ZOONOTIC TUBERCULOSIS: A COMPREHENSIVE OVERVIEW

Abstract

Zoonotic tuberculosis, caused primarily by *Mycobacterium bovis* and occasionally *Mycobacterium caprae* and other non-tuberculous mycobacteria, is an intricate and multifaceted public health concern. The disease primarily affects livestock such as cattle, goats, and buffalo, which serve as reservoirs for the bacterium, leading to the potential for human infection through direct or indirect contact with infected animals or consumption of contaminated animal products. This chapter provides a comprehensive examination of zoonotic tuberculosis, covering its historical context, epidemiology, transmission dynamics, clinical manifestations, diagnosis, treatment, prevention, and control strategies.

Keywords: Zoonotic tuberculosis, *Mycobacterium bovis*

Author

Dipal Bhatt
Smt. L. P. Patel Institute of Medical Laboratory Technology
Bhaikaka University,
Karamsad, Gujarat, India
dipalm@charutarhealth.org

I. INTRODUCTION

Zoonotic tuberculosis, also known as *Mycobacterium bovis* tuberculosis, is a form of tuberculosis (TB) that can infect both humans and animals. It is caused by the bacterium *Mycobacterium bovis* and is transmitted primarily through the consumption of contaminated animal products, close contact with infected animals, or through environmental exposure to contaminated materials. Here is a historical perspective on zoonotic tuberculosis:

Historical Perspective

1. **Ancient Times:** Tuberculosis is one of the oldest diseases known to humanity. Evidence of TB has been found in ancient Egyptian mummies dating back to 2400 BC, indicating its long history in human populations. While the zoonotic transmission of TB was not well understood in ancient times, it is believed that people who lived closely with animals, such as cattle, might have been at risk of contracting bovine tuberculosis[1].

2. **Development of Veterinary Medicine (19th Century):** The 19th century saw significant developments in veterinary medicine and the recognition of *Mycobacterium bovis* as the cause of tuberculosis in cattle. The link between bovine TB and human TB was established during this period, although the zoonotic transmission route was not fully understood[2].

3. **Tuberculosis Control Efforts (20th Century):** In the early 20th century, efforts to control tuberculosis in both humans and animals intensified. This included the development of the tuberculin skin test to diagnose TB in cattle and the pasteurization of milk to reduce the risk of transmission through dairy products. Public health campaigns to control tuberculosis in humans also led to improvements in overall hygiene and sanitation, which indirectly reduced the risk of zoonotic transmission[3].

4. **Zoonotic Tuberculosis in Modern Times:** In many developed countries, the incidence of zoonotic tuberculosis has significantly decreased due to rigorous testing and culling of infected cattle herds and the pasteurization of milk. However, zoonotic TB remains a concern in some parts of the world, especially in regions with inadequate control measures, limited access to healthcare, and consumption of raw or unpasteurized dairy products[4]. The World Health Organization (WHO) and other international agencies continue to work on controlling zoonotic tuberculosis through vaccination programs, improved diagnostics, and public health education[5].

5. **Emerging Challenges:** Zoonotic tuberculosis continues to be a concern, particularly in regions where the disease is endemic in livestock populations. The emergence of drug-resistant strains of *Mycobacterium bovis* poses a new challenge to TB control efforts in both humans and animals. One Health approaches, which emphasize the interconnectedness of human, animal, and environmental health, are gaining prominence in addressing zoonotic diseases like bovine TB[6].

II. EPIDEMIOLOGY OF ZOONOTIC TUBERCULOSIS

1. **Global Distribution:** Zoonotic tuberculosis, primarily caused by Mycobacterium bovis, has a global distribution, but the prevalence and impact of the disease can vary significantly by region. Here's an overview of the global distribution of zoonotic tuberculosis:

   - **Africa:** Zoonotic tuberculosis is relatively common in many African countries, particularly those with a high prevalence of bovine tuberculosis in livestock. In these regions, the disease often affects both humans and cattle. The consumption of unpasteurized milk and close contact with infected animals are common risk factors[7].

   - **Asia:** Several Asian countries, including India, China, and some Southeast Asian nations, have reported cases of zoonotic tuberculosis. In these regions, cultural practices such as consumption of raw milk and close proximity to livestock contribute to the transmission of the disease.

   - **Europe:** Zoonotic tuberculosis is also present in parts of Europe, with some countries, like Spain and the United Kingdom, experiencing sporadic cases. Wildlife reservoirs, such as badgers and deer, have been implicated in transmission to cattle and humans in some European regions[8].

   - **North America:** In North America, zoonotic tuberculosis is less common than in some other regions, but it still exists. In the United States, for example, sporadic cases of *M.bovis* infection in humans have been reported, often linked to contact with infected wildlife like deer[9].

   - **South America:** Several South American countries, such as Argentina and Brazil, have reported cases of zoonotic tuberculosis. In these regions, cattle farming is prevalent, and consumption of unpasteurized milk or dairy products is a known risk factor.
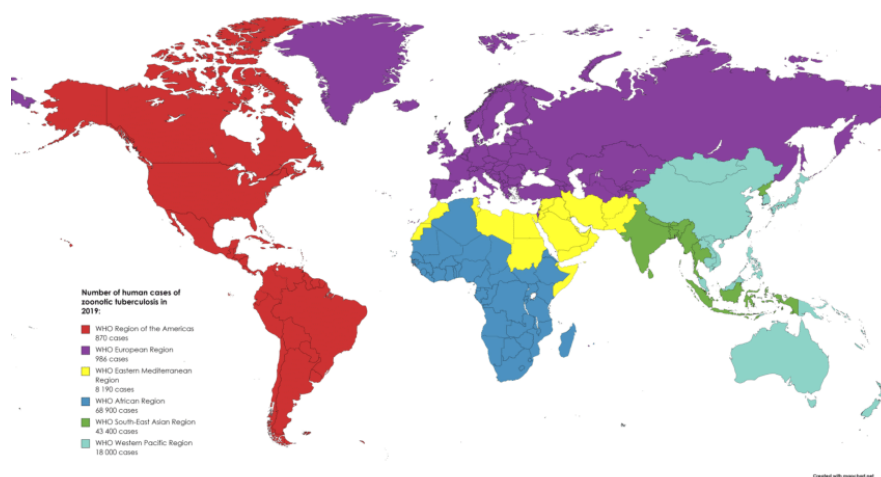

Figure 1: Global Distribution of Zoonotic Tuberculosis[10]

- **Oceania:** Zoonotic tuberculosis has been reported in countries like Australia and New Zealand, where it primarily affects livestock. Efforts to control the disease in these regions have included vaccination of wildlife reservoirs like possums.

- **Middle East:** Some Middle Eastern countries have reported zoonotic tuberculosis cases, with a focus on control measures in livestock populations and raising awareness about safe milk consumption.

