Tuberculosis in Brazil: Epidemiological aspects, diagnosis, and treatment

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ABSTRACT

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis, considering that this comorbidity represents a public health problem, it is of paramount importance to understand the associated clinical, epidemiological, and economic factors due to its high prevalence in Brazil. The objective of this study was to review the literature on the epidemiological aspects, risk factors, diagnosis, and treatment related to tuberculosis in Brazil. The bibliographic research was developed from the analysis of scientific articles, obtained from the VHL, National Library of Medicine and SCIELO databases. Tuberculosis is an infectious, chronic, granulomatous and necrotizing disease caused by the acid-fast bacillus. The most common form of presentation is pulmonary, and susceptibility to the disease is influenced by multiple factors: age, nutritional status, infection with the human immunodeficiency virus, habits and lifestyle, poor income and education, inadequate housing, population density, and fragility of systems. The best form of control is through early diagnosis. This diagnosis can be made through clinical, bacteriological, radiological and histopathological data. Sputum smear microscopy is performed using 2 to 3 samples collected in the morning in order to detect sputum smear microscopy patients. Culture in solid and/or liquid medium is used to evaluate the presence of mycobacteria and enable their identification. The standard therapy of the disease consists of the use of Rifampicin, Isoniazid Pyrazinamide and Ethambutol (RIPE) for 2 months and (IR) for 4 months. The effective implementation of prophylactic measures is essential to reduce the burden of tuberculosis in Brazil. This context highlights the need to strengthen tuberculosis control actions in all spheres of the health system, with a focus on early diagnosis, treatment adherence, and prophylaxis measures.

Keywords: Tuberculosis, Bacterial resistance, Epidemiology, Diagnosis, Treatment.

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INTRODUCTION

Tuberculosis (TB) is an infectious, chronic, granulomatous, and necrotizing disease caused by the acid-fast bacillus (AFB) *Mycobacterium tuberculosis*, also known as Koch's bacillus. (BRAZIL, 2019).

TB continues to be an important public health problem in Brazil, with the disease presenting an incidence rate that defies control and eradication efforts. In 2020, Brazil recorded a rate of 30.7 cases per 100,000 inhabitants, placing the country among the 30 with the highest concentration of the disease in the world (BRASIL, 2021). The epidemiology of tuberculosis in Brazil is marked by regional inequalities, with the highest incidence rates observed in the North and Northeast regions (FARAH *et al*., 2020).

The diagnosis of tuberculosis is a challenge, especially in vulnerable populations. The use of diagnostic methods such as sputum smear microscopy, culture, and new molecular tests, such as the GeneXpert rapid molecular test, improves early detection, but there are still gaps to be filled in the diagnostic coverage of the disease (SILVA *et al*., 2019). In addition, co-infection with the human immunodeficiency virus (HIV) further complicates the diagnosis and, consequently, the treatment of tuberculosis, requiring integrated and multidisciplinary approaches (MACHADO *et al*., 2020).

The treatment of tuberculosis in Brazil follows the guidelines of the National Tuberculosis Control Program and involves the use of multidrug therapy for a minimum period of six months with drugs such as isoniazid, rifampicin, pyrazinamide, and ethambutol. However, adherence to treatment presents challenges, largely due to the stigma associated with the disease, side effects of medications, and the complexity of the therapeutic regimen (CARDOSO *et al*., 2021). Drug resistance, notably multidrug-resistant tuberculosis (MDR), is another growing concern that requires surveillance and new treatment strategies (CAMPOS *et al*., 2022).

Finally, tuberculosis prophylaxis, which includes BCG vaccination and prophylactic treatment in individuals at higher risk of developing the disease, is essential for controlling transmission. The effective implementation of these prophylactic measures is essential to reduce the burden of tuberculosis in Brazil (LIMA *et al*., 2019). This context highlights the need to strengthen tuberculosis control actions in all spheres of the health system, with a focus on early diagnosis, treatment adherence, and prophylaxis measures.

