Chapter 44

Vaccination and Alternate Control Strategies to Control *Mycobacterium* Species

Amina Umar[1], Soha Fatima[2], Nimra Tabassum[2], Hassaan Bin Sajid[2], Husnain Hayder[1], Nouman Tariq[1], Abubakar Amjad[1], Muhammad Suleman[1], Muthhar Ali[1] and Muhammad Rizwan*[3]

[1]Faculty of Veterinary Science, University of Agriculture Faisalabad
[2]CABB Department, University of Agriculture Faisalabad
[3]Department of Clinical Medicine and Surgery, Faculty of Veterinary Science, University of Agriculture Faisalabad
*Corresponding author: rizwanjavaid3361@yahoo.com

ABSTRACT

Tuberculosis is a disease caused by *Mycobacterium species* that results in severe illnesses and poses a danger to worldwide health because of their complicated pathogenicity as well as widespread epidemiology and ability to damage the immune system. Managing numerous bacterial infections which mainly concentrate on immunization as well as nontraditional measures, were discovered in this chapter. For the prevention of infections, different inoculation options are studied along with the detailed cycle of disease as well as epidemiological trends of diverse mycobacterial bacteria. A rare of these procedures consist of the usage of both live as well as dead mycobacteria along with protein-based as well as DNA vaccines that can help to deteriorate damaging strains such as *Mycobacterium bovis*. The occurrence of mycobacterial diseases requires more necessary action, despite the progress in vaccine advancement. A hopeful alternative is phage therapy, which attacks and destroys *Mycobacteria* using bacteriophages. Procedures of immunotherapy are being examined for their capability to improve the host's protected response mostly includes the use of cytokines such as interleukin-2 also Granulocyte-Macrophage as well Colony-Stimulating Factor along with interleukin-24 and interleukin-32. Antibody to control tuberculosis is occasionally observed as an important component of a comprehensive therapeutic method. To control the spread of disease-causing mycobacterial infections, genetic resistance methods in hosts along with environmental and management plans designed to lower the contact and spread. This chapter aims to add valuable contribution to worldwide efforts to reduce the load of these pathogens by integrating these numerous plans in a direction to advance the knowledge of present involvements as well as excite the formation of innovative approaches to fight *Mycobacterium* species in both humans as well as veterinary medicine.

KEYWORDS
Bacteria, Tuberculosis, *Mycobacterium*, Alternatives, Vaccination

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INTRODUCTION

Various collections of bacteria involved in *Mycobacterium* species are liable for important diseases in humans as well as animals, for example, tuberculosis (TB) and Leprosy (Barletta and Steffen, 2022a). Stoppage and control of these diseases are important for public health along with veterinary medicine (Palma et al., 2020). This chapter explores managing mycobacterial infections through vaccination strategies and alternative control measures.

The Mycobacteriaceae family has a genus of bacteria with it called *Mycobacterium*. *Mycobacterium* species have many features like no spore-forming and not a motile bacterium with a bacillus formation (Parija, 2023). Pleomorphism is another feature, which means they can change their formation from round to rod-shaped (Pavlova et al., 2022). They are similar to gram-positive bacteria as well as they need staining of acid-fast to differentiate from other bacterial species (Ullberg and Özenci, 2020). The genus *Mycobacterium* comprises different bacteria that could be disease-causing pathogenic, saprophytic as well as opportunistic, or may be nonpathogenic (Rigouts and Cogneau, 2021).

The fame of *Mycobacterium* species is for causing a disease called tuberculosis, which mostly affects the human breathing system. Yet a variety of other diseases were also caused like affecting different organs and systems (Adamowicz et al., 2023). For example, widespread cutaneal problems in humans are caused by *M. ulcerans*, while cutaneous, hypodermic, and internal infections are due to *M. abscessus* (Tan et al., 2020). Furthermore, species that cause disease in both humans and animals are *M. avium* complex, *M. kansasii* as well as *M. bovis* (Stabel et al., 2021). Various reptiles, fish,

birds, and mammals were also affected by other *Mycobacterium* species.

As predicted one-third of the world's people are diseased by *Mycobacterium tuberculosis* making Tuberculosis (TB) an important worldwide health issue. Presently, there are around 1.5 million fatalities along with 9 million new infections yearly. To protect children from getting severe TB, the only licensed TB vaccine available is the Bacille Calmette Guerin (BCG) vaccine. But in adults, its efficiency against lung TB ranges from 0 to 80% depending on topographical location. Another important factor is that it is not appropriate for persons whose immune systems are compromised. There is an immense need for improving TB vaccines because vaccination is known as the most operative method for preventing and controlling infectious diseases.

After COVID-19, TB is one of the important causes of mortalities from infectious diseases around the cosmos. COVID-19 has a bad impact on TB-related health services that involves late analysis and treatment as well as new vaccinations wrong way up the previous declining trends in TB deaths (Allué-Guardia et al., 2023). The World Health Organization (WHO) developed the End TB Plan in 2015 whose aim is to reduce the deaths cases along with costs related to tuberculosis worldwide. According to strategy, the goal set for 2025 includes a 75 percent decrease in the number of deaths as well as a 50% drop in TB cases in comparison to 2015. A 95% decrease in TB deaths as well as a 90 percent decrease in TB cases will be achieved by 2035. Nevertheless, to meet these striving targets many countries are currently not on track due to their own economic and political reasons.