2. **Host Reservoirs:** Zoonotic tuberculosis, primarily caused by Mycobacterium bovis, involves various host reservoirs, both domestic and wild animals, which can serve as a source of infection for humans. Here are some of the key host reservoirs of zoonotic tuberculosis:

- **Cattle:** Domestic cattle are the primary reservoirs for *M.bovis* and are a significant source of zoonotic tuberculosis. Infected cattle can transmit the bacterium to humans through the consumption of unpasteurized dairy products or by close contact with infected animals, particularly during the handling and milking processes.

- **Goats and Sheep:** While less common than in cattle, *M.bovis* infections can also occur in domestic goats and sheep. Humans can contract the disease from infected goats and sheep through direct contact, consumption of contaminated milk, or inhalation of aerosols containing the bacterium.

- **Wildlife:** Wild animals, particularly those in close proximity to livestock, can act as reservoirs for *M.bovis* and contribute to zoonotic transmission. In some regions, wildlife reservoirs have played a significant role in maintaining the bacterium's presence. Common wildlife reservoirs include:

  ➢ **Badgers:** In parts of Europe, badgers are known to harbor *M.bovis* and can transmit the bacterium to cattle, other wildlife, and occasionally humans.
  ➢ **Deer:** Various deer species, such as white-tailed deer and red deer, can carry *M.bovis*. This can lead to transmission to other deer and occasionally to livestock and humans.
  ➢ **Possums:** In New Zealand, the common brushtail possum is a significant wildlife reservoir of *M.bovis*, leading to transmission to livestock.

- **Other Wildlife:** Besides badgers, deer, and possums, other wildlife species like wild boars, raccoons, and buffalo have been implicated as hosts for *M.bovis* in different regions.

- **Pets and Companion Animals:** In rare cases, domestic pets such as cats and dogs can become infected with *M.bovis*, posing a potential risk to their human owners. This can occur through contact with infected wildlife or consumption of contaminated animal tissues.

- **Other Livestock:** Zoonotic tuberculosis can also be transmitted from infected cattle to other livestock species kept in close proximity, such as horses, pigs, and poultry.

- **Humans:** While humans can contract zoonotic tuberculosis from infected animals, they can also serve as reservoirs, particularly in cases of human-to-human transmission of *M.bovis*. This is more common in healthcare settings or among close contacts of an infected individual[7-9,11].

3. **Transmission Pathways:** Zoonotic tuberculosis, caused primarily by Mycobacterium bovis, can be transmitted to humans through various pathways. Understanding these transmission routes is crucial for preventing and controlling the spread of the disease. Here are the primary transmission pathways of zoonotic tuberculosis:

- **Consumption of Contaminated Animal Products**

  ➢ **Raw Milk:** One of the most common modes of zoonotic tuberculosis transmission is the consumption of unpasteurized or raw milk from infected cows, goats, or other dairy animals. *M.bovis* can be present in the milk, and when consumed without adequate pasteurization, it can infect humans.

- **Inhalation of Aerosols**

  ➢ **Respiratory Secretions:** Inhalation of aerosols containing *M.bovis* is another significant route of transmission. This can occur when infected animals cough or exhale, releasing respiratory secretions containing the bacterium into the air. People in close contact with infected animals, such as farmers, veterinarians, and abattoir workers, are at higher risk.

- **Direct Contact with Infected Animals or Tissues**

  ➢ **Physical Contact:** Close contact with infected animals or their tissues can lead to transmission. This includes activities like milking, handling, or slaughtering infected animals.
  ➢ **Open Wounds:** In some cases, *M.bovis* can enter the human body through open wounds or cuts when handling infected animals or their contaminated tissues.

- **Vector-Borne Transmission**

  ➢ **Insects:** While less common, there have been reports of potential vector-borne transmission through insect vectors like biting flies. These insects can mechanically transfer the bacterium between animals and potentially to humans.

- **Environmental Exposure**

  ➢ **Contaminated Environment:** Prolonged exposure to environments contaminated with *M.bovis*, such as barns, stables, or pastures where infected animals have been, can increase the risk of transmission through inhalation or skin contact.

- **Human-to-Human Transmission**

  - **Healthcare Settings:** In rare instances, human-to-human transmission of *M.bovis* has occurred, particularly in healthcare settings, when healthcare workers or family members come into close contact with an infected individual's respiratory secretions. This is more common in immunocompromised individuals.

- **Food Handling and Preparation**

  - **Contaminated Meat:** Handling, preparation, and consumption of undercooked or raw meat from infected animals can potentially lead to transmission, although this route is less common compared to consumption of contaminated milk[12].
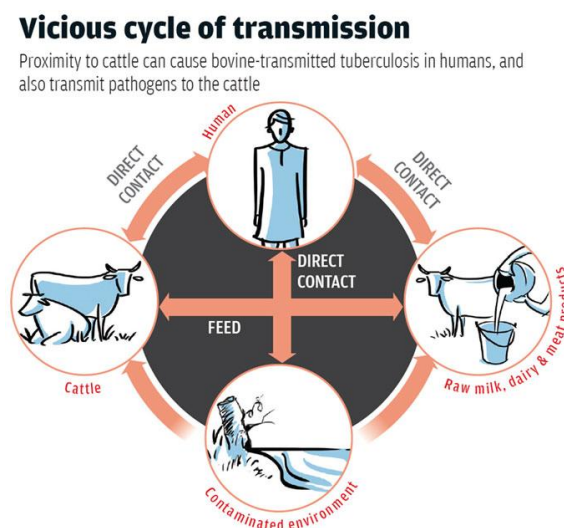

Figure 2: Transmission Pathways of *Mycobacterium bovis* [13]

III. MYCOBATERIUM *BOVIS*

1. **Bacterial Characteristics:** *Mycobacterium bovis* is a bacterium responsible for causing tuberculosis in various animal species, including cattle, and it can also infect humans. It shares several bacterial characteristics with other members of the Mycobacterium genus, but it also has some specific features. Here are the key bacterial characteristics of *Mycobacterium bovis:*

   - **Mycobacterial Cell Wall:** *Mycobacterium bovis*, like other mycobacteria, has a unique cell wall composition that is distinct from most other bacteria. The mycobacterial cell wall contains high levels of lipids, including mycolic acids, which contribute to its waxy and impermeable nature. This complex cell wall structure is responsible for the acid-fast staining property of mycobacteria.

   - **Acid-Fast Staining:** One of the hallmark characteristics of *Mycobacterium bovis* is its ability to retain stains even after being exposed to acidified alcohol during staining procedures. This property is due to the high lipid content of the cell wall and is the basis for acid-fast staining techniques used to identify mycobacterial infections.

- **Slow Growth:** *Mycobacterium bovis* is known for its slow growth rate compared to many other bacteria. It typically grows on solid media over a period of several weeks to months, making it challenging to culture and diagnose.

