below 5% nationally [30, 31].

Regarding the economic burden, in 1999, it was estimated that DOTS in India would generate economic benefits equivalent to between 0.9% & 3.3% of GDP. Number of Disability Adjusted Life Years (DALY) lost due to TB per 100,000 people in India has improved by 33% from 1990-2006. TB caused a loss of 7.9 million DALYs & a reduction of US$ 23.7 billion in economic well being that is equivalent to US$21 per capita. The cost of TB control averaged just US$26 per DALY gained over 1997-2006 & generated a return of US$ 115 per dollar spent. Thus, the return on investment has been good for the Government of India & donor programs [32, 33].

Catastrophic cost is defined in health financing literature as OOPE above a certain threshold proportion of house hold income is the reason of impoverishment for millions of people in the world [34].

In TB catastrophic cost is defined as total treatment cost (direct & indirect cost) more than or equal to (≥) 20% of pre TB annual house hold income as adverse outcomes were strongly associated with this threshold [35, 36].

Indirect costs i.e. time, income & productivity loss associated with an episode of TB & contributes a significant proportion of total treatment cost. It is included in the catastrophic cost definition along with OOPE [37].

A study published in 2024 about catastrophic costs for tuberculosis patients in India in four states namely Assam, Maharashtra, Tamil Nadu & West Bengal studied 1,482 TB patients across these four states. The study showed that high rates of catastrophic costs with 30% to 61% experienced hardship exceeding 20% of pre TB annual house hold income mainly due to diagnosis & economic loss because of unemployment during long TB treatment [38].

The total cohort 1,482 patients consisted of 529 from the general population, 526 from urban slum areas & 427 from tea garden areas. The patients were from 118 TB units & 182 tea gardens across 16 districts from the above-mentioned four states. Treatment cost or Out of Pocket Expenditures (OOPE) ranged between ₹ 32,829- ₹34,315. For urban slum dwellers, the range was ₹30,782- ₹30,806 while for tea garden workers, the range was ₹22.981- ₹29.960 [39].

The study adopted the human capital approach that measures lost productivity but does not capture indirect costs due to reduced productivity. In the output approach, the second form of modeling, reduced productivity in the form of income loss was captured & treatment costs soared to ₹30,347 for tea garden families,₹ 57,992 for urban slum dwellers & ₹61,181 for general population patients [40].

The study showed poor health insurance coverage & limited usage among study participants. Therefore improved insurance coverage & reimbursement of expenses through insurance can play a crucial role in reducing catastrophic cost [41].

The WHO report, 2022 on TB & India TB report, 2024 presumes that missing childhood TB cases impede achieving 2025 goal of eliminating TB from India. Globally, at least 1.2 million children aged less than 15 years fall ill with TB every year. Only 44% of these cases get detected. The report also mentions that TB is the leading cause of death from infectious diseases for children. The estimated mortality of children with TB who fail to receive treatment is about 22% [20, 42].

India contributes nearly 1/3rd to the global childhood TB burden. The report says while the number of TB cases notified in India has increased since 2015, notifications for childhood TB have remained constant at 6% each year. Nearly 0.34 million children in India aged less than 15 years are estimated to get TB disease every year. Children in this age group are estimated to contribute about 13% of the Tb caseload. In 2022, only 1,35,734 children were notified. Thus over 2,00,000 or about 40% children with TB were likely missed in 2022. Further, of the 3,00,000 molecular tests performed on children, just 37,000 or only 12% were bacteriological confirmed cases. In addition, the coverage of BCG vaccination fell from 92% in 2019 to 85% in 2020 to 84% in 2021 because of the COVID 19 pandemic. However, it increased to 91% in 2022 or in the post pandemic period. The falling rate led to the surge in childhood TB cases. Homoeopathy of AYUSH played an active role during the pandemic [43-45].

Additionally, only a small portion of children & extra pulmonary TB patients are successfully screened for drug resistance. Evan as the bulk of cases in children is pulmonary TB, which is easier to detect, up to 32% of TB cases are extra-pulmonary which makes TB detection further challenging [41, 44].

Way Ahead with AYUSH

The 2002 National policy on Indian Systems & Homoeopathy envisages the role of homoeopathy in National Health Programs & one such program is the RNTCP. The objectives & strategies mention about linking of the Homoeopathic therapeutic system both at institutional & community level [45].

As 10% of the population In India use Homoeopathy, using the projected population of 150 crores in the absence of a Census since 2011, it can be inferred that 15 crore population can be saved from the development of TB Diathesis & TB Miasm in their bodies. Simultaneously, the TB patients will benefit as recurrence of TB will be reduced while saving them from side effects of Chemotherapy during the course of treatment [45-47].

NFHS & TB

As already mentioned above, the tubercular miasm is around low body weight for children or children who have Low Weight for Height (W/H- Wasting) & Low Weight for Age (WA- Underweight). Similarly, for adults who have Low BMI or Low Weight in Kilograms per Height in Meter Squares (Kg/M2). This implies that those children who are Wasted & are Underweight are prone to Tuberculosis. Similarly the adults who have Low BMI are prone to Tuberculosis. The following table gives the indicators related to Wasting & Underweight in children & adults who have low BMI [48].