METHODOLOGY

This is a narrative review of the literature, with the objective of seeking updates on the epidemiological aspects, risk factors, diagnosis, and treatment related to tuberculosis in Brazil, providing information in a simplified and rapid manner. Considering the object of the study, a question guided the search process in the literature: What is the prevalence, sociodemographic and

clinical profile of patients affected by tuberculosis, and the diagnosis, treatment and prophylaxis of the disease?

To achieve the objective of the study, initially the articles referring to the topic addressed were searched in the Virtual Health Library (VHL), in the National Library of Medicine database and Scientific Electronic Library Online (SCIELO), from 2015 to 2024. For this, the following Health Sciences Descriptors (DeCS) were used: tuberculosis; epidemiology; risk factors; diagnosis; treatment. The articles were selected according to the inclusion criteria: articles published in Portuguese or English, from the last 10 years and that were within the theme. Incomplete studies that did not belong to a reliable database were excluded. Thus, 36 articles were used to prepare the research.

LITERATURE REVIEW

GENERAL ASPECTS OF TB

Tuberculosis (TB) is an infectious, chronic, granulomatous, and necrotizing disease caused by the acid-fast bacillus (AFB) *Mycobacterium tuberculosis*, also known as Koch's bacillus. (BRAZIL, 2019). The pathogen reaches the airways through the speech, cough or sneeze of the individual who has the active disease, being able to eliminate viable bacilli through aerosols (TAVARES *et al*., 2019). The most common form of presentation is pulmonary, but there are also extrapulmonary involvements. Finally, TB commonly manifests itself through a chronic course, an infectious syndrome that can generate anorexia, fever, weight loss, prostration, in addition to the symptoms of the affected site (BRASIL, 2019).

Thus, it can be stated that TB is considered a serious public health problem (MANÇANO; ZANETTI; MARCHIORI, 2022). Since 1993, the World Health Organization (WHO) has declared TB one of the world's emergencies, being a health priority that to this day remains among the top 10 causes of death from infectious diseases caused by a single agent in the world (BRASIL, 2017). In addition, important negative factors that corroborate the incidence of the disease are the appearance of multidrug-resistant strains and the co-infection of HIV-positive patients (SILVA *et al.*, 2021).

RISK FACTORS

Susceptibility to tuberculosis is influenced by multiple factors, among which the following stand out: age, nutritional status, infection with the human immunodeficiency virus (HIV), habits and lifestyle (alcoholism, smoking), poor income and education, inadequate housing and large families, population density, and fragility of the systems. In addition, it is known that individuals who are close contacts of tuberculosis patients are at high risk of developing the disease, especially in the first two years after contact and infection (SILVA *et al.* ,2018).

Taking into account the COVID-19 pandemic, tuberculosis has become a risk factor as there is a co-infection between these two diseases. Although there are few studies, analyses carried out on co-infected patients from nine different countries, mainly in Italy, concluded that there was a greater presence of these two diseases in immigrants and male patients. Another conclusion was the mortality in 10% of these co-infected patients, treated for the 2 diseases (MISHRA *et al*., 2021).

Still on the influence of the COVID-19 pandemic on the course of TB patients, researchers analyze that the simultaneity of these diseases in a patient has a high power to lead him more quickly to more severe forms of the viral disease. This is explained by the characteristic of both diseases to shake the patient's immune system. Therefore, from experience of past coronavirus outbreaks, researchers say that only severe tuberculosis should be treated in a hospital setting, and COVID-19 can promote many cases of latent PT reactivation (CRISAN-DABIJA *et al*., 2020).

PATHOGENESIS

The pathophysiology begins with the entry of the bacilli through the upper airways, reaching the alveoli, promoting the recruitment of neutrophils that are initially unable to contain the infectious process, in this way, the bacilli can multiply within their interior, to the point that they rupture and contaminate new neutrophils, at this time, new phagocytes are recruited to the site of infection, and develop an infectious focus. Therefore, the primary infection occurs at the first contact with Koch's bacillus. Thus, during this primary infection, there is great dissemination of the bacillus throughout the body in an occult way (CARDOSO *et al*., 2021; PACHECO; JACOCIUNAS, 2021).

