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Study of tuberculosis treatment

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Dedication

In the Name of God, the Most Gracious, the Most Merciful

At the beginning of this humble work, I extend my sincere thanks and praise to God Almighty, who has given me the opportunity to attain this level of knowledge, and provided me with the strength and patience to complete this humble work. I dedicate this work:

***To my dear mother**,*

You are my support, my beacon, and my source of inspiration. Your constant care and encouragement have been my greatest motivation, and every step I have taken in this academic path has been the fruit of your wise advice and encouraging words.

To my dear father,

You have always been by my side, supporting and encouraging me.Let this work be an expression of my gratitude and love for you. I ask God to protect you from all harm, and to grant your health, happiness, and a long life, so that I may repay you even a small part of your kindness.

To my sisters Rayane, Selsabyl, and my brother Adam,

For the love and affection they have showered upon me, I wish them a life filled with joy, happiness, and success.

***To my dear friends: Ikram, Khawla, Zainab, and Fawzia**,*

For their moral support and encouragement during difficult times, I wish from the bottom of my heart that our friendship will last forever.

*To my colleague, **my beautiful Imane**, who shares my name, for her effort and commitment throughout this work.*

Ms. DJERFI .I

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***To my sisters**,*

For the love and affection they have showered upon me, I wish them a life filled with joy, happiness, and success.

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Ms. BELFETHI .I

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List of abbreviations

TB:	Tuberculosis.
LTB:	Latent tuberculosis.
PTB:	Pulmonary tuberculosis.
ETB:	Extra pulmonary tuberculosis.
BK:	Koch's bacillus.
M. tuberculosis:	*Mycobacterium tuberculosis*.
M. bovis:	*Mycobacterium bovis.*
M. africanum:	*Mycobacterium africanum.*
WHO:	World Health Organization.
PTI:	Primary Tuberculosis Infection.
ETB:	Extra pulmonary tuberculosis.
CLA:	Cervical lymphadenopathy.
ADA:	Adenosine deaminase.
IGRAs:	Interferon-gamma release assays.
AFB:	Acid-fast bacilli.
CT:	Computed tomography.
TST:	Tuberculin skin test.
PCR:	Polymerase Chain Reaction.
DOT:	Directly Observed Treatment.
H:	Isoniazid.
R:	Rifampicin.
Z:	Pyrazinamide.
E:	Ethambutol.

S:	Streptomycin.
RCTs:	Randomized controlled trials.
MDR PT:	Multidrug-Resistant pulmonary tuberculosis.
PBPs:	Penicillin-binding proteins.
DM:	Diabetes mellitus.
AIDS:	Acquired Immune Deficiency Syndrome.
HIV:	Human Immunodeficiency Virus.
ART:	Rifampicin and antiretroviral therapy.
PPD:	Purified protein derivative.
IGRAs:	Interferon-gamma release assays.
BCG:	Bacillus Calmette Guérin.
FDDS:	Floating drug delivery systems.
GNPs :	Gold nanoparticles.
MSNs :	Mesoporous silica nanoparticles.
LN TB:	Lymph node TB.
PL TB:	Pleural TB.
PR TB:	Peritoneal TB.
MN TB:	Meningitis TB.
MM TB:	Mammary TB.
ML TB:	Miliary TB.
IN TB:	Intestinal TB.
CU TB:	Cutaneous TB.
UG TB:	Urogenital TB.
OA TB:	Osteoarticular TB.

H TB:	Hepatic TB.
EP TB:	Epiploic tuberculosis.
DOTS:	Directly Observed Treatment; Short-course.
DCD:	Mortality rate.
CRP:	C-reactive protein.
Cre A:	Creatinine.
DR-TB:	Resistant tuberculosis.
AST:	Aspartate Aminotransferase.
ALT:	Alanine Aminotransferase.
WBC:	White blood cells.
RBC:	Red blood cells.
OR:	Odds ratio.
CI:	Confidence interval.
CR1:	Complement receptor one.

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Introduction

Introduction

Respiratory diseases are among the most common health problems worldwide, encompassing a wide range of disorders that affect the respiratory system. These conditions directly impact breathing ability and quality of life, and they can range from acute and serious illnesses such as pneumonia to chronic conditions like asthma and tuberculosis. The causes of respiratory diseases vary and include infectious agents such as viruses and bacteria, as well as environmental factors like smoking and air pollution, in addition to genetic and immunological factors. Given their significance and profound impact on public health, respiratory diseases receive considerable attention in both medical and research communities. Prevention, early diagnosis, and appropriate treatment are essential factors for improving outcomes and reducing the burden of these diseases **(Juan et al., 2019)**.

Tuberculosis is one of the most common and deadly respiratory diseases, representing a longstanding global health concern. A significant number of new cases are reported annually. The etiological agent of this disease belongs to the genus *Mycobacterium*, which includes several species, some of which infect humans and others animals. The most prevalent species responsible for human tuberculosis is *Mycobacterium tuberculosis*. This pathogen primarily affects the respiratory system, especially the lungs, and in such cases, the disease is considered contagious **(Ellis et al., 2024)**.

However, *Mycobacterium tuberculosis* can also disseminate to other parts of the body, including the lymph nodes, serous membranes, bones, and the central nervous system, leading to various forms of extra-pulmonary tuberculosis. In the majority of cases, the bacilli enter the body and remain in a latent state without causing clinical symptoms. Nevertheless, under certain conditions—such as immunosuppression or poor living conditions—the infection may progress to active disease. Typical symptoms of active TB include chronic cough, fever, night sweats, and unintended weight loss **(Arju et al., 2022; Jorge et al., 2023)**.

The treatment of tuberculosis primarily relies on the use of a combination of effective antibiotics administered consistently over a defined period. In cases of active pulmonary tuberculosis, the standard first-line regimen consists of four primary drugs during the initial (intensive) phase, which typically lasts two months: isoniazid, rifampicin, pyrazinamide, and ethambutol. This is followed by a continuation phase, usually lasting an additional four months, during which isoniazid and rifampicin are administered. Strict adherence to the prescribed treatment regimen is crucial to ensure complete recovery and to prevent the emergence of drug-

resistant strains, which represent a major challenge to tuberculosis control efforts. In cases of multidrug-resistant tuberculosis, alternative second-line drug regimens are required, which are often longer in duration and associated with greater side effects and lower patient tolerance **(Jong et al., 2020; Perumal et al., 2020)**.

This work begins with a detailed bibliographic section that presents general information about tuberculosis, starting with its definition, the pathogenic agents responsible for the disease, its various forms, and modes of transmission, and concluding with the diagnostic methods employed. We then explore the therapeutic approaches used in the treatment of tuberculosis, focusing on the use of antibiotics, their potential toxicity, appropriate prescription practices, and recommended dosages. Particular attention is given to the treatment protocol adopted in Algeria, in order to highlight the specific features of the national strategy for combating this disease.

In the applied section of this work, which constitutes the second part, we conducted a field internship at the Public Hospital of Ferdjioua, in addition to three Public Primary Health Care Centers located in Mila, Ferdjioua, and Deraâhi Bousselah localities. This was done to ensure comprehensive coverage of all tuberculosis follow-up centers within the province. During this internship, we carried out a descriptive and analytical study of patient records. We began by analyzing the clinical data of the patients as well as the recorded biological markers, with particular attention to their evolution throughout the treatment period. This analysis aimed to enhance our understanding of the clinical manifestations of tuberculosis and its various patterns, while also assessing the effectiveness of the treatment protocol in place. Furthermore, we considered the risk factors associated with treatment failure. Finally, we explored the potential existence of biological markers that may assist in predicting treatment outcomes.

Part one

Bibliographic synthesis

Chapter one

Introduction to tuberculosis

I.1. General Information of tuberculosis

I.1.1. History of tuberculosis

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* bacteria **(Bazin, 2011)**, which has persisted for thousands of years and is widely spread across the globe. It is estimated that around 2 billion people have been exposed to this bacterium, with approximately 10.4 million new cases being recorded annually **(Mac Donald et al., 2015)**. Tuberculosis is considered a life-threatening disease, responsible for the death of about 1.4 million people each year **(Salvioli, 2001)**.

The origins of TB date back more than 150 million years, and it has been shown that *Mycobacterium tuberculosis*, the causative agent of the disease, requires specific environmental conditions for its spread and development **(Hayman, 1984)**. It is possible that the first strain of Mycobacterium infected early human ancestors in East Africa around three million years ago **(Gutierrez, 2005)**, and the common ancestor of modern strains may have appeared between 20,000 and 15,000 years ago **(kapur et al., 1994; Borsch et al., 2002)**. According to studies of ancient Egyptian mummies, skeletal deformities associated with TB suggest the presence of the disease in that era, as also depicted in ancient Egyptian art **(Morse et al., 1964; Zimmerman, 1979)**. The earliest written records of TB come from India and China, dating back 3,300 and 2,300 years, respectively **(Brown, 1941)**. References to TB were also found in ancient Hebrew texts **(Daniel et al., 1999)**. In ancient Greece, he was known as "phthisis," and Hippocrates described it as a fatal disease. In Roman times, it was mentioned by many physicians, though without recognizing its connection to extra-pulmonary manifestations **(Daniel, 2006; Pease, 1940)**. The disease continued to spread across Europe throughout the 8th to 19th centuries **(Roberts et al., 2003)**.

In the middle Ages, scrofula was a deadly disease, and it was widely believed that the king's touch could cure the illness, known as the "king's evil" **(Murray et al., 2016)**. Over time, the disease was better understood, and medical procedures such as the removal of infected glands were developed **(Baroukh, 1996)**. Specialized treatment areas were also organized, and patients were isolated to prevent the spread of the disease **(Sabatini, 2004)**.

In the 19th century, tuberculosis was a real scourge, and in the absence of effective treatment, patients had to rest in sanatoriums. However, the 20th century brought major advances: in 1907, a TB sensitivity test was developed **(Daniel, 2006)**, followed in 1921 by the development of the bacillus Calmette guérin (BCG) vaccine **(Tan Siang and Erika, 2012)**. The

discovery of the first effective antibiotics between 1943 and 1952 by Selman Abraham Waksman marked a decisive turning point in the fight against this disease **(Daniel, 2005)**.

Between 1950 and 1963, new treatments were developed, such as isoniazid (1952), pyrazinamide (1954), ethambutol (1961) and rifampicin (1963), which still constitute the basis of anti-tuberculosis treatments today **(Webb and Davies, 1998)**. Despite a sharp decline in cases over the decades, TB remains a threat.

In 1993, the World Health Organization declared it a global emergency due to its resurgence in several countries **(Dye et al, 2005)**.

Today, the disease can be treated effectively provided that the patient strictly follows his or her treatment regimen and does not encounter a resistant strain.

I.1.2. Discovery of tuberculosis

Tuberculosis is also known as "the robber of youth" due to the high mortality rate among young people in Western Europe. It became an epidemic in the 18th century with a significant increase in the number of deaths caused by surrounding conditions such as poor diet, poor sanitation, and poorly ventilated houses **(Barberis et al., 2017)**.

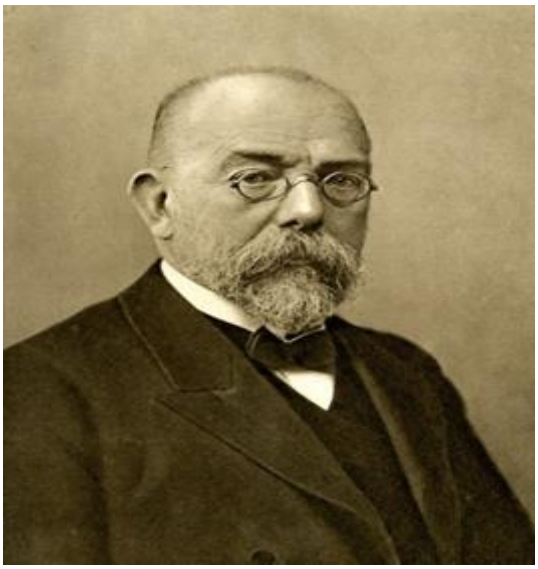

Figure 01: Robert Koch (**Grad Mann, 2005)**.

TB continues to claim many lives annually and has been a subject of inquiry for many scientists and researchers. The discovery of the main cause of TB by the German doctor Robert Koch in 1882 **(Fig. 01)**, on the 24th of March, was a pivotal event in understanding the disease and developing an effective treatment for it. It is considered one of the greatest medical achievements in human history, as he discovered the bacillus responsible for the disease,

Mycobacterium tuberculosis. Only 17 days after announcing his discovery, the details of his research were published in a prestigious scientific journal, which was a remarkable achievement compared to today's publishing standards, and it provided undeniable proof of the cause of TB. Following this, Koch's postulates were formulated, which became a standard in microbiological medicine. This discovery impressed scientists and experts, gaining widespread acceptance in the global scientific community. In 1905, Koch was awarded the Nobel Prize in Physiology or Medicine in recognition of his significant contribution to the field **(John et al., 2015)**.

I.1.3. Definition of tuberculosis

Among the diseases known to humans throughout history, tuberculosis is considered one of the oldest and most dangerous diseases to have affected humanity, causing a staggering number of deaths from ancient times to the present day across the world. This disease is caused by the bacterium *Mycobacterium tuberculosis* **(Arvind et al., 2020)**.

TB varies according to its effect on the body. In some cases, the body becomes infected with the *Mycobacterium* bacteria, but she remain dormant within the body, preventing any symptoms of the disease from appearing. This is due to the immune system's ability to contain the pathogen and prevent it from multiplying. People with latent tuberculosis (LTB) do not experience any symptoms, but they can develop active disease at any time, especially if their immune system weakens **(Table. 01)**. It is important to note that this form of the disease is not contagious to healthy individuals, as latent tuberculosis does not spread to others. **(Jesus et al., 2022)**.

Table 1: Tuberculosis infection (Latent) and tuberculosis disease (Active Pulmonary TB) (**Fraisse, 2020).**

latent Infection	Tuberculosis disease (Active Tuberculosis)
No symptom. Generally normal radio. Generally negative respiratory sampling. No contagion.	Symptom (cough, fever, sweat, night, weight loss). Generally abnormal radio. Generally positive respiratory sampling. Contagion (before treatment)

In the vast majority of cases, the infection primarily affects the lungs, which is referred to as pulmonary tuberculosis (PTB), the most common type. This type of TB is transmitted through the air via sneezing or coughing, as the bacteria are spread through droplets of water vapor expelled from the lungs **(Fig. 02) (Sarah et al., 2017)**. In some cases, TB bacteria can spread to other organs in the body, and the symptoms of the disease vary depending on the affected organ. These organs may include the bones, lymph nodes, kidneys, intestines, stomach, brain, and others, this type is called extra pulmonary tuberculosis (ETB) **(Marjorie et al., 2005; Surendra et al., 2021)**.

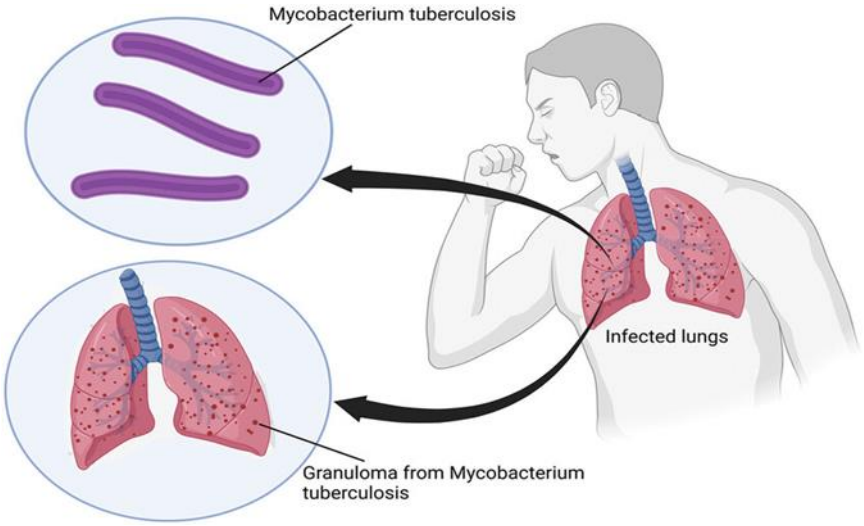

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Figure 2: Infection by *Mycobacterium tuberculosis* **(Sakula, 1983).**

I.2. The Etiological Agent

I.2.1. *Mycobacterium tuberculosis*

The bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*) or Koch's bacillus (BK) is a rod-shaped bacterium responsible for tuberculosis **(Nicole et al., 2020)**. It is characterized by its resistance to acids **(Shelby et al., 2024)**, which makes it easier to diagnose using specific staining tests such as the "Ziehl-Neelsen" test **(fig. 3) (Ariel et al., 2022)**.

The bacterium TB is asporogenous, strictly aerobic meaning it requires oxygen to grow, and thrives at an optimal temperature of 37°C, making the human body a suitable environment for its growth and reproduction. This bacterium is characterized by slow growth compared to other bacteria, with colonies taking 2 to 6 weeks to appear on specialized solid media such as Loffler’s agar, Middlebrooks agar, or Lowenstein-Jensen agar. The colonies appear with a

rough, granular texture, usually white or creamy, or yellow due to pigment production. The bacterium is non-motile as it lacks flagella. Its cell membrane contains a large amount of lipids, particularly mycolic acids, which provide it with strong resistance against chemicals, disinfectants, and antibiotics **(Khaoula et al., 2022)**.

The genome of *M. tuberculosis* is relatively small compared to other bacteria, but it contains many genes associated with antibiotic resistance, pathogenicity, and survival within the host. These genetic traits play a crucial role in the bacterium's ability to establish and persist in its primary habitat, the human body, particularly the lungs. Furthermore, the bacterium can also infect other parts of the body and survive by forming granulomas, a strategy that allows it to evade the immune system and continue to persist despite challenges such as antibiotic treatment **(fig. 4) (Matsu et al., 2020)**.

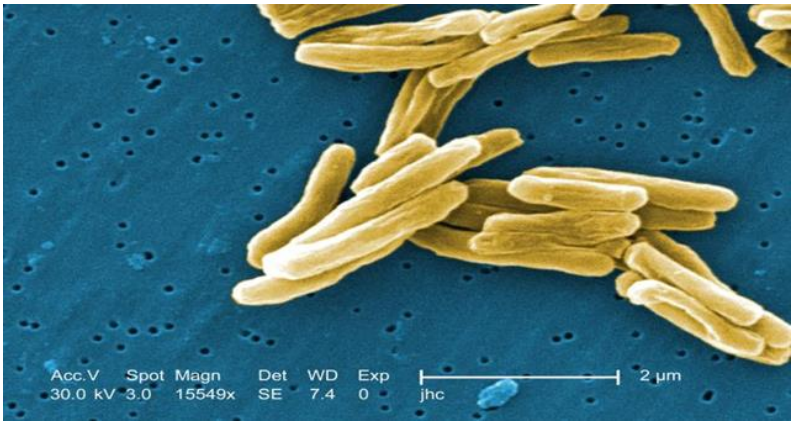


Figure 3: Lava does Broncho alveolar, coloration de Ziehl-Neelsen, 100X **(Ariel et al., 2022)**.

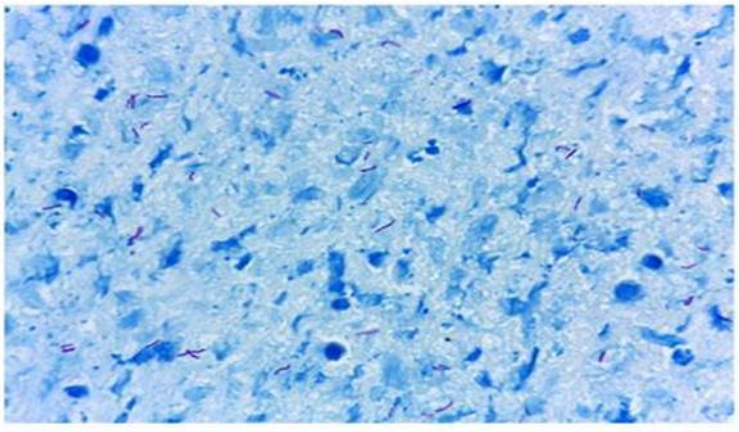


Figure 4: Scanning electron microscopy of *Mycobacterium tuberculosis* **(Todar, 2020)**.

I.2.1.1. Classification

The classification of living organisms is a system designed to organize and categorize these organisms into groups based on their shared characteristics. Classification relies on criteria such as morphology, genetics, and ecological behaviors. In the field of microbiology, the classification of bacteria, like *M. tuberculosis*, helps to understand their evolutionary relationships, biological characteristics, and pathogenic potential. It also aids in determining appropriate diagnostic and therapeutic strategies to combat diseases such as tuberculosis.

The classification of *M. tuberculosis* is as follows:

Kingdom: Bacteria

Phylum: *Actinobacteria*

Class: Actinobacteria

Order: Actinomycetales

Family: Mycobacteriaceae

Genus: *Mycobacterium*

Species: *Mycobacterium tuberculosis*

I.2.2. Mycobacterium bovis

Mycobacterium bovis (*M. bovis*) is a bacterium closely related to *M. tuberculosis*, causing tuberculosis in animals, especially cattle, and can be transmitted to humans, leading to bovine tuberculosis. Although it is less common in humans compared to *M. tuberculosis*, it can cause pulmonary or extra pulmonary infections, especially in individuals who come into contact with infected animals or consume unpasteurized milk. This bacterium grows slowly and is acid-fast due to the lipid content in its cell wall. The bacterium is transmitted through respiratory droplets or by consuming contaminated animal products. The disease is treated with antibiotics such as revamping and isoniazid, although this bacterium is resistant to pyrazinamide. Prevention includes regular testing of cattle, reducing the consumption of unpasteurized milk, and using the vaccine against *M. tuberculosis*, which provides some protection against *M. bovis* **(Áine et al., 2022)**.