Effective vaccination along with alternative control methods are important because *Mycobacterium spp*. hurt human as well as animal health (Balseiro et al., 2020). Bacillus Calmette-Guerin (BCG) vaccine is currently available which offers some defense against tuberculosis but is not much curative against other *Mycobacterium* infections. Immunotherapies and new vaccines need more research to give wider as well as more effective defense (Fatima et al., 2020). Various alternative methods include phage therapy along with antimicrobial peptides, a different vaccine in combination with immunomodulators as well as some managemental and genetic modifications that show promise in managing *Mycobacterium* infections (Allué-Guardia et al., 2021). To reduce the spread and brutality of diseases caused by *Mycobacterium spp*. implementation of these strategies is necessary.

An Overview of *Mycobacterium* Species

A varied group of bacterial species that show different levels of disease in humans as well as animals is included in the *Mycobacteriaceae* family which shows different host reservoirs along with growth patterns in agar (Barletta and Steffen, 2022b). Usually, *Mycobacteriaceae* bacteria have different characteristics they are aerobic as well as no spore formation along with Gram-positive in nature, and are unable to be motile having acid-fast bacilli with a curved shape that may show some branches due to the presence of mycolic acid cell wall (Romagnoli et al., 2020). A complex cell wall structure is seen in members of the *Mycobacterium* genus that causes low absorbency. Ziehl-Neelsen acid-fast staining procedure is used to differentiate it from other bacterial species (Dulberger et al., 2020).

There are mainly two groups included in the *Mycobacterium* genus that can be differentiated by noticing their growth rates. *Mycobacterium bovis*, *Mycobacterium tuberculosis* as well as *Mycobacterium leprae* are included in slow-growing *Mycobacteria* and they are answerable for bovine TB (BTB), human TB (TB), and leprosy (Byrne et al., 2020). While opportunistic or non-pathogenic bacteria are included in the fast-growing group that bacteria like *Mycobacterium smegmatis*.

MTBC which means *Mycobacterium tuberculosis* complex is a group of bacteria from the *Mycobacteriaceae* family that includes *M. tuberculosis* as well as *M. africanum* also including *M. bovis*, *M. canettii* along with *M. microti* and some other species *M. pinnipedii*, in addition with *M. caprae* (Kanabalan et al., 2021). Additionally, two new species *M. orygis* and *M. mungi*, are also added to the *Mycobacterium tuberculosis* complex (Islam et al., 2023). Some *Mycobacterium species* cause disease in particular animals which includes *M. bovis* cause disease in bovines (Bespiatykh et al., 2021), M. caprae cause disease in small ruminants including goats and sheep*, M. pinnipedii* usually affects sea creatures like sea lions or seals, *M. microti* infect the voles and *M. orygis* develop an infection in oryxes (Delghandi et al., 2020).

Pathogenesis and Epidemiology

To develop operative control strategies for the prevention of mycobacterial disease the understanding of pathology as well as epidemiology is important (O'Brien et al., 2021). Localized infections or systemic distribution of Mycobacterial infection occur when bacteria enter the host body by inhaling or ingestion that involve the respiratory system or digestive system respectively. The key feature that is involved in pathogenesis is bacteria's capability to live and reproduce within macrophages of Immune cells (Mir et al., 2022). Spread of disease occurs via straight contact, dirty food with water, or aerosolized droplets that enter through the mouth or nose.

The *mycobacterial* species that cause disease in animals especially those that have zoonotic importance and also cause diseases in humans were the primary focuses in the epidemiology of *mycobacteria* (Gebreyes et al., 2020). *M. bovis* is a bacterium that causes disease in cattle but can be spread to humans and develop zoonotic infections. Some other mycobacterial species such as *M. avium* an opportunistic bacterium in both animals and humans often linked with environmental causes (To et al., 2020).

The factors that influenced mycobacterial epidemiology include animal farming practices, environmental circumstances as well as the presence of a reservoir of wildlife species (Pereira et al., 2020). Managing disease in both

animals as well as humans requires an understanding of transmission, control measures, and risk factors is vital. Changes in environmental circumstances along with their effect on the appearance and spread of infection require continuous research to evolve better solutions (Destoumieux-Garzón et al., 2022).

Gross Pathologic Features of MTC Disease

The Latin term "tuberculum" which has meaning of lump or nodule is the main word from which the word "tuberculosis" is derived (Yousaf Kazmi, 2022). The lumps or nodules that form in the disease tuberculosis are called "tubercles". The most important gross lesion in tuberculosis that can be seen by the naked eye is a fixed, yellow to white or maybe grayish tubercle, and size is between pinpoint to some centimeters in width in immunocompromised animals the lacerations may be more diffused (Borham et al., 2022).

