A REVIEW ON PHARMACOTHERAPY AND MANAGEMENT OF TUBERCULOSIS

A. BHARATH KUMAR, KUMAR B, RAMESH D, GOBINATH M

Department of Pharmacy Practice, Ratnam institute of Pharmacy, Nellore. 524002

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Abstract: Tuberculosis (TB) is a disease caused by bacteria called Mycobacterium tuberculosis. The bacteria usually attack the lungs, but they can also damage other parts of the body. TB spreads through the air when a person with TB of the lungs or throat coughs, sneezes, or talks. The tuberculosis causes weakness of the immune system. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. It is spread through the air when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. Most infections do not have symptoms, known as latent tuberculosis. About one in ten latent infections eventually progresses to active disease which, if left untreated, kills more than 50% of those so infected. TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within endosomes of alveolar macrophages. Macrophages identify the bacterium as "foreign" and attempt to eliminate it by phagocytosis. During this process, the entire bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called a phagosome. The bacteria reach the vital organs and reach the blood stream and Formation of granuloma lesion. General signs and symptoms include fever, chills, night sweats, loss of appetite, weight loss, and fatigue. Significant nail clubbing may also occur. Isoniazid, rifampicin, pyrazinamide, Ethambutol, macrolides, fluoroquinolones are used to treat the disease. Diagnosis of TB relies on radiology (commonly chest X-rays), as well as microscopic examination, nucleic acid amplification test, mantoux test, Quanti feron TB assay Blood gama interferon assay, sputum examination, Ziehl neelsen staining and microbiological culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) and/or blood tests.

Keywords: Phagosome, Phagocytosis, Macrophages, Replication, Ziehl neelsen.
INTRODUCTION

Mycobacterium Tuberculosis, the causative agent of Tuberculosis (TB), is one of the world’s most Devastating human pathogens. In 2004, 49 million People developed active TB and approximately 2 million people died from it, making this disease the second leading cause of infectious disease mortality worldwide. Central to the success of M. tuberculosis as a pathogen is its ability to persist within humans for long periods in a clinically latent state: roughly 95% of the people who become infected develop a latent infection. The magnitude of this disease reservoir is estimated to be approximately 2 billion people or roughly one-third of the global population. The problem is made worse by the interaction of M. tuberculosis and HIV and the two infections intersect in the world’s poorest countries, magnifying the death toll. As a result, TB is the leading cause of death in HIV-infected individuals. Infection with HIV increases the risk of TB and also increases the risk of reactivating latent disease to over 20 times that in HIV-negative people as immune suppression. M. Tuberculosis infection also worsens HIV: people living with HIV and active TB tend to have higher viral loads and die sooner than those without TB. Furthermore, anti-TB drugs, mainly rifampicin, have important interactions with antiretroviral drugs, while HIV treatment in people co infected with mycobacteria can lead to the potentially fatal immune reconstitution inflammatory syndrome. All of this makes TB control a priority issue around the globe. Worsens HIV: People living with HIV and active TB tend to have higher viral loads and die sooner than those without TB. Furthermore, anti-TB drugs, mainly rifampicin, have important interactions with antiretroviral drugs, while HIV treatment in people co infected with mycobacteria can lead to the potentially fatal immune reconstitution inflammatory syndrome all of this makes TB control apriority issue around the globe.\[1\]

Fig 1 Interaction of Tuberculosis with host.
TB (tuberculosis) is an communicable infectious disease that affects the alveoli of the lungs. Although it can affect almost any part of the body.

- About 150 years ago, it caused about one in eight of all deaths in the UK, but by the 1980s, with better housing and nutrition and effective treatments, it had become uncommon in the UK with 5086 cases in 1987.

- However, TB had not been wiped out completely. Over the last 20 years numbers in the UK have been rising slowly. About 9000 people now get TB each year – around one person in every 7000 of the population[2].

- TB is not easily caught – you have to be in fairly prolonged close contact with someone with TB (for example, living in the same household) – but everybody should be aware of the symptoms of the disease so they can seek treatment as soon as possible.

- TB is curable with a course of special antibiotics. In 1700, John Jacob Manget1 described a form of disseminated tuberculosis (TB) and likened the tiny tubercles evident on gross pathological examination to that of innumerable millet seeds in size and appearance. He coined the term miliary TB (derived from the Latin word *miliarius*, meaning related to millet seed) to denote this fatal form of disseminated TB. Miliary TB results from a massive lympho adenopathy.

- In the dissemination from *Mycobacterium tuberculosis* laden focus. Miliary TB still remains a perplexing disease that continues to elude the most erudite and experienced clinicians and is a diagnostic and therapeutic challenge. Mortality from this disease has remained high despite effective therapy being available.

**History**

- Tuberculosis has been present in humans since antiquity. The earliest unambiguous detection of *M. tuberculosis* involves evidence of the disease in the remains of bison dated to around 17,000 years ago However, whether tuberculosis originated in bovines, then was
transferred to humans, or whether it diverged from a common ancestor, is currently unclear.

- A comparison of the genes of *M. tuberculosis* complex (MTBC) in humans to MTBC in animals suggests humans did not acquire MTBC from animals during animal domestication.