M. bovis utilizes the host's mycophagy mechanism to enhance its intracellular survival and reduce the immune response against it. Mycophagy is a process in which damaged mitochondria are removed from the cells, but *M. bovis* exploits this process in an unconventional way by inducing it to suppress Xenophagy, an immune response in which the body recognizes and destroys foreign entities. Studies indicate that the induction of mycophagy enhances the survival of the bacteria inside macrophages, increasing its ability to survive and grow. On the other hand, inhibiting mycophagy reduces *M. bovis* ability to persist within the cells. These findings highlight how bacteria can manipulate host cell mechanisms to promote their survival, providing a deeper understanding of the strategies *M. bovis* uses to persist in the host, which can help in developing new strategies to combat infection. **(Yinjuan et al., 2022)**.

I.2.3. Mycobacterium africanum

Mycobacterium africanum (M. africanum) is a type of bacteria closely related to *M. tuberculosis* and is a major cause of PTB in West Africa. This type usually causes a less severe form of TB compared to *M. tuberculosis*, but it can still be fatal if left untreated. It can be difficult to differentiate it from *M. tuberculosis* in diagnosis, requiring specific laboratory tests. *M. africanum* is typically treated the same way as TB, using a combination of antibiotics such as isoniazid, rifampicin, ethambutol, and pyrazinamide **(Marta et al., 2022)**.

The *M. africanum* strains have been classified into two main genetic types: L5 and L6, based on genetic differences in their genomes compared to *M. tuberculosis*. *M. africanum* strains are characterized by deletions in specific genomic regions such as RD9, RD711, and RD702, allowing them to be distinguished from *M. tuberculosis* using techniques like Spoligotyping (Spacer Oligonucleotide Typing) and genomic sequencing. Recent studies suggest that L6 strains may have originated from an animal reservoir, evolving to adapt to different host species. This indicates that L6 strains could have been generalist pathogens before becoming specialized in animal reservoirs, which contributes to their geographic restriction primarily in certain regions **(Marta et al., 2022)**.

A study on the response of macrophages to *M. africanum* infection showed that different strains of *M. africanum* induced varying cytokine responses, with some strains causing strong and others weak responses. The strains also triggered less IFN-β production compared to *M. tuberculosis*. Additionally, the lack of type I IFN signalling reduced bacterial load in the lungs. Regarding adaptive immune responses, *M. africanum* caused a weaker immune response, which may explain the slower progression of infection and tissue protection **(Marta et al., 2022)**.

I.3. Pathophysiology and mode of transmission

I.3.1. The pathophysiology of Tuberculosis

The infection with *M. tuberculosis* begins when the bacteria enter the lungs through inhalation of airborne droplets containing the bacteria, which are released into the air by an infected person through coughing or sneezing. Another person can inhale these small droplets containing the bacilli, allowing the bacteria to enter the respiratory system and reach the lungs. Once the bacilli reach the lungs, they travel to the lower respiratory tract, specifically to the alveoli, where gas exchange occurs. Here, the bacteria are attacked by immune cells known as macrophages, which attempt to engulf and eliminate the bacteria as part of the initial immune response. However, what makes *M. tuberculosis* unique is its ability to survive within these macrophages. It has mechanisms that prevent its destruction within these cells, allowing it to slowly multiply inside them **(fig. 5**) **(Kathryn et al., 2023)**.

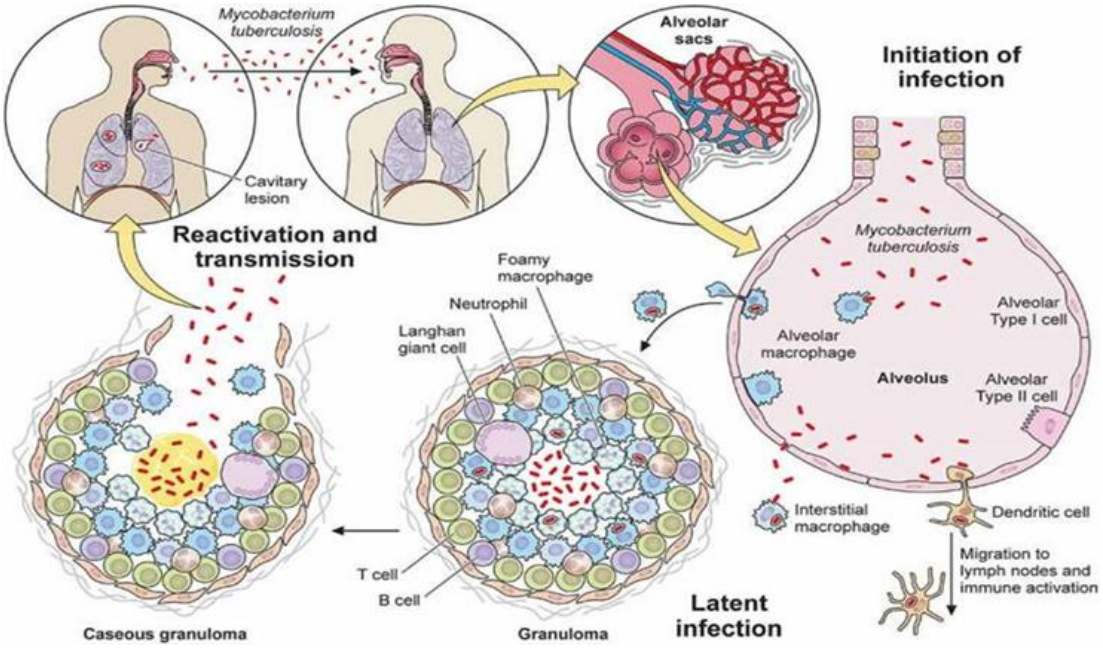


Figure 5: Overview of *M. tuberculosis* infection **(Kathryn et al., 2023)**.

In response to this infection, the immune system attempts to contain the spread of the bacteria by forming granulomas clusters of immune cells around the bacilli. This process creates a "barrier" that traps the bacteria, leading to what is called an inflammatory response. These granulomas often remain dormant or inactive for long periods, sometimes years, without the

disease progressing or symptoms appearing. This condition is known as "latent infection," where the bacteria remain in the body without causing disease but can become active later. However, if the immune system becomes weakened, the bacteria may reactivate and begin multiplying again. In this case, the disease progresses to "active tuberculosis," where the bacilli multiply rapidly, leading to symptoms such as persistent coughing, fever, night sweats, and weight loss. Furthermore, the bacteria can spread to other organs in the body such as the kidneys, brain, bones, and lymph nodes, resulting in more complex complications that can threaten the patient's life. **(Kathryn and al., 2023)**.

I.3.2. Protein virulence factor

M. tuberculosis uses several mechanisms to survive inside the human body and reduce the host's immune response. The proteins secreted by *M. tuberculosis* modify the activity of TLR2 receptors, which decreases the innate immune response and disrupts the immune system's ability to recognize the bacteria. These proteins also affect cytokine production, helping to modulate the immune response and reduce inflammation. Additionally, *M. tuberculosis* interferes with the function of the phagosome within immune cells like macrophages, allowing the bacteria to survive inside the cells without being destroyed. *M. tuberculosis* also affects the process of autophagy within immune cells, helping it avoid destruction and enhancing its survival inside the body. Finally, *M. tuberculosis* modifies cell death pathways within host cells to avoid being eliminated, which further promotes its survival within the host and allows it to multiply slowly **(fig. 6) (Kathryn et al., 2023)**.

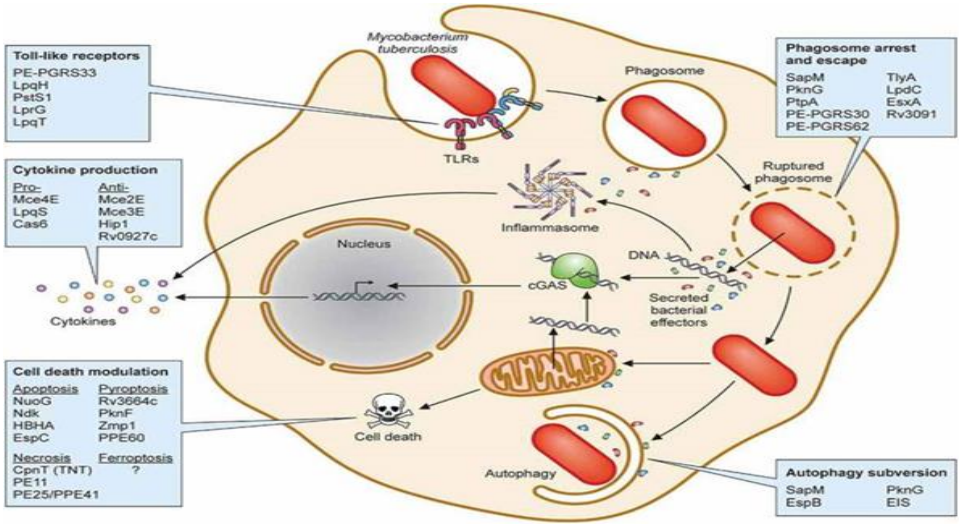


Figure 6: virulence factors of *M. tuberculosis* **(Kathy et al., 2023)**.

I.3.3. Modes of transmission and triggering factors

There are several factors that increase the risk of developing tuberculosis. First, a weakened immune system is one of the main factors, as being infected with the human immunodeficiency virus (HIV) virus or taking immunosuppressive drugs, such as those used in cancer treatment, increases the likelihood of contracting TB. Additionally, people who live or work with someone with active TB in enclosed or poorly ventilated environments are more likely to be exposed to the infection. Malnutrition also weakens the immune system, increasing the risk of TB, particularly in individuals who suffer from vitamin and mineral deficiencies. Other factors that increase the risk include smoking and excessive alcohol consumption, as smoking damages the lungs and makes them more susceptible to infection, while alcohol affects the body's ability to fight diseases. Furthermore, living in poor conditions, such as in shelters, prisons, or overcrowded areas, increases the likelihood of contracting TB due to the higher chances of exposure to the infection. Traveling to regions with high rates of TB also poses a greater risk of infection. Finally, chronic diseases such as diabetes and heart disease can weaken the immune system, making individuals more susceptible to TB **(Manoj et al., 2023)**.

PTB spreads through the air when a person inhales droplets released by an infected person during coughing or sneezing. The bacteria causing TB are carried in tiny particles that spread in the air, making it easier for the disease to transmit in crowded or enclosed spaces **(Zuqin et al, 2020)**. In addition, in some rare cases, he can be transmitted through drinking contaminated milk from infected animals, as the bacteria may be present in unpasteurized milk. **(Áine et al, 2022)**. As for transmission through contaminated surfaces or tools, the likelihood is very low, as TB bacteria cannot survive on surfaces for long and lose their ability to infect quickly once they dry. Therefore, transmission through surfaces or contaminated tools is extremely rare. **(Dominique, 2001)**.

I.4. Epidemiology of tuberculosis

I.4.1. Geographic distribution of tuberculosis

Tuberculosis is a public health disease due to its epidemic potential. Listed as notifiable disease, it is subject to rigorous surveillance in order to prevent any epidemic. This vigilance is all the more necessary as the incidence and prevalence of the infection remain worrying in some countries. TB is the second leading cause of death among infectious diseases, after COVID-19 and before acquired immune deficiency syndrome (AIDS) **(Pai et al.; 2022)**.

I.4.1.1. In the world

TB is among the top ten causes of death worldwide. Its expansion is closely linked to factors such as poverty, overcrowding and poor living conditions, as well as other adverse socio-demographic and socio-economic factors **(Frame et al, 2006)**.

In 2019, approximately 10 million people developed active TB, including 6.2 million men, 3.2 million women and almost 1 million children (550 000 boys and 490 000 girls). The

The majority of tuberculosis cases occur in South-East Asia (around 44%), followed by Africa (25%) and the Western Pacific (18%), while lower proportions are seen in the Eastern Mediterranean (7.7%), the Americas (2.8%), and Europe (2.7%). Countries such as India (27%), China (9%), and Indonesia (8%) are particularly burdened by TB **(Kyu et al., 2018)**.

In 2020, about 86% of new TB cases were reported from 30 high-burden countries, with two-thirds concentrated in India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa **(Sulis and Migliori, 2020)**.

In 2021, the global number of TB cases rose to 10.6 million, a 4.5% increase compared to 2020. Moreover, 1.6 million people died, including around 187,000 with HIV coinfection **(Glaziou, 2022**).

Drug-resistant TB also showed an upward trend, with an estimated 450,000 new cases of rifampicin-resistant TB a 3% increase over the previous year. This marks a reversal in previous declining trends **(Udwadia et al., 2023)**.

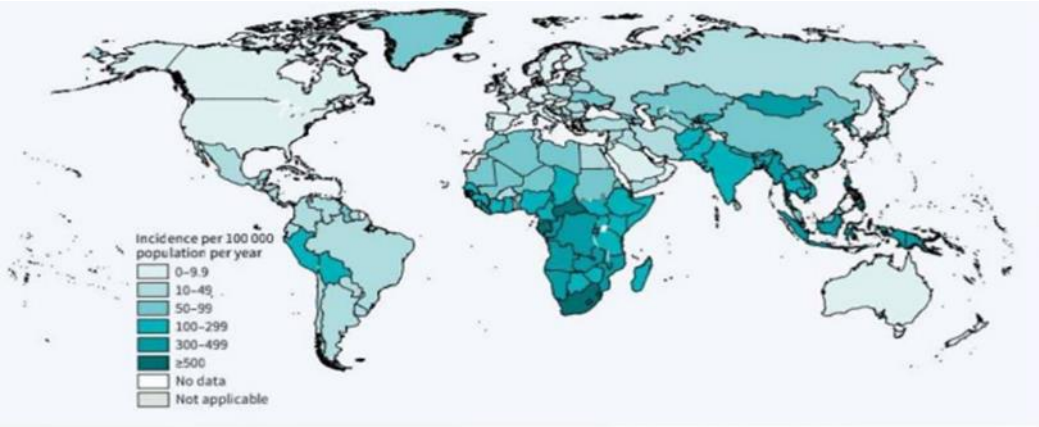


Figure 7: Estimated incidence rates of tuberculosis 2021 (rate per 100,000) **(Ghebreyesus and Kasaeva, 2022)**.

I.4.1.2. In Africa

In North Africa, the geographical distribution of TB is divided into three distinct zones: Morocco, northern Algeria and Tunisia in the west; eastern Egypt, along the Nile; and a central region in southwestern Libya, just above the Tropic of Capricorn **(Bodnar et al., 2001)**.

In sub-Saharan Africa, which accounted for 11% of the world's population in 2002, 24% of all TB cases and 26% of contagious PTB cases were reported that year. While the average global incidence of contagious TB is estimated at 63 cases per 100,000 population, it is 149 cases per 100,000 in sub-Saharan Africa.

Despite the existence of effective prevention and treatment measures, such as chemotherapy and vaccination, TB continues to increase worldwide. According to World Health Organization (WHO) estimates, the annual incidence of the disease increased from 7.3 million cases in 1996 to 8.8 million in 2002. Projections indicated 9 million cases in 2005 and a continued increase to 10 million cases. **(Boulabal et al., 2004)**.

I.4.1.3. In Algeria

Algeria, considered a country with a high prevalence of TB, recognized this disease as a public health priority in 1964. In response, a national tuberculosis control program was established in 1969, accompanied by a large-scale BCG vaccination campaign, which continued until 1972. That same year, the Algerian state introduced completely free care for TB patients and made BCG vaccination mandatory **(Boudjedjou and Guerin., 2018)**.

Before 1962, the incidence of TB in Algeria was close to 300 cases per 100,000 inhabitants. After independence, a significant reduction in the annual risk of infection was observed until the early 1990s, when the incidence increased again due to various socio-economic problems **(Alihlassa, 2018)**.

In 2018, Algeria recorded **23,078 cases** of TB, distributed as follows:

- **7,053 cases** of pulmonary tuberculosis (30.6%), including 5,750 cases of contagious TB, with an incidence of 13.8 cases per 100,000 inhabitants.
- **16,025 cases** of extra pulmonary tuberculosis (69.4%), with an incidence

- Of 38.4 cases per 100,000 inhabitants. Nearly 75% of cases concerned lymph node and pleural forms **((Brahimi et al., 2020)**.

In 2022, **18,421 cases** of tuberculosis were recorded, including 4,600 cases (25.26%) of PTB, including 4,485 cases of contagious TB. A continuous decline in the number of cases has been observed over more than ten years. In addition, 13,769 cases (74.74%) of extra-pulmonary tuberculosis were recorded **(Saihi, 2023)**.

In general, areas with high urbanization have a higher incidence than rural areas. Furthermore, the western region of Algeria has a higher incidence compared to other regions of the country **(Fig. 08) (Hamid, 2016)**.

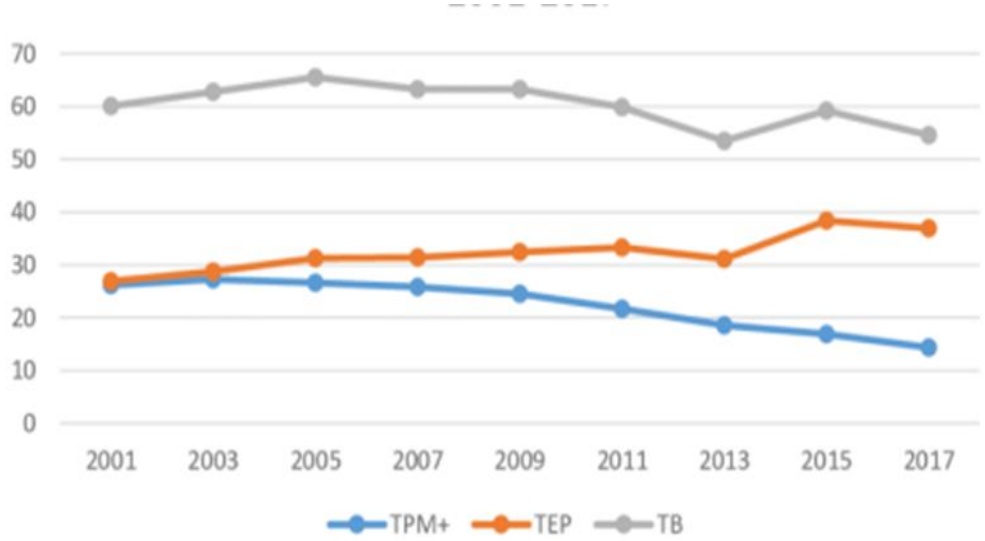


Figure 8: The incidence of tuberculosis in Algeria, 2001-2017**. TPM+:** tuberculosis pulmonary à microscopy positive, **TEP:** tuberculosis extra-pulmonary, **TB:** tuberculosis (pulmonary) (**Bentata, 2018)**.

- **Analysis of Tuberculosis Incidence Trends in Algeria (2001–2017)**

The incidence curve of tuberculosis in Algeria from 2001 to 2017 highlights three key epidemiological indicators: smear-positive pulmonary tuberculosis (TPM+), extra pulmonary tuberculosis **,** and the overall tuberculosis cases **.** The recorded data demonstrate a steady and gradual decline in the incidence rate of TPM+, decreasing from approximately 28 cases per 100,000 population in 2001 to less than 15 cases per 100,000 in 2017. This reduction reflects the effectiveness of national programs focused on early diagnosis and prompt treatment of infectious cases **(Bentata, 2018)**.

Conversely, a gradual increase in the incidence rate of extra pulmonary tuberculosis was observed during the same period, rising from about 28 to 38 cases per 100,000 population, with notable spikes after 2013. This increase can be attributed to advancements in diagnostic techniques as well as emerging health and social factors, including immunosuppression associated with chronic diseases **(Sahu et al., 2020; Bentata, 2018)**.

Meanwhile, the total number of tuberculosis cases remained relatively stable, ranging between 55 and 65 cases per 100,000 population, with a slight decline in 2013 followed by a subsequent rise in the following years. This trend indicates that tuberculosis continues to pose a significant public health challenge in Algeria, necessitating intensified preventive and therapeutic efforts, especially targeting extra pulmonary TB, which is often difficult to diagnose at early stages **(World Health Organization, 2023; Ministère de la Santé Algeria, 2025)**.

These findings underscore the importance of adopting a comprehensive health approach that emphasizes strengthening early diagnostic capacities for extra pulmonary tuberculosis cases alongside supporting existing strategies to combat pulmonary tuberculosis, all within the framework of a national integrated vision aimed at eradicating the disease **(World Bank, 2023; Bentata, 2018)**.

I.5. The forms of tuberculosis

I.5.1. Pulmonary tuberculosis

I.5.1.1. Definition

Pulmonary tuberculosis is the most common and highly contagious form of the disease, primarily due to its airborne transmission. Although it mainly affects the lungs, it can also spread to other parts of the body, giving rise to various extra pulmonary forms of TB **(Ait-Khaled, 2010)**. PTB usually attacks the lungs, but also the pleura, the TB bacillus destroys lung tissue, creating cavities. The disease therefore remains localized in the lungs **(Jones and Niederweis, 2011)**.

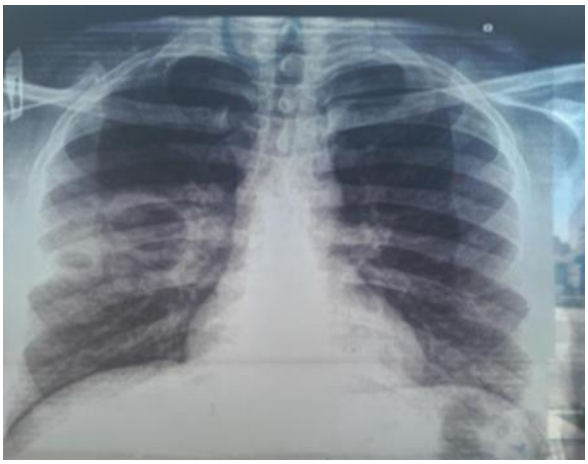


Figure 9: Chest radiograph of pulmonary tuberculosis **(Hôpitaux généraux Hakim Saadane, 2023)**.