In cattle, the culprit bacteria is *M. bovis* which causes Tuberculosis. The nasal and oral routes are mostly seen but by skin contact, inherited and genital routes were also seen in some cases. In the start sub lobular or maybe lobular lacerations are seen that spread to the respiratory lymph nodes (Tiwary et al., 2022). Calcified caseated lesions developed in the lungs and lymph nodes. Caseating bronchopneumonia occurs due merging of nodules in the lungs. Cavitations along with ulcers in the trachea or bronchi are commonly seen in long-lasting cases. In the fulminating course of disease miliary lung lesions are also seen (Stephenson and Byard, 2020). Pleural involvement occurs when the disease spreads to the serosal layer having sessile, pedunculated, or sometimes cauliflower-like erections that lastly calcify and result in forming solid white nodules. Therefore, pearl disease is the name given to pleural tuberculosis (Borham et al., 2022b). The infection spreads to main organs like lymph nodes, skeletal muscles as well as serous membranes together with the peritoneum membrane as well as pericardium layer along with meninges in the nervous system. In advanced respiratory disease and the oral route of infection nodules and ulceration may be existing in the upper portion of the digestive tract and abomasum. Small and large intestines of cattle were also affected by ulcerative lesions (Esteves et al., 2021). There few cases where dermal infections were seen and it restricted to the place of lymph nodes. The uterus or epididymis may be diseased through genital contaminations but these are not common. The newborn fetus is infected through congenital tuberculosis and the disease is spread via umbilical vessels that involve hepatic and abdominal lymph nodes which can turn into general disease. MTC causes inflammation of the uterus that leads to endometritis in the dam and is essential for the transfer of congenital infection (Figueiredo et al., 2021). Although recurrent abortions and infertility result due to extensive uterine disease. The mammary glands shed bacteria in milk due to MTC infection that result in spread and contamination of milk.

There are rare cases in which cattle are affected by ulcerative lymphangitis which is commonly known as "skin tuberculosis." The precise information about which type of organism causes the disease is not known yet, nevertheless, compatibility with *M. bovis* or *M. kansasii* is seen due to low numbers of acid-fast bacilli under the microscope (Konieczny and Pomorska-Mól, 2023). The lesion appears first as subcutaneous nodules attached to the skin. Ulcerative nodules are mostly seen with other nodules that mostly form sideways to the lymphatic system. Lesions are cured after bursting and evacuating the material inside but sometimes nodules unite to form huge masses of connective tissue and pus-filled substance (Naafs et al., 2020). Local lymph nodes were not involved in this and the culturing and identification of animals is not possible. Tuberculin skin tests may or may not show results in infected animals (Srinivasan et al., 2020). Principally *M. bovis* sometimes causes disease in Sheep and goats and leads to MTC disease but normal or natural cases are very rare (Mahomed et al., 2023).

Proliferative enteritis occurs in horses due to organisms of the MAIC causing a disease closely similar to Johne's disease in cattle (O'Connell et al., 2023). Lesions are mostly seen in the intestinal tract but in severe cases, distribution of crudely nodular lesions is seen in the respiratory organs, some parts of the liver and spleen, tissues of the mammary gland as well as vertebrae of the cervical region, and skin is also involved (Urs et al., 2024). Involvement of reproductive system or nervous system lesions is occasional if it occurs.

Vaccination Strategies

Attenuation of Virulent Strains of *Mycobacterium Bovis*

The effectiveness of Bacillus Calmette-Guérin (BCG) was measured experientially. This weekend vaccine requires a single dose most of the time but some may need a booster for optimum protection (Setiabudiawan et al., 2022). All strains of BCG have a 9.5 kilobase (kb) deletion showed during recent genetic analysis and when it is related to infectious strains of *M. bovis* as well as *M. tuberculosis* it includes nine genes. Removing some genes involved in virulence or encrypting enzymes for serious metabolic pathways from infectious strains of *M. bovis* as well as *M. tuberculosis* should advance the BCG vaccine (Seral et al., 2024). In terms of antigenic outline, these mutants may look like infectious strains more closely than that of BCG henceforth showing improved vaccine effectiveness. Methods like jumping gene mutagenesis, and prohibited recombination along allelomorphic exchange have now been developed in molecular biology to deactivate genes in *M. bovis* along with this some screening methods have been recognized to categorize weakened mutants (Sukhija et al., 2023). To dodge any opportunity of return to an infectious strain through alteration an attenuated vaccine would be obligatory to have removal in two different genes to make it used fully in the field. To differentiate between vaccinated animals and those diseased with *M. bovis* would require advanced immunological screening methods. An immunological test makes a separation between vaccinated and non-vaccinated animals could be formed if the novel vaccine strain also

has one or more gene removals, the products of which DTH or another immunological response could be inspected (Aida et al., 2021). A wild-type *M. bovis* strain's esat-6 gene has been removed. In the primary trials, this mutant's vaccination triggered guinea pigs to respond powerfully to PPD-B but not to ESAT-6 protein in a skin test. A forceful reaction to PPD and ESAT-6 was seen in animals inoculated with the wild-type strain of *M. bovis*.