Survey	*Indicator*	*Performance of the Indicator in Percentage*
NFHS 5	U5 Children who are wasted	19.3
NFHS 5	U5 Children who are severely wasted	7.7
NFHS 5	U5 Children who are underweight	32.1
NFHS 5	Women aged 15-49 years whose BMI is below normal (<18.5kg/m^2)	18.7
NFHS 5	Men aged 15-49 years whose BMI is below normal (<18.5kg/m^2)	16.2

Table 1: NFHS indicators on wasting & underweight in children, Low BMI in adults [48].

This means when these percentages are converted to numbers, the burden of TB can be extrapolated. Taking the projected score of India to 150 million, 15% of these populations are the total number of U5 children. Hence, 150*15/100= 22.5 million. Out of these 22.5 million, about 20% or 1/5th are wasted. This means 4.5 million U5 children are wasted & are prone to TB. Similarly, out of these 22.5 million, about 8% are severely wasted or are more prone to TB. So 22.5*8/100= 1.8 million are severely prone to TB. Hence, the total number of U5 children that are prone to TB are 6.3 million [53-57].

Regarding women & men in the age group of 15-49, the census tells us that they constitute about 1/3rd of the population. So women in this age group are 50 million. Out of these 50 million, about 20% (rounding up 18.7) or 10 million have low BMI & are prone to TB. Similarly, 16% of 50 million men will be 8 million & hence 8 million men in the age group of 15-49 are prone to TB. So the total number of adults that are prone to TB are 18 million [53-57].

Integration of Homoeopathy in the nutritional intervention programs of central & state governments will reduce the impact of tubercular diathesis & tubercular miasm in the bodies of these children & adults [53-57].

About Kanamycin & side effects

As mentioned above, Kanamycin is an antibiotic of Aminoglycoside group that is used for serious bacterial infections & hence was also used for the treatment of TB. The issue with this antibiotic is that it causes damage to hearing, sense of balance & kidneys. It was removed from the treatment regimen of TB [58].

It is here that the Homoeopathic therapeutic system of AYUSH has a role while reducing the impact of the side effects & giving the body no side effects during the course of treatment [53-57].

Attaining Universal Health Coverage through the active inclusion of AYUSH in India is a sustainable way to deal with the perennial issue of TB. As mentioned above, through the eyes of Medical Pluralism, homoeopathy has an active role to offer [53-57].

ATP & TB

The energy mechanism of the body that converts Adenosine Diphosphate (ADP) to Adenosine Triphosphate (ATP) has helped scientists to deal with MDR TB. ATP Synthase is the enzyme that does the process. ATP synthase has two parts that are F_0 & F_1 that bare situated within the inner mitochondrial membrane & Thylakoid membrane that has CF_0 & CF_1. F_0 is the portion that is embedded inside the mitochondrial membrane in Eukaryotes. Thylakoid membrane is in plants & plasmic membrane is in Prokaryotes. Studies show that signing & synthesizing various drug molecules targeting ATP Synthase the enzyme critical for energy production in TB bacteria. ATP Synthase produces ATP from ADP & inorganic phosphate that helps in bacterium survival [59-62].

Using this development, drugs like ATP Synthase inhibitors like 'Sudoterb' of Lupin Laboratories, India & 'Sirturo' of Koen Andries at Jansen Pharmaceuticals have been approved by Food & Drugs Administration (FDA) in 2012 for MDR TB [59-62].

Conclusion

Epidemiology puts TB in the secular trend as the issue of TB is multi contry, multi dimensional, multi factorial, multi types & pluralistic in nature there by throwing challenges to the stakeholders of TB for centuries now.

Homoeopathy has a way to deal with the TB in the body before the TB bacteria wins the battle. That means till the point of Ghon focus. Another prime advantage is that during the course of Chemotherapy, Homoeopathy will catalyze the immunity of the body while reducing the side effects of the Chemotherapy in the body.

When the case becomes complex through the emergence of DR, MDR & XDR, again Homoeopathy of AYUSH has a role to help the body to overcome these issues as a complementary therapeutic system while helping the body to catalyze the immunity & helping the body to optimize the benefits of the nutritional interventions that are critical in TB intervention.

What is most beneficial is that Homoeopathy can cover masses as it encompasses all the qualities of Essential Medicine (ED). Active integration of Homoeopathy of AYUSH will help the country to achieve the Sustainable Development Goal related to TB by the next 6years.

Acknowledgement

The lead author thanks all the coauthors who are Homoeopaths for their contribution in the Homoeopathic section & all other coauthors for their contribution in the non Homoeopathic section. Professor Shankar Das was the Ph.D. guide of the lead author & Professor D.P. Singh was the teacher of the lead author at Tata Institute of Social Sciences, Mumbai during 2011-2018 & 1995-1997 respectively. Professor Dwivedi is the coordinator of the program at Lucknow university where the lead author currently teaches as a faculty.

Declaration

The lead author declares that the Homoeopathic integration mentioned here is only suggestive in nature.

Funding

There was no funding received for the article.

Conflict of Interest

There is no conflict of interest regarding the article.

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