A Review On Recent Updates On Drug Resistance In Mycobacterium Tuberculosis

Sandhya Bhagwat Puri, Geeta Satish Kedare, Gayatri Kishor Bawsiwal, Rohini Sunil Nandre, Punam Vishnu Gadekar

Aditya College Of Pharmacy, Beed

Abstract:-

Personal information is any information that relates to a specific person and could identify them.[1,2] This includes an individual's name, signature, address, phone number, date of birth, sensitive information, credit information, employee record information, photographs, internet protocol (IP) addresses, voice print and facial recognition biometrics, and location information from a mobile device.[3] Personal information is also known as personally identifiable information (PII) or personal data.[4,2] The term "sensitive information" refers to personal information that includes information or an opinion about an individual's health, racial or ethnic origin, political opinions, religious beliefs, sexual orientation, criminal record, or membership in a trade union.[3]The Privacy Act 1988 doesn't cover the personal information of someone who has died.[3]

Tuberculosis (TB) is a disease that affects people worldwide. Here are some key facts from the search results:

- In 2021, an estimated 10.6 million people fell ill with TB worldwide, and 1.6 million people died from TB (including 187,000 among HIV-positive people).[1]
- TB is the 13th leading cause of death worldwide and the second leading infectious killer after COVID-19 (above HIV and AIDS)
- People living with HIV are 16 times more likely to fall ill with TB disease than people without HIV. TB is the leading cause of death among people with HIV.[1]
- TB occurs in every part of the world. In 2021, the largest number of new TB cases occurred in WHO's South-East Asian Region (46%), followed by the African Region (23%) and the Western Pacific (18%) .[1,2]
- In the United States, there were 7,882 TB cases reported in 2021, with an incidence rate of 2.4 cases per 100,000 persons. There were 600 TB-related deaths reported in 2020.[2,3]
- A black hole is an astronomical object that has such strong gravity that not even light can escape it.[1,4]
- Most black holes form from the remnants of a large star that dies in a supernova explosion, and the resulting gravitational field is incredibly powerful.[4]
- Neutron stars are another type of astronomical object that can form after a supernova explosion. They are made almost entirely of neutrons and are incredibly dense.[1,2]

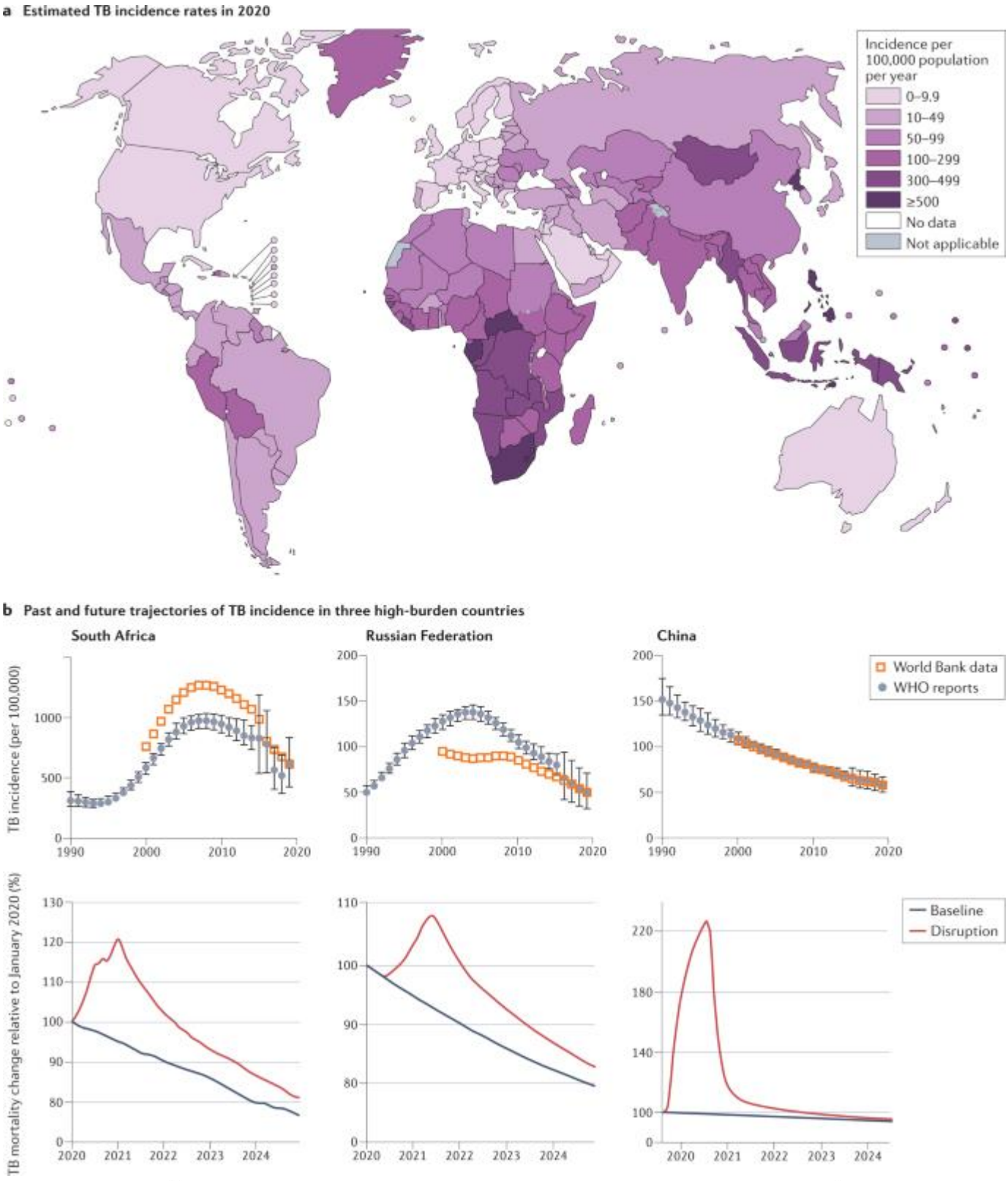
Keyword:- Mycobacterium tuberculosis, Project to Accelerate New Treatments for Tuberculosis (PAN-TB) , Extensively drug-resistant TB (XDR TB), Multidrug-resistant tuberculosis (MDR TB)