- As was previously believed. Both strains of the tuberculosis bacteria share a common ancestor, which could have infected humans as early as the Neolithic Revolution. Skeletal remains show prehistoric humans (4000 BC) had TB.

- Researchers have found tubercular decay in the spines of Egyptian mummies dating from 3000–2400 BC. *Phthisis* is a Greek word for consumption, an old term for pulmonary tuberculosis; around 460 BC.

- Hippocrates identified phthisis as the most widespread disease of the times. It was said to involve fever and the coughing up of blood, which was almost always fatal. Genetic studies suggest TB was present in the Americas from about 100 AD.

- Before the Industrial Revolution, folklore often associated tuberculosis with vampires. When one member of a family died from it, the other infected members would lose their health slowly.

- People believed this was caused by the original person with TB draining the life from the other family members.

- Although the pulmonary form associated with tubercles was established as pathology by Dr Richard Morton in 1689 due to the variety of its symptoms, TB was not identified as a single disease until the 1820s, and was not named tuberculosis until 1839 by J. L. Schönlein.

- During 1838–1845, Dr. John Croghan, the owner of Mammoth Cave, brought a number of people with tuberculosis into the cave in the hope of curing the disease with the constant temperature and purity of the cave air; they died within a year. Hermann Brehmer opened the first TB sanatorium in 1859 in Görbersdorf.

- Egyptian mummies with severe skeletal deformities suggest that TB has existed since antiquity (Pott's disease).

- After the plague devastated Europe during the Middle Ages, TB (the “white plague”) began to take its heavy toll.

- TB affected famous kings and political figures (e.g., King Edward VI, King Louis VIII of France, John Calvin, Cardinal Richelieu, Napoleon II).
• TB, also called writer's or artist's disease, killed, among others, Nicolo Paganini, Robert Louis Stevenson, Franz Kafka, George Orwell, all five Brontë sisters, Thomas Mann, Albert Camus, and Igor Stravinsky.

• The Nobel Prize for Medicine for TB-related work was given to the following:
  
  • Dr. Robert Koch (fig. 1) for the discovery of TB bacillus (1905).
  
  • Dr. Gerhard Domagk for the discovery of the first antibacterial drug (Prontosil); also pioneered anti-TB drug development (1947).
  
  • Dr. Selman Waksman for the development of streptomycin as an anti-TB drug (1952)
  
  • In 1993, the World Health Organization (WHO) declared TB a global emergency, the only disease ever so designated. In 2003, WHO reported a continued TB Pandemic.

**Risk factors**

• HIV positive patients

• People consume drugs via parentral route

• Patients suffering from leukemia

• People who ever recently undergone organ transplanstation

• Patients on anti TNF alpha therapy

• Those suffering from silicosis

• Genetics

• Alcohol

• Smoking

• Diabetes milletus

**Epidemology**

• In 2007, the prevalence of TB per 100,000 people was highest in sub-Saharan Africa, and was also relatively high in Asia.

• Roughly one-third of the world's population has been infected with *M. tuberculosis* with new infections occurring in about 1% of the population each year .

• However, most infections with *M. tuberculosis* do not cause TB disease, and 90–95% of infections remain asymptomatic.
• In 2012, an estimated 8.6 million chronic cases were active. In 2010, 8.8 million new cases of TB were diagnosed, and 1.20-1.45 million deaths occurred, most of these occurring in developing countries. Of these 1.45 million deaths, about 0.35 million occur in those coinfected with HIV\(^3\).

![Annual number of new reported TB cases](image)

• Tuberculosis is the second-most common cause of death from infectious disease (after those due to HIV/AIDS).

• The absolute number of tuberculosis cases ("prevalence") has been decreasing since 2005, while new cases ("incidence") have decreased since 2002.

• China has achieved particularly dramatic progress, with about an 80% reduction in its TB mortality rate between 1990 and 2010. Tuberculosis is more common in developing countries.

• About 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the US population test positive.

• Hopes of totally controlling the disease have been dramatically dampened because of a number of factors, including the difficulty of developing an effective vaccine.

• The expensive and time-consuming diagnostic process, the necessity of many months of treatment, the increase in HIV-associated tuberculosis, and the emergence of drug-resistant cases in the 1980s.

• In 2007, the country with the highest estimated incidence rate of TB was Swaziland, with 1,200 cases per 100,000 people.

• India had the largest total incidence, with an estimated 2.0 million new cases. In developed countries, tuberculosis is less common and is found mainly in urban areas. Rates per 100,000 people in different areas of the world were: globally 178, Africa 332, the Americas...
In Canada and Australia, tuberculosis is many times more common among the aboriginal peoples, especially in remote areas. In the United States the Aborigines have a fivefold greater mortality from TB, and racial and ethnic minorities accounted for 84% of all reported TB cases.

The incidence of TB varies with age. In Africa, it primarily affects adolescents and young adults.

However, in countries where incidence rates have declined dramatically (such as the United States), TB is mainly a disease of older people and the immunocompromised (risk factors are listed above).

Worldwide, 22 "high-burden" states or countries together experience 80% of cases as well as 83% of deaths.