- **Aerobic and Non-Motile:** *Mycobacterium bovis* is an aerobic bacterium, which means it requires oxygen for growth. It is non-motile and does not possess flagella for movement.

- **Resistance to Environmental Stress:** *Mycobacterium bovis* can survive for extended periods in the environment, especially in contaminated soil, water, and on fomites. This resistance to environmental stress contributes to its persistence and potential for transmission.

- **High Genetic Similarity to *M. tuberculosis*:** *Mycobacterium bovis* is closely related to Mycobacterium *tuberculosis*, the bacterium responsible for causing tuberculosis in humans. They share a significant degree of genetic similarity, and many of the genes involved in virulence and pathogenicity are conserved between the two species.

- **Pathogenicity:** *Mycobacterium bovis* is a highly pathogenic bacterium that can cause tuberculosis in a wide range of mammals, including cattle, deer, badgers, and humans. It typically infects the respiratory system but can also cause extrapulmonary infections.

- **Zoonotic Potential:** One of the significant characteristics of *Mycobacterium bovis* is its zoonotic potential. It can be transmitted from infected animals, particularly cattle, to humans, leading to zoonotic tuberculosis. This zoonotic transmission is a public health concern in regions where bovine tuberculosis is prevalent.

- **Vaccine Use:** The Bacillus Calmette-Guérin (BCG) vaccine, which is derived from a strain of *Mycobacterium bovis*, is used for immunizing against tuberculosis in humans. BCG vaccination provides varying levels of protection against tuberculosis, especially in children.

- **Antibiotic Resistance:** Some strains of *Mycobacterium bovis* may display resistance to certain antibiotics, making treatment of infections more challenging[14].

2. **Genetic Diversity:** *Mycobacterium bovis*, the bacterium responsible for bovine tuberculosis and a zoonotic agent that can infect humans, exhibits genetic diversity similar to other pathogenic mycobacteria within the Mycobacterium tuberculosis complex. This genetic diversity can have important implications for disease epidemiology, diagnosis, treatment, and control. Here are some key aspects of the genetic diversity of *Mycobacterium bovis*:

- **Genomic Diversity:** *Mycobacterium bovis* has a diverse genomic makeup, with genetic variations occurring in different regions of its chromosome. These genetic differences can lead to variations in virulence, host specificity, and drug susceptibility among different strains of *M.bovis*.

- **Spoligotyping:** Spoligotyping is a widely used molecular typing method for Mycobacterium tuberculosis complex strains, including *M.bovis*. It relies on the detection of unique patterns of spacer sequences in the direct repeat (DR) region of the genome. Spoligotyping can help identify specific *M.bovis* strains and trace the source of infections.

- **MIRU-VNTR Typing:** Mycobacterial Interspersed Repetitive Units-Variable Number Tandem Repeats (MIRU-VNTR) typing is another molecular typing technique used to assess the genetic diversity of *M.bovis*. It involves the analysis of variable number tandem repeats in specific genetic loci, providing a high-resolution method for strain differentiation

- **Lineage Diversity:** *Mycobacterium bovis* is classified into several genetic lineages, some of which are more prevalent in specific geographic regions. These lineages can exhibit differences in pathogenicity and virulence. For example, the African 1 and African 2 lineages are commonly found in Africa, while the European 1 lineage is predominant in Europe.

- **Regional Variation:** The genetic diversity of *M.bovis* can vary significantly by region. Different regions may have distinct strains of *M.bovis*, and the distribution of these strains can be influenced by factors such as livestock populations, trade, and local control measures.

- **Drug Resistance:** Genetic diversity in *M.bovis* can also manifest as variations in drug resistance. Some strains may exhibit resistance to anti-tuberculosis drugs, making treatment more challenging.

- **Host Adaptation:** *Mycobacterium bovis* has the ability to adapt to different host species, leading to variations in pathogenicity and host specificity. This host adaptation can result in distinct genetic profiles among strains infecting different animal species.

- **Transmission Dynamics:** Understanding the genetic diversity of *M.bovis* is crucial for studying the transmission dynamics of bovine tuberculosis, especially in regions with a high prevalence of the disease. Genetic typing can help trace the source of infections and identify potential transmission routes.

- **Vaccine Development:** Knowledge of genetic diversity can inform vaccine development efforts. The Bacillus Calmette-Guérin (BCG) vaccine, derived from a strain of *Mycobacterium bovis*, may vary in efficacy against different *M.bovis* strains, highlighting the importance of considering strain diversity in vaccine design.

- **Control Strategies:** Tailoring control strategies to the specific genetic diversity of *M.bovis* in a given region can enhance the effectiveness of disease control efforts. Targeted interventions, such as testing and culling of infected animals and vaccination programs, may be influenced by strain diversity[15].

IV. CLINICAL MANIFESTATIONS IN HUMANS

1. **Pulmonary and Extrapulmonary Infections:** *Mycobacterium bovis* is a zoonotic pathogen that can cause tuberculosis in humans, often referred to as "zoonotic tuberculosis" or "bovine tuberculosis" when it originates from infected animals, particularly cattle. The clinical manifestations of *Mycobacterium bovis* infection in humans are generally similar to those caused by Mycobacterium tuberculosis, the primary agent of human tuberculosis.

- **Pulmonary Tuberculosis:** Pulmonary tuberculosis is the most common clinical presentation of *Mycobacterium bovis* infection in humans. It typically manifests with symptoms such as:

  - ➤ **Cough:** A persistent cough that may produce sputum, which can sometimes be blood-tinged.
  - ➤ **Fever:** Low-grade fever, often in the late afternoon or evening (known as "evening fever").
  - ➤ **Night Sweats:** Profuse sweating, particularly during the night.
  - ➤ **Weight Loss:** Unintentional weight loss and loss of appetite.
  - ➤ **Fatigue:** Generalized weakness and fatigue.
  - ➤ **Chest Pain:** Pain or discomfort in the chest, which can be associated with pleuritic pain if the pleura is involved.

- **Extrapulmonary Tuberculosis:** In some cases, *Mycobacterium bovis* can cause extrapulmonary tuberculosis, where the infection spreads to other parts of the body. Common sites of extrapulmonary involvement include lymph nodes (cervical or peripheral lymphadenitis), bones, joints, and the gastrointestinal tract.

- **Gastrointestinal Tuberculosis:** Gastrointestinal tuberculosis, including abdominal pain, diarrhea, and intestinal perforation, can occur due to *M.bovis* infection, especially if contaminated dairy products have been consumed.

- **Disseminated Tuberculosis:** In severe cases, *Mycobacterium bovis* infection can disseminate throughout the body, leading to miliary tuberculosis. This condition is characterized by widespread, tiny tubercles (granulomas) in various organs and can be life-threatening.

