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Tuberculosis: Pathogenesis, Treatment, And Public Health Challenges

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Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains a leading infectious disease globally, presenting significant challenges to public health systems. This review provides an exhaustive examination of the pathogenesis, clinical manifestations, and diagnostic methodologies associated with TB. Furthermore, it evaluates contemporary treatment regimens, including first-line and second-line pharmacotherapies, and addresses the emergence of drug-resistant strains. The socio-economic impact of TB, alongside public health strategies for its control and prevention, is critically analyzed. This review aims to furnish a holistic understanding of TB, encompassing its biological, clinical, and socio-economic dimensions, and to discuss future directions in research and policy-making to combat this persistent global health threat.

Key Words: Tuberculosis, Drug-resistant tuberculosis, Treatment regimens, Global Health

1.Introduction:

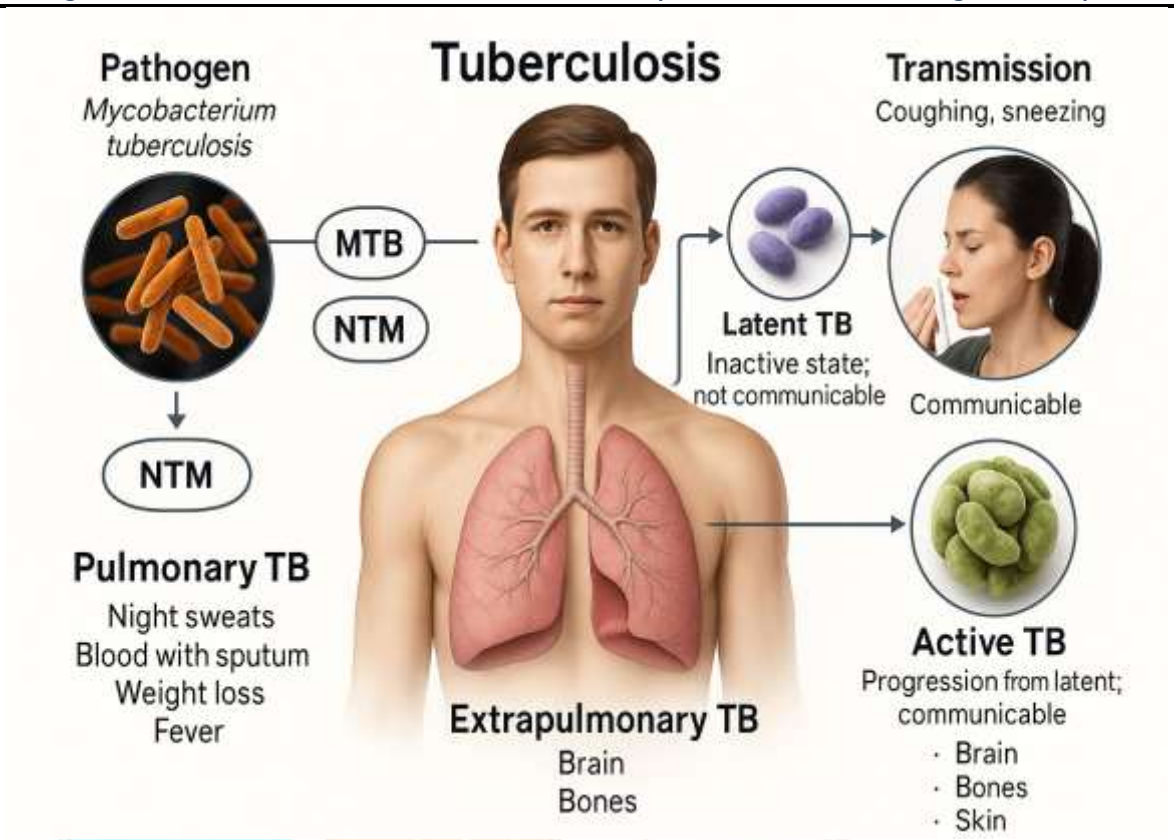
Tuberculosis is a disease caused by Mycobacterium tuberculosis also referred as Mtb, is one of the most highly contagious disease which can be spread through cough, sneeze [7, 21]. Every year, 10 million people suffer from tuberculosis Despite being a preventable and curable disease, 1.5 million people die from TB each year – making it the one the world's most fatal disease. There are group of species which can cause who TB referred to as M. tuberculosis complex (MTBC) and it consist of around 8 Species besides MTBC and MTB which are: -M. Africanum, M. Bovis, M. Microti, M. Canetti. **NTMs are: -**M. Kansassi, M. Leprae, M. Avium., M. Kansasii

Now, M. Africanum, M. Bovis, M. Microti, and M. Canetti are TB causing pathogens while remaining 4 M. Kansassi, M. Leprae, and M. Avium. M. Kansasii are referred to as "NTM" (nontuberculous mycobacteria) which are responsible for causing diseases which resemble TB.

