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Unveiling insights into bovine tuberculosis: A comprehensive review

Aswin Rafif Khairullah[1], Ikechukwu Benjamin Moses[2], Muhammad Khaliim Jati Kusala[1], Wiwiek Tyasningsih[3], Siti Rani Ayuti[4], Fedik Abdul Rantam[3], Ima Fauziah[1], Otto Sahat Martua Silaen[5], Yulianna Puspitasari[3]*, Suhita Aryaloka[6], Hartanto Mulyo Raharjo[3], Abdullah Hasib[7], Sheila Marty Yanestria[8] and Nanis Nurhidayah[1]

[1]*Research Center for Veterinary Science, National Research and Innovation Agency (BRIN), Bogor, Indonesia*
[2]*Department of Applied Microbiology, Faculty of Science, Ebonyi State University, Abakaliki, Nigeria*
[3]*Division of Veterinary Microbiology, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia*
[4]*Faculty of Veterinary Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia*
[5]*Doctoral Program in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia*
[6]*Master Program of Veterinary Agribusiness, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia*
[7]*School of Agriculture and Food Sustainability, The University of Queensland, Gatton, Australia*
[8]*Faculty of Veterinary Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia*

Abstract

The frequent zoonotic disease known as "bovine tuberculosis" is brought on by the *Mycobacterium bovis* bacteria, which can infect both people and animals. The aim of this review article is to provide an explanation of the etiology, history, epidemiology, pathogenesis, clinical symptoms, diagnosis, transmission, risk factors, public health importance, economic impact, treatment, and control of bovine tuberculosis. Primarily, bovine tuberculosis affects cattle, but other animals may also be affected. Bovine tuberculosis is present throughout the world, with the exception of Antarctica. Cattle that contract bovine tuberculosis might suffer from a persistent, crippling illness. In the early stages of the disease, there are no symptoms. The tuberculin test is the primary method for detecting bovine tuberculosis in cows. Depending on its localized site in the infected animal, *M. bovis* can be found in respiratory secretions, milk, urine, feces, vaginal secretions, semen, feces, and exudates from lesions (such as lymph node drainage and some skin lesions). This illness generally lowers cattle productivity and could have a negative financial impact on the livestock business, particularly the dairy industry. The most effective first-line anti-tuberculosis chemotherapy consists of isoniazid, ethambutol, rifampin, and streptomycin. Second-line drugs used against bovine tuberculosis include ethionamide, capreomycin, thioacetazone, and cycloserine. To successfully control and eradicate bovine tuberculosis, developed nations have implemented routine testing and culling of infected animals under national mandatory programs.
Keywords: Bovine tuberculosis, Cattle, Infectious disease, *M. bovis*, Public health.

Introduction

For more than a century, members of the genus *Mycobacterium* have been the source of the infectious disease tuberculosis, which poses a serious threat to both human and animal health (Borham *et al*., 2022). Currently, this illness is the cause of more deaths than any other bacterial illness. Over 2 billion people, or one-third of the global population, are infected with this bacterium, and between 1.5 and 2 million people die from tuberculosis each year (Houben and Dodd, 2016). This illness is credited as being the primary cause of infectious disease-related deaths worldwide. There are three forms of tuberculosis, which affects different species: human, poultry, and bovine tuberculosis (Dhama *et al*., 2011; Bihon *et al*., 2021).

Bovine tuberculosis, due to *Mycobacterium bovis*, is a serious infectious disease that affects a wide range of domesticated and wild animals with grave economic and public health challenges (Kasir *et al*., 2023).

The frequent zoonotic disease known as "bovine tuberculosis" is brought on by the *Mycobacterium bovis* bacteria, which can infect both people and animals (Kasir *et al*., 2023). Livestock-transmitted bovine tuberculosis has grown to be a serious infectious disease that can cross species boundaries (Broughan *et al*., 2016). The development of granulomatous nodules known as tubercles, which are indicative of bovine tuberculosis, is largely dependent on the infection route (Palmer *et al*., 2022). Bovine tuberculosis is a global disease that affects the cattle-producing industry greatly economically. However, the requirement for

***Corresponding Author:** Yulianna Puspitasari. Division of Veterinary Microbiology, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: *yulianna-puspitasari@fkh.unair.ac.id*

pasteurization of milk, tuberculin testing of cow skin, and culling of diseased cattle has resulted in a dramatic drop in the incidence of human tuberculosis caused by *M. bovis* in developed countries (Palmer *et al*., 2012).

These bacteria can produce aerosolized droplets that infected animals can cough up or exhale, which susceptible animals or people can subsequently inhale (Hanif and Garcia-Contreras, 2012). The risk of exposure is highest in spaces that are enclosed, such as warehouses. The most typical way of transmission for veterinary professionals who treat sick animals as well as agricultural and livestock workers is inhaling droplets (Mohamed, 2019). Shared drinking troughs containing the saliva and other excrement of diseased animals increase the risk of infection amongst livestock (Bouchez-Zacria *et al*., 2018). Furthermore, adding animals frequently raises the risk of introducing disease and having a large animal population raises the risk of the disease spreading throughout the herd (Skuce *et al*., 2012).