- **Immunocompromised Individuals:** Immunocompromised individuals, such as those with HIV/AIDS, are at a higher risk of developing severe forms of *Mycobacterium bovis* infection, including disseminated disease.

- **Molecular Typing:** In some cases, molecular typing methods, such as spoligotyping and MIRU-VNTR typing, may be used to distinguish *Mycobacterium bovis* from Mycobacterium tuberculosis and determine its specific lineage. This information can be valuable for epidemiological investigations.

    It's important to note that the clinical presentation of *Mycobacterium bovis* infection can overlap with that of *Mycobacterium tuberculosis*. Diagnosis typically

involves laboratory tests, including sputum culture and molecular assays, to confirm the presence of the bacterium and differentiate between species.

2. **Atypical Presentations:** *Mycobacterium bovis* can cause atypical presentations of tuberculosis in humans, which may not follow the typical clinical patterns seen with Mycobacterium tuberculosis. These atypical presentations can make diagnosis and management more challenging. Here are some examples of atypical presentations of *Mycobacterium bovis* infection:

- **Gastrointestinal Tuberculosis:** *Mycobacterium bovis* infection can lead to gastrointestinal tuberculosis, which may manifest with symptoms such as abdominal pain, chronic diarrhea, weight loss, and malabsorption. This form of tuberculosis is often associated with the consumption of contaminated dairy products, especially unpasteurized milk.

- **Osteoarticular Tuberculosis:** Osteoarticular tuberculosis caused by *M.bovis* can affect bones and joints, leading to symptoms like joint pain, swelling, stiffness, and decreased range of motion. It can mimic other joint disorders and may be more challenging to diagnose.

- **Pleural Tuberculosis:** While pleural involvement is more commonly associated with *Mycobacterium tuberculosis*, *Mycobacterium bovis* can also cause pleural tuberculosis. Symptoms may include pleuritic chest pain and pleural effusion.

- **Skin and Soft Tissue Infections:** *Mycobacterium bovis* can lead to cutaneous tuberculosis, resulting in skin lesions, ulcers, or abscesses. These skin and soft tissue infections can be mistaken for other skin conditions.

- **Genitourinary Tuberculosis:** In rare cases, *Mycobacterium bovis* can infect the genitourinary system, causing conditions such as renal tuberculosis. This can result in symptoms like hematuria, flank pain, and urinary tract infections.

- **Miliary Tuberculosis:** *Mycobacterium bovis* can cause miliary tuberculosis, a severe form of disseminated tuberculosis in which the infection spreads throughout the body. It can involve multiple organs and present with a wide range of non-specific symptoms, making diagnosis challenging.

- **Immunocompromised Individuals:** Atypical presentations of *Mycobacterium bovis* infection may be more common in immunocompromised individuals, such as those with HIV/AIDS. In such cases, the infection can be more severe and may affect various organ systems.

- **Negative Tuberculin Skin Test:** Some individuals with *Mycobacterium bovis* infection may have a negative reaction to the tuberculin skin test (Mantoux test), which is commonly used for diagnosing tuberculosis. This can complicate diagnosis, as a negative skin test does not rule out infection.

- **Vaccine Strain:** In regions where the Bacillus Calmette-Guérin (BCG) vaccine is commonly administered, individuals may develop skin or lymph node reactions at the vaccination site. These reactions can resemble cutaneous or lymphatic tuberculosis and may be caused by the vaccine strain of *Mycobacterium bovis*[16].

Due to the potential for atypical presentations and the challenges in diagnosis, healthcare providers should consider a broad range of clinical and epidemiological factors when evaluating patients for possible *Mycobacterium bovis* infection. Molecular typing methods and culture techniques can help confirm the specific strain and guide treatment decisions. Additionally, a detailed patient history, including dietary habits and exposure to livestock, can be critical in suspected cases of zoonotic tuberculosis caused by *Mycobacterium bovis*.

V. DIAGNOSIS OF ZOONOTIC TUBERCULOSIS

1. **Laboratory Methods**

- **Clinical Evaluation:** A thorough clinical assessment is essential to identify symptoms and risk factors associated with tuberculosis, including exposure to potentially infected animals or consumption of unpasteurized dairy products. Common symptoms of zoonotic tuberculosis in humans include cough, fever, night sweats, weight loss, fatigue, and, in some cases, specific extrapulmonary symptoms depending on the site of infection.

- **Medical History:** Taking a detailed medical history is crucial, including information about the patient's occupation, travel history, dietary habits (especially consumption of raw or unpasteurized milk), and any known contact with infected animals.

- **Tuberculin Skin Test (Mantoux Test):** A tuberculin skin test (Mantoux test) can help assess exposure to Mycobacterium tuberculosis complex bacteria, including *Mycobacterium bovis*. However, it may not reliably distinguish between different mycobacterial species.

- **Chest X-ray and Imaging:** Imaging studies, such as chest X-rays or CT scans, can help identify pulmonary involvement and extrapulmonary manifestations of tuberculosis.

- **Sputum Examination:** Collecting sputum samples for acid-fast bacilli (AFB) staining and culture is a common method for diagnosing pulmonary tuberculosis. It can help confirm the presence of *Mycobacterium bovis* or other tuberculosis-causing bacteria.

- **Extrapulmonary Specimen Collection**: In cases of suspected extrapulmonary tuberculosis (e.g., lymphadenitis, gastrointestinal involvement), samples from the affected site may be collected for microscopy, culture, and molecular testing.

- **Microscopy**

  - **Acid-Fast Bacilli (AFB) Staining:** AFB staining is a rapid and commonly used method for tuberculosis diagnosis. Clinical specimens, such as sputum or tissue samples, are stained with specific dyes that adhere to mycobacterial cell walls, making them visible under a microscope. While AFB staining can indicate mycobacterial infection, it does not distinguish between different mycobacterial species.

- **Culture**

  - **Mycobacterial Culture:** Culturing clinical specimens on specialized media is the gold standard for diagnosing zoonotic tuberculosis. Mycobacterium bovis grows slowly, so cultures are incubated for several weeks to months. Common culture media include Lowenstein-Jensen and Middlebrook agar. The presence of colonies with characteristic mycobacterial growth confirms the diagnosis.

- **Molecular Tests**

  - **Polymerase Chain Reaction (PCR):** PCR assays are highly sensitive and specific for detecting *Mycobacterium bovis* DNA in clinical specimens. They can differentiate between different Mycobacterium species and identify drug resistance mutations if needed. PCR-based tests are valuable for rapid diagnosis and strain differentiation.
  - **Nucleic Acid Amplification Tests (NAATs):** NAATs, including real-time PCR and loop-mediated isothermal amplification (LAMP), offer rapid and sensitive detection of *Mycobacterium bovis* DNA. They are often used for both pulmonary and extrapulmonary samples[18].