I.5.1.2. Types of pulmonary Tuberculosis

I.5.1.2.1 Primary Tuberculosis Infection (PTI)

Primary tuberculosis infection most often goes unnoticed, although it can sometimes cause mild deterioration of general condition, accompanied by moderate fever and asthenia. Rarer manifestations, such as serofibrinous pleurisy, erythema nod sum, or phlyctenular keratoconjunctivitis, can also occur.

The diagnosis of latent tuberculosis, corresponding to the persistence of the Mycobacterium tuberculosis complex after primary infection, is based on the exclusion of active tuberculosis. This requires a thorough history, a rigorous clinical examination, and a chest X-ray. A primary infection can progress directly to an active form, particularly in immunocompromised individuals (e.g., those with HIV infection) or in the elderly **(Chaker, 2022)**.

I.5.1.2.2. Post-primary or secondary infection

This is the most common form of active TB, typically presenting with a gradual onset of pulmonary symptoms. Patients often exhibit nonspecific general signs such as fatigue (asthenia), weight loss, shortness of breath (dyspnoea), and a persistent cough.

Some symptoms are more suggestive, such as a low-grade evening fever (vesperal fever) frequently accompanied by night sweats. The cough may be associated with hemoptysis, which tends to alarm the patient and thus leads to an earlier diagnosis. In some cases, mucopurulent

sputum highly indicative of tuberculosis may also be present. Chest pain may be reported, particularly in cases involving pleural effusion or pneumothorax. The non-specific nature of general symptoms can often delay the diagnosis **(Chaker, 2022)**.

I.5.2. extra-pulmonary Tuberculosis

Extra pulmonary tuberculosis is a type of TB that does not affect the lungs but can infect other parts of the body; it can spread through the blood or lymph from the lungs to other parts of the body **(fig. 10) (Ali et al., 2022)**. Its symptoms and diagnosis vary depending on the affected organ. Such as the lymph nodes, bones, joints, kidneys, nervous system, and sometimes other tissues. ETB is less common than PTB, but it still poses a health threat in some regions, especially in countries where TB rates are generally high **(Thomas ET all., 2023)**. We can restrict the areas of TB infection to the following locations.

- Serous tuberculosis
- Visceral tuberculosis
- Lymph node tuberculosis
- Osseous and osteoarticular tuberculosis
- Cutaneous and mucosal tuberculosis

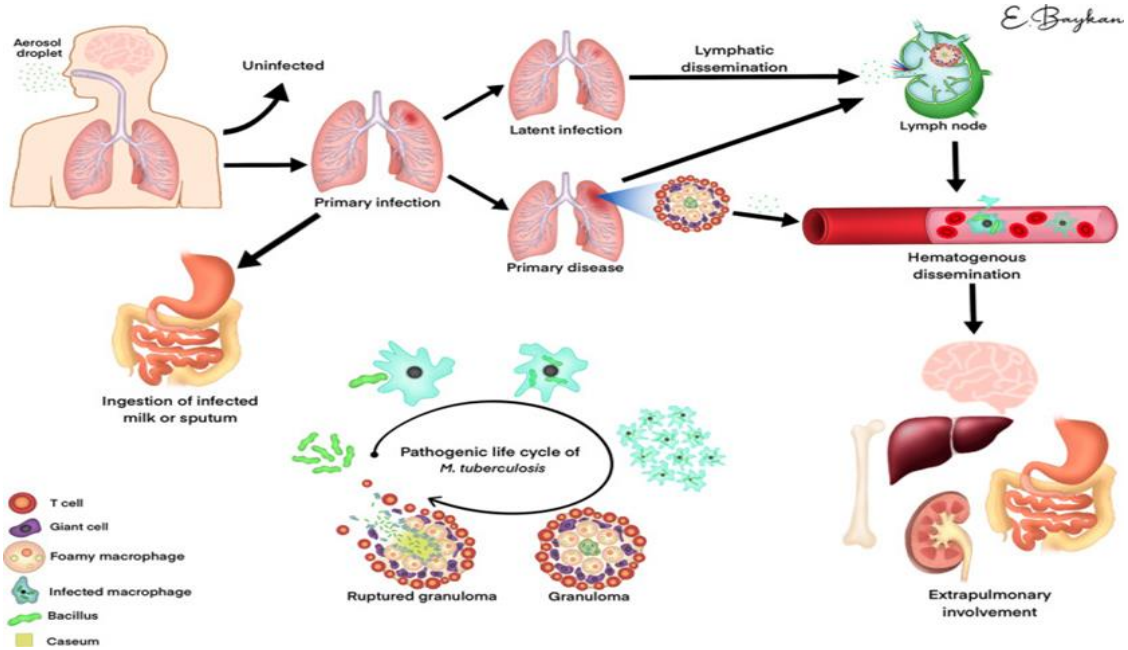


Figure 10: Pathogenic life cycle and extra pulmonary dissemination of *M. tuberculosis* **(Ali and al., 2022)**.

I.5.2.1. Lymph node tuberculosis

Lymph nodes represent between 30 and 60% of all ETB cases. Cervical lymph nodes are the most frequently affected, followed by the mediastinal, axillary, inguinal, epitrochlear, and mesenteric lymph nodes. TB then manifests as the appearance of lymphadenopathy **(Figure. 11) (Lanoix et al., 2011)**.

- **Tuberculous cervical**

Cervical lymphadenopathy (CLA) is a common disease occurring in patients of all ages, with an annual incidence of 0.6–0.7% for the general population **(Chau, 2003; Sakr, 2016)**. The most common etiologies are reactive hyperplasia (38–79%) and TB lymphadenitis (4–34%) in benign cases and metastatic carcinoma (50–94%) and lymphomas (5–41%) in malignant cases **(Bandoh, 2016; Han, 2018)**. Referral patterns and treatment strategies for deferent types of CLA are all distinct; thus, accurate identification of the specific etiology is essential for subsequent medical management **(Chau, 2003; West, 2016)**.

However, the differential diagnosis of CLA is challenging, especially in patients without reliable medical history and characteristic symptoms, which is commonly seen in underdeveloped areas of developing countries **(Choi, 2016)**.

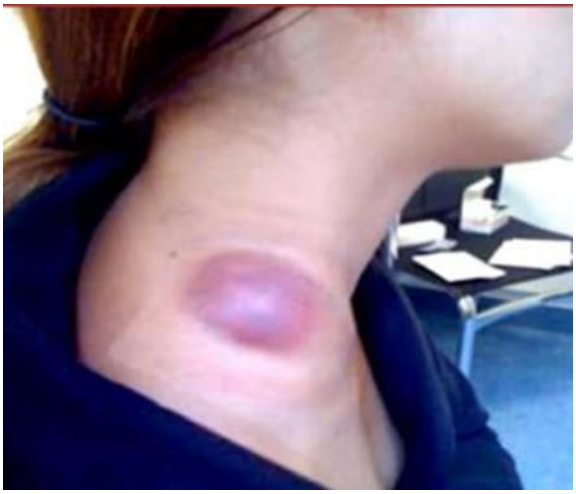


Figure 11: Appearance of lymph node tuberculosis **(Mazza et al., 2012)**.

I.5.2.2. Osteoarticular tuberculosis

This form of TBC can affect any joint, although it primarily affects large joints such as the hip, knee, and elbow. It results in functional impairment, reduced range of motion, and non-

painful swelling of the joint, usually caused by the presence of a cold abscess **(Ait Khaled and Enarson, 1999)**

I.5.2.2.1. Tuberculosis of the spine (Pott's disease)

TB spondylodiscitis, or Pott's disease, is the most common TB osteoarticular disease in developing countries. Vertebral involvement is most often of haematogenous origin. The infection first affects the highly vascularized cancellous bone, then spreads to the intervertebral disc and adjacent vertebrae. Initial symptoms include spinal pain accompanied by general symptoms (fever, weakness, weight loss, and night sweats). The diagnostic methods of choice are spinal imaging by CT or MRI. A biopsy provides bacteriological evidence **(Fig. 12) (Mazza et al., 2012)**.

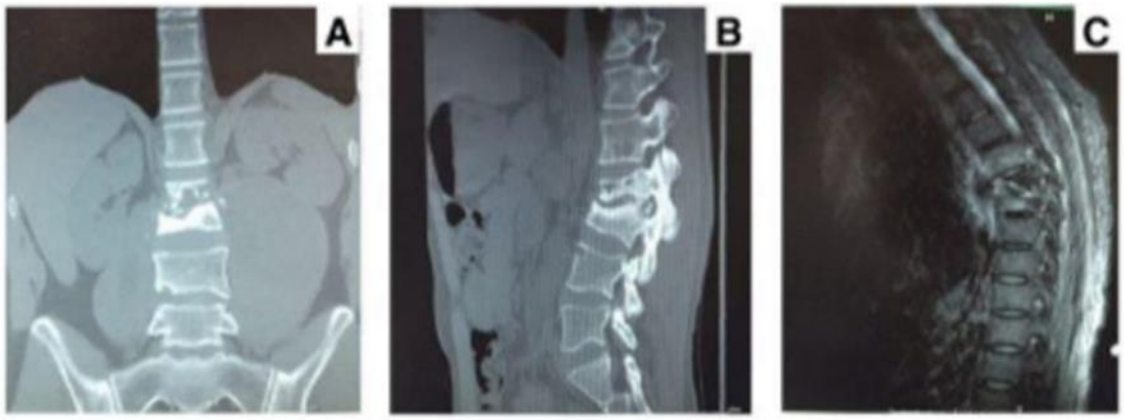


Figure12: CT and MRI of spinal tuberculosis. **A.** CT of spinal tuberculosis: anteroposterior position; **B**. CT of spinal tuberculosis: lateral position; **C**. MRI of spinal tuberculosis (**Qian et al., 2018)**.

I.5.2.2.2. Tuberculous Osteoarthritis

Joint involvement by TB occurs primarily in the large joints of the hip, elbow, or knee, but can affect any joint, including the interphalangeal joints or small bones of the feet **(Ludwig and Lazarus., 2007)**. Joint fluid aspiration and synovial biopsy provide bacteriological or histological confirmation of the diagnosis **(Ketata et al., 2014)**.

I.5.2.2.3. Tuberculosis of other bones

TB of long bones clinically and radiologically suggests chronic osteomyelitis With fistula **(Ketata et al., 2014).** TB of flat bones (cranial vault and rib) manifests itself with the appearance of cold abscesses, and radiographs reveal one or more cysts **(Ketata et al., 2014)**.

I.5.2.3. Urogenital tuberculosis

Urogenital tuberculosis accounts for approximately 15% of ETB forms. It results from haematogenous dissemination and can affect the entire urogenital system. Renal involvement is the most common, often silent, but can cause pain and haematuria in advanced stages. The infection can spread to the urinary tract and genitals.

In women, it mainly affects women of reproductive age, often causing infertility due to involvement of the fallopian tubes and endometrium. It is rarely accompanied by urinary involvement (5% of cases) and manifests as pelvic pain and menstrual disorders .In men, the epididymis is the most common site, which can develop into an abscess or fistula. The prostate, testicles and seminal vesicles may also be affected **(Chaker, 2022; Ait Khaled and Enarson, 1999)**.

I.5.2.4. Serous tuberculosis

Involvement of the serous membranes in TB is one of the common forms of ETB, ranking second after lymph node TB in terms of prevalence. This includes various infections such as pleural, pericardial, and peritoneal tuberculosis, which affect the serous tissues that cover internal organs. Although less common than PTB, it still presents a challenge in diagnosis and treatment due to the diversity of symptoms and the potential for serious complications **(Azadeh et al., 2023)**.

I.5.2.4.1. Peritoneal tuberculosis

Peritoneal tuberculosis is a rare form of TB that affects the peritoneal membrane (peritoneum) **(fig. 13)**, which lines the abdominal organs. This type of TB results from the spread of *M. tuberculosis* to the peritoneum, either hematogenously from a primary pulmonary focus or by direct extension from adjacent infected organs such as lymph nodes or the intestines. Peritoneal TB is characterized by nonspecific symptoms including abdominal pain, ascites, weight loss, fever, and general fatigue, which often complicates the diagnosis and may lead to

it being mistaken for malignancy or chronic inflammatory diseases. Diagnosis relies on a combination of methods, including analysis of ascetic fluid, imaging studies, and laparoscopy with histological examination of biopsy samples. Treatment follows the standard protocols used for TB, and early diagnosis and initiation of therapy are crucial to reduce morbidity and mortality **(Elena et al., 2023; Imhokhai et al., 2021)**.

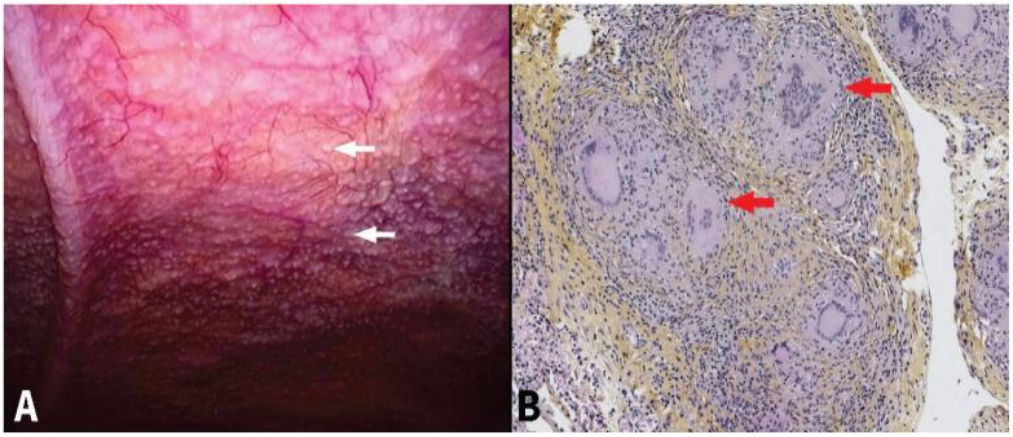


Figure 13: (A) Photograph showing white tubercular deposits (white arrows) on the parietal peritoneum. **(B)** Microscopy of peritoneal biopsy sample showing numerous non-necrotizing granulomas (red arrows). Hématoxyline phlox ne saffron stain. Original magnification × 100 **(Imhokhai et al., 2021)**.

I.5.2.4.2. Pleural Tuberculosis

Pleural tuberculosis is a form of ETB that affects the pleural membrane surrounding the lungs. It often results from the spread of *M. tuberculosis* from a primary pulmonary focus. The condition is characterized by symptoms such as chest pain, dry cough, fever, and weight loss. It is commonly associated with an exudative pleural effusion that is rich in lymphocytes. Due to the low number of bacilli present in pleural fluid, diagnosis can be challenging. It typically relies on fluid analysis, markers such as adenosine deaminase (ADA), and molecular techniques like polymerase chain reaction (PCR). In some cases, a pleural biopsy may be necessary to confirm the diagnosis. Treatment involves standard anti-tuberculosis medications. In more complex cases, drainage of the fluid or surgical intervention may be required **(Jane et al., 2021)**.

I.5.2.4.3. Tuberculous meningitis

Tuberculous meningitis is a form of ETB that occurs primarily in immunocompromised patients, children, and the elderly its onset is generally more gradual than that of bacterial

meningitis. Initial symptoms include persistent fever, general fatigue, myalgia, headache, and a deterioration in general condition, which precede the appearance of signs of meningeal irritation **(Mazza, 2012; Chaker, 2022)**.

I.5.2.5. Visceral tuberculosis

Abdominal TB is a medical condition that can mimic malignant tumours, making diagnosis difficult and often-delaying appropriate treatment. The disease presents in various forms depending on the affected organ. It may appear as genital TB, impacting the reproductive organs and potentially leading to infertility, or as intestinal TB, which affects the digestive tract and causes chronic abdominal pain and weight loss. In more severe cases, it can develop into cerebral TB, involving the central nervous system and posing serious neurological risks. The disease can also affect the kidneys, known as renal tuberculosis, leading to chronic urinary tract inflammation, or spread to the liver (hepatic TB), impairing its vital functions. Additionally, splenic TB may occur, influencing the immune system. Due to the wide range of manifestations and the overlap with other conditions, diagnosis often requires advanced imaging techniques and histological examinations to confirm the disease and formulate an effective treatment plan **(Chandan et al., 2023)**.

I.5.2.5.1. Genitaled tuberculosis

Female genital TB is a common cause of infertility, often affecting the fallopian tubes and endometrium after the infection spreads from other parts of the body **(fig. 14)**. Many women show no clear symptoms and the condition is typically discovered during infertility investigations or when there are pelvic pain and menstrual irregularities. Diagnosis relies on a combination of endoscopic, microbiological, and histological tests. Early treatment is crucial to prevent permanent damage, though the disease may still lead to fertility complications even after treatment, along with the psychological impact of social stigma **(Christine et al., 2022)**.

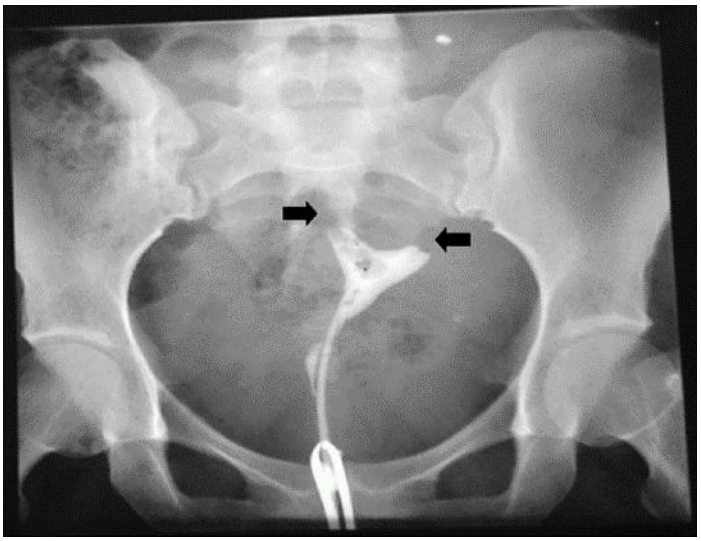
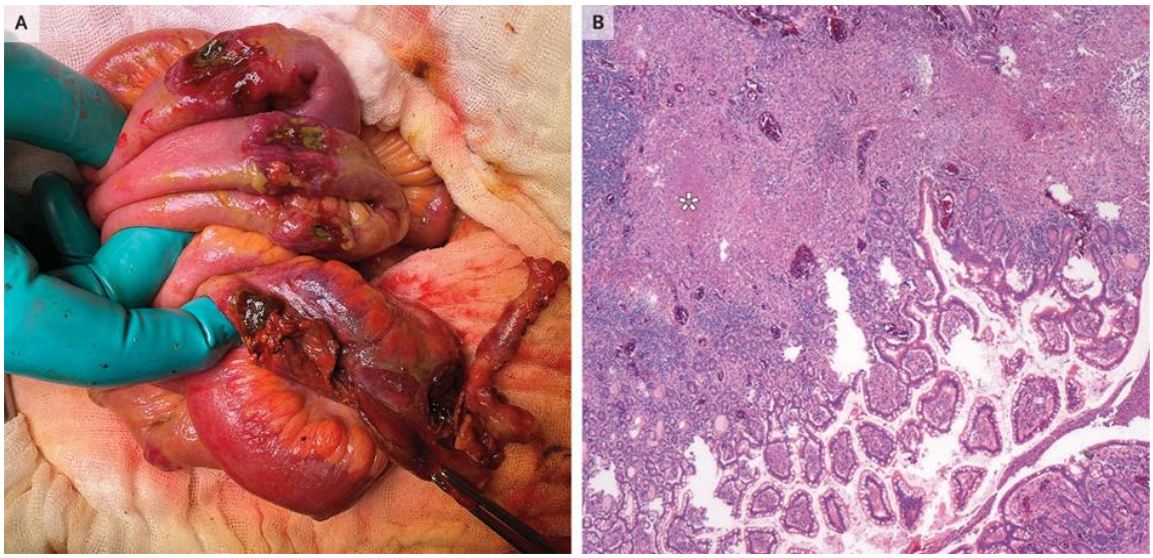


Figure 14: Hysterosalpingography shows a blockage in both fallopian tubes, as indicated by the arrows **(Jai Bhagwan et al., 2018)**.

I.5.2.5.2. Intestinal Tuberculosis

Intestinal TB is a form of ETB that affects the gastrointestinal tract **(fig 15)**. Although it is relatively rare, this type of TB poses a significant diagnostic challenge due to its strong resemblance to other diseases such as Crohn's disease and intestinal cancer. The symptoms of intestinal TB are often nonspecific and may include abdominal pain, weight loss, chronic fever, and either diarrhea or constipation. Delayed or incorrect diagnosis can lead to serious complications such as intestinal obstruction or perforation. Therefore, diagnosis relies on a combination of clinical, endoscopic, histological, and radiological examinations, in addition to modern molecular tests, to ensure accurate differentiation and appropriate treatment **(Esther et al., 2018)**.



Figur15 : Intestinal Tuberculosis **(Luis et al., 2022)**.

I.5.2.5.3. Cerebral tuberculosis

TB meningitis is one of the most severe forms of ETB, despite its rarity, and is associated with high rates of mortality and neurological complications. One of its most serious outcomes is stroke, caused by inflammation of cerebral blood vessels, which can lead to focal paralysis or altered consciousness. The challenge lies in the diversity of symptoms and the unclear mechanisms of vascular damage. Although the standard anti-tuberculosis four-drug therapy combined with corticosteroids is used, it often fails to prevent vascular complications, highlighting the importance of early diagnosis and prompt treatment to avoid permanent damage **(Tala et al., 2020; Robert et al., 2017)**.