According to estimates, culling losses from this disease can account for 30%–50% of the difference between dairy or beef cattle's market value and their worth at slaughter (Pérez-Morote *et al*., 2020). A major contributing factor to zoonotic *M. bovis* infections in humans is the consumption of raw or unpasteurized animal products, inhalation of bacterium-containing droplets, and contact with diseased carcasses (Luciano and Roess, 2020). The precise incidence of *M. bovis*-caused bovine tuberculosis in humans is challenging to ascertain because of technological challenges in isolating the microbe. Given that people and animals coexist in the same environment and often live in rural regions, bovine tuberculosis in humans is becoming a bigger problem in emerging nations (Malama *et al*., 2013).

According to research, bovine tuberculosis is still prevalent in underdeveloped and developing nations, and *M. bovis* is thought to be the causative agent of 10%–15% of human tuberculosis cases (Getahun *et al*., 2020). There is a wide range of effects on *M. bovis* infection, and the risk of transmission of this disease is dependent on host, pathogen, and environmental factors (Allen *et al*., 2021). *Mycobacterium bovis* is thought to primarily infect cattle, despite the fact that the disease has been isolated from many other livestock and animal species so there is a risk of human transmission that could affect public health (Devi *et al*., 2021). The incidence and consequences of bovine tuberculosis may still be underestimated globally since many nations lack robust surveillance systems and epidemiological research is scarce (Luciano and Roess, 2020).

Interspecies disease transmission is among the least studied aspects of disease ecology. One of these pathogens is the causative agent of tuberculosis in cattle, *M. bovis*. The aim of this review article is to provide an explanation of the etiology, history, epidemiology, pathogenesis, clinical symptoms, diagnosis, transmission, risk factors, public health importance, economic impact, treatment, and control of bovine tuberculosis.

Etiology

Mycobacterium bovis serves as the etiological agent for bovine tuberculosis (Kasir *et al*., 2023). *Mycobacterium bovis* grows best in frozen tissue, but tissue preservatives such as sodium tetraborate prevent this bacterium from growing (Borham *et al*., 2022). This microbe is facultative intracellular, obligate aerobic, non-motile, and does not create spores. Its dimensions are 1–10 μm in length and 0.2–0.6 μm in breadth, and it takes 15–20 hours to generate (Nava-Vargas *et al*., 2021). The incubation time for *M. bovis* is 3 weeks. *Mycobacterium bovis* can endure for several months in the environment, particularly in conditions that are chilly, gloomy, and damp (Allen *et al*., 2021). The microbe's survival period varies according on sunlight exposure, ranging from 18 to 332 days at 12°C to 24°C.

History

Since thousands of years ago, it has been known that numerous mammals are afflicted with tuberculosis. This disease is thought to be the leading cause of death in the past 200 years when weighed against other serious illnesses (Borham *et al*., 2022). The cause of tuberculosis in humans, *Mycobacterium tuberculosis*, was found by Koch in 1882 (Cambau and Drancourt, 2014). However, Smith distinguished *M. bovis* from *M. tuberculosis* in 1898 (Mitermite *et al*., 2023). The loss of productivity, sickness, and death caused by bovine tuberculosis, along with the possible zoonotic hazard, make it a highly significant economic concern (Rahman *et al*., 2020). Cost monitoring is also very important from an economic standpoint. Regional disease foci that are not thought to be free of bovine tuberculosis still persist in the US, Australia, and several European nations, despite the fact that the illness poses a significant threat in emerging nations (Fitzgerald and Kaneene, 2013). In addition, the cattle business in the UK continues to face significant challenges due to the widespread prevalence of bovine tuberculosis (Allen *et al*., 2018).

Epidemiology

Bovine tuberculosis is present throughout the world, with the exception of Antarctica (Ramos *et al*., 2020). Worldwide, more than 50 million cattle are likely exposed to bovine tuberculosis (*Srinivasan et al*., 2021). India has been noted to be a country with the largest infected herds worldwide with an estimated bovine tuberculosis prevalence of 7.3% among farm and dairy cattle (Ramanujam and Palaniyandi, 2023).

Although bovine tuberculosis was formerly widespread, management initiatives have eradicated or almost completely eradicated the illness in many nations' livestock populations. According to current statistics, the following nations are free of bovine tuberculosis:

Australia, Sweden, the Czech Republic, Norway, Austria, Switzerland, Luxembourg, Jamaica, Latvia, Slovakia, Iceland, Estonia, Canada, Lithuania, Finland, Barbados, Denmark, and Singapore (Humblet *et al*., 2009). There are initiatives in place to eradicate bovine tuberculosis in the United States, New Zealand, Japan, and several European nations (Borham *et al*., 2022). Though it can also infect other livestock including goats, sheep, and camels as well as wild animals such as civets, possums, and deer, bovine tuberculosis is still a serious infectious illness in some places where it affects cattle (Mohamed, 2019).

In underdeveloped nations with inadequate control efforts, this disease continues to pose a risk to public health and produces substantial economic challenges for the livestock industry (Little, 2019). In Africa, 82% of people and 85% of cattle reside in regions where bovine tuberculosis in cattle has been reported (Ghebremariam *et al*., 2016). The main causes of the spread of domestic ruminant populations and the variations in milk production within the African ecological zone are the reasons that are mentioned in relation to the dissemination of bovine tuberculosis in Africa (De Garine-Wichatitsky *et al*., 2013). This element may have a major impact on the spread of bovine tuberculosis, along with variations in the production strategies used to manage animals across the African continent, such as pastoralism, agro-pastoralism, mixed farming, and intense dairy farming (Renwick *et al*., 2007; Pokam *et al*., 2019).