The loss of some metabolic activity in a strain is shown by auxotrophy, or the incapability to grow in a slight medium. Although the method has been functional to several bacterial diseases with victory to create weakened strains with vaccine potentials (Seif et al., 2020). In initial attempts to determine the usefulness of this approach, several attenuated strains of *M. bovis* were developed by chemical mutagenesis of a liquid culture with nitrosoguanidine. Following the screening of strains for auxotrophy, the auxotrophs were tested for virulence in guinea pigs. Two of these auxotrophic *M. bovis* strains, which were shown to be attenuated in guinea pigs, were tested for the protection of cattle against bovine tuberculosis. The calves in this experiment showed solid IFN-Y responses to PPD-A before vaccination, which may have shown that they were exposed to mycobacteria (Cooke et al., 2023). When BCG-vaccinated and control groups were compared, particularly fewer animals established tuberculous lesions following inoculation with any of the two auxotrophic *M. bovis* strains. The calf's previous contact to ambient mycobacteria may have role in BCG's failure to defend the cattle in this trial. The inoculations made from auxotrophic strains had 1-2 x 10° CFU/dose of living microorganisms, which was about 1 log1o extra than the BCG preparation (Conlan et al., 2021). Given that dosages of range 104–106 CFU BCG can produce equal amounts of resistance, it is unsure that this played a part in the enhancement of vaccine effectiveness. The newly-derived weakened *M. bovis* strains' overall efficacy in this setup is inspiring. These two auxotrophic strains required genetic changes that could be exposed despite rigorous hard work (Peres and Brock, 2022).

Many mutants of *M. bovis* have been formed by prohibited recombination to make weakened strains of the bacterium with precise deletions. In guinea pigs, it was confirmed that four mutants that were selected because they could not grow in a slight medium were attenuated. Two of these mutants formed a level of defense similar to that formed by BCG when exposed to infectious M. bovis (Gunasena et al., 2022). A 2bp chromosomal removal existed in one of these mutants, but a 15 kb big DNA removal including twelve genes existed in the future. The efficacy of these two strains as inoculations has freshly been examined in possums. Eight weeks after the strains were dermally vaccinated at an amount of 109 CFU, the possums were tested with virulent *M. bovis* spray. Upon post-mortem eight weeks after the test, the possums vaccinated with BCG or one of the auxotrophic strains showed far fewer lung lacerations and minimized body weight loss in contrast to the non-vaccinated controls (Telford and Goethert, 2020). Only the receivers of the auxotrophic strain inoculation, as opposed to the controls, had a spleen microbial count that was prominently lower. The possum model may help evolve better tuberculosis inoculations because few if any, new vaccinations verified in mouse or guinea-pig replicas prove more defense against tuberculosis than the BCG vaccine. This type of inoculation often produces prolonged (Balseiro et al., 2020b) and long-lasting resistance with fewer doses and has a robust and wide-ranging resistant response but has a risk of return to virulency in some cases as well is not appropriate for animals whose immune system is compromised.

Use of Live Vectors

Genes encoding mycobacterial antigens have been expressed using living vectors, such as the vaccinia virus as well as attenuated *Salmonella* strains. Nevertheless, the effectiveness of these vaccines against *M. bovis* has not been estimated. Meanwhile, most live vectors may be given oral or parenteral route, use of these for wildlife vaccination is remarkable (Osterloh, 2022). Fifty percent of the badgers that administered a dose of a live recombinant injection orally were protected against rabies. Boosting of the immune system by via M. bovis DNA vaccines may be achieved effectively using live viral vectors having mycobacterial genes, later this major boosting method has been confirmed to be fruitful in inducing healthy CMI responses to specific antigens of bacteria.

Killed Mycobacteria

The usage of dead mycobacterial vaccinations is supposed to be harmless than that of live, weakened *M. bovis* vaccines. Administration of this killed vaccine involves a single dose or maybe a sequence of doses which is dependent on the definite vaccine as well as the creature's time of life along with health status (Sefidi-Heris et al., 2020). However, conventional vaccines having killed mycobacteria joined with an oil accessory provoke a Th2-type immune response and offer a slight defense. It has been recommended to use a lifeless *M. vaccac* for tuberculosis immunoprophylaxis. It is supposed that *M. vaccac* applies its defensive assistance by making CMI responses to common mycobacterial antigens as well as by preventing the Koch phenomena of tissue necrotizing elements. In the direction to estimate the efficacy of the dead *M. vaccae* vaccine, calves were administered a sub-cut injection of vaccination having 109 CFU of the (Milián-Suazo et al., 2022) inoculation, surveyed by a trial with *M. bovis*. On comparison of the results the calves immunized with BCG have no protection for tuberculosis. Moreover, vaccinating badgers against tuberculosis with killed *M. vaccae* did not yield any defense. If *M. vaccae* was administered alone intraconjunctivally or through oral route in an initial trial including possums did not show any defense against *M. bovis*. But, defense against the *M. bovis* challenge was produced by the combination of both dead *M. vaccae* and live BCG. Later the spleen microbial count was significantly lesser with this mixture than with BCG (Noguera-Ortega et al., 2020). This study advocates that removing *M. vaccae* could advance the efficacy of the BCG injection as well as the efficacy of the BCG vaccine. This type of vaccine is safe for immunocompromised animals as well as it is unchanging and can be kept for an extended period but it often needs several doses to attain full protection as well as may not deliver robust or long-lasting protection as live vaccines are considered its disadvantages.