Introduction:-

Tuberculosis (TB) is a bacterial disease caused by Mycobacterium tuberculosis that can affect any organ in the body, but pulmonary tuberculosis is the most common form and is infectious[1,2,3]

- TB is spread from one person to another through airborne transmission when an infected person coughs, sneezes, or sings, releasing tiny droplets with the bacteria into the air that can be inhaled by another person.[1,2]
- Drinking non-sterilized milk from infected cows can also transmit the disease, but this mode of transmission plays only a minor role in the natural history of the disease in humans[1]
- Symptoms of TB disease include coughing, chest pain, fever, night sweats, weight loss, tiredness, and not feeling well in general.[1,3,4]
- TB can be fatal if not treated properly.[3,5]
- Treatment regimens for TB consist of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months, and there are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB.[1]
- In 2018, it was estimated that one quarter of the world's population had a latent infection of TB, and new infections occur in about 1% of the population each year[1]
- In 2020, an estimated 10 million people developed active TB, resulting in 1.5 million deaths, making it the second leading cause of death from an infectious disease after COVID-19.[1,4]
- Most TB cases occur in the regions of South-East Asia, Africa, and the Western Pacific, with more than 50% of cases being diagnosed in seven countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, and Bangladesh.[1,4]
- By 2021, the number of new cases each year was decreasing by around 2% annually.[1,4]
- About 80% of people in many Asian and African countries test positive, while 5–10% of people in the United States test positive via the tuberculin test.[1,4]
- TB has been present in humans since ancient times.[1,6]

Worldwise statics :



Tuberculosis: Classification

• **Pulmonary tuberculosis**, i.e., tuberculosis of the lungs, is the most frequent form of the disease, and over 80% of cases belong to this type. This form of tuberculosis can be infectious[7]

• **Extra-pulmonary tuberculosis**, i.e., tuberculosis affecting organs other than the lungs, most frequently the pleura, lymph nodes, spine and other bones and joints, the genitourinary tract, the nervous system and abdomen. Tuberculosis may affect any organ and may even become disseminated. This type of tuberculosis usually not infectious[7]

Tuberculosis: Types

- Active TB Disease. Active TB is an illness in which the TB bacteria are rapidly multiplying and invading different organs of the body. [8]
- Miliary TB. Miliary TB is a rare form of active disease that occurs when TB bacteria find their way into the bloodstream.[8]
- Latent TB Infection.[8]