TB is a disease which mainly targets lungs causing pulmonary disorder but can attack and cause harm to other organs aswell leading to extrapulmonary TB. Like: - osteotuberculosis, neurotuberculosis, skin TB

TB Bacteria can remain in inactive state for years without showing any significant symptoms causing Latent TB (LTBI). About 10% of these evolve into active TB which if not detected on time lead to increase in mortality rate. In case of Active TB symptoms which can be observed are: Night Sweats, Loss of Weight, Blood with Sputum, FEVER

Now TB itself is a communicable disease which can spread via sneezing and coughing of infected patient however LTBI is not communicable [21]



1.1Types Of TB Patients-

A. New TB Patient: Patients who have never been diagnosed with tb earlier or treated for it or patients who have taken anti-TB drug for less than 1 month
B. Previously Treated TB Patient: Patients who have been treated with Anti-Tb drugs for 1 month or more
C. Relapse patients: Patients which were cured and of removed from anti-TB drugs but are now suffering from recurring episode of TB.
D. Treatment after failure patients: Patients treated for TB but whose treatment failed
E. Treatment after loss to follow up patients: Patients declared to loss after follow up previously referred to as “treatment after default patients
F. Other previously treated patients: Patients whose outcome post TB treatment is unknown or undocumented

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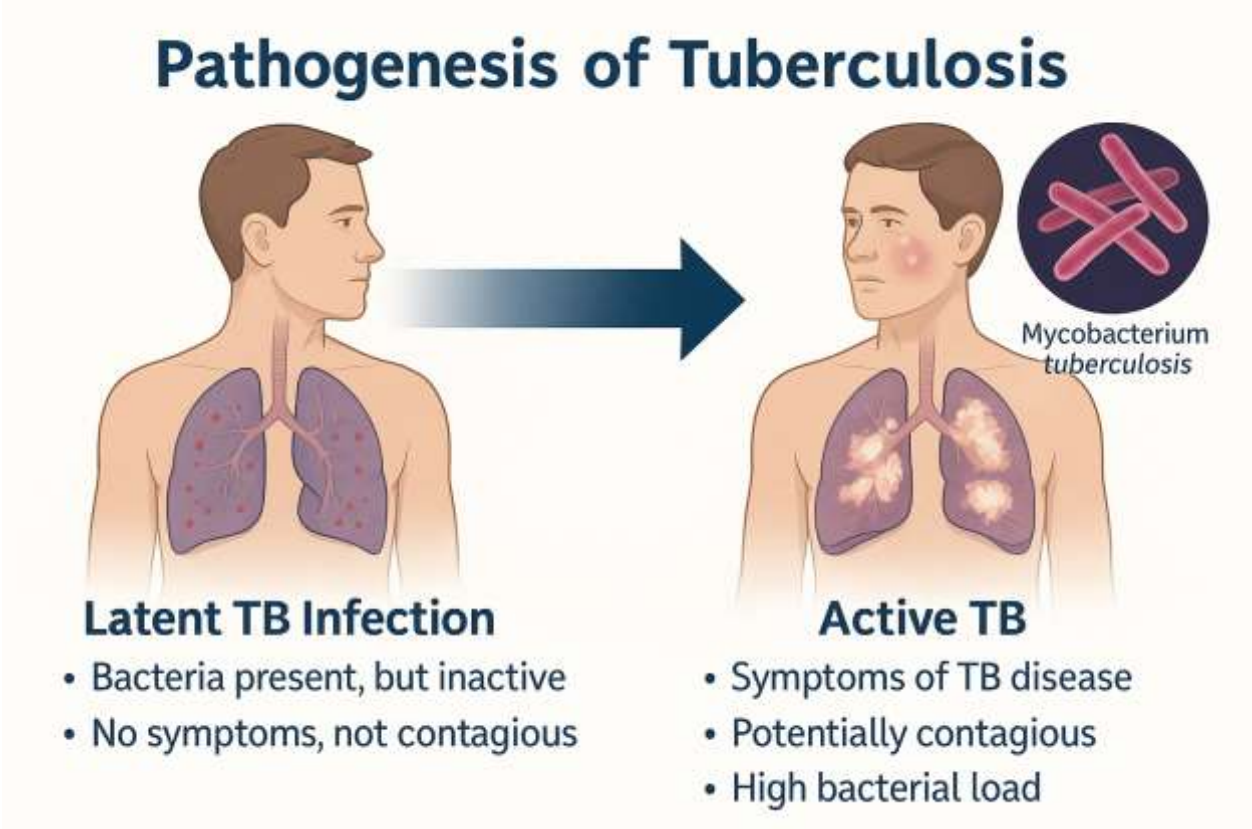
1.2Epidemiology of TB:

TB is a highly contagious disease which affect lungs and is caused by bacteria Mycobacterium Tuberculosis it is spreads via air when infected person sneezes or coughs.

It has been estimated by WHO that about a 1/4th (quarter) of world population has been infected with TB and about those 5-10% have not developed the symptoms will develop them and get infected by TB those who have been infected but have not fell ill yet act as carrier of disease [22]



2 Pathogenesis of Tuberculosis

It is observed in most patients TB infection results in chronic condition or a lifelong standoff, where TB bacteria can stay in Latent (inactive) state showing no symptoms except when body generates immune response to TB antigens it is estimated about 1/3rd of World population is infected with TB.
In about 5-10% infected individuals latent TB develops into active TB it is characterized by high bacterial load and this leads up to 1.7Millions death per year which is highest and higher than any other single bacteria pathogen.
Now certain diseases like H.I.V (Human Immunodeficiency Virus) can significantly increase risk of acquiring / developing TB as it compromises body's immune system as if it was not enough itself it can lead developing drug-resistant strains of TB which can potentially make it tougher to treat TB and can hinder effective treatment
Even though significant progress has been made in field of TB over 130 years since when it was 1st identified by Robert Koch year 1882 on 24th March many questions about TB are yet to be answered.
Now current vaccine being administered for TB, BCG (Bacillus Calmette-Guérin) has been in use since 1921 which means it has been administered for about 103 years and has been administered to approximately 3.5 billion people but yet it can't reliably prevent TB in adults indicating need for better and more efficient and affective TB vaccines. [17]

2. Clinical Manifestation and Diagnosis of T.B:

A) In children: From a clinical standpoint of view childhood TB. Does not show any signs or specific symptoms but it progresses and gets worse over time and in children suffering with PTB it can get misdiagnosed as LTBI [2,11,3] Symptoms in case Paediatrics TB are-

- Fatigue
- Loss of appetite
- night sweats, weakness
- weight loss
- evening fever.

Now when the disease reaches lung it can cause coughing in child which may be productive or no productive coughing. Main symptom for Pediatric TB is Coughing be it Productive or Nonproductive. It is also necessary to consider that TB can affect other organs and not only lungs. IT is estimated in 20% children that tb has extrapulmonary manifestation.

B) In HIV Affected Patients: In case HIV affected individual symptoms of TB are influenced by the amount of degree Immunosuppression and is similar to that of a normal patient. [20,19,10].

C) In Normal Patients and Development: It has been observed that there is difference in development of TB in various patients due to different immune response and cellular activity]. It can be said to mainly comprise of 4 stages: -

i. Latent Stage: can also be referred to as inactive stage where TB is not active. In this stage of TB, no symptoms are visible there is no microbiological or radiological activity to determine or identify that TB is present however it may progress during this period

ii. Primary Stage: Primary pulmonary TB is generally Asymptomatic which means it does not show its symptoms now the only visible symptoms occur sub clinically symptoms which occur can be self-assessed though its limited can include paratracheal lymphadenopathy which is commonly associated with TB it occurs due to spread of bacilli from Lungs to Lymphatic system

iii. Primary Progressive Tuberculosis: Active TB only develops into 5-10% People suffering from it or those who have been exposed to bacteria *M tuberculosis.* As patient progresses to active TB, they show non-specific symptoms. which can include 1. Progressive Fatigue 2. Loss of Appetite, 3. Wasting (Loss of Fat and Lean Muscle), Wasting occurs due to immune response of the body, Sputum can also contain blood due to hemoptysis

iv. Extrapulmonary Tuberculosis: Pulmonary system is most common location for TB but 20% of immunocompetent patient suffers from Extrapulmonary Tuberculosis, Risk of Extrapulmonary disease increase with immuno-suppression and most dangerous location is CNS where infection can lead to meningitis or space occupying tuberculomas which can lead Tubercular meningitis. [4]