Mycobacterial Protein Vaccines

Using defensive protein antigens formed by live mycobacteria is the focus of an alternative approach. Probably, sub-unit immunizations would not make hindrance with investigative trials along with have their efficacy be impacted by animals being sensitive to environmental *mycobacteria* earlier (Amoroso et al., 2021). This vaccine requires many doses for full immunity as well and booster doses are also needed. It is found that proteins present in culture remain made from *M. tuberculosis* powerfully stimulate not only the T lymphocytes in patients having human tuberculosis as well as in experimentally diseased mice and also seen in cattle. The skill of antigens present in culture remains to provide defense has been exposed in several research by using tiny animal models (Ábalos et al., 2022). The highest levels of defense against aerogenic trial with *M. tuberculosis* were obtained by vaccinating mice as well as guinea pigs with culture filtrate proteins (CFP) obtained from tuberculosis. Likewise, it has been exposed that a CFP inoculation produced from *M. bovis* significantly defends mice against virulent *M. bovis*. When *M. tuberculosis* CFP was joined with adjuvants such as dimethyldeoctadecylammonium chloride (DDA) and administered in mice established cellular defense to mycobacterial antigens while the same combination in cattle did not show positive but a slight IFN-Y response was seen (Kaur et al., 2019). Although the administration of a diethyl aminoethyl (DEAE) dextran adjuvant in cattle helped make considerable antigen-specific antibodies as well as IL-2 responses. An *M. bovis-prepared* culture filtrate protein (CFP) vaccine along with lipid A adjuvant that comprised of the recombinant cytokine bovine IL-2 significantly improved antigen-specific antibody responses but minimum stimulation for antigen-specific IFN-y responses in cattle (Wedlock et al., 2000). In tested cattle, this inoculation reduced the overall mean tuberculous lung laceration value and did not reason for any tuberculin skin-test reactivity in the final test. while compared to non-immunized animals, these animals showed an advanced occurrence of extra-thoracic disease distribution.

These data demonstrate how challenging it is to bring strong antigen-specific IFN-Y results in cattle by using low-dose adjuvants. same adjuvants have not yielded the same results when used in cattle or small animal models. None of the sub-unit vaccines currently have formed antigen-specific IFN-y results in cattle up to this point that are equal to those formed by weakened *M. bovis* injections (Lowenthal et al., 1998). To enhance or produce better results for antigen-specific IFN-y responses, preparations with the most superior adjuvants along with the addition of other cytokines such as IL-12 or IL-18 make significant improvement. This type of subunit vaccine is safer than live vaccines because they do not have live pathogens and can be personalized to take in only the most immunogenic parts of the pathogen but may need adjuvants to improve the resistant response and provide shorter time protection as associated with live inoculations (Portielje et al., 2003).

DNA Vaccines

Although the uncomplicated idea behind DNA immunization is fairly straightforward and this kind of knowledge has freshly been established since the early 1990s. This type of injection is administered in a sequence with precise medicating procedures based on the vaccine. An expression of plasmid comprising a part of DNA encrypting a bacterial antigen is how a DNA vaccination is made (Li et al., 2020). The bacterial disease-causing antigen gene is enlarged in an altered bacterium employing this plasmid DNA and the host is vaccinated with the decontaminated plasmid DNA that possibly holds the antigen gene. A living cell is instantly transfected by this plasmid DNA. Inside the nucleus, this antigen-containing gene is decoded into RNA after this the RNA in the cytoplasm is translated into protein (Valizadeh et al., 2022). Eventually, the bacterial protein produced immunization in the host's cells and letting the initiation of strong humoral and cell-mediated responses that are strong and defensive.

In defense of the contradiction of tuberculosis in small animal models used in experiments shows that DNA vaccines have significant capacity. Important features of the TB disease while encrypting a solo protein or maybe epitope these inoculations have the potential to cause strong memory responses such as bringing IFN-y as well as cytotoxic T cell responses and help to provide protection (Duong et al., 2023). Protection is enhanced if Adjuvant molecules such as DNA CpG parts are involved in the vaccine as well and defense is also amplified if the DNA vaccine encodes for numerous proteins otherwise epitopes. DNA inoculations for tuberculosis have been revealed in a mouse model to be able to treat a disease which was a good achievement and news for application in wildlife. The element such as numerous vaccinations seems to be obligatory as a problem. Two of these immunizations produced immune serum globulin G1 (IgG1)-influenced humoral responses along with $CD4^+$ T cell responses while IFN-Y is modest, which is seen in a recent study led in cattle (Abo-Elyazeed et al., 2023). Key advantages of this type of vaccine are that it is unchanging and can be formed quickly and it brings both humoral and cellular protection responses but it is still comparatively new and less broadly used in veterinary medicine as well as regulatory support methods can be long (Montero et al., 2024).