Symptoms

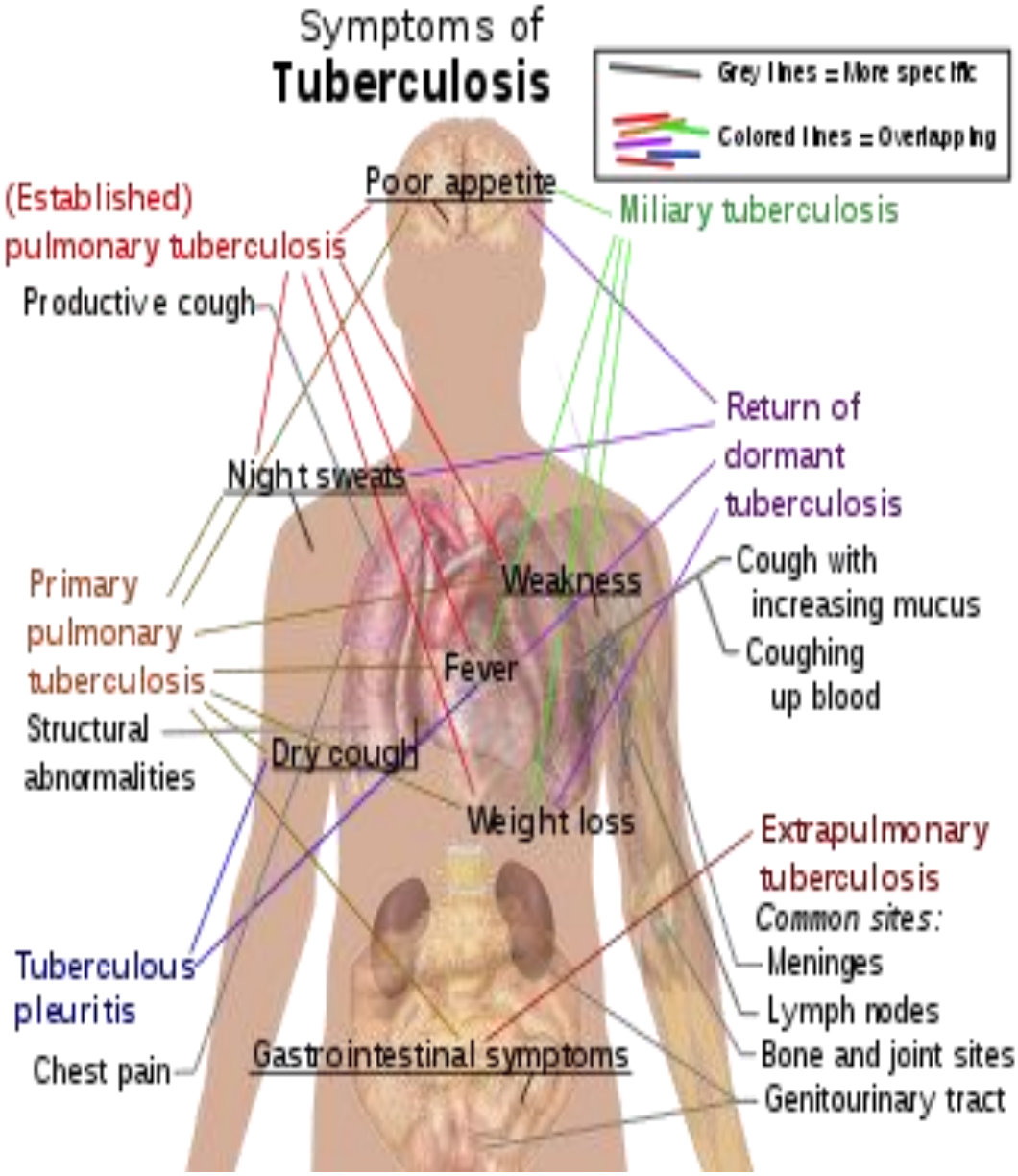


Figure no.;-1 Symtoms related to GI tract

Pathogenesis

About 90% of those infected with *M. tuberculosis* have asymptomatic, latent TB infections (sometimes called LTBI), with only a 10% lifetime chance that the latent infection will progress to overt, active tuberculous disease. In those with HIV, the risk of developing active TB increases to nearly 10% a year. If effective treatment is not given, the death rate for active TB cases is up to 66%. [11]