After 2 to 10 weeks, a granulomatous focus is formed, which can be called a "primary focus" or Ghon's nodule, which will contain the bacillus in its latent form. In 90% of cases, the infection will be effectively controlled at that time, and the patient will remain asymptomatic in a state of latency. Delayed activation, or reactivation, can occur in immunosuppressive conditions or with the development of comorbidities. This reactivation of the disease in a host with pre-existing immunity generates an intense inflammatory response, with the formation of caseous granulomas and pulmonary cavitation, which is the classic form of the disease (CARDOSO *et al*., 2021).

Primary tuberculosis can be divided into three, the typical primary tuberculosis, which is more common in children between 2 and 12 years of age, who will present with a small area of pneumonitis. Progressive primary, which occurs in patients who become infected with a large number of bacilli or with depressed immune defenses, in which the primary focus will evolve to a large area of pulmonary granulomatous inflammation. And the miliary form, which is a common type in children under two years of age and not vaccinated with BCG or severely immunosuppressed, in this form the bacilli are not contained and the primary focus continues to proliferate and

disseminate bacilli in the blood, if not treated early can lead to the child's death (MASSABNI; BONINI, 2019; CARDOSO *et al*., 2021; SILVA *et al.*, 2021)

The other type of presentation of the disease is post-primary tuberculosis, which develops in patients infected for more than 3 years, with a higher incidence in adolescents and adults. This subtype can occur through two mechanisms, namely the reactivation of a latent focus after an event that weakened the immune defense or by reinfection inhalation of a new bacillary inoculum. The symptoms of tuberculosis are usually related to where the bacteria are located, and respiratory symptoms such as dry and bloody cough, chest pain when coughing, and difficulty breathing are more common (MELO *et al*., 2020; CARDOSO *et al.*, 2021)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The best way to control Tuberculosis is through its early diagnosis. This diagnosis can be given through clinical, bacteriological, radiological, and histopathological data (BRASIL, 2019). Bacteriological methods include sputum smear microscopy, culture, and molecular tests. Sputum smear microscopy (AFB) is performed using 2 to 3 sputum samples collected in the morning in order to detect smear-positive patients. Culture in solid and/or liquid medium is used to evaluate the presence of mycobacteria and enable their identification. Rapid molecular tests (RMT-TB) are indicated to validate the diagnosis of new cases, as well as to evaluate rifampicin resistance (COSTA *et al.*, 2018).

The radiological approach is evaluated through chest X-ray and tomography. These methods are essential to analyze patterns related to disease presentation, evolution, and resolution by treatment. Chest X-ray (BP and left profile), which is the method of choice due to its accessibility, may present patterns such as nodules, masses, consolidation, pleural effusion, or interstitial process. CT is capable of detecting more specific alterations of tuberculosis and is usually indicated after a normal radiographic presentation (SILVA *et al.*, 2021). The histopathological method is important especially for the diffuse and extrapulmonary forms of TB, it should be considered that the histopathological lesion compatible with the diagnosis is granuloma with caseous necrosis (BRASIL, 2019).

Pulmonary tuberculosis includes some differential diagnoses, especially in cases that present with a prolonged cough, such as consumptive syndromes, pneumonia, silicosis, fungal or bacterial infections, pulmonary embolism, among others, thus requiring the use of the diagnostic methods already mentioned for its differentiation. In addition, there are: the pleural form that should include lymphomas and neoplastic effusions in its diagnosis; the lymph node form which should include lymphoproliferative diseases; the meningoencephalic form which should include bacterial, fungal

and viral diseases of the central nervous system; and the osteoarticular form that should include septic arthritis and osteomyelitis (BRASIL, 2019).

TREATMENT OF PULMONARY TUBERCULOSIS

The treatment of pulmonary tuberculosis, as in many diseases, is more effective when there is an early diagnosis. However, studies have shown that many cases of Tuberculosis are treated late due to a longer delay on the part of the patient, when it takes a long time to seek recourse. There is a delay in diagnosis and treatment, but patient delay has been shown to be the major cause of late treatment of the pulmonary form of Tuberculosis, requiring patients to be more informed about the symptoms, as well as active research (BELLO *et al*., 2019).