In the field of veterinary medicine, vaccines of all types are vital particularly when it arises to control disease like Tuberculosis caused by Mycobacterium Bovis. The choice of a vaccine is based on a numeral variables like nature of the illness as well as the planned resistant response and the aimed animal type (Vannini et al., 2021).

Alternative Control Strategies

In addition to vaccination, alternative strategies play a crucial role in controlling mycobacterial infections.

Table 1: Vaccination Strategies Against *Mycobacterial* Species

Type of Vaccine	Dose	Mode of Action	References
Inactivated (Killed)	Single dose or series of doses	Stimulates immune response by introducing inactivated pathogens, prompting antibody production without causing disease.	(Tovey and Lallemand, 2010)
Live Attenuated	Usually, a single dose, may require a booster	Mimics natural infection, eliciting a strong immune response with both antibodies and cellular immunity.	(Mok and Chan, 2020)
Subunit	Often requires multiple doses with boosters	Presents key antigens to the immune system, leading to antibody production without risk of disease.	(Foged, 2011)
DNA	Typically, in a series, specific dosing guidelines	Host cells take up DNA, produce antigens, and trigger an immune response.	(Reyes-Sandoval and Ertl, 2001)
mRNA	Usually requires two doses	Cells produce the antigen from mRNA, leading to an immune response similar to live attenuated vaccines.	(Kowalzik et al., 2021)
Toxoid	Initial doses followed by boosters	Introduces inactivated toxins, prompting the body to produce antibodies against the toxin.	(Moylett and Hanson, 2003)

Phage Therapy

Phage therapy's goal is to fight tuberculosis along with other destructive mycobacterial diseases by using bacteriophages as a weapon. Bacteriophages are one of the most important techniques which have natural bacteria-killing capabilities. Bacteriophages are much more selective than antibiotics as well as they can remove mycobacteria without risking the body's helpful microbes (Khusro et al., 2016). when inoculated into the human body these bacteriophages stick to mycobacteria and start transporting their genome to them and after that, the phage increases till it lyses or breaks the bacteria. These newly formed phages will move to other uninfected ones till their individual population also goes destroyed and every disease-causing mycobacterium will have been removed (Ouyang et al., 2023).

Because of its important feature in which phage precisely targets antibiotic-resistant Mycobacterium strains it has numerous benefits. There is a lot of potential seen in phage therapy because of its excellent results in antibiotic-resistant bacteria (Hatfull et al., 2022). Also, bacteriophages can modify itself according to bacteria's resistance and remain to be effective against them. Phage medication is now being studied and the results are inspiring. It can be an active weapon against mycobacterial diseases meanwhile it offers an unfailing, effective, and safe substitute for outdated antibiotics (Melo et al., 2020).

Immunotherapy

Immunotherapy aims to enhance the host's immune response to control mycobacterial infections.

Cytokines

Proteins termed cytokines influence the development, delivery as well as the function of cells and help in directing the activities of the innate as well as adaptive protected systems (Arango Duque and Descoteaux, 2014). Although the recombinant human interferon (rhuIFN-γ) in addition to recombinant human interleukin-2 (rhuIL-2) along with α-tumor necrosis factor (TNF-α), as well as recombinant human granulocyte-macrophage colony-stimulating factor (rhuGM-CSF), are the most important cytokines used in medical applications or clinical experiments but the brief half-life along with high price of cytokine immunotherapy are its disadvantages (Mi et al., 2021a).

Interleukin-2

Th1-type immunization response cytokine IL-2 is elaborate in both immune cell activation as well as control. A study discloses that IL-2 can aim an alteration in the way genes are expressed in MTB-encouraged peripheral blood mononuclear cells (PBMCs) along with this can remove or reduce mucus germs in around 60% of people affected with MDR-TB who are also getting (Daichou et al., 1999). Yet, everyday intradermal inoculation of rhuIL-2 could not show signs or improve bacillar clearance in persons with drug-prone TB, according to information from a double-blind controlled medical trial. So, there is changeability in the scientific results of rhuIL-2 in combination with chemotherapy for MDR-TB or stubborn pulmonary tuberculosis (PTB) (Mealey et al., 2008). Additionally, rhuIL-2 immunoadjuvant treatment was safe for PTB/MDR-TB affected people along with improving the growth and revolution of CD4+ T cells as well as NK cells, thus growing the amount of sputum that is bacteria-negative in TB patients (Mi et al., 2021b). Yet, no visible enhancement was seen in radiographic variations in TB patients. In China, a 24-month multicenter, huge-sample potential scientific investigation is being led to assess the properties of rhuIL-2 adjuvant treatment for MDR-TB (Sheng et al., 2022).