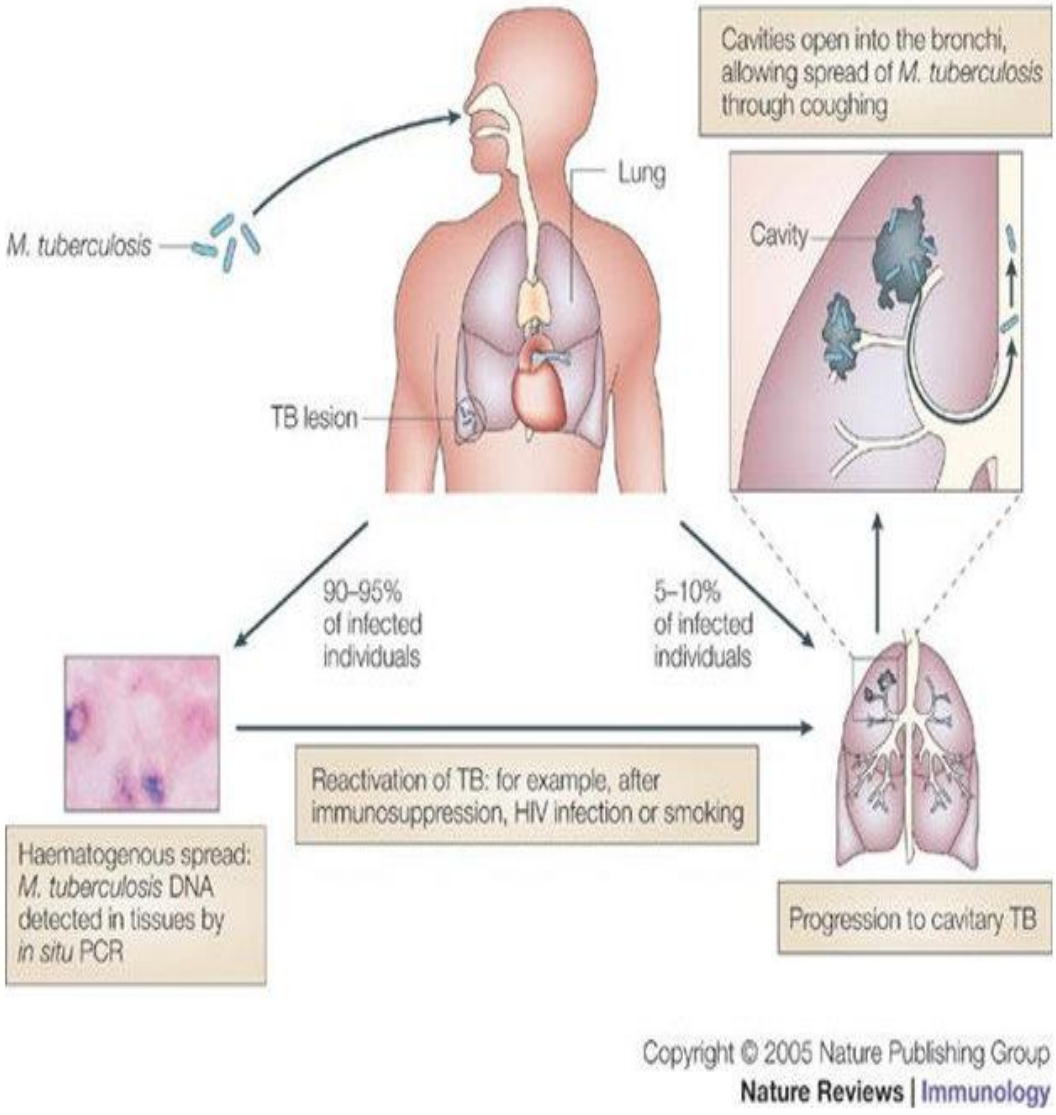


Figure no.:-2 Pathogenesis of MT

Diagnosis:

To diagnose a tuberculosis (TB) infection, a healthcare provider will perform a physical exam that includes listening to the patient's breathing with a stethoscope, checking for swollen lymph nodes, and asking questions about symptoms.[12]

. TB tests are ordered if TB is suspected, if the patient was likely exposed to a person with active TB disease, or if the patient has health risks for active TB disease.[12]

. The healthcare provider will determine whether a skin test or blood test is the best option.[12]

.The most commonly used diagnostic tool for TB is a skin test, also known as the Mantoux tuberculin skin test.[13,14,15]

. A small amount of a substance called tuberculin is injected just below the skin on the inside of the forearm. Within 48 to 72 hours, a healthcare worker will check the arm for swelling at the injection site. The size of the raised skin is used to determine a positive or negative test. A positive test indicates that the patient likely has either a latent TB infection or active TB disease.[12,13,14,15]

. People who had a TB vaccination might get a positive test even if they have no infection. A negative test means that the patient's body didn't react to the test, but it doesn't necessarily mean they don't have an infection.[12,13,14,15]

.Other tests, such as a chest X-ray and a sample of sputum, are needed to see whether the patient has TB disease.[12,16,17]

. A chest X-ray can show irregular patches in the lungs that are typical of active TB disease.[13,16

. If the chest X-ray shows signs of TB, the healthcare provider might take samples of the mucus that comes up when the patient coughs, also called sputum. Lab tests can detect the bacteria in the sputum if the patient has active TB disease in their lungs or voice box.[14,16,17]

. Other lab tests that may be ordered include a breath test, a procedure to remove sputum from the lungs with a special tube, a urine test, and a test of the fluid around the spine and brain, called cerebrospinal fluid.[12]

Non-pharmacological management:

. Tuberculosis is a serious disease that requires proper medical treatment. However, there are some non-pharmacological management strategies that can help improve the outcomes of tuberculosis treatment. Here are some tips from the provided search results:

1. Quit smoking: Smoking is associated with an increased risk of tuberculous infection and of progression from tuberculous infection to tuberculosis disease, increased disease severity, delayed sputum smear conversion, and increased risk of unfavorable treatment outcomes. Health care workers should advise smokers to quit, and counseling to stop smoking should be part of tuberculosis care.[18]

2. Eat a healthy diet: Sunflower seeds, nuts, chia seeds, pumpkin seeds, and flaxseeds are great sources of zinc, which can help fight against diseases like TB. Fruits and vegetables like orange, mango, sweet pumpkin, and carrots, guava, amla, tomato, nuts, and seeds are an excellent source of Vitamin A, C, and E, and should be included in the daily diet regime of a TB patient. Pineapple juice is also very effective in treating tuberculosis, as it helps to reduce mucus formation and provides faster recovery.[19]

3. Maintain a strong immune system: If you are healthy, you probably have a strong immune system and your body can fight off infections from bacteria or viruses easily. So if you breathe in TB bacteria, your immune system would probably kill them off straight away, without you ever getting ill or knowing about it.[23]