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Fig 4 Showing Asia is more Prone to TB
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**Prognosis**

Age-standardized death from tuberculosis per 100,000 inhabitants in 2004

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<tr>
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**Transmission**

- When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets 0.5 to 5.0 µm in diameter[^4].

- A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (the inhalation of fewer than 10 bacteria may cause an infection. People with prolonged, frequent, or close contact with people with TB are at particularly high risk of becoming infected, with an estimated 22% infection rate.

- A person with active but untreated tuberculosis may infect 10–15 (or more) other people per year. Transmission should only occur from people with active TB – those with latent infection are not thought to be contagious.

- The probability of transmission from one person to another depends upon several factors, including the number of infectious droplets expelled by the carrier, the effectiveness of ventilation, the duration of exposure, the virulence of the *M. tuberculosis* strain, the level of immunity in the uninfected person, and others.
Pathophysiology

- *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%. TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within endosomes of alveolar macrophages.

- Macrophages identify the bacterium as “foreign” and attempt to eliminate it by phagocytosis.

- During this process, the entire bacterium is enveloped by the macrophage and stored temporarily in a membrane-bound vesicle called a phagosome.

- The phagosome then combines with a lysosome to create a phagolysosome[4]. In the phagolysosome, the cell attempts to use reactive oxygen species and acid to kill the bacterium. However, *M. tuberculosis* has a thick, waxy mycolic acid capsule that protects it from these toxic substances.

- *M. tuberculosis* actually reproduces inside the macrophage and will eventually kill the immune cell.

- The primary site of infection in the lungs, known as the "Ghon focus", is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe.[1] Tuberculosis of the lungs may also occur via infection from the blood stream. This is known as a Simon focus and is typically found in the top of the lung.

- This hematogenous transmission can also spread infection to more distant sites, such as peripheral lymph nodes, the kidneys, the brain, and the bones.
All parts of the body can be affected by the disease, though for unknown reasons it rarely affects the heart, skeletal muscles, pancreas, or thyroid. Tuberculosis is classified as one of the granulomatous inflammatory diseases.

Macrophages, T lymphocytes, B lymphocytes, and fibroblasts aggregate to form granulomas, with lymphocytes surrounding the infected macrophages. When other macrophages attack the infected macrophage, they fuse together to form a giant multinucleated cell in the alveolar lumen.

The granuloma prevents dissemination of the mycobacteria and provides a local environment for interaction of cells of the immune system.

Bacteria inside the granuloma can become dormant, resulting in latent infection. Another feature of the granulomas is the development of abnormal cell death (necrosis) in the center of tubercles.
To the naked eye, this has the texture of soft, white cheese and is termed caseous necrosis\(^5\).

TB bacteria gain entry to the blood stream from an area of damaged tissue, they can spread throughout the body and set up many foci of infection.

**Flow chart of Pathophysiology of Tuberculosis**

1. **M. Tuberculosis**
   - Enter into the alveoli the lungs
   - Macrophages, T-lymphocytes, B-lymphocytes, Gama interferons
   - Reach the all the vital organs, systemic circulation
   - Complete destruction of immune system
   - Formation of granuloma lesion
   - Tuberculosis
Signs and symptoms

Clinical manifestations of TB in the lungs

- A bad cough that lasts 3 weeks or longer
- Weight loss
- Loss of appetite
- Coughing up blood or mucus
- Weakness or fatigue
- Fever
- Night sweats
- Hemoptyisis
- Hemolysis
- Chest pain
- Hoarseness of voice
- Different sites of infection
- Fatigue
- Nail clubbing

Causes of Tuberculosis

- Mycobacteria

![Mycobacterium Tuberculae](image)

**Fig 6** Micobacterium Tuberculae

- The main cause of TB is *Mycobacterium tuberculosis*, a small, aerobic, non motile bacillus.
- The high lipid content of this pathogen accounts for many of its unique clinical characteristics.
- It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than an hour.
- Mycobacteria have an outer membrane lipid bilayer. If a Gram stain is performed, MTB either stains very weakly "Gram-positive" or does not retain dye as a result of the high lipid and mycolic acid content of its cell wall.
- MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured in the laboratory[^6].
- Using histological stains on expectorated samples from phlegm (also called "sputum"), scientists can identify MTB under a regular (light) microscope.
- Since MTB retains certain stains even after being treated with acidic solution, it is classified as an acid-fast bacillus (AFB).
- The most common acid-fast staining techniques are the Ziehl–Neelsen stain, which dyes AFBs a bright red that stands out clearly against a blue background, and the auramine-rhodamine stain followed by fluorescence microscopy.
• The *M. tuberculosis* complex (MTBC) includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canetti*, and *M. microti*. *M. africanum* is not widespread, but it is a significant cause of tuberculosis in parts of Africa.

• *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has largely eliminated this as a public health problem in developed countries.

• *M. canetti* is rare and seems to be limited to the Horn of Africa, although a few cases have been seen in African emigrants.

• *M. microti* is also rare and is mostly seen in immuno deficient people, although the prevalence of this pathogen has possibly been significantly underestimated.