- **Serological Tests:** Serological tests are available but are generally less specific and sensitive than other diagnostic methods for tuberculosis. They are not commonly used for routine diagnosis but may have research or epidemiological applications.

- **Immunological Tests:** Interferon-Gamma Release Assays (IGRAs): IGRAs, such as the QuantiFERON-TB Gold test, can aid in the diagnosis of tuberculosis by detecting a specific immune response to Mycobacterium tuberculosis complex antigens. While IGRAs are not species-specific, they can help identify individuals exposed to mycobacterial infections.

- **Histopathology and Biopsy:** Histopathological examination: Examination of tissue biopsies can reveal characteristic granulomas and acid-fast bacilli. It is often used in the diagnosis of extrapulmonary tuberculosis when clinical specimens are difficult to obtain.

- **Genetic Typing Methods:** Spoligotyping and MIRU-VNTR Typing: These molecular typing methods help differentiate between *Mycobacterium bovis* and Mycobacterium tuberculosis strains. They are valuable for epidemiological investigations and source tracing.

- **Cytology:** Cytological examination: In cases of zoonotic tuberculosis with extrapulmonary involvement (e.g., lymphadenitis), cytological examination of aspirated fluid or fine-needle biopsy specimens may reveal the presence of mycobacteria.

- **Drug Susceptibility Testing (DST):** Determining the drug susceptibility of *Mycobacterium bovis* strains is essential for guiding treatment decisions. DST involves testing the susceptibility of the bacterium to various anti-tuberculosis drugs[17].

  Effective diagnosis of zoonotic tuberculosis often requires a combination of these laboratory methods, depending on the clinical presentation and available specimens. A multidisciplinary approach involving clinicians, microbiologists, and epidemiologists is crucial for accurate diagnosis and appropriate patient management. Additionally, the One Health approach, which considers both human and animal health aspects, is important for addressing zoonotic tuberculosis comprehensively.

2. **Challenges in Diagnosis:** The diagnosis of zoonotic tuberculosis, caused by *Mycobacterium bovis*, presents several challenges due to its unique characteristics and the need for a comprehensive One Health approach. Here are some of the key challenges in diagnosing zoonotic tuberculosis:

- **Atypical Clinical Presentation:** Zoonotic tuberculosis can present with atypical clinical symptoms that mimic other diseases, making diagnosis more challenging. This is particularly true for extrapulmonary forms of the disease.

- **Similarity to *M. tuberculosis*:** *Mycobacterium bovis* is closely related to *Mycobacterium tuberculosis*, and the clinical, radiological, and histological features of the diseases they cause can be very similar. Distinguishing between the two species can be difficult without specialized laboratory tests.

- **Mantoux test Limitations:** The tuberculin skin test (Mantoux test) may not reliably distinguish between infections with *M.bovis* and *M. tuberculosis*, as both can elicit a positive response. This limits its utility in differentiating zoonotic tuberculosis.

- **Specialized Laboratory Facilities:** Diagnosis often requires specialized laboratory facilities for culturing and identifying *Mycobacterium bovis*. These facilities may not be readily available in all regions, leading to delays in diagnosis.

- **Slow Growth:** *Mycobacterium bovis* has a slow growth rate in culture, requiring several weeks to months for colonies to appear. This can delay the confirmation of diagnosis.

- **Lack of Species-Specific Serological Tests:** Unlike some other pathogens, there are no widely used serological tests that can definitively differentiate *Mycobacterium bovis* from Mycobacterium tuberculosis. This can hinder rapid diagnosis.

- **Complexity of Extrapulmonary Cases:** Extrapulmonary forms of zoonotic tuberculosis can be particularly challenging to diagnose. Obtaining appropriate specimens for testing and distinguishing tuberculosis from other granulomatous diseases can be difficult.

- **Low Prevalence in Humans:** In many regions, zoonotic tuberculosis is relatively rare in humans compared to tuberculosis caused by *M. tuberculosis*. This low prevalence can reduce awareness and familiarity among healthcare providers.

- **Interference from BCG Vaccination:** In regions where the Bacillus Calmette-Guérin (BCG) vaccine is commonly administered, individuals may have a positive response to tuberculin skin tests due to vaccination, which can complicate diagnosis.

- **Co-Infections and Immunocompromised Patients:** Co-infections with other pathogens and the presence of immunocompromised individuals, such as those with HIV/AIDS, can complicate diagnosis and the interpretation of test results.

- **Veterinary and Epidemiological Investigations:** To understand the source of zoonotic tuberculosis transmission, thorough epidemiological investigations and veterinary assessments are often necessary. Coordinating between human and animal health sectors can be challenging.

- **Global Health Disparities:** Diagnosis of zoonotic tuberculosis is more challenging in regions with limited healthcare infrastructure and resources, where access to specialized tests and expertise may be lacking[18].

VI. TREATMENT AND MANAGEMENT

1. **Antibiotic Therapy:** The treatment of zoonotic tuberculosis, caused by *Mycobacterium bovis*, typically involves a combination of antibiotics, similar to the treatment regimens used for tuberculosis caused by Mycobacterium tuberculosis. It's important to note that *Mycobacterium bovis* is susceptible to many of the same antibiotics used in the treatment of human tuberculosis. The specific choice of antibiotics and the duration of treatment may vary depending on factors such as the patient's clinical presentation, drug susceptibility testing (DST) results, and the extent of the disease. Here is a general guideline for antibiotic therapy in the treatment of zoonotic tuberculosis:

- **First-Line Antituberculosis Drugs:** The first-line drugs used in the treatment of zoonotic tuberculosis are the same as those used for *Mycobacterium tuberculosis*. They include:

  - **Isoniazid (INH):** Typically, a cornerstone of the regimen.
  - **Rifampicin (RIF):** Often combined with INH.
  - **Pyrazinamide (PZA):** Usually included in the initial phase of treatment.
  - **Ethambutol (EMB):** Frequently used in the initial phase and may be continued in the continuation phase.

- **Duration of Treatment:** The standard duration of treatment for zoonotic tuberculosis is usually 6 to 9 months. However, the exact duration can vary based on factors such as the patient's clinical response, site of infection, and drug resistance profile.

- **Drug Susceptibility Testing (DST):** DST should be performed to determine the susceptibility of the *Mycobacterium bovis* strain to antituberculosis drugs. This helps guide the selection of appropriate antibiotics and treatment duration.

- **Second-Line Drugs:** In cases of drug resistance or treatment failure, second-line antituberculosis drugs may be considered. These drugs include: Fluoroquinolones (e.g., moxifloxacin), Injectable drugs (e.g., amikacin, kanamycin), Other drugs (e.g., ethionamide, cycloserine). The choice of second-line drugs should be based on DST results and expert guidance.

- **Monitoring and Follow-Up:** Patients receiving treatment for zoonotic tuberculosis should be closely monitored for treatment response and potential adverse effects of the medications. Regular follow-up visits are essential.