Granulocyte-Macrophage Colony-Stimulating Factor

A monomeric glycoprotein is produced by macrophages including T cells along with mast cells as well as natural killer cells plus endothelial cells and fibroblasts. GM-CSF is a cytokine that has protection and controlling effects. It has been verified that GM-CSF hinders M. *tuberculosis* growth in human WBC especially mononuclear macrophages (Wałajtys-Rode and Dzik, 2017). In the handling of active PTB (APTB), rhuGM-CSF adjuvant immunotherapy verified superior protection as

well as acceptability in affected people which is proved by the outcomes of a phase II experimental trial. Moreover, the mucus microorganisms rapidly turned negative in the eighth week of medication (Y. Zhang et al., 2012a). Moreover, in the MDR-TB mouse model, immunization through IL-2 along with GM-CSF may increase the cure rate of the mice and lesser the microbial burden in the respiratory system as well as spleen and lung lesions, henceforth boosting the efficacy of the initial-line anti-TB medicines. When injected as a solo dose, recombinant GM-CSF adenoviruses (AdGM-CSF) in a mouse model significantly lesser the lung microbial load in contrast to old-style chemotherapy (Francisco-Cruz et al., 2013). This is a new technique found in gene therapy.

Interleukin-24

The IL-10 cytokine family has a new suppressor gene fellow known as IL-24. The silent features like its preserved assembly, chromosomal site, as well as cytokine-like possessions, make it a novel suppressor of IL-24 (Abdalla et al., 2016). According to a study *M. tuberclosis* disease has been exposed to suppress IL-24 appearance in human PBMCs along with minor IL-24 stages in the blood serum of TB patients that may increase TB vulnerability and involve in the development of long-lasting TB (Wilson et al., 2010). Depending upon the initial visit of neutrophils IL-24 can trigger the IL-24 receptor signaling path of $CD8^+$ T cells to make high levels of interferon-γ (IFN-γ) to destroy *M. Tuberclosis*. According to a study IL-24 medication of the mice TB model confirmed an anti-TB effect which demonstrates that IL-24 may be a new immunotherapy treatment (Mi et al., 2021c).

Interleukin-32

An important secretory protein that involved in involved in innate as well as adaptive immune responses is IL-32 which is a cytokine mainly formed by immune cells including T cells along with NK cells and epithelial cells. It initiates the formation of vital inflammatory features in macrophages which include TNF-α also has IL-1β as well as IL-6 MIP-2, and IL-8 whose main function is eliminating *M. Tuberculosis* (Gautam and Pandit, 2021). Consequently, TNF-α can be amplified and cell decease can be stimulated by the increased influence of IL-32 in innate immunity against the disease tuberculosis. According to a recent investigation, heat-killed *M. Tuberclosis* stimulus of human PBMCs can raise the *M. Tuberclosis* clearing capabilities of human monocyte-macrophages by making the formation of a noteworthy quantity of IL-32 (Park et al., 2014). Human IL-32γ formed by type II alveolar consonant epithelial cells from transgenetic mice is significantly lesser than lung *M. tuberculosis*. Additionally, next the down regulation of endogenic IL-32 expression in human THP-1 macrophages by siRNA interfering there was a extensive growth in intracellular *M. Tuberclosis* as well as intracellular inflammatory markers such TNF-α and IL-1β has been seen (Refai et al., 2018). IL-32γ was downregulated whereas IL-32β was amplified in the *M. Tuberclosis* diseased PBMCs of the healthy control group the results indicate that IL-32 helps to stop *M. Tuberclosis* infection. The qualified richness of IL-32 isoforms may have an influence on this result. Afterward, IL-32 is a fresh immunotherapy that displays potential for making protection mechanisms along with stopping *M. Tuberclosis* development (Montoya et al., 2014).

Table 2: Cytokines Used in Immunotherapy for Mycobacterial Infections

Cytokine	Mechanism of Action	Therapeutic Potential	Challenges	References
Interleukin-2 (IL-2)	Enhances T-cell proliferation and activation	Boosts immune response, useful in combination therapy	Toxicity at high doses, cost	(Dhupkar and Gordon, 2017)
Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Stimulates macrophage activation and differentiation	Promotes mycobacterial killing, enhances vaccine efficacy	Limited effectiveness as monotherapy	(Y. Zhang et al., 2012b)
Interleukin-24 (IL-24)	Induces apoptosis in infected cells	Targets infected cells, minimizes damage to healthy cells	Delivery to target tissues, stability issues	(Panneerselvam et al., 2013)
Interleukin-32 (IL-32)	Modulates immune response promotes pathogen clearance	Reduces bacterial load, supports long-term immunity	Inflammatory side effects, dosage optimization	(Sasindran and Torrelles, 2011)

Anti-TB Antibodies

It is generally recognized that the cellular immune response acts as a main role in stopping tuberculosis additionally the importance of humoral immunity in tuberculosis is argumentative (Redford et al., 2011). However further research in recent years has confirmed that antibodies also offer a protective influence in contradiction to tuberculosis protection (Rijnink et al., 2021). Immunological damage caused by dangerous molecules can be prevented by the application of M. Tuberculosis antigen-specific antibodies and inflammatory response for example phagosome maturing as well as intracellular bactericidal action may prompted (X. Zhang et al., 2017).