• Other known pathogenic mycobacteria include *M. leprae*, *M. avium*, and *M. kansasii*. The latter two species are classified as "nontuberculous mycobacteria" (NTM). NTM cause neither TB nor leprosy, but they do cause pulmonary diseases that resemble TB[^7^]

**Diagnosis of Tuberculosis**

![Fig 7 M. tuberculosis (stained red) in sputum](image)

**Active tuberculosis**

• Diagnosing active tuberculosis based merely on signs and symptoms is difficult, as is diagnosing the disease in those who are immuno suppressed.

• A diagnosis of TB should, however, be considered in those with signs of lung disease or constitutional symptoms lasting longer than two weeks.

• A chest X-ray and multiple sputum cultures for acid-fast bacilli are typically part of the initial evaluation.
Interferon-γ release assays and tuberculin skin tests are of little use in the developing world.

A definitive diagnosis of TB is made by identifying *M. tuberculosis* in a clinical sample (e.g. sputum, pus, or a tissue biopsy).

Nucleic acid amplification tests and adenosine deaminase testing may allow rapid diagnosis of TB.

These tests, however, are not routinely recommended, as they rarely alter how a person is treated. Blood tests to detect antibodies are not specific or sensitive, so they are not recommended.\(^8\)

**Latent tuberculosis**

![Mantoux tuberculin skin test](image)

**Fig 8 Mantoux tuberculin skin test**

**Latent Tuberculosis**

- The Mantoux tuberculin skin test is often used to screen people at high risk for TB.
- Those who have been previously immunized may have a false-positive test result.
- The test may be falsely negative in those with sarcoidosis, Hodgkin’s lymphoma, malnutrition, or most notably, in those who truly do have active tuberculosis.
- Interferon gamma release assays (IGRAs), on a blood sample, are recommended in those who are positive to the Mantoux test.\(^9\)
- These are not affected by immunization or most environmental mycobacteria, so they generate fewer false-positive results. However, they are affected by *M. szulgai*, *M. marinum*, and *M. kansasii*.
- IGRAs may increase sensitivity when used in addition to the skin test, but may be less sensitive than the skin test when used alone.

**Diagnosis of Tuberculosis Tests**

- Radiology (commonly chest X-rays)
- ECG
CT Scan (computerized tomography)
- MRI Scan (Magnetic Resonance image)
- Microscopic examination of Sputum
- Nucleic acid amplification test
- Mantoux test
- Quanti feronTB assay
- Blood gamma interferon assay
- Sputum examination
- Ziehl neelsen staining
- Microbiological culture of body fluids
- Tuberculin skin test (TST)
- Blood tests.

**Lab investigations of Tuberculosis**

- RBC
- WBC
- PLATELETS
- RETICULOCYTE COUNT
- ESR COUNT
- MCV
- PCV
- MCHC
- THYROID FUNCTION TEST
- KIDNEY FUNCTION TEST
- LIVER FUNCTION TEST
- PULMONARY FUNCTION TEST
Pharmacotherapy of Tuberculosis

First line drugs

- Isoniazid
- Pyrazinamide
- Ethambutol
- Rifampicin
- Streptomycin

Second line drugs

- Bacteriostatic drugs
  - Cycloserine
  - Ethionamide
  - Para amino Salicylic Acid

Bactericidal Drugs

- Amikacin
- Kanamycin
- Capreomycin

Newer Drugs for TB

- Ciprofloxacin
- Ofloxacin
- Norfloxacin
- Gatifloxacin
- Sparfloxacin
- Pefloxacin
- Tarofloxacin
- Levofloxacin
- Mevofloxacin
- Lomefloxacin
Moxifloxacin

Other Drugs for TB

Azithromycin

Clarithromycin

Rifabutin, Thiacezone

Management of latent TB

Treatment of latent TB infection

- Treatment of latent TB infection should be considered for people in the following groups, once active TB has been excluded by chest X-ray and examination.

People identified through screening who are:

- 35 years or younger (because of increasing risk of hepatotoxicity with age)[12]
- any age with HIV any age and a healthcare worker and are either:
  - Mantoux positive (6 mm or greater), and without prior BCG vaccination, or strongly Mantoux positive (15 mm or greater), interferon-gamma positive, and with prior BCG vaccination.

Children aged 1–15 years identified through opportunistic screening to be

- Strongly Mantoux positive (15 mm or greater), and interferon-gamma positive (if this test has been performed), and without prior BCG vaccination.
- People with evidence of TB scars on chest X-ray, and without a history of adequate Treatment.

People with HIV who are in close contact with people with sputum-smear positive

Respiratory TB should have active disease excluded and then be given treatment for latent TB infection.

Tuberculosis: NICE clinical guideline

Treatment for latent TB infection should not be started in close contacts of people with sputum-smear-positive MDR TB who are strongly Mantoux positive (15 mm or greater), as no regimen is of proven benefit, and only a small proportion of people infected will develop the disease. Long-term monitoring should be undertaken for active disease [10].