I.5.2.5.4. Hepatic tuberculosis

Hepatic TB is a rare form of ETB and is often asymptomatic, which makes its diagnosis challenging and sometimes leads to it being mistaken for malignant tumours on imaging studies. Patients may present with nonspecific symptoms such as anorexia, mild upper abdominal pain, or persistent fever, without a history of hepatitis or respiratory symptoms. Imaging modalities such as MRI or PET-CT may reveal hepatic nodules that can be misinterpreted as metastatic lesions. Image-guided liver biopsy is crucial for confirming the diagnosis, typically showing granulomatous inflammation, along with positive results for acid-fast staining or interferon-gamma release assays (IGRAs). Although PCR testing may sometimes yield false-negative results, culture of the biopsy sample may later confirm the presence of *M. tuberculosis*. Treatment is based on the standard four-drug anti-tuberculosis regimen, which often leads to

significant clinical and radiological improvement within a few months **(Carlo et al., 2023; Yuqing et al., 2024)**.

I.5.2.6. Cutaneous tuberculosis

Cutaneous TB is rare, with a frequency of 1 to 2%. Its anatomical and clinical polymorphism and the difficulty of isolating the pathogen make its diagnosis difficult **(Fig 16) (Bezioui et al., 2017)**.

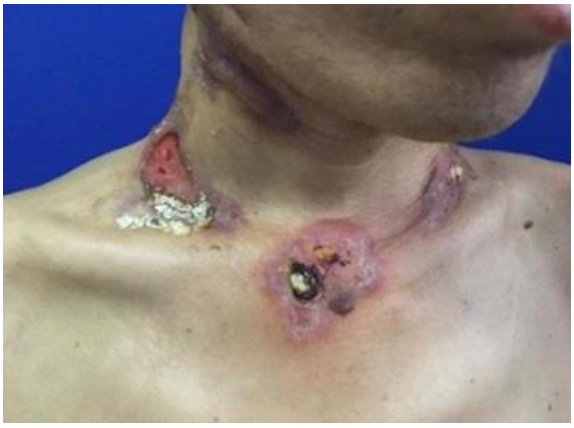


Figure 16: A 24-year-old man with erosions and abscesses of tuberculous scrofuloderma **(Chen et al., 2019)**.

I.6. Clinical manifestation of tuberculosis

Clinical Symptoms of TB vary depending on the type of the disease (pulmonary or extra pulmonary) and the stages the patient goes through. In the case of PTB, the symptoms begin gradually and include a persistent cough lasting more than three weeks, which may be accompanied by sputum or blood in advanced cases (haemoptysis). The patient may also experience chest pain and difficulty breathing (dyspnoea). Other common symptoms include a low-grade fever that is usually worse at night, along with night sweats, which are a distinctive sign of TB. The patient also experiences unexplained weight loss, loss of appetite (anorexia), and general fatigue with severe body weakness. As for ETB, symptoms vary depending on the affected organs. If the lymph nodes are involved, the patient may suffer from swollen lymph nodes. In the case of bone and joint involvement, there may be back pain or joint pain. In the case of neurological involvement, symptoms like headache and confusion may occur, particularly if the disease affects the central nervous system (such as meningitis). If the genitourinary system is affected, the patient may experience blood in the urine or difficulty urinating. Symptoms vary depending on the affected organ, but all of them indicate chronic inflammation caused by the immune system's response to the infection **(Sarah et al., 2017; Laneke et al., 2020; Esther et al., 2018)**.

I.7. Risk Factors for tuberculosis

Tuberculosis is an infectious disease that spreads through the air. The risk of infection is influenced by various individual and community-level factors. On an individual level, the risk increases for young children and the elderly due to weaker immune systems. Additionally, conditions such as HIV/AIDS, diabetes, malnutrition, or the use of immunosuppressive drugs can compromise the body's ability to fight the infection. Certain behaviors, including smoking, alcohol consumption, and drug use, also contribute to a higher risk of developing TB.On a community level, poor living conditions such as poverty, malnutrition, overcrowding, and poor ventilation especially in places like prisons and refugee camps facilitate the spread of the disease. Low levels of education, lack of awareness, and limited access to healthcare services, particularly in high-burden areas or among displaced persons and refugees, lead to delayed diagnosis and treatment, further exacerbating the spread of TB **(Nayana et al., 2023; Melsew et al., 2018; Denise et al., 2018)**.

I.8. Diagnosis of Tuberculosis

TB is a serious infectious disease caused by the bacterium *M. tuberculosis*. Diagnosis is based on clinical symptoms, laboratory tests such as sputum examination and culture, and molecular tests such as Gene pert, which have contributed to accelerated detection of the disease and drug resistance **(Pai et al ., 2021)**.

I.8.1. Bacteriological diagnosis

Microbiology plays a key role in the diagnosis and treatment of TB. It helps confirm the diagnosis by identifying the pathogen BK, in pathological samples **(Bouheraoua, 2013)**. In cases of pulmonary tuberculosis, it facilitates the detection of bacillus-carrying individuals, the main vectors of disease transmission **(Souidi, 2014)**.

I.8.1.1. Direct examination by microscopy (sputum)

I.8.1.1.1. Sputum collection

In cases where PTB is suspected, it is recommended, whenever possible, to collect three sputum samples. The first, known as the "on-the-spot" sample, is collected immediately after the consultation, under the supervision of a nurse. The nurse must explain to the patient that the sputum should be produced following a deep and forceful cough in order to obtain secretions originating from the bronchi **(Fig. 17)**.

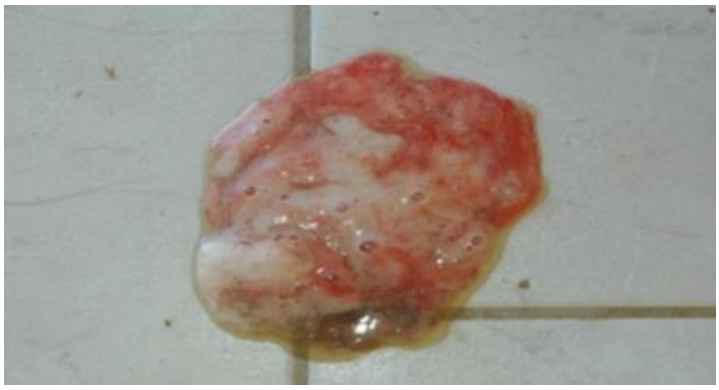


Figure 17: Bloody sputum from a patient suffering from pulmonary tuberculosis at the Boussif laboratory in Oujda **(Souidi, 2014)**.

The nurse then provides the patient with a second container intended for collecting an early morning sample, to be obtained by the patient upon waking the following day. Finally, when the patient returns with this sample, a third sputum specimen is collected on the spot. **(Gopi, 2007)**.

I.8.1.1.2. Classical Methods with microscopic observation

Samples may also be obtained through gastric lavage (containing swallowed bronchial secretions) or by bronchial aspiration. In cases where ETB is suspected, specimen collection particularly biopsies is performed based on the anatomical site affected by the disease **(Ratovonirina, 2017)**.

A smear is then prepared by spreading the biological specimen onto a thin glass slide, followed by staining to reveal the characteristic resistance of mycobacteria to acid-alcohol decolorization. Two staining methods are commonly used for this purpose: the Ziehl-Neelsen method and auramine staining (fluorochrome) **(Fig. 18)**.

Figure 18: Preparation and staining of sputum slides for microscopic examination **(Self-portrait)** .

Direct microscopic examination can only detect acid-fast bacilli (AFB) in a sample if their concentration is at least 0.5 to 1.1 bacilli per microliter **(fig. 19) (Saltini, 2006)**.

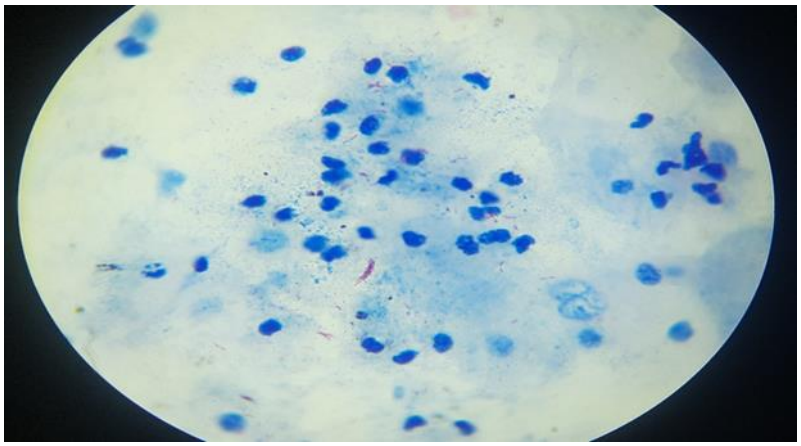


Figure19: Observation of Bk on the microscope **(Self-portrait)**.

I.8.1.2. Cultivation

Bacteriological culture has significantly higher sensitivity compared to direct microscopic examination **(Gopi, 2007)**. It should be performed systematically, as it enables the identification of isolated mycobacteria and the subsequent performance of drug susceptibility testing **(Houidi, 2016)**.

Due to the slow growth rate of most *M. tuberculosis* species with a doubling time of approximately 20 hours enriched culture media are required.

Samples likely to be contaminated with commensal flora, such as sputum, urine, abscess pus, or lymph node secretions, must undergo decontamination prior to inoculation. In contrast, specimens considered sterile (e.g., pleural, peritoneal, or pericardial fluid, joint effusions, surgical biopsies, or lymph node aspirates) can be cultured directly without prior decontamination **(Meyssonnier, 2012)**.

The Löwenstein-Jensen solid medium, which is egg-based, is the most commonly used culture medium. In primary cultures, M. tuberculosis colonies typically appear between the 21st and 28th day **(Kassa and Messaoudi., 2017)**.

Upon colony emergence, microscopic examination is conducted to confirm the presence of acid-fast bacilli. If confirmed, the culture is deemed positive, and the results are reported quantitatively based on the number of colonies per tube **(Ais and Ais., 2018)**.

I.8.2. Radiological diagnosis

TB is often referred to as the "great imitator" in medical imaging because it can mimic a wide range of pulmonary pathologies. However, certain radiological signs are highly suggestive of the disease **(Meyssonnier, 2012; Wright and Zignol, 2012)**.

The use of imaging tests such as chest X-ray, computed tomography (CT), or other thoracic imaging techniques will depend on the clinical manifestations observed **(Coulon and Piette, 2008)**. Typical features of TB include nodular opacities, sometimes confluent, peribronchovascular infiltrates, and cavitations. The most frequently affected areas are the posterior segment of the upper lobe and the apical segment of the lower lobe (Brändli et al., 2003). presents as a macro nodular opacity, usually 1 to 4 cm in diameter. It may remain stable or evolve over time

I.8.3. Immunological diagnosis

I.8.3.1. tuberculin skin test (TST) (intradermal reaction)

The Monteux test, also known as the intradermal tuberculin reaction, is a skin test designed to assess the delayed hypersensitivity reaction induced by mycobacterial antigens *(M. tuberculosis* complex, BCG, and certain atypical mycobacteria). It is the only truly quantitative test, involving the intradermal injection of 0.10 ml of purified tuberculin on the anterior surface of the forearm. The injection must be strictly intradermal and without any bleeding. The formation of an "orange peel" papule (**Fig. 20)** confirms the proper intradermal placement of the injection. The results are read after 72 to 96 hours by measuring the largest diameter (in millimetres) of the induration at the injection site **(Fig. 21) (Majdaoui, 2016)**.

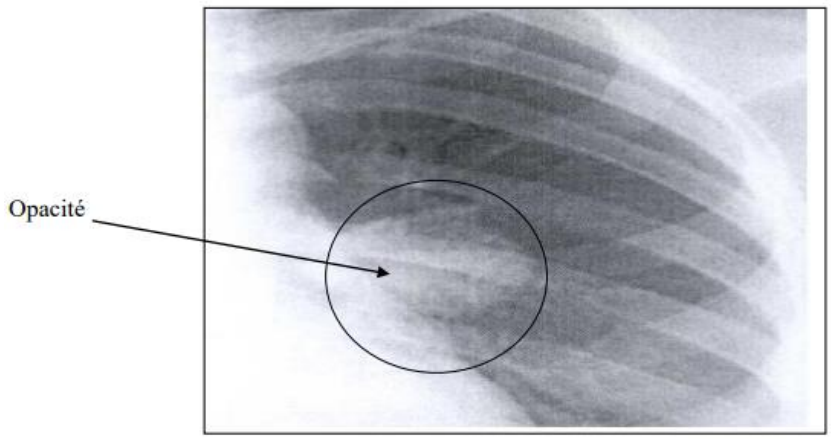


Figure 20: Large opacity with left hilar projection of regular contours **(Souidi, 2014)**.

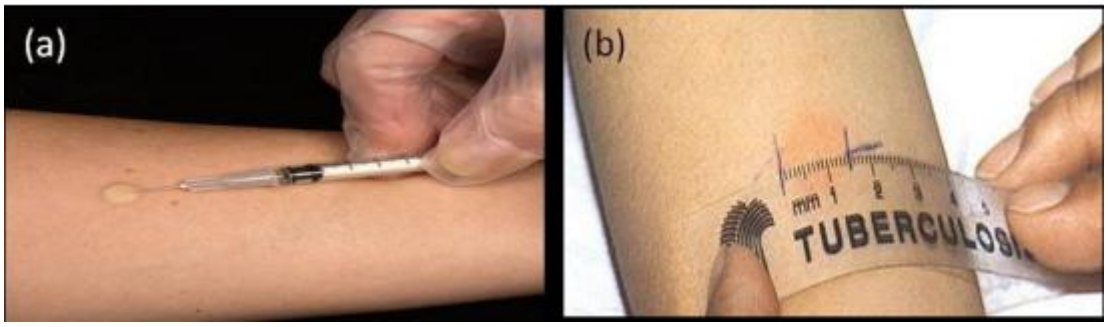


Figure 21: Tuberculin Skin Test :**(a)** Technique for intradermal injection **;(b)** Technique for interpreting the intradermal tuberculin reaction **(Gopi, 2007)**.

- The interpretation of the results should be carried out according to vaccination history **(Table. 02) (Bouklata, 2016)**.

Table 02 : Interprétation de test à la tuberculine **(Bouklata, 2016).**

Diameter (mm)	Clinical significance of tuberculosis infection
5 <	Negative
5 à 10	Possible but unlikely for atypical *mycobacteria.*
< 10	Positive: probable tuberculosis infection.

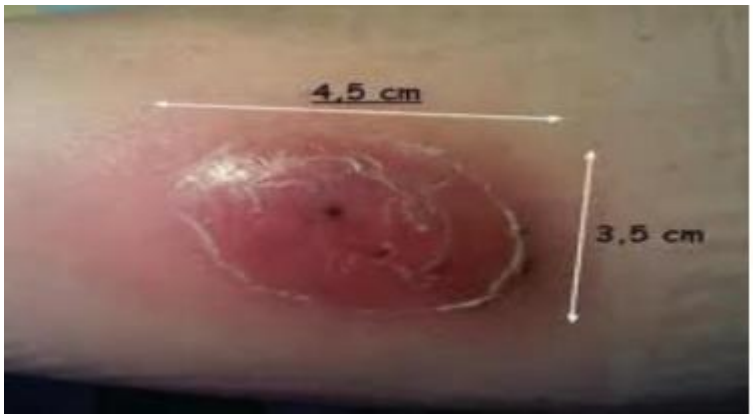


Figure 22: Positive IDR test with induration of 1cm in diameter **(Gopi, 2007)**.

I.8.3.2. - Molecular tests

In recent years, numerous molecular techniques have been developed and adapted for the diagnosis of TB, utilizing the detection of mycobacterial DNA. These methods primarily rely on gene amplification strategies. The conventional Polymerase Chain Reaction, which targets specific genetic sequences unique to *M. tuberculosis* strains, has been widely used

(D'Amato et al., 1995). More advanced approaches include real-time PCR, such as the Xpert MTB/RIF assay, offering rapid detection and drug resistance profiling **(Blakemore et al., 2010; Broccolo et al., 2003; Helb et al., 2010)**. Another promising technique is LAMP-PCR (Loop-mediated Isothermal Amplification), which facilitates the identification of nucleic acid sequences specific to tubercle bacilli in a simple and rapid manner **(Boehme et al., 2007; Cao et al., 2015)**.

While these molecular methods represent a major advancement, their direct application to clinical specimens is currently limited by suboptimal sensitivity **(Kim et al., 2009)**. Nonetheless, when performed on cultured isolates, these techniques demonstrate excellent levels of both sensitivity and specificity **(Kim et al., 2009)**.

Chapter two

Tuberculosis treatment

II. Treatment of Tuberculosis

II.1. Treatment Objectives

Tuberculosis is one of the major health challenges facing the world due to its impact on individual and public health. Despite medical advancements, eliminating TB still requires integrated efforts, including awareness, treatment adherence, and continuous follow-up. The objectives of TB treatment may have repercussions, both on an individual and community level. On the individual level, the main objective is to completely cure the patient by eliminating the TB bacteria, which prevents relapse or complications. This can only be achieved through full commitment to the treatment plan, which often lasts for several months without interruption **(Agadir et al., 2011)**.

On the public health level, patient adherence to treatment helps protect the community from the spread of infection and reduces the risk of drug-resistant strains emerging one of the biggest challenges in TB control. This, in turn, preserves the effectiveness of current medications, protects future generations from resistant TB, and eases the health and economic burden on societies **(Agadir et al., 2011)**.

II.2. Tuberculosis therapy

Treating tuberculosis is considered a complex medical challenge due to the nature of the causative bacteria, which grow slowly and can enter a dormant state within the body. This behavior necessitates long-term, multi-drug treatment to ensure complete eradication of the infection. The bacteria can be found in different locations within the body; some multiply abundantly outside the cells, particularly in lung cavities, creating an environment that promotes drug resistance. Other groups grow slowly within macrophages or are located in solid, caseous material with poor blood supply, which reduces the effectiveness of medications. An effective treatment plan typically involves first-line drugs administered over a period of 6 to 9 months in standard cases, and up to 18 months or more in cases of drug resistance. To ensure adherence and achieve full recovery, the "Directly Observed Treatment" (DOT) approach is adopted as a standard practice, along with continuous monitoring to manage any potential side effects **(Thomas et al., 2017; Ayushi et al., 2023)**.

II.2.1. Essential drugs for tuberculosis

Tuberculosis treatment initially relies on a combination of drugs designed to eliminate the bacteria in all their forms and locations within the body. This regimen typically includes key medications such as rifampin, isoniazid, pyrazinamide, ethambutol, and streptomycin. Treatment is generally divided into two phases: the first, known as the intensive phase, lasts for the initial two months and involves the use of rifampin, isoniazid, and pyrazinamide to rapidly reduce the bacterial load and prevent the development of drug resistance **(Table. 03)**. This is followed by the continuation phase, which extends for four months or longer depending on the patient's response, during which isoniazid and rifampin are used to eliminate any remaining bacteria and prevent relapse **(Thomas et al., 2017)**.

II.2.1.1. Isoniazid (H)

This medication is one of the main pillars in the treatment of tuberculosis, known for its ability to widely distribute throughout the body, easily penetrating critical tissues such as the brain, pleural membrane, peritoneum, and respiratory tract. It is metabolized in the liver, and its half-life in the bloodstream varies depending on the individual's metabolic rate, ranging from one to three hours. The drug works by inhibiting the synthesis of mycolic acid, a vital component of the bacterial cell wall, making it particularly effective against rapidly dividing bacteria and contributing to their gradual elimination **(Jindani et al., 1980; Wang et al 1972; American Thoracic Society, 2003)**.

- **Toxicity**

The use of this drug is associated with several side effects, particularly affecting the liver, where it can cause an elevation in liver enzymes, especially alanine aminotransferase. In rare cases, hepatic inflammation may develop. The drug's hepatotoxicity increases when used in combination with rifampin. Additionally, it can affect the nervous system, leading to peripheral neuropathy. Other rare side effects include seizures, dermatologic reactions, and monoamine sensitivity **(Thomas et al., 2017)**.

II.2.1.2. Rifampicin (R)

Rifampin is an antibiotic primarily used in the treatment of tuberculosis, known for its effectiveness against rapidly dividing bacteria as well as those in a partially dormant state. It works by inhibiting the RNA polymerase enzyme in *Mycobacterium tuberculosis*, thereby

stopping its replication. Rifampin is a key component in short-term treatment regimens, as it helps reduce the likelihood of relapse after recovery.

It has a high ability to penetrate various body tissues, but it reaches relatively low concentrations in the central nervous system, which may require higher doses in some cases. It is metabolized in the liver and stimulates the cytochrome P-450 enzymes, which can reduce the effectiveness of other medications **(Mitchison, 2000; American Thoracic Society, 2003)**.

- **Toxicity**

Rifampin is one of the essential antibiotics for treating tuberculosis, but it may cause some side effects, the most significant of which is cholesteric hepatic toxicity, characterized by elevated levels of bilirubin and alkaline phosphatase. Additionally, some patients may experience a transient rash with itching, along with a change in the colour of bodily fluids to orange. In rare cases, a flu-like syndrome or thrombocytopenia may occur **(Steele et al., 1991; American Thoracic Society, 2003; Paula et al., 1998)**.

II.2.1.3. Pyrazinamide (Z)

Pyrazinamide is considered one of the key components in the treatment of tuberculosis, playing a vital role in eliminating dormant bacteria that thrive in acidic environments within the body. This drug weakens the bacterial cell membrane and disrupts its essential functions, making it highly effective in targeting persistent organisms that may remain hidden after the start of treatment. Z is typically used during the initial two months of therapy to help shorten the overall treatment duration. In cases where Z is not included in the regimen, the treatment period may extend to at least nine months or more. The drug is metabolized in the liver, while its by-products are excreted by the kidneys, requiring caution when administered to patients with kidney failure. Z is also known for its ability to penetrate cerebrospinal fluid, and its effects last in the body for approximately 9 to 10 hours **(Zhang et al., 2003; Ellard et al., 1987)**.