There are significant regional variations in the prevalence of bovine tuberculosis within a nation. According to reports from South America, locations surrounding large towns with high concentrations of intense milk production are also home to the greatest incidences of bovine tuberculosis (Avila *et al*., 2018). Bovine tuberculosis prevalence has been reported to be highest in India (7.3 %), followed by Brazil (2.5 %), and China (2.4 %) (Gong *et al*., 2021; Rodrigues *et al*., 2022; Ramanujam and Palaniyandi, 2023).

In nations with advanced testing and control systems and a comprehensive set of surveillance and control methods to address cow-to-cow transmission, bovine tuberculosis is likely to be an infectious illness with a low incidence and apparent low transmission rate (Mandal *et al*., 2023). The primary reservoir for *M. bovis* is cattle (Palmer *et al*., 2012). *Mycobacterium bovis* infections primarily occur in humans who consume raw milk and dairy products, while they can also occur in the air (Ortiz *et al*., 2021). The most frequent *M. bovis* infection in children (Gallivan *et al*., 2015). This microorganism affects the tonsils and can cause digestive tract infections that lead to abdominal tuberculosis or "scrofula" or cervical lymphadenitis (Waters and Palmer, 2015). *Mycobacterium bovis* typically inhabits extrapulmonary sites in the intestines, kidneys, brain, and bones (Torres-Gonzalez *et al*., 2016).

Pathogenesis

Most of the bacilli stay in the upper respiratory tract after inhalation. Alveolar macrophages will breakdown any bacteria that make it into the alveoli. The high quantity of lipids that penetrate the cell walls and proliferate in macrophages makes tubercle bacilli resistant to phagocytosis (Kawka *et al*., 2023). *Mycobacterium* accumulation causes cell-mediated hypersensitivity and inflammatory foci. The cytokines released by activated macrophages cause tubercles, which are specific tissue lesions (Hossain and Norazmi, 2013). Avascular granulomas known as tubercles are composed of two zones: a peripheral zone containing lymphocytes and fibroblasts (epithelioid cells) and a central zone containing giant cells (Datta *et al*., 2016). The potential for illness to develop within the host is determined by the mycobacteria's capacity to proliferate and survive inside macrophages. Phagosome-lysosome fusion is prevented, which allows macrophage organisms to survive and multiply at the initial infection site (Zhai *et al*., 2019).

Mycobacteria's pathogenicity is based on their capacity to avoid phagocytic death, which is mostly brought on by components of their cell walls, such as: TDM is a surface glycolipid implicated in umbilical cord factor and serpentine growth *in vitro*; Suphatide is a sulfur-containing surface glycolipid that inhibits the fusion of phagosomes with lysosomes; bacteria's produced cAMP may also help with this; lipoarabinomannan (LAM) heteropolysaccharide, which prevents interferron gamma (IFNã) from activating macrophages and causes them to release TNFá, which raises fever, and IL-10, which reduces T cell proliferation brought on by mycobacteria; and peptidoglycan, cell wall waxes, and other glycolipids are in charge of extra processes that draw antigen-presenting cells (Rahlwes *et al*., 2023).

Mycobacteria enter macrophages throughout the body and are discharged from them (Weiss and Schaible, 2015). The host's immunological response to mycobacteria and the formation of lesions is aided by the waxy cell wall component mycolic acid. The host initiates a cell-mediated immune response by stimulating T cells and macrophages, which is followed by the development of granulomas and a delayed-type hypersensitivity reaction (Smith *et al*., 2021). Mycobacterium virulence is associated with several lipids that are absent from other bacterial species. Surface-bound mycobacterial lipids that can influence innate immunity include lipomannan (LM), LAM, phosphatidylinositol mannosides, umbilical cord factors trehalose mono- and (TMM and TDM), and phthiocerol dimycocerosates (Ghazaei, 2018). Monomycolyl glycerol, one of the recently discovered lipids, has been demonstrated to alter hypervirulence and host immunity (Andersen *et al*., 2009).

These germs are absorbed by macrophages and then undergo intracellular replication (Maphasa *et al*., 2021). In an attempt to conceal contaminated macrophages with fibrous tissue, the body forms granulomas and tubercles. Granulomas are often spherical, hard, yellow, or gray, and have a diameter of 1–3 cm. Dried cellular debris that is yellow, caseous, or necrotic makes up the granuloma's core in one portion (Carrisoza-Urbina *et al*., 2019). The infection can cause smaller tubercles, measuring 2–3 mm in diameter, and spread hematogenously to the lymph nodes and other parts of the body. The term "miliary tuberculosis" refers to the development of these tiny tubercles (Sharma *et al*., 2016).

Clinical symptoms

Cattle that contract bovine tuberculosis might suffer from a persistent, crippling illness. In the early stages of the disease, there are no symptoms. But in the later stages, there is weakness, a low-grade temperature that fluctuates, gradual emaciation, and decreased appetite (Ramos *et al*., 2015). Shortness of breath, wet cough, or trachypnea may occur if there is an infection in the lungs. The location of lesions, which are primarily observed in the upper respiratory tract, lungs, and tonsils in both affected humans and animals, demonstrates the involvement of the respiratory tract and its function in the pathogenesis of the disease (Pal *et al*., 2022). A good appetite is frequently seen in cows with progressive emaciation that is unrelated to other clinical indicators, even if some of them have severe miliary tuberculosis lesions and are clinically normal (Krajewska-Wędzina *et al*., 2022). Temperature swings and erratic appetite are typically linked to this illness. The fur on the exterior could becoming abrasive.