3.Management of Drug-Resistant TB:

Drug Resistant TB is type of TB which does not respond to standard treatment of TB a comprehensive review consisting of over 148 studies showcases that more than 318,000 people found out that 11.6% cases of TB are Drug Resistant

Isoniazid resistant tuberculosis (TB) is type of TB which does not respond to antibiotic Isoniazid which is generally used to trat TB a comprehensive review of over 98 studies shows that about 15.7% 102,000 people suffer from Isoniazid resistant TB

Rifampin resistant tuberculosis (TB) is a variation of TB which is resistant to Rifampin a comprehensive revive consisting of over 109 studies consisting of over 215,000 people found out that about 9.4% of TB cases globally are resistant to Rifampin.

[Global prevalence of drug-resistant tuberculosis: a systematic review and meta-analysis Nader Salar, 2023]

3.1 Advance in TB Diagnostics:

Smear Microscopy: For over 100 years microscopic examination of sputum sample using Ziehl-Neelsen (ZN) stain has done to diagnose TB however this tradition light microscope method not much viable as it can only detect 70-80% cases. A better option is

fluorescence microscopy: which is 10% more sensitive then Light Microscopy it allows for easier viewing of TB bacteria at a lower magnification. However, it had its own downsides like it can only be used in dark rooms and that mercury bulb needed constant changing and was replaced by

LED fluorescence microscopy: uses LED (Light Emitting Diode) instead of Mercury Lamp which gives it way better lifespan lasting about 10,000 Hours (6,00,000 Minutes) making it more economical and affordable in long and according to W.H.O it is 10% more accurate then Smear Microscopy [Innovative laboratory methods for improved tuberculosis diagnosis and drug-susceptibility testing Nathan Mugenyi]

3.3) Ongoing Clinical Trials:

C-Tb is a diagnostic tool developed for TB developed by SSI, DENMARK. IT uses specific proteins from TB bacteria to detect immune response proteins are recombinant proteins ESAT-6 and CFP-10. These proteins are part of the TB bacteria but not its BCG vaccine hence allowing for a better differentiation. Dose finding trial was held between February to November 2010 at St. George's University of London, UK. It consisted of 38 Adults which were diagnosed with Active TB recruited from outpatient clinics in South West London

And patients were divided into 3 groups consisting of 12 members each where Group 1 received 0.01mg of either preserved or unpreserved C-Tb, injected based on randomization.

Conclusion whereas Group 2 and 3 Received 0.1 mg of C-Tb based on safety evaluations from the first group. pain from injections was evaluated using a Visual Analogue Scale (VAS), from 0 mm (no pain) to 100 mm (worst pain) in follow-up.

Specificity Trial of C-TB

Was conducted in Surrey Clinical Research Centre, Guildford, UK. From May to November 2011 and consisted of 151 participants which were adults and had received BCG vaccine

[1]

6.Computational Tools in Tuberculosis Research:

Bioinformatics and Genomic Analysis

A) Isolated and Genotyping

12 Mycobacterium tuberculosis complex also referred to as MTBC isolates were utilized in this study which consisted of 6 reference strands and 6 clinical isolates which were previously described by Zhu EL 2016 these 6 standard strains were reference and was produced from ATCC specifically for genome sequencing reason rains were cultured in Lowenstein-Jensen media or Middlebrook 7H10 media supplemented with 10% Oleic Albumin Dextrose Catalase (OADC, Becton Dickinson), glycerol, and 0.05% Tween 80. This Genotyping was conducted using the VNTR-15 scheme as outlined in the MIRU-VNTRplus database and deployed following markers