- **Toxicity**

Hepatotoxicity is considered one of the most well-known side effects associated with the use of pyrazinamide, particularly when used in combination with other ant tubercular drugs, despite its high efficacy in treating tuberculosis. Other adverse effects include elevated serum uric acid levels, which typically do not necessitate discontinuation of therapy unless there is a prior history of gout. Patients may also experience bothersome symptoms such as nausea,

vomiting, photosensitivity-induced dermatitis, a mild skin rash, and joint pain **(Døssing et al., 1996; Yee et al., 2003; Snider et al., 1984; Cullen et al., 1956)**.

II.2.1.4. Ethambutol (E)

Ethambutol is used as part of standard tuberculosis treatment protocols, helping to control the disease by inhibiting bacterial growth rather than directly killing the bacteria. Its main benefit lies in reducing the risk of developing resistance to other drugs, especially in the early stages of treatment when drug susceptibility test results are not yet available. This medication is taken orally and is primarily excreted through the kidneys, requiring dose adjustments in cases of renal impairment. Although it is effective in treating pulmonary TB, its efficacy is limited in cases involving the central nervous system. Additionally, it may affect the optic nerve, making regular vision check-ups important throughout the treatment period **(Donald et al., 2010; Pilheu et al., 1971)**.

- **Toxicity**

Peripheral neuritis and skin rash are rare adverse effects that may occur during the course of treatment. The most commonly observed toxicity, however, is optic neuritis, which typically arises following prolonged use of the drug or in the presence of renal insufficiency. Initial symptoms include difficulty in distinguishing colours, particularly red and green, which may progress to worsening visual impairment. In most cases, vision returns to normal upon discontinuation of the medication **(Leibold et al., 1966; Varughese et al., 1986; American Thoracic Society., 2003)**.

II.2.1.5. Streptomycin (S)

Streptomycin is a drug from the aminoglycoside group, primarily used to treat tuberculosis. It is highly effective against active bacteria that proliferate in non-cellular tissues, but it is less effective in cases of tuberculosis where the bacteria are inside cells. The drug works by inhibiting protein production inside bacterial cells, leading to the destruction of the bacteria.. It is administered via injection only, as it is not available in tablet or syrup form. The dosage is determined based on the patient's health needs and can be adjusted accordingly. In some areas with high tuberculosis prevalence, resistance to the drug may develop, requiring the search for alternatives or modifications in treatment approaches **(Thomas et al., 2017)**.

❖ **Toxicity**

In certain therapeutic cases, vestibular disturbances and hearing loss may occur, a condition known as ototoxicity. This typically arises with the administration of high doses of the drug and is more likely to affect elderly patients. Less common adverse effects include nephrotoxicity, circumoral paraesthesia, hypokalaemia, and hypomagnesemia **(Feldman et al., 1954; Joint Committee on the Study of Streptomycin., 1947)**.

Table 3: Minor Side Effects of First-Line Antituberculosis Drugs **(Agadir et al., 2011)**.

Drugs	Side effects
Isoniazid	Euphoria Insomnia and facial acne Paresthesia of the lower limbs
Rifampicin	Digestive disorders Facial acne
Pyrazinamide	Arthralgia, anorexia
Ethambutol	Nausea
Streptomycin	Facial tightness Nausea, Dizziness

II.2.2. Alternative Medications

In cases of treatment failure with second-line drugs or relapse of the disease, the cause is often due to bacteria resistant to the antibiotics previously used, either inherently resistant or acquired through irregular or incorrect use of these antibiotics. In such cases, new antibiotics are used, which are generally less effective and cause more severe side effects than the primary

antibiotics. These drugs are prescribed exclusively by specialized doctors in university hospitals, as they require careful and continuous supervision. **(Agadir et al., 2011)**.

II.2.2.1. Ethionamide

Ethionamide is considered an effective medication used in the treatment of tuberculosis cases that do not respond to conventional therapies. It is classified as a second-line anti-tuberculosis drug. Introduced into medical use in the 1950s, its utilization has expanded with the increasing incidence of drug-resistant pulmonary tuberculosis. Despite its effectiveness in eliminating the bacteria that cause TB, Ethionamide is associated with several known side effects, including gastrointestinal disturbances, mood changes, and effects on the liver and nervous system. However, visual disturbances remain among its rare complications **(Jain et al., 2020; Mohammad et al., 2020)**.

II.2.2.2. Ofloxacine

Ofloxacine is an antibiotic from the fluoroquinolone group, known for its bactericidal activity through the inhibition of DNA gyrase, an enzyme essential for the replication of *M . tuberculosis*, including strains resistant to first-line drugs. Studies have shown that it has moderate to high early bactericidal activity, making it a promising candidate for shortening the duration of TB treatment, especially in low-bacterial-load forms such as tuberculous lymphadenitis. While the use of Ofloxacine in TB treatment is promising, fluoroquinolone resistance is an increasing concern, highlighting the importance of performing molecular drug susceptibility testing before its use particularly in extra pulmonary TB cases, where diagnosis is more challenging. Ofloxacine has also been associated with certain adverse drug reactions, necessitating close monitoring of patients during treatment to ensure safety and adherence **(Syed et al., 2024)**.

II.2.2.3. Kanamycin

Kanamycin is an antibiotic discovered and developed in the 1950s, known for its broad-spectrum activity against various bacteria, including *M. tuberculosis* resistant to streptomycin. Although kanamycin showed effective bactericidal activity against *M. tuberculosis* in laboratory tests, no randomized controlled trials (RCTs) have definitively proven its efficacy in treating tuberculosis, unlike streptomycin, which was proven effective through such trials. Kanamycin is primarily used in the treatment of drug-resistant TB or severe cases of lung

disease, but it can cause serious side effects such as ototoxicity and nephrotoxicity **(Peter, 2021)**.

II.2.2.4. Cycloserine

Cycloserine is an antibacterial drug used in the treatment of multidrug-resistant TB and has been in use since the 1950s. It works by inhibiting enzymes responsible for the formation of the bacterial cell wall, contributing to the destruction of the tuberculosis-causing bacteria. Despite its effectiveness in treating MDR-TB, its use is limited due to neurological side effects, including seizures in about 10% of patients. However, Cycloserine is considered important in the treatment of drug-resistant TB, as it does not show cross-resistance with other drugs. It has been recommended as a second-line medication for treating MDR-TB in recent guidelines, although its role in treating XDR-TB remains unclear **(Table. 04) (Yang et al., 2019)**.

Table 4: Major and minor side effects of second-line anti-tuberculosis drugs **(Agadir et al., 2011)**.

Drugs	Minor effects	Major effects
Ethionamide	Anorexia, excessive salivation, nausea, vomiting, sulfurous belching, metallic taste	Psychotic disorders (hallucinations or depressive syndrome) Hypoglycemia
Ofloxacine	Common digestive problems (anorexia, nausea, vomiting) Nervous problems (dizziness, headaches)	Achilles tendonitis
Kanamycin	Deafness, dizziness and nephrotoxicity)	
Cycloserine	Neurological disorders (tremor, dizziness, headaches and speech difficulties or insomnia)	Generalized hypersensitivity or Hepatitis Leading to suicide

II.3. Standardized therapy regimens and their indication

II.3.1. The various phases of therapeutic management

Treatment of drug-susceptible tuberculosis consists of two phases:

II.3.1.1. Intensive Phase

Two months, based on a combination of recommended first-line drugs. This intensive phase eliminates most bacilli and reduces the impact of the few bacilli that are resistant to ant tuberculosis drugs due to spontaneous mutations. The role of this intensive phase is to reduce the risk of treatment failure **(Agadir et al., 2011)**.

II.3.1.2.Continuation phase

Is important because it ensures that the patient is permanently cured and that no relapse will occur after treatment is stopped. This phase does not require as much medication as the intensive phase, but its duration must be long enough (usually four months) to guarantee the patient's permanent cure **(Agadir et al., 2011)**.

II.3.2. Therapeutic diets

Until 2010, the National Tuberculosis Control Program adopted the classification of tuberculosis cases by category in order to standardize anti-tuberculosis chemotherapy regimens **(Souidi, 2014).** Thus, these cases were classified into four categories **(Table. 05)**.

Table 5: Treatment categories and corresponding chemotherapy regimens **(Lakehal, 2014)**.

Category de Treatment	**Group of maladies**	**Phase initial**	**Phase d'entretien**
PT **TB ceveral**	Find out more about TP in positive frottis. New to TP in positive cultureseulement. Use the TP to enter the fruit there are also some parenchymate uses Develops non-cavities. Primarily infected with the condition Pulmonary Forme severs of the TP and TEP	**2 HRZE**	**4 HR**
PT	This type of TP is characterized by a basic effect treatment: Rechute Reprise development after interruption premature Echec	**2 SHRZE / 1 HRZE**	**5 HRE**
TEP	Primary symptomatic infection without pulmonary disease. Formes Common from TEP (pleurésies, ascite, osseuse).	**2 HRZ**	**4 HR**
PTC **PT MDR**	Chronic cases (after failure or relapse of second-line treatment) Cases of PT with multi-resistant bacilli.	**Standardized or individualized third-line regimens**	

PT: Pulmonary Tuberculosis; **EPT:** Extra pulmonary tuberculosis; **TB:** Tuberculosis. ; **MDR PT**: Multidrug-Resistant pulmonary tuberculosis.

- **Category I: (2 Months RHZE / 4 Months RH regime)**

This group comprises new cases of smear-positive PTB that should be treated with chemotherapy as a priority.

In addition to this main group, we must include:

- Severe forms of ETB.
- New cases of smear-negative and culture-positive PTB.
- New cases of smear-negative PTB with cultures not performed or not available **(Agadir et al., 2011)**.

- **Category II: (Regime 2 Months SHRZE / 1 Month HRZE / 5 Months RHE)**

This group corresponds to the group of progressive relapses, failures, and relapses of PTB, observed after an initial course of chemotherapy. These cases are always bacteriologically positive (by direct microscopy and/or culture) **(Agadir et al., 2011)**.

- **Category III :(Regimen 2 Months RHZ / 4 Months RH)**

This group is that of cases of simple ETB and primary infections without pulmonary involvement visible on chest X-ray **(Agadir et al., 2011)**.

- **Category IV : (Regimen 3 Months EthOKCZ/ 18 Months EthOZ)**

The chronic case group corresponds to patients with smear-positive PTB who have already undergone supervised retreatment without success these cases represent category II failures.

These are generally multidrug-resistant cases, particularly those resistant to isoniazid and rifampicin. The management of these patients is complex and requires the exclusive intervention of a university hospital pulmonologist, who is the only one authorized to prescribe medications specific to this resistant form of the disease **(El Garch, 2011)**.

II.3.3. The relapse

Relapse or recurrence is defined by an increase in the size of a residual lymph node or the appearance of one or more lymph nodes after a complete course of anti-tuberculosis chemotherapy and a phase of clinical remission. This is either a reactivation of the TB strain or a de novo infection by another strain **(Park et al., 2019)**.

If the treating physician suspects failure or relapse, samples should be repeated to definitively confirm failure based on bacteriological and/or histological evidence and decide whether to continue treatment or perform surgery in addition to chemotherapy. Some authors emphasize the need to distinguish between a true relapse (positive culture, which is not always easy to confirm) and a paradoxical post-treatment reaction **(Park et al., 2019; Lee , 2015)**.

II.4. Treatment Management and Doses

Tuberculosis is an infectious disease that requires long-term, systematic treatment to ensure complete recovery and prevent the development of drug resistance. The importance of treatment lies not only in selecting the appropriate drugs, but also in determining the precise dosages of each drug based on the patient's weight, age, and general health condition. Any deviation in dosages whether overdosing or underdoing can lead to treatment failure or the emergence of resistant strains.

The treatment protocol for TB relies on the use of a combination of drugs at precisely defined doses, typically including: rifampicin, isoniazid, pyrazinamide, and ethambutol. These doses vary depending on the stage of treatment (intensive or maintenance) and the type of TB (susceptible or drug-resistant **(Table. 06)**. Hence, it is essential to understand the mechanism of dose determination and its vital role in the success of the treatment plan **(Agadir et al., 2011)**.

Table 6: New tuberculosis treatment (The number of sentences on the screen for the original quote) **(Agadir et al., 2011)**.

Weight of sick (kg)	RHZE 150/75/400/275mg	RHZ 150/75/400 mg	RH 150/75 mg
30 – 39	2	2	2
40 – 54	3	3	3
55 – 70	4	4	4
> 71	5	5	5

II.5. Drug Resistance in *Mycobacterium tuberculosis*

The development of drug resistance in *M. tuberculosis* poses a major obstacle to global TB control efforts. Resistance typically arises through the stepwise accumulation of genetic mutations, particularly in genes targeted by first-line anti-TB drugs such as isoniazid and rifampicin, leading to multidrug-resistant strains. Further acquisition of resistance to fluoroquinolones and second-line injectable agents results in extensively drug-resistant TB. Contributing factors include prolonged treatment regimens, poor patient adherence, latent infections, and host-related conditions such as immunosuppression and malnutrition. In addition to classical mutation-driven mechanisms, *M. tuberculosis* employs non-genetic strategies including efflux pumps, metabolic dormancy, and adaptation to the host microenvironment, enhancing its ability to withstand antimicrobial pressures. These complexities highlight the urgent need for novel therapeutic approaches targeting both bacterial and host-mediated resistance pathways **(fig. 19) (Dipanwita et al., 2024)**.

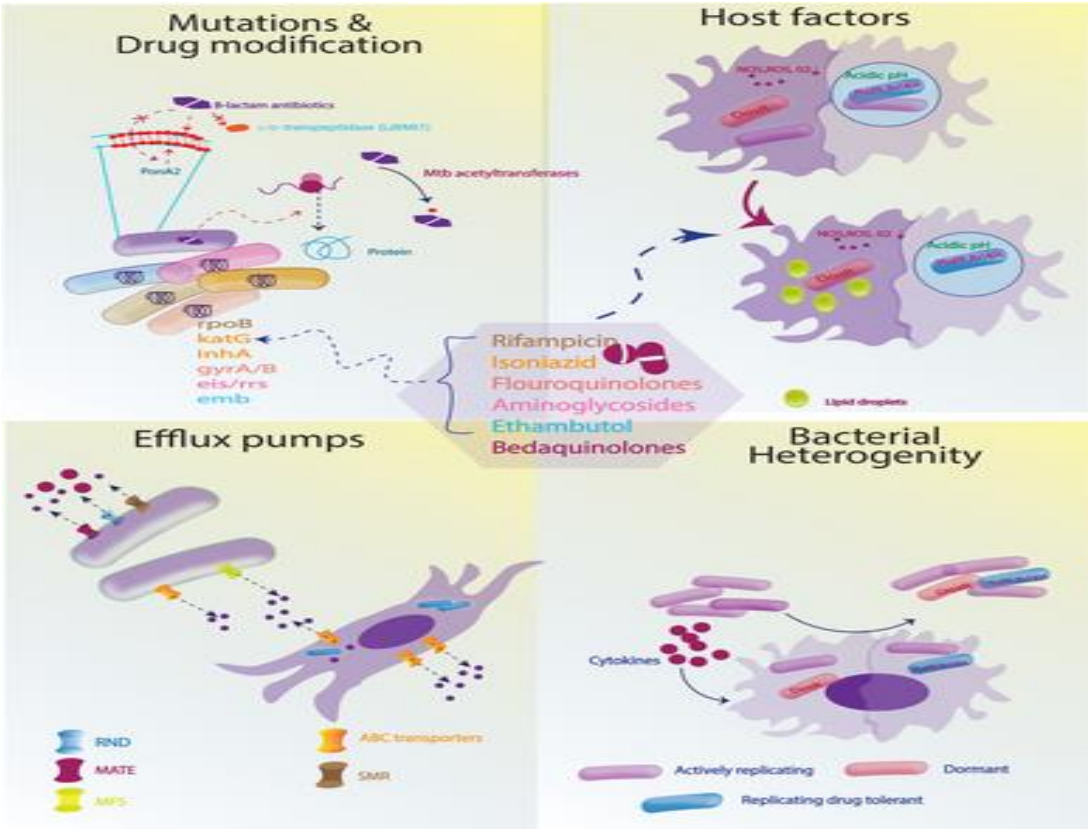


Figure 23: Mechanisms of drug tolerance and resistance in *M. tuberculosis* **(Dipanwita et al., 2024)**.

II.5.1. Mechanisms of drug resistance in M. tuberculosis

II.5.1.1. Passive resistance mechanism

Passive resistance is one of the natural mechanisms employed by *M. tuberculosis* to withstand antibiotics. It is manifested in the bacterium's structural properties, where these factors collectively create an internal environment that protects the bacteria and provides it with an inherent ability to tolerate various drugs **(Tasha et al., 2013)**. Among these mechanisms, we can mention:

- *M. tuberculosis* has a thick and complex cell wall composed of three main layers: peptidoglycan, arabinogalactan, and mycolic acids, which form a barrier that prevents the effective penetration of many antibiotics **(Luke et al., 2015; Jackson et al., 1999)**.
- The bacterium exhibits a slow growth rate, which reduces the effectiveness of antibiotics, as it decreases the likelihood of being targeted during cell division **(Claudia et al., 2004)**.

- The limited presence of porin proteins restricts the uptake of nutrients and antibiotics, thereby enhancing the overall drug tolerance of the bacterium **(Maha et al., 2013; Shi et all., 2014; Shi et al., 2011)**.
- *M. tuberculosis* exhibits intrinsic resistance to β-lactam antibiotics by utilizing alternative enzymes, specifically l,d-transpeptidases, instead of the conventional penicillin-binding proteins targeted by these drugs, rendering β-lactams largely ineffective. Additionally, mutations or loss of function in certain PBPs, such as PonA2, can further influence the bacterium's susceptibility to β-lactam antibiotics **(Mohammad et al., 2017; Cordillot et al., 2013)**.

II.5.1.2. Specialized resistance mechanisms

Despite advances in tuberculosis treatment, *M. tuberculosis* remains a major medical challenge due to its complex and multifaceted resistance mechanisms. These mechanisms include alterations in the structural configuration of target proteins, which reduce the efficacy of antibiotics like macrolides and lincosamides, facilitated by the *M. tuberculosis* enzymes that methylates ribosomal RNA, hindering antibiotic binding. Additionally, *M. tuberculosis* employs biochemical strategies such as drug inactivation through acetylation, particularly with aminoglycosides, mediated by the EIS enzyme, which also enhances survival within host macrophages. The bacterium also utilizes efflux pumps to expel antibiotics from the cell, reducing their intracellular concentration and promoting resistance. Genetic mutations, such as those in the rpoB gene, further contribute to resistance by altering drug-binding sites, with strains like Beijing showing rapid mutation during active infection. Unlike other bacteria, *M. tuberculosis* primarily acquires resistance through chromosomal mutations rather than horizontal gene transfer. Moreover, resistance mutations often come with a biological cost, decreasing bacterial fitness in the absence of drugs, but compensatory mutations in genes like rpoA, rpoC, gyrA, and gyrB can restore fitness and even reverse resistance, allowing the bacterium to regain drug sensitivity **(Dipanwita et al., 2024)**.

II.6. Drug Interactions

II.6.1. Drug Interactions between Diabetes and Tuberculosis

Both diabetes mellitus (DM) and tuberculosis represent major global public health challenges, placing an increasing burden on healthcare systems, particularly in low- and middle-income countries. TB remains a serious infectious disease that continues to claim many lives,

especially among individuals with weakened immune systems. On the other hand, DM contributes to this threat by impairing immune function, thereby increasing the risk of developing TB by up to threefold. Research has shown that individuals with diabetes are more susceptible to active TB and often face poorer treatment outcomes, including higher rates of treatment failure, relapse, and mortality **(Edison et al., 2022)**.

The comorbidity between DM and TB presents a complex therapeutic challenge, as the use of multiple medications increases the risk of drug interactions. TB drugs such as rifampin and ethambutol may interact with diabetes medications like metformin through their effects on organic anion and cation transporters OAT and OCT. For example, rifampin may inhibit OAT1, affecting the absorption of other drugs, while ethambutol inhibits OCT1, altering the absorption of metformin. Additionally, the metabolic products of ethambutol may interact with other drugs such as metformin or lamivudine, commonly used in associated conditions like diabetes or viral infections, as they are substrates for hOCT3 and hOST1 transporters. These interactions may impact drug absorption or elimination, increasing the risk of toxicity or reducing effectiveness. Therefore, treatment requires careful monitoring and regular evaluation to minimize these interactions and protect patient health **(Xiao lei et al., 2013; Masud et al., 2016**).

II.6.2. Interactions between Tuberculosis and HIV

Acquired Immune Deficiency Syndrome is a chronic condition resulting from infection with the Human Immunodeficiency Virus, which progressively weakens the immune system and makes the body more vulnerable to opportunistic infections chief among them, tuberculosis. TB is the leading cause of death among people living with HIV, and studies indicate that the relationship between the two diseases is mutually reinforcing: HIV accelerates the progression of latent TB to active disease, while TB increases HIV replication and further weakens immune function. Evidence from Ethiopia and Ghana shows that mortality rates among co-infected individuals are high, attributed to factors such as older age, poor functional status, low CD4 counts, opportunistic infections, and advanced stages of AIDS. Managing both diseases simultaneously presents clinical challenges, as potential drug interactions between TB medications like rifampicin and antiretroviral therapy (ART) for HIV may reduce treatment effectiveness or increase toxicity. Therefore, effective management of HIV-TB co-infection requires early screening, integrated treatment approaches, and careful medical follow-up to improve survival and quality of life **(Lorena AT AL., 2024; Shun et al., 2024; Sisay et al., 2024; Martin et al., 2024)**.