Though their eyes stay bright and attentive, affected animals tend to become more submissive and lethargic (Ayele *et al*., 2004). These broad indicators frequently become more noticeable following the cow's delivery. The hallmark of lung involvement is a persistent cough brought on by bronchopneumonia. The cough only happens once or twice at a time, is moist, and not very uncomfortable; it is more frequently triggered in the morning and during chilly weather (Bhatt *et al*., 2012). It is important to rule out bovine tuberculosis when there is a persistent loss of appetite and health, reduced milk production, and a crippling illness with or without respiratory symptoms.

In more severe situations, swollen lymph nodes may impede the digestive system, blood vessels, or airways. Head and neck lymph nodes may seem affected and occasionally rupture, releasing fluid (Skuce *et al*., 2012). Occasionally occurring diarrhea and constipation are signs of gastrointestinal tract involvement (Malikowski *et al*., 2018). Bloating may be brought on by pressure on the esophageal mediastinal glands, which are swollen. Dysphagia results from enlargement of the retropharyngeal glands (Rana *et al*., 2013). In the latter stages of tuberculosis, extreme emaciation and acute respiratory distress are possible. Male genitalia are rarely afflicted by lesions, although female genitalia can experience them occasionally (Borham *et al*., 2022). The significance of tuberculous mastitis stems from its potential harm to public health, its ability to spread to the clavicle, and the challenge of distinguishing it from other types of mastitis (Farrokh *et al*., 2019).

Descriptive statistics and regression models are used in data analysis to demonstrate that the majority of tuberculosis lesions are found in the respiratory system's lymph nodes and lungs (Tulu *et al*., 2021). Typically, the disease has a protracted course and takes months or years to manifest symptoms. Clinical indicators that are frequently observed include anorexia, big, conspicuous lymph nodes, diarrhea, udder induration, recurring cough, weakness, loss of appetite, weight loss, and fluctuating temperature (Islam *et al*., 2021). Although it is mostly a crippling chronic illness, it can occasionally be acute and advance quickly (Menin *et al*., 2013).

The majority of infected livestock may be detected early because symptoms of infection are uncommon in nations with disease eradication initiatives (Good and Duignan, 2011). In the latter stages, gradual emaciation with fever, weakness, and irregular appetite are typical signs (Ramos *et al*., 2015). When exercising in cold weather in the morning, animals suffering from pulmonary disease typically have a more severe cough and may even get tachypnea or dyspnea (Sichewo *et al*., 2020). In their later stages, animals may experience respiratory problems and severe malnutrition. Animals become disoriented, unable to climb, and observed roaming around during the day in the later stages of the disease (Tschopp *et al*., 2009).

Human tuberculosis, which is caused by *M. bovis*, is typically a persistent and crippling illness. In the early stages of the disease, there are no symptoms (Torres-Gonzalez *et al*., 2016). Nevertheless, gradual emaciation, low-grade fever that fluctuates, weakness, a decrease in appetite, and nocturnal sweats characterize the last stages (Allen *et al*., 2021). Dyspnea, chest pain, wet cough, and tachypnea can all be symptoms of lung infection. Changes in temperature and changes in appetite are typically linked to this illness (Good *et al*., 2018).

Diagnosis

Clinical diagnosis

Clinical signs are used to make a provisional diagnosis of bovine tuberculosis. Cattle with bovine tuberculosis typically take months to show clinical symptoms. Additionally, infections can lie latent for years before resurfacing in old age or during stressful situations. Clinical indicators of an *M. bovis* infection include low-grade fever, persistent weakness, wet cough, and swollen local lymph nodes (Lema and Dame, 2022).

Post mortem diagnosis

To detect tubercles, the lymph nodes, particularly those connected to the head, chest, and belly, are closely inspected during the postmortem examination (Ramos *et al*., 2015). The progressively developing tubercles, known as granulomas, in every bodily tissue and organ are indicative of severe pathological alterations in the carcass. These granulomas typically have a yellowish hue, are caseous or calcified, and are frequently encapsulated (Carrisoza-Urbina *et al*., 2019). Certain species, like deer, have lesions that more closely resemble abscesses than ordinary tubercles (Gormley and Corner, 2018). Certain tubercles are so tiny that they must be sliced open to be seen with the naked eye. Tubercles in cattle are typically seen in the lymph nodes on the head and chest. This typically affects the surface of bodily cavities, the lungs, the spleen, and the liver (Palmer *et al*., 2022).

Tuberculin skin test (TST)

The TST involves injecting *M. bovis* pure protein derivative (PPD) tuberculin subcutaneously, followed three days later by looking for swelling (delayed hypersensitivity) at the injection site (Coad *et al*., 2010). For many years, the TST has been an effective epidemiological and diagnostic tool for managing tuberculosis in cows (Carneiro *et al*., 2021). The injection is referred to as tuberculin. The protein solution found in the cell walls of *mycobacterium* species is utilized to produce tuberculin (Maitra *et al*., 2019). The injection of this protein solution into the skin of an infected animal triggers a local inflammatory reaction by the body's sensitized immune system, which results in the telltale signals of a positive tuberculin test (Encinales *et al*., 2010). There would not be an inflammatory response in animals who have not been exposed to bovine tuberculosis.

IFNɣ assay test

This test is usually carried out in the laboratory by using freshly collected blood samples. It involves measuring the level of a type of ctytokine (an immunological messenger protein) which is called "interferon gamma (IFNɣ)". The white blood cells of cattle release IFNɣ when they are infected with tuberculosis after stimulation with bovine and avian tuberculins. Blood samples from cattle infected with bovine tuberculosis can be used to measure the IFNɣ level (Ghielmetti *et al*., 2021).