1.Mtub04
2. ETRC
3. MIRU04
4. MIRU40
5. MIRU10
6. MIRU16
7. Mtub21
8. QUB11b
9. ETRA,
10. Mtub30
11.MIRU26
12.MIRU31
13. Mtub39
14. QUB26
15. QUB4156

These are all the locus of MIRU-VNTR whose products were individually amplified and were subjected to elctrophesis on an agarose gel as suggest by Fabre et al 2004 and there copy number were calculated via Bio numeric software and the complete Genome SNP was
performed using Mega 6.06 software. [8]

B) Genome Structure and Identification of Specific Genes and SNPs:

Genome Structure and Identification of Specific Genes and SNPs involve

First calculating ANI and the ANI was calculated using Genome tool to determine the genetical similarity between various genomes of the isolates now these multiple alignments of genomes sewer conducted with mauve multiple alignment software using progressive alignment option of software was generated by Mauve and was parsed using a custom Perl script.

SNP's which were found out in the repetitive region of genomes were removed and not included in the analysis to enhance the accuracy and were defined as exact replica of repetitive sequence of 25 base pairs identified using Repeat-Masker tool.

Gene sequences which were used were downloaded annotated using the Rapid Annotation using Subsystem Technology (RAST) server it allowed for the identification of genes unique to specific species of groups, which helped in more comprehensive understanding of genetic differences and specific traits among the isolates and the

ANI was calculated using Genome tool to determine genetic similarity between various genomes of the isolates now these multiple alignments of genomic sewer conducted with mauve multiple alignment software using progressive alignment option of software output file generated by Mauve was parsed using a custom Perl script.

c) Genomic DNA Extraction, Sequencing, Correction, and Re-Annotation

Genomic DNA from 12 MTBC strains was extracted using the TIANamp Bacteria Genomic DNA Kit this DNA was first sequenced using PacBio Single-Molecule Real-Time (SMRT) Technology to correct any errors which have been made by PacBio sequencing the isolates were re-sequenced using next generation sequencing it an Illumina Genome Analyzer 2X. Paired-end libraries were prepared from 5 µg of genomic DNA using the TruSeq DNA sample prep kit A (Illumina Inc., San Diego), and sequencing was done with a read length of 2 × 150 nucleotides on an Illumina GAIIx instrument. Image analysis and base calling were performed using the standard Illumina pipeline and raw sequencing reads were trimmed and the raw sequencing reads were trimmed at a Phred score threshold of 20 to ensure high quality. These filtered reads were mapped onto the genome sequences assembled using the Hierarchical Genome Assembly Process (HGAP.3) algorithm in SMRT Portal and BWA version 0.5.9, then converted to sorted BAM format using SAM tools v0.1.9. The coverage ranged from 157× to 394×, averaging 255×. Pilon v1.13 was used to polish the genome sequences, resulting in 9,493 insertions and 133 deletions. The raw Illumina sequencing reads were deposited in the NCBI Sequence Read Archive (SRP064893) and the Genome Sequence Archive of the BIG Data Center (PRJCA000307). At the end 12 Genome sequences were re-annotated using RAST, an automated tool for annotating. [9,]

6.2) Computational Drug Discovery and Design:

Finding for molecules acting against Mtb involves high throughput screening and computational methods thus a database called CDD Tb and has been developed to collect both public and private public data which helps in facilitating data mining and collaboration the public data paired with cheminformatics approach were used to create model to distinguish between active and inactive compound. Comparison between compounds were made with list of FDA-approved drugs, focusing on the polar surface area and pKa of active compounds as significant activity determinants, while hydrophobicity was not always significant. Bayesian classification models for 220,463 molecules were generated and tested which help in determining and identifying active or inactive substructures. Computational pharmacophores based on known Mtb drugs successfully mapped and retrieved active compounds from Mtb datasets this study helped gain in-depth knowledge into molecular properties and feature such a 1D molecular Descriptors and 2d molecular descriptors [8]