II.7. Latent Tuberculosis Treatment

There are various diagnostic methods used to detect latent tuberculosis infection, ranging from traditional to advanced techniques. One of the most widely used tests is the tuberculin skin test, which relies on a localized immune response following the intradermal injection of a purified protein derivative (PPD) of *M. tuberculosis*. Despite its broad use, the accuracy of TST is reduced in individuals who have received the BCG vaccine or have had previous exposure to non-tuberculous mycobacteria, and it may yield false-negative results in immunocompromised patients. In contrast, interferon-gamma release assays (IGRAs), such as Quanta FERON-TB Gold and T-SPOT.TB, represent an important advancement, measuring IFN-γ secretion by T cells in response to MTB-specific antigens such as ESAT-6 and CFP-10. Although IGRAs demonstrate relatively higher sensitivity and specificity, they still cannot reliably differentiate between latent and active TB.

Studies have shown that combining IGRA and TST improves diagnostic accuracy, particularly in immunosuppressed individuals. Further diagnostic advancements are under investigation, including immune biomarkers like CD161+ T cells, blood cell ratio analysis, and methylation profiling of alveolar immune cells, which show promise for early-stage LTB detection. Additionally, low-cost and easy-to-use molecular tests such as “Gene pop” are being developed for use in resource-limited settings. Despite these advances, a major challenge remains in developing a definitive diagnostic test with sufficient sensitivity and specificity to accurately distinguish between latent and active TB **(Christian et al., 2023)**.

Regarding treatment, several effective antimicrobial regimens are available for managing LTB, varying in duration and drug combination. Among the preferred short-course therapies is the once-weekly combination of isoniazid (900 mg) and rifapentine (900 mg) for three months. Another widely used option includes the daily combination of isoniazid (900 mg) and rifampicin (600 mg) for 3–4 months. Rifampicin monotherapy (600 mg daily for 3–4 months) is also favoured due to its lower risk of hepatotoxicity. Alternatively, isoniazid monotherapy (5–10 mg/kg, up to 300 mg daily) for 6–12 months remains a long-standing regimen, although it is associated with a higher risk of liver toxicity. This variety of therapeutic options allows for tailored treatment plans based on individual patient needs, balancing efficacy, safety, and adherence **(Christian et al., 2023)**.

II.8. Preventive Treatment

It has many protective measures that are used in the anti-tuberculosis system: BCG vaccination and prophylaxis **(Sahnoune, 2011).**

II.8.1. BCG vaccination

The Bacillus Calmette–Guérin vaccine is a live attenuated bacterial vaccine derived from a strain of M. bovis, originally isolated by Edmond Nocard from a TB mastitis lesion in a cow. This strain was subsequently cultured and attenuated beginning in 1908 by Albert Calmette and Camille Guerin. In Algeria, BCG vaccination was made mandatory as of 1969 **(Zehani, 2016).**

The BCG vaccine provides varying degrees of protection against TB, particularly its most common form, PTB. However, it has been demonstrated that the vaccine offers consistent and effective protection against disseminated forms of the disease, especially TB meningitis **(WHO, 2018).**

- **Children who need to be vaccinated with BCG**

  - ✓ All viable infants born in a hospital maternity ward, urban polyclinic, or private clinic, regardless of their birth weight, before discharge from the maternity ward.
  - ✓ All infants born at home, who must be presented by their parents, either spontaneously or at the request of the municipality that registered them in the civil registry, to the vaccination center (basic health unit or PMI center) closest to their home, within the first month following birth.
  - ✓ All children aged 0 to 14 years inclusive, without a vaccination scar, when they present to a health facility (particularly during the first DTP-Hib vaccination at the third month of age).
  - ✓ In all cases, vaccination is administered without prior tuberculin testing **(Agadir et al. 2011).**

II.8.2. Chemoprophylaxis

Chemoprophylaxis allows the development of TB maladies to prevent déjà infections. It is the main function of children of up to 5 years, asymptomatiques that comes into contact with Detroit with a PTB diagnosing device noting that this substance is still alive **(Agadir et al., 2011).**

In general, this prophylaxis consists of the administration of isoniazid seul, a dose of 5 mg/kg every day, after a period of six months, and that's what makes the vaccine status due to the BCG **(Sahnoune, 2011).** In national contexts, this application may be large in risk groups, in the context of exposure and public health policies.

II.9. Advanced Strategies in Tuberculosis Treatment and Diagnosis

Modern approaches to combating tuberculosis aim to enhance drug efficacy and enable faster, more accurate detection. Among the most notable strategies are floating drug delivery systems (FDDS), which improve drug retention in the stomach for prolonged periods, thereby increasing the absorption of drugs such as rifampicin. Additionally, floating microspheres loaded with rifampicin and quercetin have been developed, demonstrating good stability and enhanced bioavailability. Furthermore, gold nanoparticles (GNPs) are used in TB treatment due to their ability to inhibit the growth of M. tuberculosis and their synergistic effects when combined with other nanomaterials such as mesoporous silica nanoparticles (MSNs). These nanoparticles are also utilized in rapid diagnostics, with GNP-based immunoassays capable of differentiating M. tuberculosis from M. bovis. These innovative techniques offer promising solutions for TB management, both by improving treatment efficacy and expediting diagnosis **(Ayushi et al., 2023)**.

Objectives of the study

Objectives of the Study

The aim of this study was first to describe the demographic and epidemiological characteristics of the TB patients, evaluating the effectiveness of diagnostic and treatment methods on different form of TB, as well as identifying the factors influencing the spread of the disease or complicating its cases. We secondly assessed TB treatment outcomes and the factors, either clinical or biological parameters, affecting treatment success among TB patients in Mila district (Northeastern Algeria). We also provide practical recommendations that will contribute to enhancing the effectiveness of health interventions, improving patient management and diagnosis methods, and predicting the early effectiveness of treatment, thereby supporting local efforts in prevention and control of TB.

Part two

Practical part

Chaptre Three

Materiel and Method

III. Material and methods

III. 1. Study Design and Duration

As part of academic training, a retrospective study was conducted, aiming to analysed particularly treatment data of patients diagnosed with tuberculosis from various regions of Mila Province. This study was carried out during the field training period, which extended from February to May, 2025.

III. 2. Study Location

This study was conducted in three public health institutions distributed across various municipalities of Mila Province, in addition to the department of pulmonology at the "Mohamed Meddahi" Public Hospital, located in the municipality of Ferdjioua, Mila Province. The study was carried out in these separate healthcare facilities with the aim of covering a broad geographical and representative range, in order to accurately reflect the epidemiological situation within the province.

III. 2. 1. Study Area

Mila Province is located in the northeastern of Algeria. It is bordered to the north by Jijel Province, to the northeast by Skikda, to the east by Constantine, to the southeast by Oum El Bouaghi, to the south by Batna, and to the west by Sétif. The province covers an area of 9,375 km² and is administratively divided into 13 districts (daïras) comprising 32 municipalities. According to the 2008 census, Mila Province had a total population of 766,886, resulting in a population density of approximately 225 inhabitants per km². These demographic and geographic indicators provide an essential basis for understanding the population distribution and territorial structure of the studied area. The province's postal code is 43000, and its telephone area code is 031.

III.2.2.1 Public Hospital Mohamed Meddahi – Ferdjioua

III.2.2.1.1 Hospital Location

The “Mohamed Meddahi” Public Hospital based in Ferdjioua city is located in the eastern part of the city, within Mila Province. Strategically positioned in the city center **(Fig. 24)**.

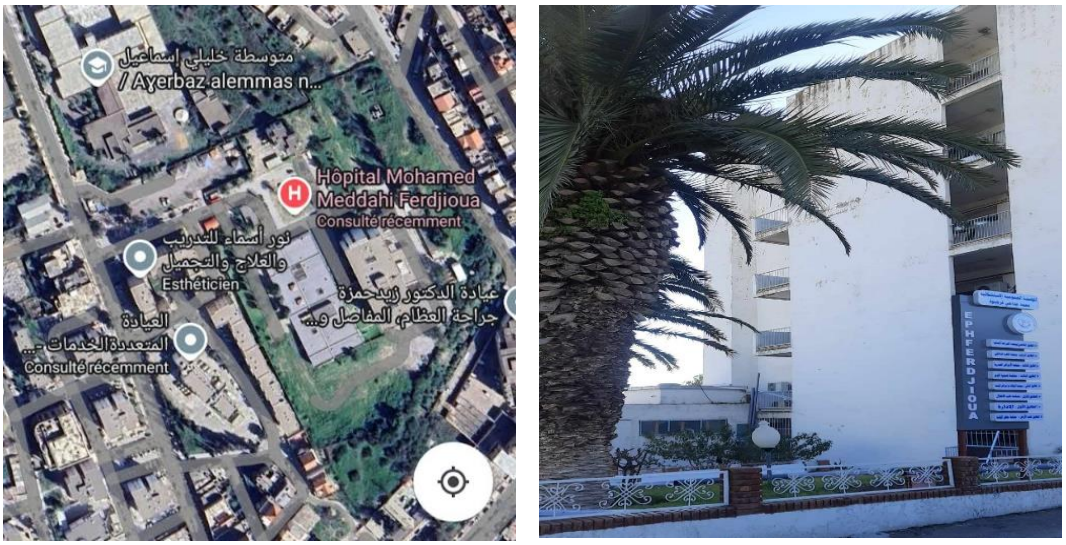


Figure 24: Mohamed Meddahi Public Hospital – Ferdjioua

III.2.2.1.2 Hospital Overview

Based on the ministerial decree dated December 20, 2009, which defines the internal structure of public hospital establishments, “Mohamed Meddahi” hospital is organized into four subdivisions: subdivision of health services, subdivision of human resources, subdivision of finance and logistics and subdivision of medical equipment maintenance and related devices.

The hospital is structured to ensure the efficient delivery of medical care and administrative services. It operates with a diverse and comprehensive approach to healthcare, reflected in its eleven main departments:

- General Surgery Department, which includes separate units for male and female surgeries.
- Internal Medicine Department, comprising male internal medicine, female internal medicine, and a medical oncology unit.
- Pneumo-Phthisiology Department, divided into specialized male and female units.

- Gynecology and Obstetrics Department, offering services in both gynecology and obstetrics.
- Pediatrics Department, which includes general pediatrics and neonatology units.
- Nephrology and Hemodialysis Department, with distinct units for nephrology and hemodialysis treatments.
- Emergency Medical and Surgical Department, encompassing triage, reception, and the operating block.
- Central Laboratory, containing microbiology and biochemistry units.
- Pharmacy Department, responsible for the management, distribution, and proper handling of pharmaceutical products.
- Epidemiology Department, which focuses on health information management and hospital hygiene.

This organizational structure highlights the hospital's capacity to provide a wide array of specialized medical services, ensuring that it plays a vital and integral role in the healthcare system of the region.

III.2.2.2. The public primary healthcare institution Deraahi Bousselah

III.2.2.2.1. Healthcare institution location

The public primary healthcare institution "Deraahi Bousselah" is located in the municipality of Draahi Bousalah, within the Bouhatem district of Mila Province, Algeria. Positioned within a semi-rural setting, the clinic plays a critical role in delivering essential healthcare services to a dispersed population across several localities in the region. Its strategic location allows it to serve as the first point of contact for medical care in the area, offering accessible primary health services to residents of "Deraahi Bousselah" and nearby municipalities**(Fig. 25)**

Figure 25: The Public Primary Healthcare Institution – Deraahi Bousselah **(Google map)**

III.2.2.2.2. Healthcare institution overview

In accordance with the structure defined by the Algerian Ministry of health for primary healthcare institutions, the “Deraahi Bousselah" primary health institution is organized to deliver decentralized and community-focused health services. It operates under the supervision of the Mila Direction of health and population, ensuring alignment with national health strategies. The institution includes several key units designed to meet the basic and preventive healthcare needs of the community:

- General Medicine Unit, which provides routine consultations, diagnosis, and treatment for common illnesses.
- Maternal and Child Health Unit, offering prenatal care, family planning, vaccinations, and child development monitoring.
- Emergency and First Aid Unit, handling minor emergencies and stabilizing patients before referral to higher-level hospitals if necessary.
- Immunization and Preventive Care Unit, focused on vaccination campaigns, school health programs, and awareness initiatives.
- Dental Care Unit, which provides basic dental consultations, preventive care, and minor procedures.

- Chronic Disease Follow-Up Unit, responsible for monitoring patients with long-term conditions such as diabetes and hypertension.
- Medical Imaging Room, equipped with basic radiology services for diagnostics.
- Pharmacy; which ensures the availability and proper distribution of essential medicines prescribed within the clinic.
- Administrative Department, managing patient records, logistics, and coordination with other health institutions.

This organizational setup ensures the efficient functioning of the institution as a vital hub for community health, focusing on prevention, early diagnosis, and continuity of care. The "Deraahi Bousselah" clinic significantly contributes to the overall public health strategy in the Mila Province, particularly in semi-rural and underserved areas.

III.2.2.3. The Public primary health institution Bouarroudj, Mila

III.2.2.3.1. Center Location

The public primary health care center is located in the city of Mila, located in eastern Algeria. Its strategic location in a densely populated urban area makes it a key hub for providing basic health services to the city's residents and its suburbs. The centre's easy accessibility by various means of transportation enhances its ability to respond quickly to citizens' daily health needs **(Fig. 26)**.

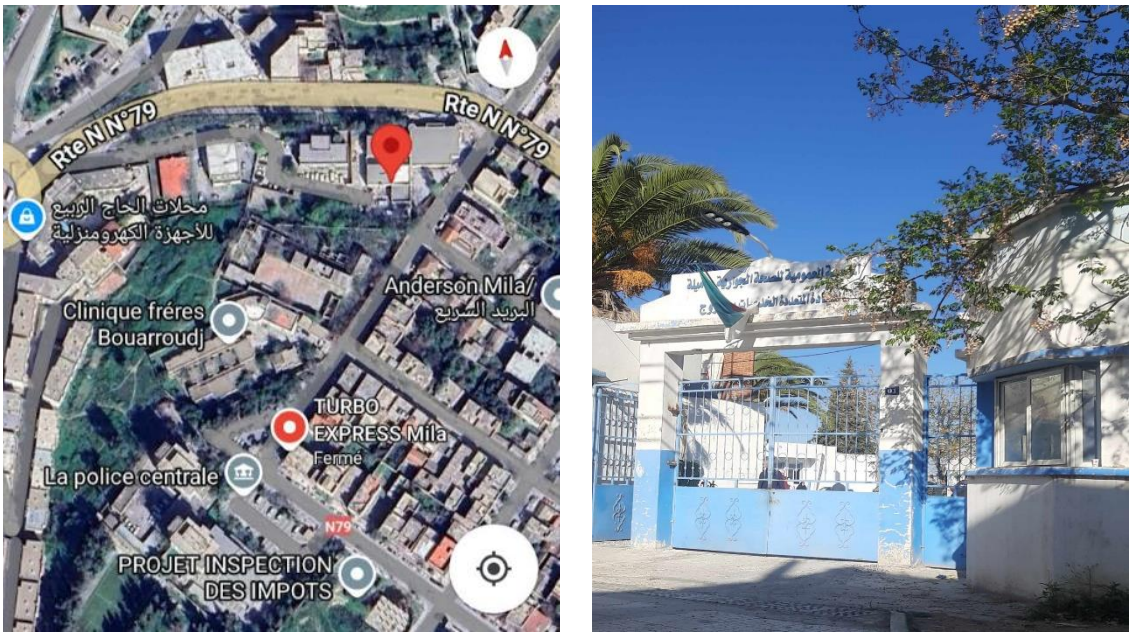


Figure 26: The Public Primary Healthcare Facility – Bouarroudj, Mila **(Google map).**

III.2.2.3.2. Center Overview

In accordance with the joint ministerial decree dated December 20, 2009, which defines the internal structure of public primary healthcare institutions, the Mila Primary Healthcare Center is designed to provide comprehensive services in prevention, diagnosis, treatment, and health education.

The center is organized into several essential units:

- General Medicine Unit: Provides daily medical consultations, diagnoses common conditions, and refers patients to specialists when necessary.
- Maternal and Child Health Unit: Focuses on prenatal care, postnatal follow-up, and child immunization as per the national vaccination program.
- Dental Care Unit: Offers preventive and restorative dental services, including routine check-ups and basic treatments.
- Emergency Unit: Manages minor emergencies, providing first aid and stabilizing patients for referral to higher-level hospitals if needed.
- Chronic Disease Follow-Up Unit: Ensures continuous care for patients with chronic conditions such as diabetes, hypertension, and asthma.
- Preventive and Immunization Unit: Organizes vaccination campaigns and conducts health awareness programs in schools and neighbourhoods.
- Radiology Room: Equipped to provide basic imaging services to support clinical diagnosis.
- Pharmacy: Responsible for ensuring the availability and proper dispensing of essential medications as prescribed by healthcare providers.
- Administrative Services: Manages patient records, appointment scheduling, and coordination with other healthcare institutions in the province.

This center is a cornerstone of the healthcare system in Mila Province, playing a crucial role in providing quality, accessible, and comprehensive healthcare services. It contributes significantly to early intervention, preventive care, and the overall health promotion efforts in the region.

III.2.2.4. Public Community Health Institution of Ferdjioua

III.2.2.4.1. Institution Location

The Ferdjioua Public Neighbourhood Health Institution is located in the Ferdjioua municipality, Mila Province, Algeria. The institution enjoys a strategic location in a densely populated area, directly below the Meddahi Hospital, making it easily accessible to the residents of Ferdjioua and the surrounding rural areas. Its location enhances its role as a major provider of primary healthcare services, serving as the first point of contact for patients seeking medical assistance after completing their hospitalization **(Fig. 27)**.

Figure 27: Public Community Health Institution of Ferdjioua **(Google map).**

III.2.2.4.2. Institution Overview

In accordance with the Joint Ministerial Decree of December 20, 2009, which establishes the regulatory framework for public community health institutions in Algeria, the Ferdjioua Institution is designed to ensure the efficient and effective delivery of a wide range of primary healthcare services. The institution consists of several basic units designed to meet both preventive and curative healthcare needs:

- General Medicine Unit: Provides general consultations, diagnostics, and outpatient care, forming the basis of primary medical services.
- Maternal and Child Health Unit: Provides comprehensive maternal care, prenatal and postnatal services, child immunizations, and growth monitoring.

- Dental Care Unit: Performs preventive and restorative dental procedures, focusing on oral health at the community level.
- Chronic Diseases Unit: Focuses on long-term follow-up and management of non-communicable diseases, including diabetes, hypertension, and cardiovascular disease.
- Preventive Care and Immunization Unit: Implements national immunization programs and leads health awareness campaigns throughout the community.
- Radiology Room: Facilitates initial diagnostic imaging to meet the needs of local patients.
- Pharmacy Unit: Ensures the availability, controlled storage, and distribution of essential prescription medications within the facility.
- Administrative Services: Manages patient records, scheduling, coordination with external healthcare providers, and internal operations.

This integrated, community-focused structure enables the Ferdjioua Neighborhood Public Health Foundation to provide responsive, equitable, and sustainable healthcare services. It plays a pivotal role in supporting the health system of the Mila Province by addressing local health challenges and improving health outcomes.

III.3. Methodology

III.3.1. Data Collection and Investigation

As part of our study, we collected and analysed clinical data of tuberculosis patients who were either hospitalized at Mohamed Meddahi Hospital or diagnosed and monitored for treatment in public health institutions, including the Public Community Health Establishments of Bouarroudj (Mila), Deraahi Bousselah, and Ferdjioua. This investigation involved a comprehensive review of archived medical records listed in the tuberculosis patient registry, covering a nine-year period from 2016 to 2024.

Our analysis focused on a range of clinical variables, including gender, age, geographic area of residence, general health condition, presence of comorbidities, type of tuberculosis, treatment regimens, and treatment outcomes. In addition, several biological and laboratory parameters were evaluated, such as blood glucose, serum creatinine, blood urea nitrogen, uric acid, prothrombin time, international normalized ratio, liver enzymes (ALT, AST), total, direct, and indirect bilirubin, acid-fast bacilli smear, HIV serology, and complete blood count.

Finally, we assessed the duration of treatment and documented mortality rates among the patients during the study period.

III.3.2. Selection Criteria

III.3.2.1. Inclusion Criteria

In the context of this study, specific and well-defined inclusion criteria were applied. The selected sample consisted of patients with confirmed tuberculosis, regardless of their age or gender. This included individuals who were either hospitalized or monitored at various public health facilities.

Diagnosis confirmation was based on several diagnostic methods, primarily the presence of characteristic radiological signs on chest computed tomography scans, or positive microscopic detection of *Mycobacterium tuberculosis* in sputum or respiratory secretions.

Bacteriological confirmation was also obtained through culture of clinical samples on appropriate media. In addition, molecular techniques such as PCR were used for the genetic identification of the pathogen. For extra pulmonary tuberculosis, diagnosis was confirmed through biopsy of the affected tissue followed by laboratory identification of the causative agent.

III.3.2.1. Exclusion Criteria

All cases in which tuberculosis infection was not clearly confirmed using standard diagnostic methods such as radiological imaging, microscopic examination, or bacteriological culture were excluded from the study. Additionally, patients whose medical records lacked essential clinical or biological data required for statistical analysis such as age, gender, place of residence, type of tuberculosis, treatment initiation and completion dates, duration of treatment, and other relevant variables were also excluded. Furthermore, cases that had been diagnosed with tuberculosis but did not undergo regular medical follow-up, whether in hospitals or public health institutions, were excluded due to the potential impact on the reliability and validity of the study findings.

III.3.3. Study Population

Our study included 717 patients who were diagnosed and followed up in various public health institutions across the Wilaya of Mila during the period from 2016 to 2024. Tuberculosis infection was confirmed using standard diagnostic methods, including radiological imaging, microscopic examination, bacteriological culture, and, in some cases, molecular testing such as PCR, particularly in cases requiring greater diagnostic precision. Clinical data were collected from official medical records maintained by the relevant health services, with the aim of analysing and studying the information according to established scientific and statistical standards.