- **Patient Adherence:** Ensuring that patients adhere to their treatment regimen is critical for successful therapy. Healthcare providers should educate patients about the importance of completing the entire course of treatment.

- **Surgical Intervention:** In some cases, surgical intervention may be necessary to manage complications of zoonotic tuberculosis, such as the drainage of abscesses or the removal of necrotic tissue.

- **Multidisciplinary Approach:** A multidisciplinary approach involving clinicians, microbiologists, epidemiologists, and veterinarians is crucial for the effective management of zoonotic tuberculosis[20].

  It's important to emphasize that the choice of antibiotics and treatment duration should be individualized based on the patient's specific circumstances and the drug susceptibility profile of the infecting strain. Additionally, the treatment of zoonotic tuberculosis often involves collaboration between the human and animal health sectors to control the disease at its source and prevent further transmission[19].

2. **Drug – Resistant Strains:** Drug-resistant strains of zoonotic tuberculosis, caused by *Mycobacterium bovis*, pose a significant challenge for both human and animal health. These drug-resistant strains can emerge due to various factors, including inadequate treatment, improper use of antibiotics, and genetic mutations within the bacterium. Here are the key types of drug resistance in zoonotic tuberculosis:

   - **Multi-Drug Resistant (MDR) Zoonotic Tuberculosis:** MDR zoonotic tuberculosis is defined by resistance to at least two of the most potent first-line antituberculosis drugs: isoniazid (INH) and rifampicin (RIF).

     Patients infected with MDR *Mycobacterium bovis* strains require treatment with second-line antibiotics, which are often less effective, more toxic, and more

expensive than first-line drugs. MDR zoonotic tuberculosis is a significant concern as it complicates treatment and increases the risk of treatment failure.

- **Extensively Drug-Resistant (XDR) Zoonotic Tuberculosis:** XDR zoonotic tuberculosis is characterized by resistance not only to INH and RIF but also to at least one fluoroquinolone and one of the three second-line injectable drugs (amikacin, kanamycin, or capreomycin). XDR strains are even more challenging to treat, as they are resistant to both first- and second-line drugs, leaving limited treatment options.

- **Pre-Extensively Drug-Resistant (Pre-XDR) Zoonotic Tuberculosis:** Pre-XDR zoonotic tuberculosis refers to strains that are resistant to either INH and RIF or a fluoroquinolone and a second-line injectable drug but not both. While not as resistant as XDR strains, Pre-XDR strains still pose significant treatment challenges and can limit treatment options.

- **Mono-Drug Resistance:** Some *Mycobacterium bovis* strains may develop resistance to a single antituberculosis drug, such as isoniazid or rifampicin. Mono-drug resistance can complicate treatment, as it may necessitate changes in the standard treatment regimen.

- **Poly-Drug Resistance:** Poly-drug resistance refers to resistance to multiple antituberculosis drugs but not meeting the criteria for MDR, XDR, or Pre-XDR. These strains may respond to some antibiotics, but the choice of drugs should be guided by DST results.

- **Genetic Mechanisms of Resistance:** Drug-resistant strains of zoonotic tuberculosis can develop due to mutations in specific genes responsible for drug activation or target modification. Resistance can also occur through mechanisms such as efflux pumps that expel drugs from bacterial cells[20].

Managing drug-resistant strains of zoonotic tuberculosis requires specialized treatment regimens based on the results of drug susceptibility testing (DST). Treatment typically involves combinations of second-line antibiotics, and the duration may be extended. The management of drug-resistant zoonotic tuberculosis should be carried out in consultation with experts in tuberculosis treatment, and close monitoring of treatment response and adverse effects is essential

VII. PREVENTION AND CONTROL

The prevalence and control of zoonotic tuberculosis, caused by Mycobacterium bovis, vary by region and are influenced by a range of factors, including the prevalence of bovine tuberculosis in livestock, human behaviors and practices, healthcare infrastructure, and public health interventions. Here's an overview of prevalence and control measures:

1. **Prevalence**

   - **Global Prevalence:** The prevalence of zoonotic tuberculosis varies widely across different regions of the world. In some areas, zoonotic tuberculosis is a significant public health concern, while in others, it is relatively rare.

   - **Endemic Regions:** Zoonotic tuberculosis tends to be more prevalent in regions where bovine tuberculosis is endemic in livestock. These regions may include parts of Africa, Asia, and Latin America.

   - **High-Risk Populations:** Certain populations are at higher risk of zoonotic tuberculosis, including individuals involved in agriculture, dairy farming, and livestock handling. Consumption of raw or unpasteurized dairy products from infected animals also poses a risk.

   - **Co-Infection with HIV/AIDS:** The prevalence of zoonotic tuberculosis is often higher among individuals living with HIV/AIDS, as their weakened immune systems make them more susceptible to infection.

2. **Control Measures**

   - **One Health Approach:** The most effective approach to control zoonotic tuberculosis involves collaboration between human health, animal health, and environmental sectors. The "One Health" approach recognizes that human and animal health are interconnected.

   - **Animal Health Measures:** Testing and Culling: Infected animals are identified through testing (e.g., skin tests or blood tests) and may be culled to prevent further spread.

   - **Vaccination:** In some regions, vaccination of livestock with the Bacillus Calmette-Guérin (BCG) vaccine or other bovine tuberculosis vaccines can help reduce the prevalence of *Mycobacterium bovis* in animals. Improved Biosecurity: Implementing biosecurity measures on farms and in slaughterhouses can help reduce the risk of transmission from animals to humans.

   - **Food Safety and Hygiene:** Public health education campaigns emphasize the importance of pasteurization and proper cooking of dairy products and meat to kill *Mycobacterium bovis* and prevent transmission through consumption.

   - **Surveillance and Testing:** Ongoing surveillance programs in livestock and wildlife populations are crucial for early detection and control efforts. Diagnostic testing of humans with tuberculosis symptoms should include tests to identify *Mycobacterium bovis*.

   - **Treatment of Human Cases:** Prompt diagnosis and treatment of zoonotic tuberculosis cases are essential to prevent further transmission. Treatment typically

involves a combination of antituberculosis drugs, which may vary based on drug susceptibility testing.

- **Contact Investigations:** Identifying and testing individuals who have had close contact with confirmed zoonotic tuberculosis cases is important to identify additional cases and sources of transmission.

- **Public Health Education:** Raising awareness among the general population about the risks associated with consuming raw or unpasteurized dairy products and proper hygiene practices when handling animals can help reduce transmission.

- **Global Collaboration:** International organizations, such as the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organization for Animal Health (OIE), play a vital role in coordinating efforts to control zoonotic tuberculosis on a global scale[21-22].