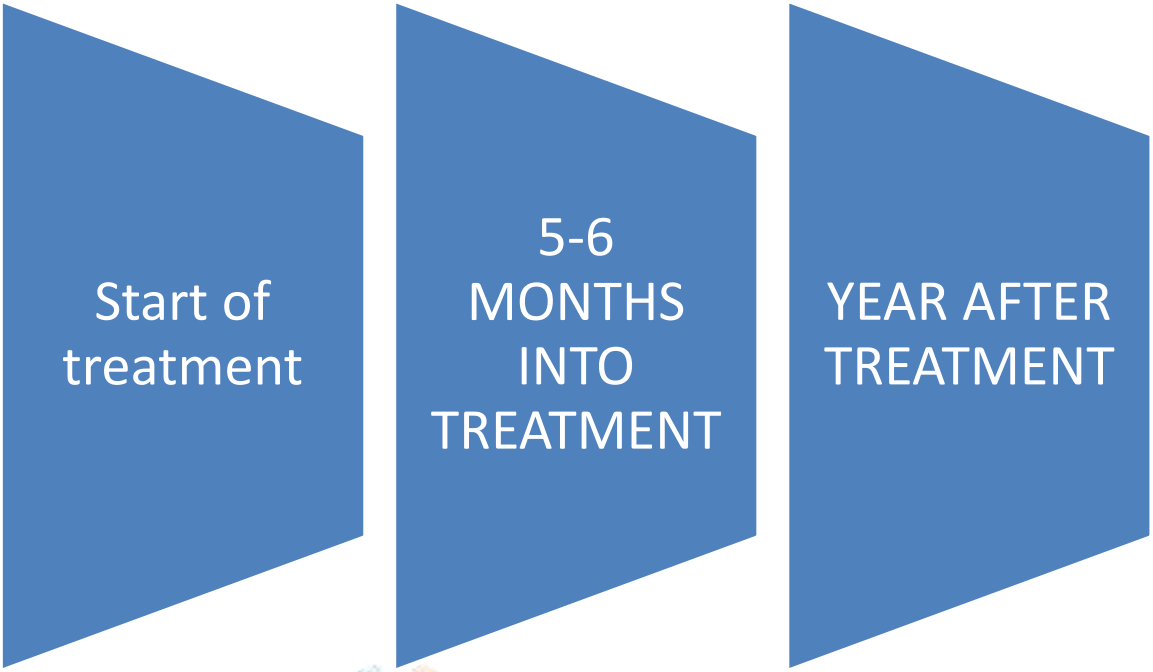
7.Public Health Implications:

7.1 Socio-Economic Impact of Tuberculosis (Indian Perspective):

Criteria for Study (Study, Participants, Interviews and instruments)

The particular study involved adult patients (18 years old and older) receiving or going through TB treat at government hospitals and healthcare facilities participants selected were patients who were 2 months in to

their TB treatment they were interview in following order: -



Aim of this analysis was focused on period from onset symptoms of TB to end of its Treatment
Aim here mainly was to asses economic burden not including after treatment.
Questionnaire used in this survey was based of W.H.O guidelines for TB patient cost survey,
Interview helped gained insight on: -

- Time in and out of pocket expense like expense for patient visits, hospital stays and drug pickups
- Expenses for additional food and nutritional supplements
- Socioeconomic details of patient their background income and ownership details
- Coping strategies like borrowing money or selling assets

Interview Process the interview took place between March 2019 to September 2022.
Helped us understand:

A) Health Seeking Behaviour:

Average duration from onset of duration of TB symptoms to beginning of treatment was 7 weeks (49 Days) for tea garden families while for urban slum dwellers it was 9 weeks (63 Days) most participants form general population and urban slum dwellers approximately 72%-75% went to a private healthcare provider on an average these patients made 8-11 trips to different healthcare provider before getting TB diagnosis.

B) Outcome of Treatment:

1.1 Adverse treatment which includes death and relapse ranged from 12% to 14% while discontinuation of treatment among the 2 was highest among Urban slums at 5% and highest death were for participant from tea garden families at 8%. Control and Prevention Strategies

C) Income:

It was observed that pre-Tb household income was higher in general population at in 20,831 and in 16,984 for urban slum dwellers and in 9,560 for tea garden dwellers and people saw loss in income during the treatment but didn't hit baseline and recovered in post treatment

D) Missed Follow-up's and Their cause:

Study showed that about 6% of general population missed follow up in which most common reason at 2.5% was death and 2nd most being refusal at 1.7% and major reason for missing among urban slum dweller participants was wrong credentials at 2.5% and death at 1.7%. [Catastrophic costs for tuberculosis patients in India: Impact of methodological choices Susmita Chatterjee].