The treatment outcomes of tuberculosis patients were classified based on their response to therapy as follows:

Cured: Patients who completed the full course of treatment and were confirmed bacteriologically negative at the end of therapy.

Completed: Refers to patients who adhered to and completed the treatment regimen, although no final laboratory confirmation of recovery was available.

Treatment failed: Applies to patients who, despite adhering to the prescribed treatment, remained bacteriologically positive after five months of therapy.

Treatment Default: Includes patients who began treatment but discontinued it for a prolonged period, while the disease remained active.

Died: Encompasses patients who died from any cause during the course of tuberculosis treatment.

Transfer-out patients: Refers to patients whose treatment outcomes could not be determined due to transfer to another healthcare facility or district.

Relapse: It is the condition in which a patient is considered cured of the disease, but after a period of stopping treatment, the symptoms return again.

According to the World Health Organization standards, tuberculosis treatment outcomes are classified into two main categories:

- **Successful Treatment Outcome:** Refers to cases in which patients have completed the full course of treatment, achieved clinical recovery with resolution of symptoms, and obtained negative results on smear microscopy at the end of treatment.
- **Unsuccessful Treatment Outcome:** Includes patients who did not exhibit an effective response to therapy, resulting in treatment failure, those who died during the course of treatment, as well as patients who experienced a relapse after initial recovery.

III.3.4. Clinical and Biological Data Analysis

The clinical data and biological parameters were compiled into Excel sheets to create a dedicated database, which will later be used for result interpretation. Initially, the clinical data were analysed in a comprehensive manner, followed by comparisons across different categories based on gender, mortality rates, and other relevant variables identified according to the study objectives. These analyses will be used to draw conclusions regarding the impact of various factors on patient outcomes.

III.3.5. Statistical Data Analysis

Statistical analysis was performed using the IBM SPSS. Descriptive statistics were presented in the form of frequencies and means ± standard deviation. Categorical variables were compared using the $\chi 2$ test, while continuous variables were compared using the Student (t-test). A p value of less than 0.05 was considered statistically significant. Graphical analyses were conducted using SPSS software.

Chapter four

Results and discussion

Results and Discussion

In this study, a comprehensive analysis of treatment efficacy and outcomes on tuberculosis patients was monitored during the course of their treatment, with the aim of evaluating the effectiveness of the treatment provided in public health institutions. The study included, furthermore, an assessment of the prevalence of comorbidities, as well as the change in different biological parameters that occurred throughout the period of treatment. Additionally, the progression of tuberculosis over eight year's period (from 2016 to 2024) was assessed, with a particular focus on temporal trends in disease incidence.

Otherwise, we compared the efficacy of tuberculosis therapy as well as the variation of different clinical and biochemical characteristics in women versus men in order to deduce a probable influence of gender on the successfulness of the therapy. Finally, a comparative analysis was also performed between patients who successfully completed the treatment and recovered and those for whom treatment therapy was fail, in order to identify the factors influencing treatment outcomes.

IV.1. Overview on clinical and biological patients characteristics

Our study included 717 patients who diagnosed with various forms of tuberculosis. To facilitate accurate interpretation and analysis of the findings, different clinical or biological data are expressed as frequency or as mean values with standard deviation (mean ± SD). As part of this study, the clinical data collected represent a fundamental component for analyzing therapeutic protocols and monitoring patients' clinical improvement during and after treatment.

Our study indicated a variation in tuberculosis incidence across the years. The highest number of cases was recorded in 2020, with 97 cases of which 63 cases were identified among women while 34 cases were among men. The number of cases was stabilized from 2020 to 2023 and a decline in the number of cases was observed thereafter, reaching its lowest point in 2024, with 46 cases (36 cases among women and only 10 cases among men) **(Fig. 28)**. By examining the findings reported by Dennis et al., a 4.5% increase in global TB cases was observed between 2020 and 2021, along with a 3.6% rise in the TB incidence rate during the same period **(Dennis et al., 2023)**. This timeframe coincided with the COVID -19 pandemic, which is likely to have contributed to these increases. The pandemic led to a decline in TB case notifications, resulting in delays in diagnosis and treatment, and a disruption of health services due to the overwhelming pressure on healthcare systems. Additionally, fear of infection discouraged individuals from visiting healthcare facilities, further reducing opportunities for early detection.

The pandemic also caused a decline in preventive activities and vaccination coverage, due to the interruption of TB preventive treatment programs and community-based monitoring, thereby facilitating further spread of the disease **(Dennis et al., 2023)**.

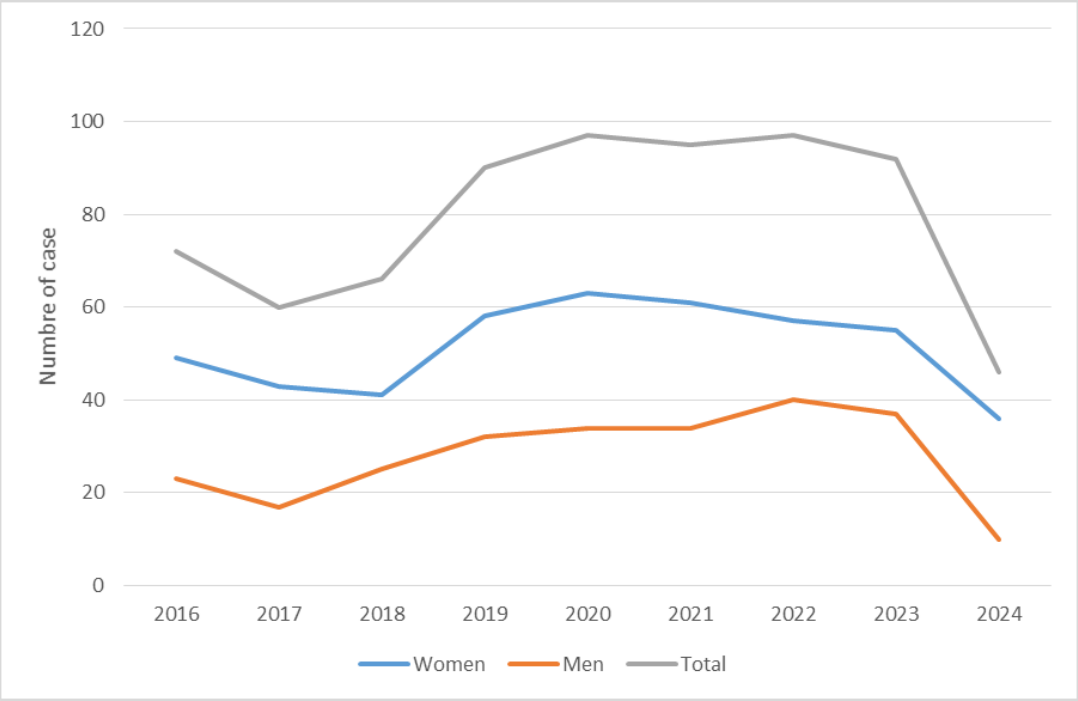


Figure 28: The number of tuberculosis cases each year.

Otherwise, our results showed a clear predominance of female patients compared to males **(Fig. 29)**. The study showed that 465 of patients was women, representing 65% of the total patients, while 252 were men (35%). Although many studies indicate that, the incidence of tuberculosis is higher among men than women, other research has shown the opposite that women may have a greater susceptibility to contracting tuberculosis **(Suman et al., 2021)**. Based on these constatations, we assume that tuberculosis may have a bidirectional pattern in terms of infection. In the study conducted by Suman et al. and based on the variation in tuberculosis incidence by gender, significant differences were found in the rates and number of cases between females and males. A total of 527 cases of pulmonary tuberculosis were recorded among females compared to 398 cases among males, with a ratio of 1:1.47 (P = 0.0001). Additionally, 84 cases of extra pulmonary tuberculosis were reported in females, compared to 46 cases in males, with a ratio of 1:1.8 (P = 0.0001). Furthermore, the study recorded 405 cases of tuberculosis in females under the age of 40, compared to 284 cases in males within the same age group **(Suman et al., 2021)**. On the other hand, findings from the study conducted by

Omara et al. indicated that the incidence of tuberculosis among females in the western provinces of Pakistan was approximately 35% higher than among males, with the increase in female cases ranging from 30% to 50% compared to males **(Omara et al., 2012)**. This may be attributed to a combination of social, environmental, and health-related factors, such as continuous exposure to indoor smoke and pollution, poor nutrition and weakened immunity, vitamin D deficiency due to limited sunlight exposure, and immune system changes during pregnancy. Practices such as early marriage and high fertility rates also contribute to increased susceptibility, in addition to the fact that women with new tuberculosis infections are more likely to progress rapidly to active disease compared to men **(Omara et al., 2012)**. In another study conducted by Hai Viet and colleagues on gender-based disparities in tuberculosis incidence in Vietnam, the results showed that the number of TB cases among men was 694, accounting for 52.6%, while among women, there were 625 cases, representing 47.4%. The study also revealed that symptoms tended to be more severe in men than in women. This disparity was attributed to several factors, including behavioral and environmental risks such as smoking and alcohol consumption, which are more prevalent among men. Additionally, men were found to be less likely to seek healthcare services compared to women. Biological factors may also contribute to this difference. For instance, male sex hormones such as testosterone may impair immune responses, whereas females may benefit from having an extra X chromosome, which carries immune-related genes **(Hai Viet et al., 2023)**.

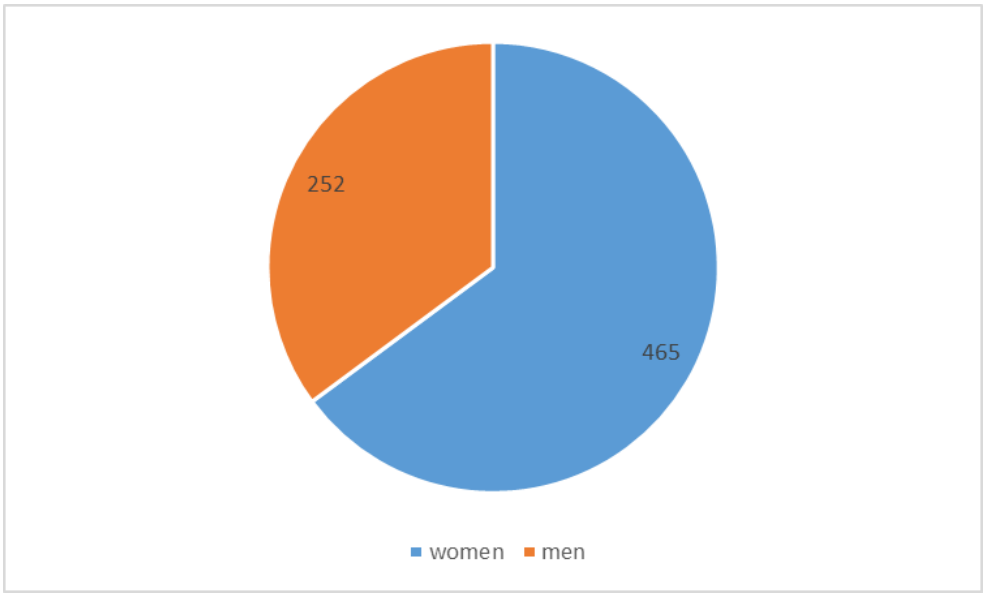


Figure 29: Distribution of patients by gender.

Our results showed that ages of patients ranged from 18 to 99 years, with a mean of 43.62 ± 19.73 years. The highest number of tuberculosis cases was showed among individuals aged between 18 and 30 years, (235 out of total cases which represents 32.86 %). The 30 to 39 age group with 148 cases (20.68%) followed this, and the age group over 70 years with 116 cases (16.21%) **(Fig. 30)**. In the study by Dong et al. who studied the TB incidence rates, a peak in TB incidence was observed in the age group of 20-24 years and they have a likelihood of contracting tuberculosis that was 1.73 to 3.03 times higher compared to the reference group (**Dong et al., 2022)**. Moreover, in another study conducted by Abiot et al., it was found that the highest incidence rate was in the age group of 25 to 34 years, which supports our findings that this age group is the most vulnerable to contracting tuberculosis **(Abiot et al., 2023)**. In another study conducted by Zhenguo et al., it was showed that the incidence of tuberculosis is higher among the elderly, with the majority of participants falling within the 70-79 age group, accounting for 49.79%. This is attributed to the decline of the immune system with age, as well as the presence of comorbid conditions, which increases the body's susceptibility to infection **(Zhenguo et al., 2025)**.

Additionally, it is worth noting that the results of our study showed that the incidence of tuberculosis was higher among women compared to men across all age groups **(Fig. 30)**. These findings are consistent with those of a study conducted by Wrishmeen et al. in Afghanistan, where higher apparent tuberculosis rates were recorded among women across different age groups, which contrasts with what is observed in many other countries. This disparity may be attributed to the social and cultural roles that women play in society, which may contribute to increased exposure to risk factors associated with tuberculosis **(Wrishmeen et al., 2012)**.

However, this gender gap began to narrow with advancing age, as an increase in the number of tuberculosis cases among men was observed in the age group over 70 years, leading to a convergence of tuberculosis rates between the genders in this age group. This convergence is likely due to biological changes associated with aging in men, in addition to cumulative health and behavioral factors such as smoking, the presence of chronic diseases, and limited access to healthcare services in earlier stages of life. This finding aligns with the results of Fernandes et al. in their research **(Fernandes and al., 2018)**.

These results highlight the importance of considering gender differences when analysing the burden of tuberculosis, especially in advanced age groups, to ensure that health interventions are directed in a more effective and equitable manner **(Fernandes and al., 2018)**.

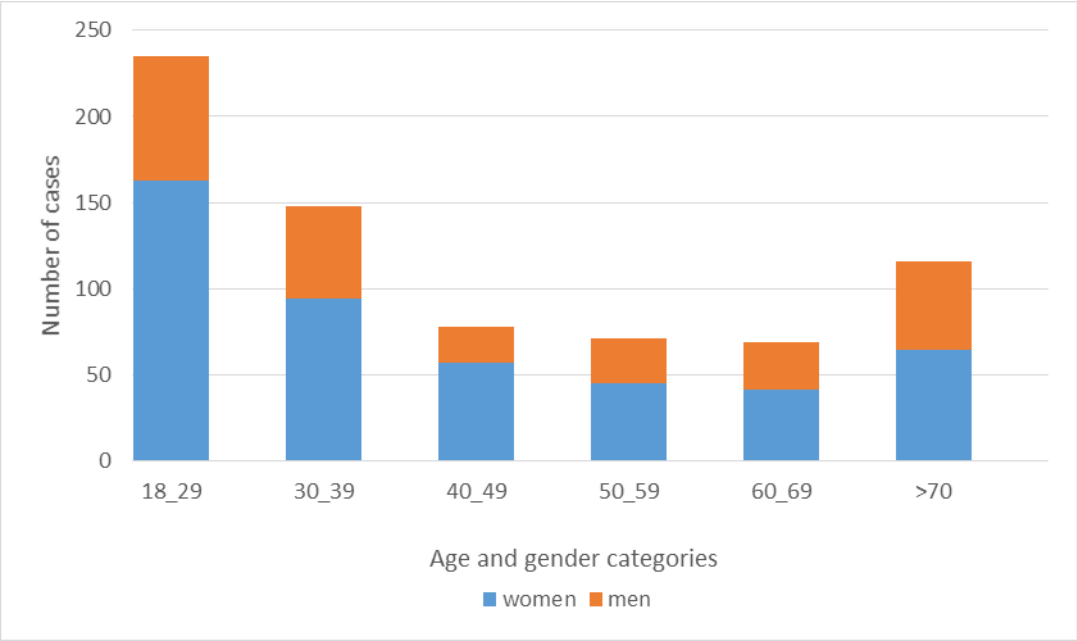


Figure 30: Distribution of the age group of patients by gender.

Regarding the types of tuberculosis, our findings showed that the highest proportion was recorded among cases of extra pulmonary tuberculous lymphadenitis, accounting for 36.26%, which corresponds to 260 cases out of the total. This was followed by pulmonary tuberculosis, representing 33.05%, or 237 cases **(Fig. 31)**. Several studies, including the one conducted by Radha et al., have shown that tuberculous lymphadenitis is the most common form of extra pulmonary tuberculosis, representing for approximately 35% to 40% of cases. Among these, cervical lymph nodes are the most frequently affected site, observed in about 60% to 90% of cases, particularly among individuals with a prior history of tuberculosis **(Radha et al., 2021)**. The elevated number of extra pulmonary TB cases observed in our study may be attributed to the fact that the majority of the surveyed areas were rural. In such regions, livestock rearing and the consumption of fresh milk and dairy products are common practices, which increases the likelihood of infection with this form of TB. Furthermore, the lack of health awareness and the generally low educational levels in these areas may also contribute to the spread of such types of the disease.

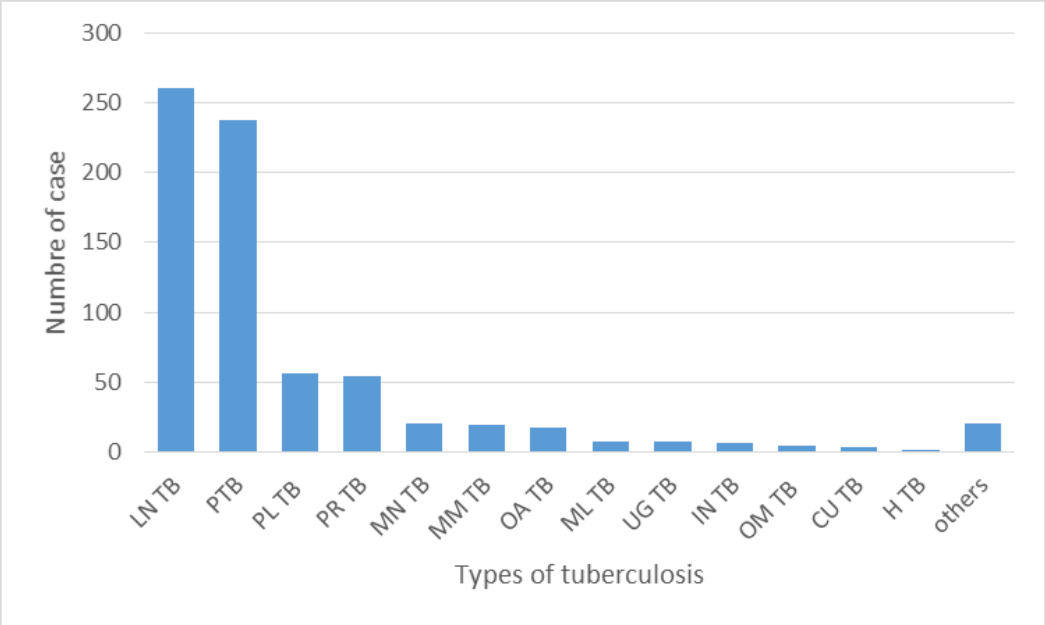


Figure 31: Number of case for each type of tuberculosis. **PTB:** Pulmonary TB, **LN TB**: Lymph node TB, **PL TB:** Pleural TB, **PR TB:** Peritoneal TB, **MN TB:** Meningitis TB, **MM TB:** Mammary TB, **ML TB:** Miliary TB, **IN TB:** Intestinal TB, **CU TB:** Cutaneous TB, **UG TB:** Urogenital TB, **OA TB:** Osteoarticular TB, **H TB** hepatic TB, **EP TB:** Epiploic tuberculosis.

The results of our study showed that the majority of patients (64.15%) received treatment for a period ranging from 3 to 6 months, which aligns with the world health organization recommended duration for drug-sensitive tuberculosis **(Table 7)**. In a study conducted in west Nusa Tenggara, Indonesia, it was reported that approximately 70% of patients completed treatment within this standard duration **(Ginting et al., 2024)**. Similarly, a study carried out in Motta Town, Ethiopia, indicated that most patients received treatment for 6 months, and it emphasized that successful outcomes were associated with full adherence to this duration **(Tadesse et al., 2023)**.

On the other hand, 21.19% of patients in our study received treatment for 7 to 9 months, while 8.36% underwent treatment for more than 10 months. These extended durations are likely indicative of complicated cases such as extra-pulmonary tuberculosis or poor initial drug response. This pattern was also observed in Bosaso TB Hospital in Somalia, where prolonged treatment durations were linked to comorbidities or suspected drug resistance (Ali et al., 2023). Furthermore, a study conducted in rural hospitals in the Eastern Cape, South Africa, emphasized that although treatment duration sometimes extended due to social challenges or limited healthcare infrastructure, adherence to the 6-month regimen remained essential for treatment success **(Mhlaba et al., 2024)**.

The small percentage of patients (0.97%) who received treatment for less than 3 months may reflect early treatment discontinuation or death in the initial stages. This issue was also documented in the Ethiopian and South African studies, where poor adherence or lack of follow-up was strongly associated with treatment failure. **(Tadesse et al., 2023; Mhlaba et al., 2024)**.

Table 7: Demographic and clinical characteristics of the TB patients.