    The control of zoonotic tuberculosis requires a concerted effort from multiple stakeholders, including governments, healthcare providers, veterinarians, researchers, and communities. By implementing a multifaceted approach that addresses both human and animal health aspects, the prevalence of zoonotic tuberculosis can be reduced, and the risks to public health mitigated.

VIII. FUTURE DIRECTIONS IN ZOONOTIC TUBERCULOSIS RESEARCH

1. **Emerging Threats:** As research on zoonotic tuberculosis (TB) continues to evolve, several emerging threats and challenges have come to the forefront. These challenges highlight the need for ongoing vigilance, research, and collaboration to address zoonotic TB effectively. Some of the emerging threats in zoonotic TB research include:

- **Antimicrobial Resistance (AMR):** The emergence of drug-resistant strains of *Mycobacterium bovis* poses a significant threat. These resistant strains can complicate treatment, increase the risk of treatment failure, and potentially lead to the development of extensively drug-resistant (XDR) zoonotic TB.

- **Zoonotic TB in Wildlife:** Understanding the role of wildlife reservoirs in zoonotic TB transmission is becoming increasingly important. Certain wildlife species, such as badgers, deer, and possums, can harbor *Mycobacterium bovis* and potentially transmit the disease to livestock and humans.

- **Genomic Diversity:** The genomic diversity of *Mycobacterium bovis* strains is an emerging area of concern. Research is needed to characterize different strains, track their transmission dynamics, and determine their potential to adapt to new hosts and environments.

- **Climate Change and Environmental Factors:** Climate change and alterations in environmental conditions can affect the distribution and prevalence of zoonotic TB. Changes in temperature and precipitation patterns may impact the behavior of wildlife reservoirs, livestock, and the persistence of *Mycobacterium bovis* in the environment.

- **Urbanization and Human-Livestock Interactions:** Urbanization and changing patterns of human-livestock interactions may increase the risk of zoonotic TB transmission. As urban areas expand and encroach on previously rural areas, there is a potential for increased contact between humans and infected animals.

- **Population Movements:** Human population movements, including migration and displacement, can facilitate the spread of zoonotic TB. Displaced populations may face challenges in accessing healthcare and veterinary services.

- **Co-Infections and Immunocompromised Populations:** Co-infections with other pathogens, such as HIV, can increase the susceptibility of individuals to zoonotic TB. Research on the interaction between zoonotic TB and other diseases is essential, especially in immunocompromised populations.

- **Rapid Urbanization and Informal Settlements:** Rapid urbanization often leads to informal settlements with poor living conditions. In such settings, zoonotic TB can spread more easily due to overcrowding, inadequate sanitation, and limited access to healthcare.

- **Global Trade and Food Supply Chains:** The global movement of livestock and animal products can contribute to the spread of zoonotic TB. Monitoring and regulating international trade in animals and animal products are crucial.

- **Economic and Sociopolitical Factors:** Economic disparities and sociopolitical factors can affect the control of zoonotic TB. Limited resources, conflicts, and political instability may hinder surveillance, prevention, and treatment efforts.

- **Antibiotic Use in Livestock:** The use of antibiotics in livestock farming may contribute to the emergence of antibiotic-resistant *Mycobacterium bovis* strains. Research into the impact of antibiotic use on zoonotic TB is important.

  Addressing these emerging threats in zoonotic TB research requires a multidisciplinary approach that spans human health, animal health, environmental science, and social sciences. Collaboration between researchers, healthcare providers, veterinarians, policymakers, and communities are essential to develop effective strategies for prevention, control, and mitigation of zoonotic TB risks. Additionally, ongoing surveillance and monitoring are crucial to detect and respond to new challenges as they arise[19].

2. **Innovation in Diagnostics and Therapeutics:** Innovation in diagnostics and therapeutics for zoonotic tuberculosis (TB) research is critical to improve our ability to detect, treat, and prevent this disease effectively. Here are some key areas of innovation in zoonotic TB research:

   - **Diagnostics**

     ➢ **Point-of-Care Tests:** Developing rapid and accurate point-of-care diagnostic tests that can detect *Mycobacterium bovis* and differentiate it from other

Mycobacterium species is a priority. These tests should be suitable for use in resource-limited settings where zoonotic TB is prevalent.

➤ **Molecular Diagnostics:** Continued advancement in molecular diagnostic techniques, such as nucleic acid amplification tests (NAATs) and next-generation sequencing (NGS), can enhance the sensitivity and specificity of zoonotic TB diagnosis. These techniques can also help identify drug resistance mutations.

➤ **Biomarkers:** Research into host and bacterial biomarkers associated with zoonotic TB can lead to the development of non-invasive diagnostic tools. Biomarkers can aid in early detection and monitoring of the disease's progression.

➤ **Immunological Assays:** Development of improved immunological assays, such as serological tests and interferon-gamma release assays (IGRAs), for zoonotic TB diagnosis. These assays may help identify individuals exposed to *Mycobacterium bovis*.

➤ **Digital Health Solutions:** Integration of digital health technologies, such as smartphone apps and telemedicine, for remote diagnostic support, patient monitoring, and data collection. These technologies can enhance access to healthcare in remote areas.

➤ **Biosensors:** The development of biosensors capable of detecting *Mycobacterium bovis* in clinical specimens or environmental samples rapidly and with high sensitivity.

- **Therapeutics**

➤ **New Antituberculosis Drugs:** Research into novel antituberculosis drugs that are effective against zoonotic TB strains, including drug-resistant variants. Targeting specific metabolic pathways and vulnerabilities of *Mycobacterium bovis* can lead to the discovery of new drug candidates.

➤ **Host-Directed Therapies:** Exploration of host-directed therapies that modulate the host immune response to enhance protection against zoonotic TB. Such therapies may complement antibiotic treatment.

➤ **Drug Combinations:** Optimization of drug combinations for the treatment of zoonotic TB. Research on synergistic drug combinations that improve treatment outcomes and shorten the duration of therapy.

➤ **Targeted Drug Delivery:** Development of targeted drug delivery systems to improve drug distribution to infected tissues, especially in cases of extrapulmonary zoonotic TB.

➤ **Therapeutics for Drug-Resistant TB:** Development of therapeutics, including novel antibiotics and immunomodulators, specifically designed to address drug-resistant zoonotic TB, including multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains.

➤ **Vaccine Development:** Research into vaccines that can protect against zoonotic TB in both humans and livestock. Cross-protective vaccines that work against both *Mycobacterium bovis* and *Mycobacterium tuberculosis* are of particular interest.

➤ **Personalized Medicine:** Advancements in personalized medicine approaches to tailor treatment regimens based on the patient's drug susceptibility profile and immune response.

➢ **Adjuvant Therapies:** Investigation of adjuvant therapies, such as adjunctive corticosteroids, to mitigate inflammation and tissue damage associated with zoonotic TB.