Recent research, aiming to optimize the treatment of TB, developed a study on the benefits of the use of an immunomodulator, Imunoxel, as an adjuvant in the standard therapy of the disease, which consists of the use of Rifampicin, Isoniazid Pyrazinamide and Ethambutol (RIPE) for 2 months and (IR) for 4 months. This immunomodulator comes from a natural compound, it was approved in Ukraine as an adjuvant in PT, as it proves to strengthen the immune system and help the host in the fight against the bacillus (KITENGE *et al*., 2021).

The post-treatment period of PT should be monitored, with a criterion of cure when there is a negative sputum smear microscopy at the end of 6 months after the treatment instituted. However, in patients with COPD, it is worth following up with them requesting chest X-rays, since after treatment, these individuals are likely to have colonization by the fungus *Aspergillus* in the tuberculosis lesion. Thus, it is of paramount importance to monitor and guide the patient to stop smoking and undergo pulmonary rehabilitation to avoid exacerbations (HSU *et al*., 2020).

The treatment of latent tuberculosis infection (LTBI) is done using isoniazid for 9 to 13 months, and for children under 10 years of age and adults over 50 years of age, rifampicin is chosen for 4 to 6 months. Studies developed in South Korea have evidenced the need for active search for LTBI for early treatment and reduction of reactivation, since there is a phenomenon of population aging, which increases the risk of reactivation of LTBI cases. In addition, they are studying the possibility of using Isoniazid in the elderly, instead of Rifampicin (KIM; KIM, 2018).

After the individual infected with tuberculosis starts treatment, it is expected that he will not be bacilliferous, that is, transmitter after 2 weeks. However, studies have been carried out and concluded that most patients who started treatment for PT remained with positive sputum cultures after this period, which is contrary to what the literature preaches. Other infectious factors, such as reduced cough frequency, should be analyzed in other studies along with the post-treatment sputum culture pattern, to better assess therapeutic efficacy, since patients undergoing treatment also tend to have a decrease in cough (CALDERWOODI *et al*., 2021).

ANTIMICROBIAL RESISTANCE

Bacterial resistance to drugs is a challenge faced in the treatment of PT, caused by the constant use of drugs, mutations of the bacteria, low adherence to treatment, among other mechanisms. Studies show that for a greater success of the treatment, in addition to improving the causes of resistance mentioned, it is necessary to have a deeper research on the mechanism of action of drugs against the bacillus, as well as their ways of evading the action of the drug. In addition, cross-resistance, synergies or antagonisms between drugs (SINGH; CHIBALE, 2021).

The treatment of multidrug-resistant LTBI cases is still poorly studied. Thus, researchers indicate that the use of Levofloxacin in these cases produces a favorable effect because it treats well and causes few adverse effects. This was demonstrated by a prospective cohort study in Micronesia with a satisfactory result with the use of this fluoroquinolone in the treatment of LTBI in 110 contacts with multidrug-resistant strains, with a success rate of 100%. Another South African study of 184 children in contact with patients with multidrug-resistant tuberculosis also had a success rate of almost 100% treating this group with levofloxacin. However, more studies with control groups are needed (FOX *et al*., 2019).

Among the cases of antimicrobial-resistant PT, there is Multidrug-Resistant Tuberculosis (MDR-TB), which does not respond to the combination of rifampicin and isoniazid, and extensively drug-resistant tuberculosis (XDR-TB), which in addition to having a characteristic equal to MDR-TB, is also resistant to the use of fluoroquinolones and second-line injectable drugs. In view of this, research shows that the growing number of drug resistance is caused by fragility in medical systems and incorrect treatment, and there should be an expansion of community-focused programs to better manage Pulmonary Tuberculosis (SEUNG *et al,* 2015**).**

MDR-TB is usually treated over an 18-month period using capreomycin, linezolid, levofloxacin, ethambutol, pyrazinamide, and terizidone. However, researchers evaluated the combination of Bedaquiline (ATP synthase inhibitor), Pretomanid and Linezolid, and obtained a favorable result in 6 months, although these drugs have many adverse effects (CONRADIE *et al*., 2020). Another study was done with the combination of Rifampentin and Moxifloxacin for 4 months, with a favorable result (DORMAN *et al*., 2021).