People who have agreed to receive treatment for latent TB infection should be started on one of the following regimens
• either 6 months of isoniazid (6H) or 3 months of rifampicin and isoniazid (3RH) for people aged 16–35 not known to have HIV

• either 6 months of isoniazid (6H) or 3 months of rifampicin and isoniazid (3RH)

• people older than 35 in whom treatment for latent TB infection is recommended and who are not known to have HIV

• 6 months of isoniazid (6H) for people of any age who have HIV

• 6 months of rifampicin (6R) for contacts, aged 35 or younger, of people with Isoniazid-resistant TB.

• People eligible for treatment of latent TB infection, but who decline to take this treatment, should be given 'Inform and advise' information about TB and have chest X-rays 3 and 12 months later.

• Neonates who have been in close contact with people with sputum-smear positive TB who have not received at least 2 weeks' anti-tuberculosis drug treatment should be treated as follows

  • The baby should be started on isoniazid (according to the current 'British national formulary for children') for 3 months and then a Mantoux test performed after 3 months' treatment.

  • If the Mantoux test is positive (6 mm or greater) the baby should be assessed for Active TB this assessment is negative and then isoniazid should be continued for a total of 6 months.

  • If the Mantoux test is negative (less than 6 mm), it should be repeated together with an interferon-gamma test. If both are negative then isoniazid should be stopped and BCG vaccination performed.

  • Children older than 4 weeks but younger than 2 years who have not had BCG Vaccination and are in close contact with people with sputum-smear-positive TB should be treated as follows

  • The child should be started on isoniazid (according to the current 'British national formulary for children') and a Mantoux test performed.
• If the Mantoux test is positive (6 mm or greater), the child should be assessed for active TB. If active TB is ruled out, full treatment for latent TB infection should be given.

• If the Mantoux test is negative (less than 6 mm), then isoniazid should be continued for 6 weeks, and then a repeat Mantoux test together with an interferon-gamma test should be carried out.

• If the repeat tests are negative, isoniazid may be stopped and BCG vaccination performed.

• Either repeat test is positive (6 mm or greater), then the child should be assessed for active TB and consider treating for latent TB.

**BCG-vaccinated children older than 4 weeks but younger than 2 years, in close contact with people with sputum-smear-positive respiratory TB, should be treated as follows**

• The child should have a Mantoux test. If this is positive (15 mm or greater), the child should be assessed for active TB. If active TB is excluded, then treatment for latent TB infection should be given.

• If the result of the test is as expected for prior BCG (less than 15 mm), it should be repeated after 6 weeks together with an interferon-gamma test.

• If the repeat Mantoux test is also less than 15 mm, and the interferon-gamma test is also negative, no further action is needed.

• If the repeat Mantoux test becomes more strongly positive (15 mm or greater and an increase of 5 mm or more over the previous test), or the interferon-gamma test is positive, the child should be assessed for active TB.

• If active TB is excluded, treatment for latent TB infection should be given.

**For children requiring treatment for latent TB infection, a regimen of either**

• 3 months of rifampicin and isoniazid (3RH) or 6 months of isoniazid (6H) should be planned and started, unless the child is known to be HIV positive, when 6H should be given.

**Healthcare workers should be aware that certain groups of people with latent TB are at increased risk of going on to develop active TB, including People who**

• Are HIV Positive

• Are Injecting Drug Users

• Have Had Solid Organ Transplantation

• Have A Haematological Malignancy
• Have Had A Jejunoileal Bypass
• Have Chronic Renal Failure Or Receive Haemodialysis
• Have Had A Gastrectomy
• Are Receiving Anti-Tumour Necrosis Factor-Alpha Treatment
• Have Silicosis.
• Patients in These Groups Should Be Advised of the Risks and Symptoms of TB, On The Basis of An Individual Risk Assessment, Usually In A Standard Letter of The Type Referred To As 'Inform And Advise' Information.

**BCG vaccination**

• When BCG is being recommended, the benefits and risks of vaccination and remaining unvaccinated should be discussed with the person (or, if a child, with the parents), so that they can make an informed decision. This discussion should be tailored to the person, be in an appropriate language, and take into account cultural sensitivities and stigma
• People identified for BCG vaccination through occupational health, contact tracing or new entrant screening who are also considered to be at increased.
• Risk of being HIV positive, should be offered HIV testing before BCG vaccination

**BCG vaccination for Neonates**

• Neonatal BCG vaccination for any baby at increased risk of TB should be
• discussed with the parents or legal guardian
• Primary care organisations with a high incidence of TB[15] should consider
• Vaccinating all neonates soon after birth.
• In areas with a low incidence of TB15, primary care organisations should offer

**BCG vaccination to selected Neonates who**

• Were born in an area with a high incidence of TB15, or have one or more parents or grandparents who were born in a high-incidence country, or have a family history of TB in the past 5 years.

**BCG vaccination for infants and older children**

Routine BCG vaccination is not recommended for children aged 10–14.
• Healthcare professionals should opportunistically identify unvaccinated children
older than 4 weeks and younger than 16 years at increased risk of TB who would have qualified for neonatal BCG and provide Mantoux testing and BCG if Mantoux negative\cite{11}.