4. Use Arjuna: The medicinal properties of Arjuna work in relieving the symptoms of tuberculosis. Bark powder of Arjuna is used for the management of some painful conditions of tuberculosis due to its antibacterial activity. It might also have antioxidant properties and may be beneficial for pulmonary tuberculosis.[19]

It is important to note that these non-pharmacological management strategies should not replace proper medical treatment for tuberculosis. Regimens for the treatment of TB disease must contain multiple drugs to which the bacteria are susceptible, and the standard of care for initiating treatment of TB involves a combination of drugs.[25]

Pharmacological Management:

Anti-tuberculosis Drug

First Line Drugs

1. Rifampin
2. Isoniazide
3. Pyrazinamide
4. Ethambutal
5. Streptomycin

Second Line Drugs

1. Kanamycin
2. Ethionamide
3. Para amino salicylic acid

Newer Drugs

1. Ofloxacin
2. Ciprofloxacin
3. Clarithromycin
4. Rifabutin
5. Azithromycin

Treatment of all forms of active TB disease requires multiple antibiotics administered for several months. The duration of treatment is typically six to twelve months.
The approved first-line agents recommended to treat drug-susceptible TB are isoniazid, rifampin, pyrazinamide, and ethambutol.[25,26]

For drug-resistant TB, stronger medications such as fluoroquinolones, amikacin, capreomycin, and streptomycin may be used.[26,27]

Bedaquiline is a newer drug that may be added to an existing antibiotic combination.[27]
The variability of disease progression, host response, and drug resistance phenotypes complicates treatment and drug discovery but also creates opportunities to stratify patient populations and optimize preventive and therapeutic strategies.[25]

Because TB is largely a disease that occurs in resource-constrained countries, existing infrastructure only enables moderately complex interventions, which adds substantial operational and implementation challenges to the already daunting research mandate.[25]

Drug resistant:

Drug-resistant tuberculosis (TB) is a major public health challenge, and there is a need for new and improved treatment regimens. Here are some key points from the search results:

The clinical drug candidate pipeline is healthy, enabling a shift in favor of developing pan-TB or universal drug regimens to treat all forms of drug-susceptible and drug-resistant TB.[28]

The NIX-TB trial (NCT02333799) tested a 6-month three-drug regimen that delivered high cure rates in select patient populations infected with multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, which is a promising step towards developing universal regimens.[28,29,30]

New diagnostic tools are continuously being improved to help physicians and health services interpret results and provide faster and more targeted treatment for patients.[28]

The WHO published a catalogue of 17,000 M. tuberculosis mutations and their association with drug resistance, which provides a reference standard for the interpretation of mutations conferring resistance to all first-line and a variety of second-line drugs.[28]

The major challenge to eradicating drug-resistant TB is the discovery and development of universal regimens only comprising drugs with novel mechanisms of action and minimum side effects, which would not only be used to treat resistant TB but could also replace the first-line regimen.[28]

The Tuberculosis Drug Accelerator was launched in 2011 as an experiment designed to facilitate collaboration in anti-TB drug discovery by breaking down barriers among competing laboratories and institutions.[28]

Recent clinical trials have tested new drug regimens for highly drug-resistant forms of TB, such as the Nix-TB trial, which tested an all-oral XDR-TB drug regimen consisting of bedaquiline, pretomanid, and linezolid.[29,30'31]

There are ongoing efforts to advance investigational TB drug regimens to phase 2 clinical trials, such as the PAN-TB collaboration, which aims to evaluate five antimicrobial agents across two combination regimens for treating both drug-susceptible and drug-resistant TB.[30]

Evotec has received a grant for drug discovery in TB, which could lead to the development of new treatments for drug-resistant TB.[31]

Drug development properties:

Tuberculosis (TB) treatment has several challenges that make it difficult to cure. These challenges include drug, pathogen, and host factors that make TB treatment longer than any other bacterial infection of the lungs.[31]

In addition, drug tolerance fuels and synergizes with drug resistance, and single drug and regimen development tested in sequence is inherently slow while tools are emerging to rationally prioritize regimens early in the cascade.[31]

Furthermore, a surprisingly small number of drugs have been tested as preventive therapy of latent TB infection (LTBI).[31]

To address these challenges, future research could focus on the following drug development priorities:

- Prioritizing promising drug regimens.[32]
- Addressing biological knowledge gaps to optimize treatment.[32]
- Developing universal regimens that would substantially accelerate global efforts to control TB.[32]
- Developing new TB drugs and treatment regimens.[33,34]
- Prioritizing drug development teams to determine which combinations of drugs should be prioritized.[34]
- Using four-drug therapy as the standard of care for initiating treatment of TB disease.[35]
- Obtaining regulatory approval for new TB drugs.[36] These priorities can help to improve TB treatment and control, and ultimately lead to a cure for this disease.