➢ **Pharmacokinetics and Pharmacodynamics:** A better understanding of the pharmacokinetics and pharmacodynamics of antituberculosis drugs in zoonotic TB to optimize dosing regimens.

➢ **Clinical Trials:** Conducting well-designed clinical trials to evaluate the safety and efficacy of new therapeutics in zoonotic TB cases[23-24].

Innovation in diagnostics and therapeutics is crucial for addressing the challenges posed by zoonotic TB, including drug resistance and the complexities of cross-species transmission. Collaboration among researchers, healthcare providers, veterinarians, pharmaceutical companies, and governments is essential to drive these innovations and translate them into practical solutions for zoonotic TB control and prevention.

IX. CONCLUSION

Zoonotic tuberculosis represents a significant health concern at the intersection of human and animal health. It demands continued research, innovation and international cooperation to reduce its impact on both human and animal populations. By addressing zoonotic TB comprehensively, we can work towards the prevention and control of this infectious disease. Zoonotic TB is a preventable and treatable disease, but its control requires a concerted effort from all stakeholders. By taking collective action, we can reduce the burden of zoonotic TB, protect human and animal health, and works towards a safer and healthier future for communities around the world.

REFERENCES

[1] Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. Journal of preventive medicine and hygiene. 2017 Mar;58(1):E9.

[2] Good M, Duignan A. Perspectives on the history of bovine TB and the role of tuberculin in bovine TB eradication. Veterinary Medicine International. 2011 Apr 17;2011.

[3] Ramanujam H, Palaniyandi K. Bovine tuberculosis in India: the need for One Health approach and the way forward. One Health. 2023 Jan 30:100495.

[4] Srinivasan S, Easterling L, Rimal B, Niu XM, Conlan AJ, Dudas P, Kapur V. Prevalence of bovine tuberculosis in India: a systematic review and meta-analysis. Transboundary and emerging diseases. 2018 Dec;65(6):1627-40.

[5] Dean AS, Forcella S, Olea-Popelka F, El Idrissi A, Glaziou P, Benyahia A, Mumford E, Erlacher-Vindel E, Gifford G, Lubroth J, Raviglione M. A roadmap for zoonotic tuberculosis: a One Health approach to ending tuberculosis. The Lancet infectious diseases. 2018 Feb 1;18(2):137-8.

[6] Borham M, Oreiby A, El-Gedawy A, Hegazy Y, Khalifa HO, Al-Gaabary M, Matsumoto T. Review on bovine tuberculosis: An emerging disease associated with multidrug-resistant Mycobacterium species. Pathogens. 2022 Jun 21;11(7):715.

[7] Kemal J, Sibhat B, Abraham A, Terefe Y, Tulu KT, Welay K, Getahun N. Bovine tuberculosis in eastern Ethiopia: prevalence, risk factors and its public health importance. BMC Infectious Diseases. 2019 Dec;19(1):1-9.

[8] Humblet MF, Boschiroli ML, Saegerman C. Classification of worldwide bovine tuberculosis risk factors in cattle: a stratified approach. Veterinary research. 2009 Sep;40(5).

[9] De la Rua-Domenech R. Human Mycobacterium bovis infection in the United Kingdom: Incidence, risks, control measures and review of the zoonotic aspects of bovine tuberculosis. Tuberculosis. 2006 Mar 1;86(2):77-109.

[10] World Health Organization. *Global Tuberculosis Report 2019*; World Health Organization: Geneva, Switzerland, 2019

[11] Fitzgerald SD, Kaneene JB. Wildlife reservoirs of bovine tuberculosis worldwide: hosts, pathology, surveillance, and control. Veterinary pathology. 2013 May;50(3):488-99.

[12] Cosivi O, Grange JM, Daborn CJ, Raviglione MC, Fujikura T, Cousins D, Robinson RA, Huchzermeyer HF, de Kantor I, Meslin FX. Zoonotic tuberculosis due to Mycobacterium bovis in developing countries. Emerging infectious diseases. 1998 Jan;4(1):59.

[13] Kundan P, "Health Unexpected window", Down to earth, Published 2016 Oct 31. Available at https://www.downtoearth.org.in/news/health/undetected-window-56036

[14] Kanipe C, Palmer MV. Mycobacterium bovis and you: A comprehensive look at the bacteria, its similarities to Mycobacterium tuberculosis, and its relationship with human disease. Tuberculosis. 2020 Dec 1;125:102006.

[15] Guimaraes AM, Zimpel CK. Mycobacterium bovis: from genotyping to genome sequencing. Microorganisms. 2020 May 3;8(5):667.

[16] Grange JM. Mycobacterium bovis infection in human beings. Tuberculosis. 2001 Feb 1;81(1-2):71-7.

[17] Schwarz NG, Loderstaedt U, Hahn A, Hinz R, Zautner AE, Eibach D, Fischer M, Hagen RM, Frickmann H. Microbiological laboratory diagnostics of neglected zoonotic diseases (NZDs). Acta tropica. 2017 Jan 1;165:40-65.

[18] Sales ML, Fonseca AA, Sales ÉB, Cottorello AC, Issa MA, Hodon MA, Soares Filho PM, Ramalho AK, Silva MR, Lage AP, Heinemann MB. Evaluation of molecular markers for the diagnosis of Mycobacterium bovis. Folia microbiologica. 2014 Sep;59:433-8.

[19] Olea-Popelka F, Muwonge A, Perera A, Dean AS, Mumford E, Erlacher-Vindel E, Forcella S, Silk BJ, Ditiu L, El Idrissi A, Raviglione M. Zoonotic tuberculosis in human beings caused by Mycobacterium bovis—a call for action. The Lancet Infectious Diseases. 2017 Jan 1;17(1):e21-5.

[20] Anaelom NJ, Ikechukwu OJ, Sunday EW, Nnaemeka UC. Zoonotic tuberculosis: A review of epidemiology, clinical presentation, prevention and control. Journal of Public Health and Epidemiology. 2010 Sep;2(6):118-24.

[21] Teppawar RN, Chaudhari SP, Moon SL, Shinde SV, Khan WA, Patil AR. Zoonotic tuberculosis: a concern and strategies to combat. Basic biology and applications of actinobacteria. 2018 Nov 5:23-38.

[22] Centers for Disease Control and Prevention. Mycobacterium bovis (bovine tuberculosis) in humans. Centers for Disease Control and Prevention: Atlanta, Georgia. 2011:2.

[23] de Macedo Couto R, Santana GO, Ranzani OT, Waldman EA. One Health and surveillance of zoonotic tuberculosis in selected low-income, middle-income and high-income countries: A systematic review. PLOS Neglected Tropical Diseases. 2022 Jun 6;16(6):e0010428.

[24] Huang F, Zhao Y. Global control of tuberculosis: current status and future prospects. Zoonoses. 2022 Mar 23;2(1).