7.2) Control and Prevention Strategies:

Xiaojing Model of Control: Aimed to control PTB (Pulmonary Tb)

Pre Xiaojing method which means from around 2012-2018 occurrence of PTB in Kashgari prefecture increased by 18.7% per year but post implementation of Xiaojing method around year 2018-21 we saw a steep decline in PTB as decreased by 28.8% per year since its implementation. Now looking at country specific statistics:

- Shufu County 58.68% decrease
- Maigaiti Country 57.16% Decrease
- Zepu County 54.02% decrease

Factors affecting implementation of Xianjing method:

1.) Zebu county had higher number of Pub Patient with significantly improved health status post-treatment compared to Shahe County ($P<0.05$).

2.) Sache country on other had less awareness of TB drug usage and precaution hence need for more regular review and awareness campaigns.

3.) Both Shache and Zepu Counties had a significant treatment burden due to discomfort from taking or injecting TB drugs, affecting 12.8% and 8.7% of patients, respectively

In conclusion we can that Xianjing Model has been beyond effective in controlling TB in Kashgar and its success can be attributed to its simplicity and: -

- Improved education about TB to patients and it's treatments and drug usage
- Better awareness and adherence to treatment protocols
- Mass campaigning
- More transparency between Government, Healthcare Provider and patients as it reinforces trust
- Effective and aggressive policy implementation focusing on reducing treatment burden and ensuring patient understand there. [9]

Future Discussion:

A) Vaccine:

TB vaccine BCG now has been around for 100 years now and it is effective in adults but however now we need a vaccine which can cover a wider spectrum of TB and we need more effective vaccines which can target drug resistant strains of tb this all now may be possible due to advances in field of: -

Biotechnology, 2) Bioinformatics and advancements in Fields of CADD (Computer aided drug design) and new technologies' like crispr-cas-9 and RNA-Bridge

B) Enhanced Diagnostic Tools:

Consistent and continued accessibility of advanced diagnostics tools Like GeneXpert and Truenat™ systems. With special emphasis on portable and rapid diagnostic can make self TB and TB diagnostic way easier and more accessible and extra effort should be made to make it more economical so everyone can be diagnosed and it can be prevented from spreading on a rather mass scale and early diagnostic can help prevent advancement of TB into its Pulmonary and higher stages.

C) R&D For new Regime and combatting Drug Resistant TB:

With incredible advancements in field of Biotechnology and Bioinformatics new tools and software's such as Crisp-Cas-9 and RNA (Ribonucleic acid) bridge emphasis should be done on developing medicines and vaccines which can target and attach drug resistant strains of tb while providing quality of life and having next to adverse effect on patient and hybrid strains of TB Aswell.

Conclusion:

TB remain to be one of the most lethal diseases to ever exist in history of mankind as per W.H.O a total of 1.3Million people dies of TB in 2022 and TB is leading infectious killer right after COVID-19. In 2022 estimated of 10.6 million fell ill with TB globally which included 5.8Million Men, 3.5miliion women and 1.3 million children. What make Tb far more Lethal then and disease is that it has tendency to stay in inactive at that point of time it is known as Latent TB in this stage one can act as vector and spread tb via his or her cough or droplets unintentionally and infecting other around him or her as of writhing this paper $1/4^{TH}$ of world infected with TB. Now about 10% of LTBI (Inactive TB cases) transform into active TB which can occur in combination depending on the bacteria like skin TB and etc. Bigger problem than this

for Treating TB is it's Drug resistant strains hence it can be said that Tb may be a curable disease but it's complexity is unmatched and it's various strains and strands make it difficult to treat with on single vaccine or regime a lot of R&D developments need to be done on individual strains and strands and mutations of TB to counter it completely and various patterns of its evolution need to be studied evaluated that when it went from latent to pulmonary to which drug it is resistant and what mutation it is and what other organ it impacted apart from lung we need on big data collection which consist of Empirical data from patient and regulate data from health care practitioner TB under and have deeper explanation how does on contact tb and how much time takes to enter in its active stage and how it becomes resistant to a specific drug and what other regimes can be used to treat and how to make TB diagnosis and Treatment more accessible to poor and how make people more aware about and need to maintain more transparent system where patients and healthcare practitioner and patient are more in sync and transparent and make patient known about every decision and its impact.

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