Some hosts lacking in antibodies have a delicate susceptibility to tuberculosis which is shown in a meta-analysis. Antibodies have contradictory defensive effects against many *M. tuberculosis* antigenic determinants (Casadevall and Pirofski, 2006). Human anti-HBHA IgM antibodies may be able to stopover *M. tuberculosis* from penetrating the epithelial cells of TB-affected patients. Although the anti-Ag85A IgG may be able to lessen the danger of active TB along with

decreasing cavities and removing mucus microbes. The minor the level of anti-LAM as well as AM antibodies in TB patients results in the quicker the development of TB along with the advanced incidence of distribution (Abebe and Bjune, 2009).

Moreover, the phagocytosis could be improved as well as CD8+ T cells could be controlled along with tissue injury plus lung swelling and microbial load could be reduced in mice by passively vaccinating with poly or monoclonal antibodies or sometimes blood serum against *M. tuberculosis* antigen (Lawn, 2012). The intranasal otherwise intratracheal dose of anti-Acr IgA antibody otherwise pretreatment with hsIgA was found helpful in declining lung colony counts and also recover granulomatous formation in *M. tuberculosis-infected* mice. On the other hand, the extrapulmonary distribution of *M. tuberculosis* was pointedly lowered by passive transmission of anti-HBHA IgG3 or McAb 4057D2 and IgG2a McAb 3921E4 or anti-LAM IgG (Kim et al., 2011).

Like IgG immunoglobulin Y (IgY), a noteworthy antibody is present in the blood of lungfish as well as reptiles and poultry which may be used as an immune globulin for TB immunotherapy. IgY fits to the class of recognition proteins that the immune system produces in response to external substances same as another Ig (Senger et al., 2015). It has been detected that IgY can intensely increase rat PBMC spread as well as discharge of IL-2 and IFN-γ which represents that the pharmacological achievement of IgY in contradiction of *M. tuberclosis* may be intermediated by regulatory cytokine manufacturing (Tetik, 2024).

Environmental and Management Practices

Operative environmental as well as managemental practices are important for minimizing mycobacterial infections principally in livestock. It is vital to follow to significant environmental in addition managemental values in order to lower mycobacteria (Guardabassi et al., 2018). To stop the entry in addition to the spread of *mycobacteria* will start with severe biosecurity actions like restrictive access and also making sure all equipment is completely washed before usage. The key to preventing environmental infection is the daily routine of cleaning as well as decontamination of animal housing and also supplies. Keeping proper animal care and treatment is also vital although the sick animals must be set aside from healthy ones to stop the disease from scattering (Couto and Cates, 2019). Before reintroducing any novel or giving animals back to the general population it must be quarantined to make certain they are illness-free. Culling may be obligatory to protect the remaining animals in the herd in circumstances where the animals are extremely vulnerable to illness or are sick (Jagielski et al., 2014). Further dropping the risk of spread by managing the animal activities both inside and among accommodations along with the restriction of wildlife reservoirs such as mice or wild birds (Warwick et al., 2023). It is probable to proficiently resist the transmission of mycobacterial species by combination of these methods.

Genetic Resistance

A combination of genetic engineering as well as selective breeding for genetic resistance to mycobacterial infections is a worthwhile long-term method for regulating livestock viruses (Pal and Chakravarty, 2020). Animals that naturally fight mycobacterium diseases in nature are recognized and maintained by selective breeding which in turn advances these assets over following generations to yield a stronger population. Alternatively, genetic engineering introduces or modifies genes that enhance immunity against *mycobacteria* through the use of advanced pioneering biotechnological techniques similar to CRISPR (Choi and Lee, 2016). while collectively these practices lower the necessity for inoculations and antibiotics along with this it also lessens the option of drug-resistant strains of bacteria and viruses. Although it reduces the overall incidence in addition to the spread of mycobacterial contaminations in cattle. All of these activities endorse better herds and improved yield (Pickrodt et al., 2023).

Conclusion

In conclusion, handling of tuberculosis causing *Mycobacterium species* will remains a very hard task in veterinary as well as human medicine. The chapter highlights the vital importance of a comprehensive plan that join the cutting-edge substitute control procedures with important conventional vaccination strategies. The persistence of these illnesses highlights the necessity for new actions, even despite the fact that vaccine developments together with DNA, protein-based as well as live vectors, dead mycobacteria and attenuated infectious strains offer possible pathways for defense. The process of Immunotherapy which uses cytokines to enhance host protection, is a possible alternate to phage treatment that provide powerful means of protection specifically by destroying *mycobacteria*. The weapons in contrast to mycobacterial infections is more strengthened by the characteristics like genetic resistance along with environmental control as well as anti-TB antibodies. A coordinated plan by uniting these various strategies is essential to successfully fight these illnesses. Preserving the efficacy of these treatments, defending the wellbeing of humans as well as animals, although dropping the universal problem of mycobacterial sicknesses will all depend upon the current examination along with enhancement of these methods.

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