Bacterial isolation

Mycobacteria can be isolated using Lowenstein-Jensen media, while *M. bovis* can be isolated by cultivating on media (Claro-Almea *et al*., 2020). Eugenics is the term used to describe the profuse development of *M. tuberculosis* on glycerol-containing media, which gives the colony characteristics of being glossy, hard, and rough (Keating *et al*., 2005). Eugenics is another term for the growth of *M. avium* on glycerol-containing media (Mayahi *et al*., 2013). *Mycobacterium bovis* grows poorly in medium containing glycerol, a condition known as dysgenic growth, but grows effectively on media containing pyruvate in the absence of glycerol (Claro-Almea *et al*., 2020). The international gold standard for determining mycobacterial infection is still bacterial culture. However, it is difficult and time-consuming to identify *M. bovis* using culture and biochemical approaches because of its dysgenic features and slow growth (Yatbantoong and Rukkwamsuk, 2017). Furthermore, the utilization of molecular techniques is costly due to the need for sufficient laboratory resources and skilled personnel.

Molecular diagnostics

The typical test protocol for *M. bovis* can be laborious, slow, complex, inaccurate, non-reproducible, and time-consuming. It can also produce ambiguous results and be executed outside of a laboratory. However, direct detection of *M. bovis* in clinical samples is also possible using molecular methods like PCR (Mishra *et al*., 2005). PCR is very helpful for the direct detection of *M. bovis* in samples of bovine tissue and has been effectively used to identify members of the *M. tuberculosis* complex (Santos *et al*., 2020). Other studies have indicated the usefulness of multiplex-PCR as a complementation tool in differentiating *M. bovis* from other cultured *M. tuberculosis* Complex (MTC) species as they applied a multiplex-PCR to differentiate *M. bovis* from MTC by one-step amplification based on simultaneous detection of *pncA* 169C > G change in *M. bovis* and the *IS6110* present in MTC species (Spositto *et al*., 2014). Additionally, distinct *M. bovis* strains can be distinguished from one another using genetic fingerprinting methods like spoligotyping. A molecular epidemiological surveillance study of 940 positive mycobacteria growth indicator tube (MGIT) cultures that were collected from patients with suspected tuberculosis visiting an outpatient department in a hospital in India using a PCR-based and whole-genome sequencing (WGS) approach indicated that isolates consisted of *M tuberculosis* [913 (97·1%) isolates], *Mycobacterium orygis* [seven (0·7%)], *M bovis* bacillus calmette-guerin (BCG) [five (0·5%)], and non-tuberculous mycobacteria [15 (1·6%)]. Subspecies were assigned for 25 isolates by WGS, which were analyzed against 715 MTBC sequences from south Asia. Among the 715 genomes, no *M bovis* was identified. Four isolates of cattle origin were also dispersed among human sequences within *M tuberculosis* lineage 1, and the seven *M orygis* isolates from human MGIT cultures were dispersed among sequences from cattle (Duffy *et al*., 2020). This study showed that *M bovis* prevalence in humans is an inadequate proxy of zoonotic tuberculosis. Additionally, the recovery of *M orygis* from humans highlights the need to use a broadened definition, including MTBC subspecies such as *M orygis*, to investigate zoonotic tuberculosis. The identification of *M tuberculosis* in cattle also reinforces the need for One Health investigations in countries with endemic bovine tuberculosis (Duffy *et al*., 2020).

Enzyme-linked immunosorbent assay (ELISA)

Tests such as ELISA (B cell-mediated immunity) is one of the options for detecting antibodies. The degree to which certain antibodies bind to antigens is not directly measured by the ELISA technique (Waritani *et al*., 2017). The purified antigens of *M. bovis*, such as the Ag85 antigen, which comprises the majority of secreted proteins, MPB70 and MPB83 protein, which are highly homologous mycobacterial proteins with restricted distribution, are the antigens typically utilized to diagnose livestock infected with *M. bovis* (Wiker, 2009). The benefit of ELISA is its ease of use; nevertheless, its sensitivity is primarily reduced because to the weak and non-teraturing humoral response in the sap throughout illness progression (Sakamoto *et al*., 2018). ELISA may be easily automated to process a large number of samples at a comparatively low cost.

Transmission

The majority of data on zoonotic mycobacterial transmission originates from studies conducted on *M. bovis*. These germs can be found in respiratory secretions, milk, vaginal secretions, semen, urine, feces, and exudates from lesions (such as lymph node drainage and some skin lesions), depending on the location (Bolaños *et al*., 2017). The degree of infection varies between species and can happen multiple times. When the respiratory system is impacted and the disease progresses to later stages with more extensive lesions, there is an increased risk of *Mycobacterium bovis* transmission (Phillips *et al*., 2003). This bacteria spreads more easily when people are in close quarters. Additionally, the illness has been cultured from the oral secretions of certain animals, such as ferrets, which may make bites a more effective means of transmission (Palmer *et al*., 2012).