Addressing biological knowledge gaps to optimize treatment:

Persistent TB disease can be caused by several factors, including immune evasion or the ability of M. tuberculosis to persist and multiply within the host cells that are supposed to eliminate bacterial pathogens, suboptimal drug penetration at the sites of disease, and extreme drug tolerance of selected subpopulations, some located in necrotic granulomas and cavity caseum.[37,38]

These niche-specific pharmacokinetics and pharmacodynamics present a challenge to ensure optimal drug delivery to bacilli in dynamic physical loci and metabolic states.[37,38]

To optimize treatment for TB, several strategies have been proposed, including therapeutic drug monitoring, pharmacogenetics, and nutritional status considerations.[37]

There is also ongoing research on the role of existing drugs and new compounds in shortening or improving treatment for tuberculosis.[39]

One promising approach is the use of high-dose rifampicin to eradicate persistent bacteria and shorten treatment duration.[40]

Quantifying lesion-specific drug uptake and pharmacokinetics in TB patients is also necessary to optimize treatment regimens at all stages of the disease.[41]

Adaptive trial designs have been proposed to evaluate the efficacy of new drug regimens and accelerate the clinical development process.[38]

The major goals of treatment for TB disease are to cure the individual patient and minimize the risk of death and disability.[42]

However, the challenges posed by persistent TB disease and niche-specific pharmacokinetics and pharmacodynamics make it important to address biological knowledge gaps to optimize treatment and improve the effectiveness of TB treatment regimens.[37,38]

Drug combination treatment:

Tuberculosis (TB) is treated with a combination of drugs, including isoniazid, a rifamycin (rifampin or either rifapentine or rifabutin), pyrazinamide, and ethambutol.[43]

Fixed-dose combination (FDC) formulations of these drugs have been advocated to prevent the emergence of drug resistance.[44]

The Food and Drug Administration (FDA) has approved fixed-dose combinations of isoniazid and rifampin (Rifamate®) and of isoniazid, rifampin, and pyrazinamide (Rifater®) for use in the United States.[45]

A 4-drug FDC (rifampicin, isoniazid, pyrazinamide, ethambutol) has been shown to be effective and safe for the treatment of TB.[44]

Rifamycins, including rifampin, are an essential component of all short-course regimens for TB treatment.[43]

Clinicians should become familiar with the management of TB disease using these fixed-dose combination drugs, but they should also consider the higher risk of drug toxicity and adverse reactions when using fixed-dose combinations.[43]