This opportunistic vaccination should be in line with the Chief Medical Officer's

Advice on vaccinating this age group following the end of the school-based programme

Mantoux testing should not be done routinely before BCG vaccination in children younger than 6 years unless they have a history of residence or prolonged stay (more than 1 month) in a country with a high incidence of TB.

**BCG vaccination for new entrants from high-incidence areas**

*BCG vaccination should be offered to Mantoux-negative new entrants who*

- Are from high-incidence countries, and are previously unvaccinated (that is, without adequate documentation or a characteristic scar), and are aged:
  - Younger than 16 years, or 16 to 35 years \cite{19} from sub-Saharan Africa or a country with a TB incidence of 500 per 100,000.

**BCG vaccination for healthcare workers**

*BCG vaccination should be offered to healthcare workers, irrespective of age\cite{20}, who*

- Are previously unvaccinated (that is, without adequate documentation or a characteristic scar), and will have contact with patients or clinical materials are Mantoux (or interferon-gamma) negative.

**BCG vaccination for contacts of people with active TB**

*BCG vaccination should be offered to Mantoux-negative contacts of people with respiratory TB for details of contact tracing) if they are previously unvaccinated (that is, without adequate documentation or characteristic scar) and are*

- Aged 35 or younger
- Aged 36 and older and a healthcare or laboratory worker who has contact with patients or clinical materials.

**BCG vaccination for other groups**

*BCG vaccination should be offered to previously unvaccinated, Mantoux negative*

**People aged 35 or younger in the following groups at increased risk of exposure to TB, in accordance with the Green Book**

- Veterinary and other staff such as abattoir workers who handle animal species
- Known to be susceptible to TB, such as simians prison staff working directly with prisoners staff of care homes for elderly people staff of hostels for homeless people and facilities
accommodating refugees and asylum seekers people going to live or work with local people for more than 1 month in a high incidence country\[12\].

**Following diagnosis of TB in a hospital inpatient, a risk assessment should be undertaken. This should take into account**

- The degree of infectivity of the index case the length of time before the infectious patient was isolated whether other patients are unusually susceptible to infection the proximity of contact.
- Contact tracing and testing should be carried out only for patients for whom the risk is regarded as significant.

**Patients should be regarded as at risk of infection if they spent more than 8**

- Hours in the same bay as an inpatient with sputum-smear-positive TB who had a cough. The risk should be documented in the contact's clinical notes, for the attention of the contact's consultant. The contact should be given 'Inform and advice' information and their GP should be informed.

**If patients were exposed to a patient with sputum-smear-positive TB for long**

- Enough To Be Equivalent To Household Contacts Determined By Risk Assessment), Or An Exposed Patient Is Known To Be Particularly Susceptible To Infection, They Should Be Managed As Equivalent To Household.
- If An Inpatient With Sputum-Smear-Positive Tb Is Found To Have Mdr Tblf Exposed Patients Are HIV Positive.\[12\]

**Interdepartmental Working Group on Tuberculosis guidelines**

In cases of doubt when planning contact tracing after diagnosing sputum smear-

- Positive TB in an inpatient, further advice should be sought from the
- Regional or national Health Protection Agency or people experienced in the field Screening new entrants.

**Healthcare professionals, including primary care staff, responsible for screening new entrants should maintain a coordinated programme to**

- Detect Active TB and start treatment
- Detect Latent TB And Start Treatment
- Provide BCG vaccination to those in high-risk groups who are not infected and who are previously unvaccinated
• Provide Relevant Information To All New Entrants. New Entrant Screening For Tb Should Be Incorporated Within Larger Health Screening

Programmes For New Entrants, Linked To Local Services. Assessment For, And Management Of Tb In New Entrants Should Consist Of The Following

• Risk Assessment For HIV, Including HIV Prevalence Rates In The Country Of Origin,
• Which Is Then Taken Into Account For Mantoux Testing And Bcg Vaccination.
• Assessment For Active Tb If Interferon-Gamma Test Is Positive; Which Would Include A Chest X-Ray.
• Treatment For Latent Tb Infection For People Aged 35 Years Or Younger In Whom Active Tb Has Been Excluded, With A Positive Mantoux Test Inconsistent With Their Bcg History, And A Positive Interferon-Gamma Test.
• Consideration Of Bcg For Unvaccinated People Who Are Mantoux Negative
• 'Inform And Advise' Information For People Who Do Not Have Active Tb And Are Not Being Offered Bcg Or Treatment For Latent Tb Infection.

New Entrants Should Be Identified For Tb Screening From The Following Information

• Port Of Arrival Reports
• New Registrations With Primary Care
• Entry To Education (Including Universities)
• Links With Statutory And Voluntary Groups Working With New Entrants. Any Healthcare Professional Working With New Entrants Should Encourage Them

Street Homeless

• Active Case Finding Should Be Carried Out Among Street Homeless People
• (Including Those Using Direct Access Hostels For The Homeless) By Chest X-Ray
• Screening On An Opportunistic And/OR Symptomatic Basis. Simple Incentives For Attending, Such As Hot Drinks And Snacks, Should Be Considered\(^{[13]}\).
• 1.8.8.2 Healthcare Professionals Working With People With Tb Should Reinforce And Update Education About Tb, And Referral Pathways, To Primary Care Colleagues,
• Social Workers And Voluntary Workers Who Work With Homeless People.
Preventing Infection In Specific Settings

- **Healthcare Environments: New Nhs Employees**
- Employees New To the Nhs Who Will Be Working With Patients.
- Specimens Should Not Start Work Until They Have Completed A Tb Screen.
- Health Check, Or Documentary Evidence Is Provided Of Such Screening Having
- Taken Place Within The Preceding 12 Months.