Animals can also contract an infection by direct contact with infected skin wounds or mucous membranes, ingestion, or inhalation (Phipps *et al*., 2018). When causing an infection by swallowing, a far higher concentration of bacteria is typically required than when inhaling them (Ayalew *et al*., 2023). The significance of different transmission pathways differs depending on the host species. Aerosols from close contact can frequently infect cattle. In this species, ingestion-based transmission is uncommon, with the exception of breastfeeding calves of infected cows (Herrera-Rodríguez *et al*., 2013). Although it seems uncommon, dermal, genital (sexual), and congenital transmission are all possible in cattle (Skuce *et al*., 2012). Most of the time, these germs are most likely spread by aerosol; however, one cow event may have been caused by hay tainted with urine (Good and Duignan, 2011).

In a number of other animals, including camels, monkeys, and civets, inhalation transmission is also believed to predominate (Mohamed, 2020). However, it is believed that ingestion occurs most frequently in deer, horses, cats, and ferrets (Broughan *et al*., 2013). Particularly in hunting or combative species like cats and ferrets, percutaneous transmission is observed (De Garine-Wichatitsky *et al*., 2013). When cats wash their mucous membranes after feeding, they may also introduce bacteria into those membranes (O'Halloran *et al*., 2019). It is believed that dogs with kidney lesions can spread *M. bovis* through their urine in kennels (Allen *et al*., 2021). There have been reports of nosocomial transmission at veterinary clinics. In one instance, probably by hand or clothing, bacteria from an ill cat were transferred to a healthy feline patient undergoing surgery (O'Connor *et al*., 2019). Additionally, raw meat consumption has been associated with bTB transmission, especially among carnivorous domesticated, wild, and captive animals when they consume infected raw meat (Deneke *et al*., 2022).

Similar to animals, humans can contract an infection through eating, inhalation, or direct contact with wounds on their skin or mucous membranes (Phipps *et al*., 2019). Oral infection is a common form of exposure when consuming unpasteurized dairy products (Collins and More, 2022). Additionally, raw or undercooked meat and other animal tissues contain *M. bovis* (Clausi *et al*., 2021). Human cases are rarely linked to animal bites. It is possible for an infection to spread from person to person, particularly through the respiratory system (Sichewo *et al*., 2020). At least one investigation raises the possibility of *M. bovis* respiratory transmission through casual community contact, although these occurrences typically involve intimate contacts, such as family (Torres-Gonzalez *et al*., 2016). There is also a chance that *M. microti* can spread from person to person (Emmanuel *et al*., 2007). There are records of human-to-animal transmissions of *M. bovis* and *M. orygis* (Baker *et al*., 2006; Sumanth *et al*., 2023).

The factors that impact the environmental survival of *M. bovis* and its closely related species are temperature, humidity, sunlight exposure, temperature and humidity changes, competition with other microorganisms, and initial bacterial load (Barbier *et al*., 2017). Particularly in cold, dark, and moist environments, *M. bovis* can live for several months in soil and other materials (such as food and excrement) (Fine *et al*., 2011). However, the illness goes away in a matter of days or weeks, particularly in situations where it is exposed to dry conditions, high temperatures, and intense sunshine (Broughan *et al*., 2016). It has been documented that *M. bovis* can survive for up to a year in ideal laboratory settings when grown in dung or soil (Robinson, 2019). The quantity of viable *M. bovis* considerably dropped within the first two weeks of one investigation, which investigated soil, water, straw, and shelled maize stored outside in open containers (Fine *et al*., 2011). However, a tiny number of bacteria survived longer. *Mycobacterium bovis* is rarely isolated from soil or pastures grazed by infected livestock, but it is unclear whether this is due to the inactivation of the microorganism or difficulty in isolating it from locations with competing bacteria that grow more easily in cultivation.

Risk factor

In humans

Human populations living in poverty, poor socioeconomic groups, low income, low immunity (including AIDS), extreme age groups (old age and children), specific ethnic groups, migrants, and contacts with animals exposed to *M. bovis* are all thought to have a significant risk of contracting bovine tuberculosis (Toribio *et al*., 2023). In some societies around the world, the consumption of raw meat and unpasteurized milk is a deeply-rooted cultural habit. In fact, some people have the opinion that the pasteurizing and boiling process destroys the milk. Additionally, in some countries, such as Ethiopia, eating raw meat or half cooked meat such as poultry, beef, mutton, goat, and fish is very common and culturally acceptable while eating other types of meat such as pork is a cultural taboo while camel meat is acceptable in the Muslim community (Deneke *et al*., 2022). In such countries where pasteurization and poor milk and meat hygiene are not properly and widely practiced, about 10%–15 % of all human TB cases are likely caused by *M. bovis* (Deneke *et al*., 2022). The likelihood of spreading *M. bovis* also rises with proximity to and length of interaction with *M. bovis* carriers (Devi *et al*., 2021).

In animals

Cattle breed, physiological state, age, genetic resistance, sex, concurrent infections, stress, immune status, and body condition score are examples of animal-level risk factors (Kazwala *et al*., 2001). Numerous research studies have demonstrated that different breeds of cattle may differ in their susceptibility to bovine tuberculosis; one such study indicates that native zebu cattle are more resistant to the disease than foreign varieties (Vordermeier *et al*., 2012). Genetically modified animals may experience more severe hunger and housing shortages, making them more prone to illness (Mohamed, 2020). The age of the animal is one of the primary risk factors for animals that have been found by numerous research in both developed and developing nations. Age increases the length of exposure (Humblet *et al*., 2009).