Drug target:-

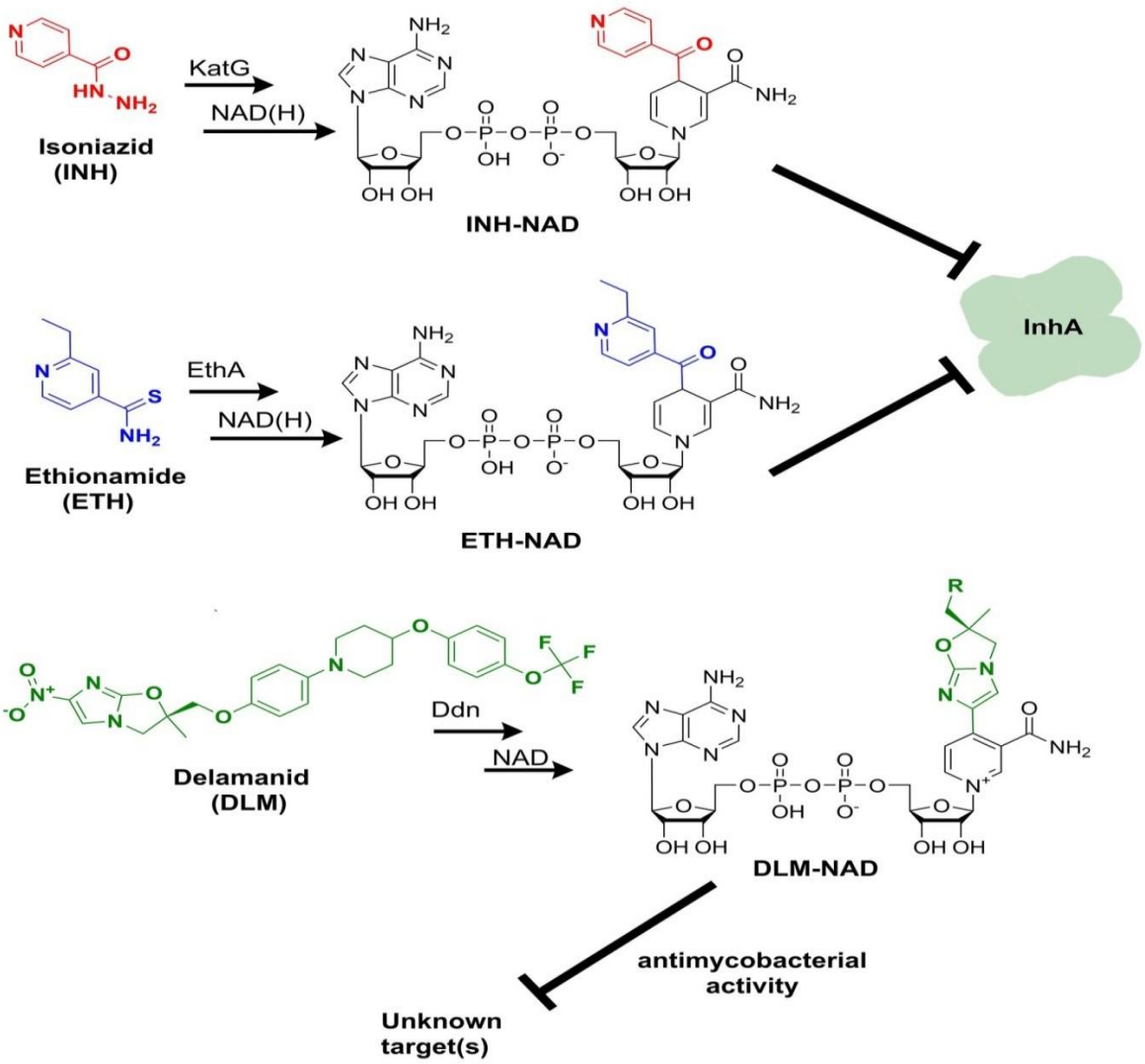


Figure no. 3 shows the formation of nicotinamide adenine dinucleotide (NAD) chemical adducts by tuberculosis (TB) drugs.[45]Prothionamide, which is a close chemical analog of ethionamide, undergoes the same transformation.[45]Pretomanid, belonging to the same class of nitroimidazoles as delamanid, may combine with NAD as well.[45]The structures of these drugs have been omitted for clarity.The formation of NAD adducts is significant because NAD biosynthesis targeting is acknowledged as a promising strategy to combat drug-susceptible, drug-resistant, and persistent tuberculosis.[46,47,48] The truncated isoniazid–nicotinamide adenine dinucleotide (oxidized) adduct is one of the most effective anti-TB drugs for prevention and treatment of TB.[48,49]

Conclusion:

Tuberculosis (TB) is a disease that is curable and preventable. Here are some key points from the search results:

TB is a global problem, with an estimated 10.6 million people falling ill with TB in 2021

Geographically, most TB cases in 2021 were in the WHO regions of South-East Asia (45%), Africa (23%), and the WesternPacific (18%)

In the United States, TB case counts and incidence rates have steadily decreased since 1992, but there was an increase in TB incidence in 2022 (2.5 cases per 100,000 persons)

Researchers found that the cells of humans and animals who have recovered from tuberculosis had prematurely aged up to 12 to 14 years, which is a possible side effect of the disease

The US government has been involved in global TB efforts, which include preventing, detecting, and treating TB, including drug-resistant TB, as well as research and development. The US TB activities reach more than 50 countries, including at least 20 of the 30 high burden countries where most new cases are occurring

The US government aims to reduce TB incidence rates by 35% relative to a 2019 baseline, a 52% reduction in TB mortality relative to a 2019 baseline, diagnosing and initiating treatment on 90% of incident (new cases of) TB and drug-resistant TB

During the COVID-19 pandemic, there were disruptions to essential TB services, which led to drops in the number of people newly diagnosed and officially reported

Reported TB incidence (cases per 100,000 persons) increased 9.4%, from 2.2 during 2020 to 2.4 during 2021 but was lower than incidence during 2019 (2.7)

Tuberculosis cases reported in the United States appear to be returning to levels seen before the COVID-19 pandemic, with an increase in TB incidence in 2022

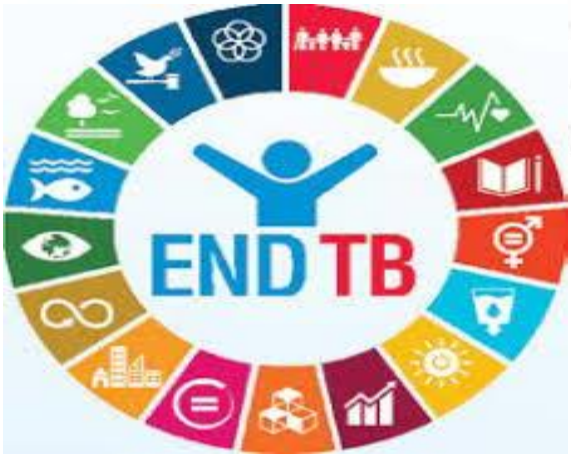
India has set an ambitious target of eliminating tuberculosis by 2025, five years ahead of the global target of 2030

The national strategic plan 2017-2025 sets the target of India reporting no more than 44 new TB cases or 65 total cases per lakh population by 2025

To achieve this goal, the government has taken several steps, including looking for cases actively among vulnerable and co-morbid populations, increasing testing capacity, and using the government's Ni-kshay portal that can help in real-time reporting of new TB cases

However, some experts believe that eliminating TB by 2025 is an impossible goal in India, especially with the world's highest TB as well as the MDR-TB burden

Nevertheless, India has demonstrated the power of its people coming together for a common cause during the COVID pandemic, and the WHO India's TB Technical Support Network has been providing technical assistance to the Ministry of Health and Family Welfare in planning, capacity building, supervision, monitoring, evaluation, and promoting research for policy development for National Tuberculosis Elimination Programme



Live free and live young! Live without TB and live forever."