Employees New To the Nhs Who Will Not Have Contact With Patients Or Clinical

- Specimens Should Not Start Work If They Have Signs Or Symptoms Of Tb.

**Health Checks For Employees New To the Nhs Who Will Have Contact With Patients Or Clinical Materials Should Include**

- Assessment Of Personal Or Family History Of Tb
- Symptom And Signs Enquiry, Possibly By Questionnaire
- Documentary Evidence Of Tb Skin Testing (Or Interferon-Gamma Testing) And/Or Bcg
- Scar Check By An Occupational Health Professional, Not Relying On The Applicant's

**Personal Assessment**

- Mantoux Result Within The Last 5 Years, If Latent Tb. Employees Who Will Be Working With Patients Or Clinical Specimens And Who Are Mantoux Negative (Less Than 6 Mm) Should Have An Individual Risk Assessment.
- For HIV Infection Before Bcg Vaccination Is Given.
- Employees New To The Nhs Should Be Offered Bcg Vaccination, Whatever Their
- Age, If They Will Have Contact With Patients And/or Clinical Specimens, Are Mantoux Negative (Less Than 6 Mm) and Have Not Been Previously Vaccinated.

**Employees of Any Age Who Are New To the Nhs And Are From Countries Of High Tb Incidence, Or Who Have Had Contact With Patients In Settings With A High Tb**

- Prevalence Should Have An Interferon-Gamma Test. If Negative, Offer Bcg
- Vaccination As With A Negative Mantoux Result And If Positive, The Person Should Be Referred For Clinical Assessment.
- For Diagnosis and Possible Treatment of Latent Infection Or Active Disease.

If A New Employee From The Uk Or Other Low-Incidence Setting, Without Prior
Bcg Vaccination, Has A Positive Mantoux And A Positive Interferon-Gamma

Test, They Should Have A Medical Assessment And A Chest X-Ray. They Should

Be Referred To A Tb Clinic For Consideration Of Tb Treatment If The Chest X-Ray Is

Abnormal, Or For Consideration Of Treatment Of Latent Tb Infection If The Chest Xray Is Normal.

If A Prospective Or Current Healthcare Worker Who Is Mantoux Negative (Less

Than 6 Mm) Declines Bcg Vaccination, The Risks Should Be Explained.

Oral Explanation Supplemented By Written Advice. He Or She Should Not Work Where
There Is A Risk Of Exposure To Tb. The Employer Will Need To Consider Each Case
Individually, Taking Account Of Employment And Health And Safety Obligations. Clinical
Students, Agency And Locum Staff And Contract Ancillary Workers Who Have Contact With
Patients Or Clinical Materials Should Be Screened For Tb To The Same Standard As New
Employees In Healthcare Environments, According To The Recommendations Set Out Above.
Documentary Evidence Of Screening To This Standard Should Be Sought From Locum
Agencies And Contractors Who Carry Out Their Own Screening. Nhs Trusts Arranging Care
For Nhs Patients In Non-Nhs Settings Should Ensure That Healthcare Workers Who Have
Contact With Patients Or Clinical Materials In These Settings Have Been Screened For Tb To
The Same Standard As New

Employees In Healthcare Environments.

Healthcare Environments: Occupational Health

These Recommendations Set The Standard For Nhs Organisations And Therefore Should
Apply In Any Setting In England And Wales Where Nhs Patients Are Treated.

Reminders Of The Symptoms Of Tb, And The Need For Prompt Reporting Of Such

Symptoms, Should Be Included With Annual Reminders About Occupational

Health For Staff Who:

Have Worked In A High-Risk Clinical Setting For 4 Weeks Or Longer.

One-Off Reminders Should Be Given After A Tb Incident On A Ward.

If No Documentary Evidence Of Prior Screening Is Available, Staff In Contact With

Patients Or Clinical Material Who Are Transferring Jobs Within The Nhs Should Be
• Screened As For New Employees The Risk Of Tb For A New Healthcare Worker Who Knows He Or She Is HIV Positive At The Time Of Recruitment Should Be Assessed As Part Of The Occupational Health Checks.

The Employer, Through The Occupational Health Department, Should Be Aware Of The Settings With Increased Risk of Exposure To Tb, And That These Pose

• Increased Risks To HIV-Positive Healthcare Workers.

Healthcare Workers Who Are Found To Be HIV Positive during Employment Should Have Medical and Occupational Assessments of Tb Risk, and May Need

• To Modify Their Work To Reduce Exposure.