Young animals may contract the infection, but symptoms don't manifest until they are adults (O'Brien *et al*., 2023). Mycobacteria can lie dormant in elderly animals for extended periods of time before reactivating. Animals often exhibit a reduced reaction to the tuberculin test as they get older (over 5 years old), as the immunological response likewise diminishes (Byrne *et al*., 2022). Management procedures or behavioral patterns may be influenced by gender-related variables. During breeding, male animals may interact with other herds more frequently, which raises the possibility of illness (Mekonnen *et al*., 2019). Insufficient feed or an inadequate diet resulting from insufficient protein, minerals, and vitamins might weaken an animal's fight against bovine tuberculosis (Carwile *et al*., 2022).

The quantity of herds, the types of livestock practices and cattle housing, animal-wildlife contact, the introduction of new cattle into the farm, herd movement and trade, and the history of bovine tuberculosis in animal groups and humans who have contracted the disease from *M. bovis* in the home are all examples of risk factors for the spread of bovine tuberculosis (Dejene *et al*., 2016). Under nomadic circumstances, herd contact and an increase in the overall size of the herd both greatly raise the risk of exposure to *M. bovis* (Skuce *et al*., 2012). Potential risk factors include the disease prevalence rate in the territory or reservoir host of the domestic animal, the size of the herd (density) of wildlife, and the history of *M. bovis* in wildlife populations in the past when there is direct wildlife interaction or sharing the environment with domestic livestock (Fitzgerald and Kaneene, 2013).

Public health importance

Since there is no clinical, radiographic, or histological distinction between tuberculosis caused by *M. tuberculosis* and *M. bovis*, tuberculosis in humans caused by *M. bovis* is typically underestimated or underdiagnosed. Although *M. bovis* is not the primary cause of tuberculosis in humans, humans can contract the disease by inhaling droplets, eating raw milk, meat, and other animal products, or by coming into direct contact with sick animals (Olea-Popelka *et al*., 2017). An estimated 10% of human tuberculosis cases are thought to be caused by *M. bovis*, with *M. tuberculosis* being the primary cause (Müller *et al*., 2013). Human tuberculosis cases caused by *M. bovis* will decrease in nations where pasteurized milk is utilized and where successful bovine tuberculosis programs are put in place (Davidson *et al*., 2017). However, disease reporting is more common in regions where cattle disease is poorly managed. The incidence rate is higher among those who work in slaughterhouses, breed livestock, and other related fields (Mia *et al*., 2022).

Human infections can result from exposure to non-cattle species. Goats, captive-bred deer, seals, and rhinoceroses have all been reported to be potential reservoirs of bovine tuberculosis (Cousins *et al*., 1993; Napp *et al*., 2013; Busch *et al*., 2017; Dwyer *et al*., 2020). Wild animals may be the source of the bacteria, particularly in nations where people frequently consume wild animal meat (De Garine-Wichatitsky *et al*., 2013). This demonstrates the high rate of tuberculosis transmission in the community, indicating the need for urgent attention from the perspectives of public health and the economy. The presence of tubercle bacilli raises the risk of lung and bladder cancer, and this condition produces chronic granulomatous disease (Fol *et al*., 2021). Bladder cytotoxicity caused by BCG cleared the path for the introduction of BCG immunotherapy as a bladder cancer treatment (Guallar-Garrido and Julián, 2020).

Economic impact

Accurately estimating the financial impact of bovine tuberculosis on animal output is extremely challenging. This illness generally lowers cattle productivity and could have a negative financial impact on the livestock business, particularly the dairy industry (Tschopp *et al*., 2021). The effect of infection risk on people is especially significant, since women and children seem to be more susceptible to the illness in nations with low socioeconomic status and inadequate veterinary and public health care (Agbalaya *et al*., 2020). All available data show that there are significant global economic losses due to bovine tuberculosis, even though estimates of the expenses connected with the disease and its control only apply to certain nations (Pérez-Morote *et al*., 2020). These losses cover costs associated with putting monitoring and control measures into place as well as losses from animal production, markets, and trading (Tschopp *et al*., 2021). The losses resulting from bovine tuberculosis are especially noteworthy when they include endangered wildlife species.

In general, there are distinct effects of bovine tuberculosis on the domestic and global economies. The most noticeable effect of bovine tuberculosis in cattle is a direct reduction in productivity, which is divided into losses from livestock and losses from slaughter (Pérez-Morote *et al*., 2020). The expenses incurred for condemnation and livestock retention make up the losses resulting from slaughter; the former represents the animal's purchase price, while the latter represents a minor fraction of the carcass value (Kapalamula *et al*., 2013). Livestock losses include lower production of milk and meat, more reproductive effort, and the expense of replacing sick animals (Borja *et al*., 2018).

Bovine tuberculosis not only directly reduces production but also has significant negative economic effects on both domestic and international trade. Due to the restriction on importing animals and animal products from nations where the illness is enzootic, bovine tuberculosis has an impact on access to international markets (Humblet *et al*., 2009). Major repercussions of this circumstance also extend to other livestock-related economic sectors. Furthermore, bovine tuberculosis can lead to inefficiencies in global markets. For instance, nations that export animal goods but are economically inefficient and disease-free will earn more money than economically efficient countries who are unable to export such items because of enzootic bovine tuberculosis (Gong *et al*., 2021). There are significant economic ramifications when this disease is found in wildlife (De Garine-Wichatitsky *et al*., 2013). In addition to being more expensive and difficult to eradicate, bovine tuberculosis has the potential to disrupt entire ecosystems, with unpredictably negative effects on a variety of private domains, including tourism and agricultural land (Kemal *et al*., 2019).