Refference:

1. https://www.mayoclinic.org/diseases-conditions/tuberculosis/symptoms-causes/syc-20351250
2. https://www.cdc.gov/tb/topic/basics/default.htm
3. https://www.cdc.gov/tb/publications/factsheets/general/tb.htm
4. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
5. https://my.clevelandclinic.org/health/diseases/11301-tuberculosis
6. https://www.wikidoc.org/index.php/Tuberculosis_classification#:~:text=The%20classification%20ranges%20from%20Class,and%20symptoms%20of%20the%20disease.
7. https://www.nationaljewish.org/conditions/tuberculosis-tb/types
8. https://www.google.com/url?sa=i&url=https%3A%2F%2Fen.wikipedia.org%2Fwiki%2FTuberculosis&psig=AOvVaw3kBELmadpIHoKVj_BPFn4P&ust=1685093212276000&source=images&cd=vfe&ved=0CBAQjhxqFwoTCPjYqcWTkP8CFQAAAAAdAAAAABAD
9. https://www.google.com/url?sa=i&url=http%3A%2F%2Fwww.southsudanmedicaljournal.com%2Farchive%2Ffebruary-2013%2Ftuberculosis-2-pathophysiology-and-microbiology-of-pulmonary-tuberculosis.html&psig=AOvVaw3hnB3tJD8IhnSOg4MaycuM&ust=1685093414789000&source=images&cd=vfe&ved=2ahUKEwimg76klJD_AhUbktgFHQgHA5YQr4kDegUIARDgAQ
10. https://www.webmd.com/lung/understanding-tuberculosis-basics
11. https://www.cdc.gov/tb/topic/testing/default.htm
12. https://www.mayoclinic.org/diseases-conditions/tuberculosis/diagnosis-treatment/drc-20351256
13. https://www.webmd.com/lung/tests-tuberculosis
14. https://my.clevelandclinic.org/health/diagnostics/22751-tuberculosis-tb-test
15. https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm
16. https://www.everydayhealth.com/tuberculosis/guide/testing/
17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8082988/
18. https://pubmed.ncbi.nlm.nih.gov/31084923/
19. https://www.cdc.gov/tb/topic/treatment/tbdisease.htm
20. https://www.lung.org/lung-health-diseases/lung-disease-lookup/tuberculosis/treating-and-managing
21. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf
22. https://www.lung.org/lung-health-diseases/lung-disease-lookup/tuberculosis/treating-and-managing
23. https://www.webmd.com/lung/understanding-tuberculosis-treatment
24. https://www.everydayhealth.com/tuberculosis/guide/treatment/
25. https://pubmed.ncbi.nlm.nih.gov/32130813/
26. https://www.tballiance.org/portfolio/trial/5089
27. https://www.tballiance.org/news/tb-alliance-launches-nix-tb-clinical-trial-test-new-xdr-tb-treatment
28. https://www.jnj.com/pan-tb-collaboration-to-advance-investigational-tuberculosis-drug-regimens-to-phase-2-clinical-trials
29. https://www.evotec.com/en/investor-relations/news/p/evotec-receives-us-66-m-grant-for-drug-discovery-in-tuberculosis-6265
30. https://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0281591
31. https://www.nature.com/articles/s41579-022-00731-y
32. https://pubmed.ncbi.nlm.nih.gov/35478222/
33. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7790895/
34. https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf
35. https://www.fda.gov/media/166142/download
36. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5204003/

37. **https://www.nature.com/articles/s41579-022-00731-y**
38. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2674232/**
39. **https://academic.oup.com/jac/article/73/3/724/4735127**
40. **https://journals.plos.org/plosmedicine/article?id=10.1371%2Fjournal.pmed.1002773**
41. **https://www.cdc.gov/tb/education/corecurr/pdf/chapter6.pdf**
42. **https://www.cdc.gov/tb/webcourses/course/chapter6/6_tb_disease_treatment_6_adherence_strategies_fixed_dose_combination_drugs.html**
43. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916937/**
44. **https://erj.ersjournals.com/content/42/3/721**
45. **https://www.researchgate.net/figure/Formation-of-nicotinamide-adenine-dinucleotide-NAD-chemical-adducts-by-tuberculosis_fig1_348780056**
46. **https://doaj.org/article/418a45e0fb0242b49aacfee47ca2599a**
47. **https://www.readcube.com/articles/10.3389/fmicb.2020.634640**
48. **https://www.sciencedirect.com/science/article/pii/S2212553115001119**
49. T https://www.mayoclinic.org/diseases-conditions/tuberculosis/symptoms-causes/syc-20351250here are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months.