This Guideline Sets Out Best Practice Guidance For The Diagnosis, Treatment, Prevention And Control Of Tb In The NHS In England And Wales. It Covers Latent Tb Infection and Active Tb Of The following Sites:

• Respiratory (Lung, Bronchus, Pleura, Thoracic Lymph Nodes)
• Meningeal
• Pericardial
• Bone And Joint
• Peripheral Lymph Nodes
• Genitourinary
• Disseminated (Including Miliary)
• The Guideline Does Not Extend To Comorbidities Such As HIV, Drug Dependencies, Diabetes,
• Hepatic Disease, Renal Disease, Or Mental Illness, Nor Does It Give Guidance On Highly Specialised
• And Individualised Activities Such As Treatment Of Multidrug-Resistant (Mdr) Tb. It Does Not Include Special Guidance For Patients Who Are Pregnant, Planning Pregnancy Or Unconscious.
• For Older People In Long-Term Care. It Considers Only The M Tuberculosis Complex Of Bacteria, And Therefore Does Not Provide Guidance On Other Mycobacterial Infections.
• This Update Looked At The Diagnosis Of Latent Tb Using M Tuberculosis-Specific Antigens (Esat-6,Cfp-10, And Tb7.7) Interferon Gamma Release Assays (Igts).
It Covers The Following Population Groups:

- Adults And Children At Increased Risk Of Infection By *M Tuberculosis* Complex (*M Tuberculosis, M Africanum, M Bovis*), Specifically If They:
  - Have Arrived or Returned From High-Prevalence Countries Within The Past 5 Years Tuberculosis.
  - Were Born In High Prevalence Countries live With People Diagnosed with Active T bhave Close Contact With People Diagnosed With Active Tb,
  - For Example At School Or workare Homeless And/Or Problem Drug Users are, Or Have A Recently Been, A Prisoner

**Approach to the Patient with Latent Tuberculosis Infection (LTBI)**

- **Clinical evaluation:** cough, chest pain, hemoptysis, fever, chills, night sweats, anorexia, weight loss, fatigue [14]
- **Past medical history**-TB treatment or exposure
- **Social history:** demographic factors increasing the risk of acquiring TB or resistant strains
- **HIV status**; voluntary testing and counseling should be offered routinely Chest radiographs (poster anterior and lateral)
- **Sputum** (three specimens) for patients with symptoms (even if chest radiograph is normal) or patients with radiologic abnormalities (images compatible with old fibrotic changes)
- **Perform baseline laboratory testing for HIV-infected patients**, pregnant and postpartum women, those with liver disease, those who use alcohol regularly
- **Those without clinical, radiologic, or microbiologic evidence of active disease:**
  - **LTBI** therapy with abnormal liver function tests at base line require continuous monitoring.

**DOTS REGIMEN THERAPY FOR TUBERCULOSIS**

<table>
<thead>
<tr>
<th>Category of Patients</th>
<th>Phases with drug</th>
<th>Regimen</th>
<th>Total Duration (months)</th>
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</thead>
<tbody>
<tr>
<td>1. seriously ill, sputum positive, extrapulmonary bacilli</td>
<td>2 HRZE, 4HR</td>
<td>2(HRZE) sub 4(HR) sub 3</td>
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II. Sputum positive failure, relapse, default

<table>
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<th>Treatment Options</th>
<th>Duration</th>
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<td>2(HRZES) 5(HRE)</td>
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</tr>
<tr>
<td>1HRZE</td>
<td></td>
</tr>
<tr>
<td>2(HRZES) 5(HRE)</td>
<td>8</td>
</tr>
<tr>
<td>1(HRZE)</td>
<td></td>
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</tbody>
</table>

III. New sputum positive, extra pulmonary TB

<table>
<thead>
<tr>
<th>Treatment Options</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 HRZ, 4HR</td>
<td>6</td>
</tr>
<tr>
<td>2(HRZE) 4(HR)</td>
<td>6</td>
</tr>
</tbody>
</table>

IV. Chronic, MDR TB

- Individual reimen

**Non Pharmacological Therapy of Tuberculosis:**

- Vaccination
- Avoid smoking
- Prevent Exposure to the pollutants
- Prevent exposure to the Smoke, fumes, Toxic gases.

**Drug interactions of TB Drugs**

- Rifampicin with Anti coagulants, barbiturates
- Isoniazid with warfarin, diazepam
- Streptomycin with cephalosporins
- Capreomycin with neuromuscular blocking agents
- Cycloserine with alcohol

**CONCLUSION**

Tuberculosis can be considered as a social infectious communicable disease. It Disturb the families Emotionally, Socially, Economically, Educationally. About 20% of TB cases World Wide Treated Successfully. Implementation of DOTS therapy by WHO Cost Effective Manner In the hospitals. About Globally 70% of The Cases detected and 80% of the cases Cured Would Reduce the Mortality. Identification and Treating the Early, Active LTBI (Latent Tuberculosis Bacilli Infection) Risk Patients prevent The Progression of the Disease. Identification And developing The Newer Drugs, Diagnostic tools, Vaccines, Therapeutic Agents will act Against the TB. Establishing TB Control services IN the World at Primary Health care Level. It will Guide Reduce the Developing Incidence of The Disease. [15]
REFERENCES