In addition, other studies have shown both a beneficial and harmful influence of the COVID-19 pandemic on bacterial resistance to antimicrobial drugs. This pandemic caused a greater dissemination of hygienic practices, such as the use of masks, social distancing, use of alcohol gel, among other measures, which makes it difficult for resistant pathogens to spread. On the other hand, the pandemic also brought with it difficulty in following up on infectious disease treatments, telemedicine with greater prescription of antimicrobials, and self-medication, which cause a greater chance of growth of resistant strains (RUSIC *et al*., 2021).

Considering the epidemiology of bacterial resistance of Koch's bacillus to antimicrobials, white and brown men, aged 25 to 44 years, had more MDR-TB strains in a study carried out between 2010-2017. Another group that developed more resistance to drugs were alcoholics, carriers of the HIV virus, and those who abandoned treatment. Thus, although there are many expenses to reduce multidrug-resistant strains of TP, there is still a high incidence of the disease in Brazil (DE OLIVEIRA *et al*., 2021).

PROFILEAXIA

In Brazil, TB is rooted in the social sphere, being a strong aggravating factor of the disease. Epidemiological data need control and prevention measures. In addition, the United Nations (UN) has included as a goal the elimination of Tuberculosis by the year 2030, as well as Brazil having instituted the National Plan for the End of Tuberculosis, where there is the intention to reduce the incidence and mortality coefficient by 2035 (BRASIL, 2018). For tuberculosis control, it is essential to interrupt the chain of transmission of the disease. Carriers of undiagnosed pulmonary TB have the power to infect a branch of 10 to 15 people per year, and if they get sick, they will maintain the transmission of the disease (WHO, 2021).

It is important to emphasize that the smaller the particle, the more chance it is to remain in the air, putting it at risk and having a greater possibility of being aspirated through the airways of individuals and infecting it (TEIXEIRA *et al.*, 2020). The Ministry of Health (MS) recommends that all identified contacts undergo tests and that they begin LTBI treatment, aiming to reduce the chance and risk of illness. It is important to emphasize that adherence to chemoprophylaxis is low worldwide, and that it is essential to exclude the active disease before the indication of LTBI treatment (BRASIL, 2019).

Another preventive measure in force is the BCG vaccine, recommended for application in the first month of the child's life and also provided for as secondary prevention with isoniazid, recommended for people who have direct contact and contact with someone with active TB (TEIXEIRA *et al.,* 2020). It is necessary to highlight the importance of home visits and educational actions with guidance for families in endemic areas, as well as individual guidance on the disease, and how to reduce the chances of contagion (ALENCAR *et al.*, 2019).

FINAL CONSIDERATIONS

In this discussion on tuberculosis, the importance of understanding the epidemiological aspects, diagnosis, treatment, and prophylaxis involving this disease of global relevance is emphasized. Tuberculosis continues to be a significant public health challenge, with millions of new cases diagnosed annually. Careful analysis of epidemiological data reveals not only the geographic

distribution of the disease, but also the most vulnerable populations, allowing the implementation of targeted strategies.

The diagnosis of tuberculosis has evolved considerably in recent years, with the incorporation of new technologies that provide greater precision and speed. Tools such as polymerase chain reaction (PCR) and early detection methods have been instrumental in reducing the rate of underdiagnosis and improving patient prognosis. However, the continuity and effectiveness of screening strategies in at-risk populations are crucial for the eradication of the disease.

The treatment of tuberculosis, although effective, requires a commitment from both health professionals and patients. Drug resistance is regrettably a growing concern, underlining the need for rigorous monitoring and research for the development of new drugs and therapeutic regimens. Promoting adherence to treatment and improving health education are indispensable components of the fight against tuberculosis.

Finally, cooperation between the health sectors, the scientific community, and civil society is key to building a future without tuberculosis. Investment in research and the dissemination of knowledge resulting from research should be encouraged to face this complex health problem. This chapter reinforces the need for a multidisciplinary and integrative approach to combat tuberculosis, providing an effective and sustainable response to the challenge presented by this infectious disease.

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