Treatment

In particular, farm, pet, and zoo animals have been treated with antibiotics for bovine tuberculosis (Robinson, 2019). However, one should be aware that clinical improvement might occur even in the absence of a bacteriological cure. Even some initially responsive animals eventually relapse, particularly when treatment is insufficient (e.g., a single medicine is used or the length of treatment is too short) (Borham *et al*., 2022). Treatment is controversial due to the possibility of medication resistance developing, the risk of germs spreading, and the potential harm to people, particularly if there are drainage lesions or an infection of the respiratory system (Palmer and Waters, 2011).

Many popular antibiotics do not affect *M. bovis* complex members. Treatment for this illness is restricted to small doses of tuberculocidal medications (Chuang *et al*., 2020). Animal treatment typically follows human-successfully implemented techniques, with two or more medications administered concurrently over several months (Meiring *et al*., 2018). It should be kept in mind while choosing antibiotics that *M. bovis* is innately resistant to pyrazinamide, with very few exceptions (de Jong *et al*., 2005). The most effective first-line anti-tuberculosis chemotherapy consists of isoniazid, ethambutol, rifampin, and streptomycin (du Toit *et al*., 2006). Second-line drugs used against bovine tuberculosis include ethionamide, capreomycin, thioacetazone, and cycloserine (Sandhu, 2011).

In regions with official control programs, vaccination against bovine tuberculosis is rarely used to control the disease because BCG can trigger a cellular immune response, which can interfere with testing methods that use PPD as the antigen (TST and interferon gamma release assay) (Balseiro *et al*., 2020). A significant challenge is the absence of diagnostic techniques to distinguish between animals that are vaccinated and those that are infected. Furthermore, there are a number of difficulties with the live attenuated BCG vaccine, including its stability in unpredictable environmental circumstances and its potential for survival in bodily tissues, secretions, and the environment (Angelidou *et al*., 2020). Nonetheless, current research using BCG in cattle indicates that giving this medication to newborns is highly successful (Hope *et al*., 2005).

Control

The prevention and control of bovine tuberculosis is necessary because sick animals lose productivity and humans are at risk of contracting the disease. However, control efforts are not implemented or are not implemented well enough in the majority of developed countries due to financial constraints, a lack of skilled professionals, a lack of political will, and a low assessment of the importance of zoonotic bovine tuberculosis in the animal and public health sectors by national governments and donor agencies (Ramanujam and Palaniyandi, 2023). To prevent person-to-person transmission, patients infected with *M. bovis* should be treated with the same public health procedures used to treat patients with infectious *M. tuberculosis* (Silva *et al*., 2013). Cattle with tuberculosis should not receive any treatment at all, and any affected livestock should be slaughtered. This is because *M. bovis* is resistant to pyrazinamide, a medication that is frequently used to treat infections in people brought on by *M. tuberculosis* complex (de Jong *et al*., 2005).

To successfully control and eradicate bovine tuberculosis, developed nations have implemented routine testing and culling of infected animals under national mandatory programs. Interestingly, many industrialized countries have reached officially tuberculosis-free status. However, infection of cattle with *M. bovis* still occurs in most countries around the world, especially in low- and middle-income countries because bTB control programs are often not implemented. This non-implementation is mostly because standard TB control through testing and culling, movement control, and slaughterhouse inspection is too expensive or ethically unacceptable, sometimes due to religious reasons (Gortázar et al., 2023). Additionally, some countries lack sufficient knowledge on the MTB complex maintenance community which draws back improvements in TB control by targeting the whole host community (Gortázar et al., 2023). For a successful bTB control, evidence of close interactions among all forms of possible hosts needs to be addressed synchronously.

Between 1953 and 1980, this program was successful in many European Union member states as well as seven countries in central Europe (Jemal, 2016). It is necessary to provide specific hygiene standards for foods of animal origin to stop diseased animals from getting into the food chain and lower the hazards connected with consuming tainted milk and meat (Tora *et al*., 2022). Systems for inspecting meat need to be improved and intended to stop the general population from consuming tainted goods. An examination must be performed both pre- and post-mortem on any animal that enters the food chain (Clausi *et al*., 2021).

The tuberculin test is the primary method for detecting bovine tuberculosis in cows (Coad *et al*., 2010). Standard bovine tuberculosis control techniques include testing and slaughterhouse inspection (Ramos *et al*., 2022). This disease will be lessened with the use of meat screening in slaughterhouses and the identification of the animals' herd origin (Abbate *et al*., 2020). The early detection of preclinical infection in animals meant for food production and the prompt removal of diseased animals from the herd will prevent future sources of infection for people and other animals, making tuberculin testing helpful in the control of bovine tuberculosis (Good and Duignan, 2011). A tuberculin test needs to be done on cattle 12 months before slaughter. Collaboration between veterinary and medical specialists is crucial in the event of a disease outbreak.

Conclusion

Bovine tuberculosis is a global disease that affects the cattle-producing industry greatly economically. However, the requirement for pasteurization of milk, tuberculin testing of cow skin, and culling of diseased cattle has resulted in a dramatic drop in the incidence of human tuberculosis caused by *M. bovis* in developed countries. The prevention and control of bovine tuberculosis is necessary because sick animals lose productivity and humans are at risk of contracting the disease.

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Author's contributions

ARK, IBM, YP, and MKJK drafted the manuscript. SRA, WT, and FAR revise and edits the manuscripts. OSMS, IF, and SA took part in preparing and critical checking this manuscript. AH, SMY, HMR, and NN edits the references. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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Data availability

All references are open access, so data can be obtained from the online web.

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