Patient Characteristics	Frequency or Mean (%)
Gender	
Men	252 (35.28%)
Women	465 (64.85%)
Age (years)	43.62 ± 19.72
Type of TB	
Pulmonary TB	233 (32.49%)
Extra-pulmonary TB	484 (67.50%)
Duration of treatment	
0–2 months	7 (0.97%)
3–6 months	460 (64.15%)
7–9 months	152 (21.19 %)
> 10 months	60 (8.36 %)
Body Weigh	
30-39	30 (4.18%)
40-54	178 (24.82%)
55-70	313 (43.65 %)
71<	159 (22.17 %)
Comorbidities	
Endocrine/Metabolic Diseases	62 (8.64 %)
Cardiovascular Diseases	47 (6.55 %)
Skin/Autoimmune Diseases	10 (1.39 %)
Miscellaneous Conditions	9 (1.25 %)
Blood Diseases and Anemia	9 (1.25 %)
Respiratory Diseases	3 (0.41 %)
Gastrointestinal Diseases	3 (0.41 %)
Neurological Diseases/Stroke	1 (0.13 %)
BK Test	
Negative	37 (46.25 %)
Positive	37 (46.25 %)
Suspicious	6 (7.5 %)
Mortality rate	39 (5.43 %)

Otherwise, assessment of biochemical parameters of TB patients in our study revealed a mean AST (TGO) level of 25.61 ± 20.40 U/L and a mean ALT (TGP) level of 20.25 ± 20.36 U/L. These values remain within normal reference ranges, suggesting no evident liver injury in most patients **(Table 8)**. Nevertheless, a notable proportion of patients showed biochemical signs suggestive of possible liver involvement, consistent with previous studies linking liver enzyme abnormalities to TB-related liver injury or drug toxicity.

As for, Zhou et al. reported that 17% of TB patients exhibited elevated rates of liver enzymes prior to treatment, particularly in extra-pulmonary TB cases, highlighting the importance of liver function monitoring (**Zhou et al., 2024**). Furthermore, Chen et al. further emphasized the role of chronic inflammation and malnutrition in hepatic alterations affecting treatment outcomes **(Chen et al., 2025)**.

Regarding glycaemia, the mean blood glucose level was 1.02 ± 2.56 g/L, with 17.76% of patients presenting elevated glucose levels. In this concern, Liu et al. demonstrated that hyperglycaemia impairs immune responses and delays TB recovery, increasing relapse risk **(Liu et al., 2023)**. Nguyen et al. explained that hyperglycemia diminishes phagocytic activity and cytokine secretion, weakening host defense **(Nguyen et al., 2025)**. Moreover, Zhao et al. underscored the critical role of optimal glycemic control in improving TB treatment outcomes among diabetic patients **(Zhao et al., 2024)**.

Although our study did not find a high prevalence of glycemic abnormalities, these findings reinforce the necessity of glycemic monitoring in TB management. Overall, assessing liver enzymes alongside glucose metabolism provides essential insights into TB's systemic effects and supports incorporating these parameters into comprehensive patient evaluations, especially in resource-limited or high-risk settings **(Ahmed et al., 2025)**.

Table 8: Biochemical characteristics of patients with Tuberculosis (Biochemical permit).

Parameters	Mean ± SD	Positive cases (%)
Creatinine (g/l) (**535**)	7,33 ± 4.97	72 (13.45 %)
Urea (g/l) **(531)**	0.40 ± 0.60	69 (12.99 %)
Glycemia (g/l) **(529)**	1.02 ± 2.56	94 (17.76 %)
AST (TGO) (UI/L) **(612)**	25.61 ± 20.40	103 (16.83 %)
ALT (TGP) (UI/L)**(606)**	20.25 ± 20.36	83 (13.69 %)
Total proteins (g/dl) **(07)**	118.71 ± 113.03	4 (57.14 %)
Gamma GT **(08)**	35.74 ± 19.61	3 (37.5 %)
Albumin (g/l) **(07)**	31.30 ± 8.88	4 (57.14 %)

Uric acid (g/l) **(311)**	54.27 ± 33.15	103 (33.11%)
Erythrocyte Sedimentation Rate (mm)**(122)**	46.78 ± 33.63	88 (72.13 %)
D-dimer (ng/ml) **(05)**	377.73 ± 597.05	3 (37.5 %)
Alkaline phosphatases(µL/l)**(379)**	138.51 ± 105.55	178 (46.96 %)
Total bilirubin (mg/l) (**507)**	6.04 ± 8.56	56 (11.04 %)
Direct bilirubin (mg/l) **(432)**	2.63 ± 7.86	346 (80.09%)
Indirect bilirubin (mg/l) **(253)**	3.22 ± 3.37	223 (88.14 %)
C-Reactive Protein mg/l **(128)**	23.14 ± 32.39	20 (15.62 %)
Blood Ionogram – Sodium (Na^+) **(19)** **(**mmol/l)	120.59 ± 47.40	3 (15.78 %)
Blood Ionogram – Potassium (K^+) **(19)** (mmol/l)	19.61 ± 88.10	2 (10.52 %)
Blood Ionogram – Chloride (Cl^-) **(11)** (mmol/l)	92.99 ± 31.13	1 (9.09 %)
Prothrombin Time (PT) (%) **(35)**	80.18 ± 20.93	9 (25.71 %)
INR (International Normalized Ratio) **(20)**	4.20 ± 13.88	17 (85 %)
Ferritine(ng/mL)**(02)**	360.17 ± 328.02	1 (50 %)
HIV Antibody Test		
Negative (Index < 1.0) **(117)**	/	117 (100 %)
Positive (Index ≥ 1.0) **(0)**	/	0

AST (TGO): Aspartate Aminotransferase, also known as **TGO** in French (Transaminase Glutamique Oxaloacétique).
ALT (TGP): Alanine Aminotransferase, also known as **TGP** in French (Transaminase Glutamique Pyruvique).

Hematological evaluations of tuberculosis patients in this study revealed significant disturbances in several complete blood count parameters **(Table 9)**. The mean hemoglobin concentration was 30.70 ± 14.50 g/dL, with decreased levels observed in 75.25% of cases (400 out of 528). The mean hematocrit was 70.73 ± 29.81%, with 34.60% of cases (181 out of 523) showing abnormal values, which may indicate the presence of anemia a common condition in TB patients. These findings are consistent with those reported by Wang et al., who associated such reductions with chronic inflammation and malnutrition **(Wang et al ., 2025).**

Additionally, the mean red blood cell (RBC) count was 9.98 ± 4.84 $\times 10^3/\mu L$, with fluctuations observed in 38.25% of cases (202 out of 528). This supports the presence of impaired erythropoiesis, as highlighted by Zhenguo et al. in their study on the hematopoietic impact of TB **(Zhenguo et al., 2025).**

The total white blood cell (WBC) count remained within normal limits (6.52 ± 4.20 $\times 10^3/\mu L$); however, 38.63% of cases (204 out of 528) showed abnormal values. Differential counts revealed a clear elevation in neutrophils (32.97 ± 31.72%) and monocytes (9.56 ± 51.28%), with abnormal rates of 66.28% and 64.05%, respectively, indicating an active innate immune response. Omair et al., who identified neutrophils and monocytes as key markers of active TB infection, confirmed this **(Omair et al, 2024)**.

In contrast, a marked decrease in lymphocyte percentages (22.16 ± 180.63%) was recorded, with abnormalities in 89.84% of cases (460 out of 512). This may reflect lymphocyte exhaustion or redistribution, both commonly observed in active TB and indicative of immune suppression, as described by both Chen et al., and Zhao et a., **(Chen et al, 2024; Zhao et al, 2024)**. A mild thrombocytosis was also observed in 24.57% of patients (129 out of 525), likely reflecting an underlying inflammatory state. According to Zhang et al., platelets play a crucial role in immune regulation during TB infection, in addition to their classical role in coagulation **(Zhang et al, 2024)**.

Table 9: Hematological profile : numerical values and corresponding parameters

Parameters	Mean ± SD	Positive cases (%)
White blood cells(10^3 /µL) **(528)**	6.52 ± 4.20	204 (38.63 %)
Neutrophils (%) (**264)**	32.97 ± 31.72	175 (66.28 %)
Lymphocytes (%) **(512)**	22.16 ± 180.63	460 (89.84 %)
Monocytes (%) **(306)**	9.56 ± 51.28	196 (64.05 %)
Eosinophils % **(257)**	3.74 ± 19.97	145 (56.42%)
Basophils (%) **(255)**	0.67 ± 3.73	34 (13.33 %)
Red blood cells (10^3 /µL) **(528)**	9.98 ± 4.84	202 (38.25 %)
Haemoglobin(g/dL) **(528)**	30.70 ± 14.50	400 (75.25 %)
Haematocrit (%) **(523)**	70.73 ± 29.81	181 (34.60 %)
MCV (ml) **(461)**	23.41 ± 9.97	137 (29.71 %)
MCH (g/dL) **(487)**	31.56 ± 38.53	156 (32.03%)
MCHC (pg) **(557)**	20.49 ± 16.42	109 (19.56 %)
RDW (Fl) **(510)**	327.75 ± 125.48	165 (46.74 %)
Platelets (10^3/µL**) (525)**	328.29 ± 124.83	129 (0.23 %)
MPV (ml**) (493)**	7.70 ± 3.59	27 (5.47 %)

MCV: Mean Corpuscular Volume**; MCHC:** Mean Corpuscular Hemoglobin Concentration**; RDW:** Red Cell Distribution Width**; MPV:** Mean Platelet Volume.

VI.1.1.Patients treatment outcomes

The figure 32 illustrates the treatment outcomes of our studied tuberculosis patients. The results showed that a highest proportion of our patients (68%) was successfully cured under standard regimen treatment. The results also showed that 24% of patients has been completed their treatment reflecting a relatively effective implementation of treatment protocols. These findings are consistent with the study by Rahman et al., which reported cure rates exceeding 70% in high-performing TB control programs **(Rahman et al., 2024)**. Similarly, Moussa et al., highlighted that adherence to the Directly Observed Treatment Short-course strategy is a critical factor in improving cure rates and reducing treatment interruption **(Moussa et al., 2025)**.

However, the observed proportions of treatment failure (1%), relapse (1%), and transfer to other facilities (1%) suggest ongoing clinical and administrative challenges. Nguyen et al., noted that relapse rates can reach 10–15%, especially in settings with a dual burden of TB and chronic conditions like diabetes **(Nguyen et al., 2025)**. Furthermore, recent findings by Chen et al. documented significant mortality during treatment particularly among patients with malnutrition or chronic liver disease potentially explaining the 5% mortality rate observed in the present study **(Chen et al., 2024)**.

Otherwise, the “treatment completed” category, which accounted for 24% of the cases, does not necessarily indicate bacteriological cure. It refers to patients who completed the prescribed course of treatment without microbiological confirmation of recovery. According to Park et al., a proportion of these patients may remain carriers of *Mycobacterium tuberculosis* in the absence of follow-up culture testing. Therefore, current literature emphasizes the importance of post-treatment monitoring, especially for patients at high risk of relapse, such as those with immune compromise or malnutrition **(Park et al., 2024**).

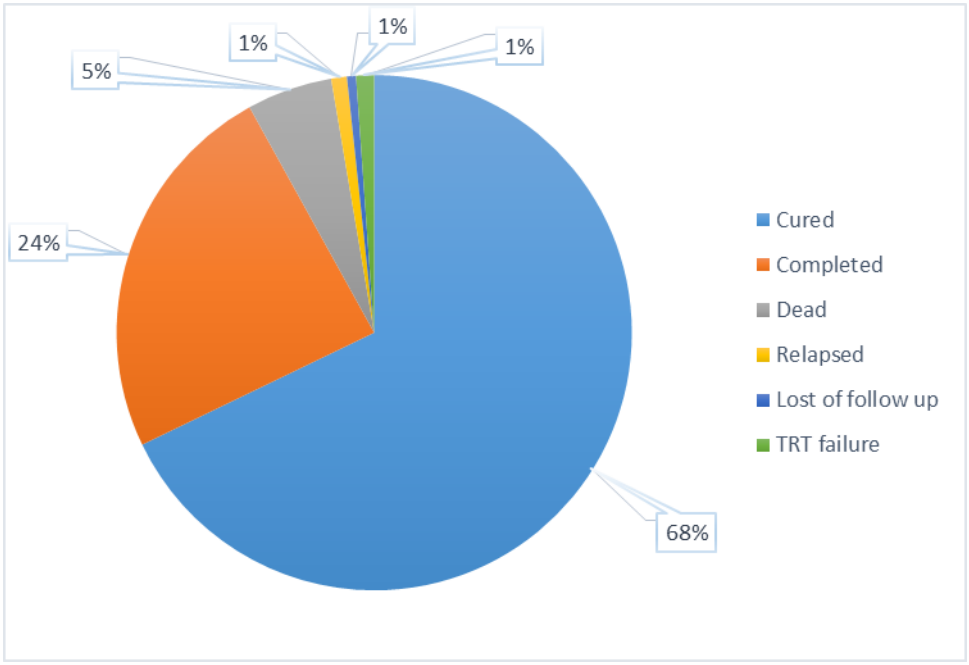


Figure 32: Relative distribution of Tuberculosis out Comes in the study sample

More interestingly, our results revealed a clearly inversed relationship between the average of treatment duration and the age range of patients **(Fig. 33)**. Specifically, it was observed that as the age increases, the treatment duration decreases. For instance, patients for whom age range varied between 30 and 49 years, the treatment duration ranged from 7.2 to 7.4 months, whereas in older age range, particularly those aged 60 and more, the average treatment duration decreased to 6.6 months and below. A study conducted by Jan et al. indicated a potential relationship between patient age and the required duration of treatment, with older patients tending to have shorter treatment periods compared to younger individuals. However, it remains inconclusive whether age has a definitive impact on treatment duration, as multiple confounding factors may influence this association **(Jan et al., 2020)**.

Several factors may account for these findings. One possible explanation is the variation in biological responses to treatment across age groups. Older adults may exhibit a faster and more effective response to certain treatments, potentially due to physiological factors such as a slower inflammatory process. Furthermore, elderly patients are often more adherent to medical advice and more consistent in taking prescribed medications compared to younger individuals, who may be more preoccupied or less regular in following treatment regimens

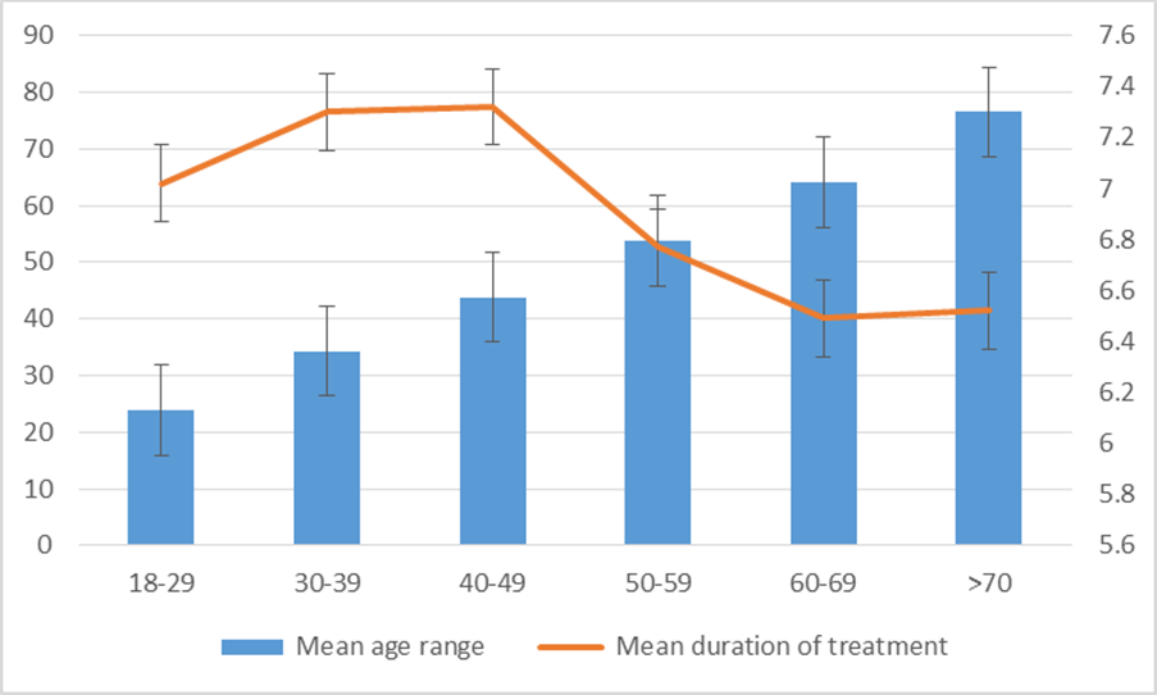


Figure 33: Relation between mean age range and mean duration of treatment.

VI.2. Clinical and risk factors comparison in women versus men

VI.2.1. The Impact of gender on age, treatment duration, and mortality among tuberculosis patients

We compared the efficacy of tuberculosis therapy as well as the variation of different clinical and biochemical characteristics in women versus men in order to deduce a probable influence of gender on the successfulness of the therapy women **(Table 10)**. Our results showed that the mean age was significantly higher among men (46.28 ±20, 70 years) compared to women (42.10 ± 19,18 years) ($p = 0.0074$). Additionally, the age group over 70 years was more represented by men rather than women ($p = 0.0223$). Based on these results, it appears that age may be an influential factor in tuberculosis treatment outcomes, particularly among men. This is supported by a recent study by Smith et al. who analysed data from seven high-income countries over different time periods. The study showed that men had significantly higher infection rates across all age groups, particularly among those over 60 **(Smith et al., 2024)**.

The study attributed this phenomenon to men being more susceptible to occupational and environmental risk factors, such as working in closed or polluted environments, along with unfavorable health behaviors such as smoking and excessive alcohol consumption, which weaken the respiratory system and make them more susceptible to TB with age. The researchers

also indicated that some biological factors, such as the effects of male hormones on the immune system, may weaken men's ability to resist infection compared to women **(Smith et al., 2024)**.

Regarding the duration of treatment, the results showed that 40.17% of men underwent treatment lasting 7 to 9 months, compared to only 8.07% of women (p = 0.0081). This suggests that men may have greater clinical complications or a poorer response to treatment. This is confirmed by a recent South Korean study conducted by Kim et al., which used national surveillance data and health insurance records to examine the relationship between gender and comorbidities in tuberculosis patients **(Kim et al., 2025)**. The study showed that males were more likely to have chronic conditions such as diabetes and hypertension, which negatively impact their response to treatment and prolong recovery. The study also noted that males often struggled with adherence to treatment, while women were more likely to attend clinics and receive medical follow-up regularly **(Kim et al., 2025)**.

On the other hand, the current study recorded a significantly high mortality rate among males than among females, as also supported by the results of a study by Mansa et al. which was conducted on a large sample of tuberculosis patients in compulsory hospitals. The study revealed that males were more likely to die during treatment **(Mwansa et al., 2019)**. The authors attributed this increase tow several factors, most notably: delayed access to health centers, advanced diagnosis, comorbidities such as HIV, nutritional deprivation, and poor adherence to treatment protocols. The study also confirmed that men often delay seeking medical care due to social and cultural factors, such as preoccupation with their economic roles, which leads them to reach advanced stages of the disease, making a full recovery difficult **(Mwansa et al., 2019)**.

Finally, the previously mentioned study by Smith et al. reinforces this trend, demonstrating that the gender disparity in mortality rates is not limited to biological factors but is also linked to different health behaviors, health education levels, and access to basic health services. All of these factors combine to explain the gap between males and females in TB treatment outcomes and underscore the need for targeted health interventions that take gender into account when planning treatment and prevention **(Smith et al., 2024)**.

Table 10: Comparison of clinical parameters in women Vs men

Patient	Women	Men	ID	x2	P-value
AGE	42.10 ± 19,18	46.28 ± 20,70	1.1210 to 7.2390		**0.0074**
AGE RANGE					
18-29	162 (35.29%)	72 (28.45%)		3.454	0.0631
30-39	93 (20.26%)	54 (21.34%)		0.117	0.7327
40-49	57 (12.41%)	21 (8.30%)		2.835	0.0922
50-59	44 (9.58%)	26 (10.27%)		0.088	0.7671
60-69	39 (8.49%)	28 (11.06%)		1.264	0.2609
>70	64 (13.94%)	52 (20.55%)		5.225	0.0223
Weigh	57.29 ± 14,59	63.32 ± 18,75	3.6955 to 8.3645		**0.0001**
Type of TB					
Pulmonary TB	116 (16.31%)	108 (15.18%)		0.571	0.4497
Extra-pulmonary TB	343 (48.24%)	144 (20.25%)		162.632	**0.0001**
Treatment duration					
0-2 months	6.8 (1.5 %)	5.06 (2%)		0.401	0.5437
3_6 months	27.17 (5.92%)	14.97 (5.92%)		0.567	1.0000
7_9 months	37.04 (8.07%)	101.6 (40.17%)		0.236	**0.0081**
>10 months	23.04 (5.1%)	12.39 (4.9%)		0.125	0.7906
Treatment outcome					
Cured	312 (73.62 %)	170 (73.91 %)		0.035	0.8521
Completed	82 (19.24%)	44 19.13 %)		0.001	0.9707
Relapsed	4 (0.93 %)	3 (1.30 %)		0.189	0.6638
Lost of follow up	2 (0.46 %)	2 (0.86 %)		0.394	0.5300
Treatment Failure	36 (8.45 %)	11 (3.43 %)		7.213	**0.0072**

VI.2.1.1. Distribution of Tuberculosis Types and Infection Rates by Gender

The results of our study revealed a clear difference and statistically significant variation in the distribution of tuberculosis forms between men and women **(Table 10)**. Firstly, regarding pulmonary tuberculosis, although the numbers were relatively close between the sexes, the majority of cases were recorded among women, with 116 cases (51.78%) of the total pulmonary TB cases, compared to 108 cases (48.21%) among men. In contrast, for extra-pulmonary

tuberculosis, the difference was more pronounced, with 343 cases (70.43%) recorded among women, compared to only 144 cases (29.56%) among men, which also represents a statistically significant difference (p = 0.0001).

These results are consistent with the findings of Lee et al., which showed that women demonstrate a more responsive immune pattern in lymphoid and peripheral tissues. This may explain the higher incidence of extra-pulmonary TB among women. Meanwhile, the higher prevalence of pulmonary TB in men may be attributed to lifestyle factors such as smoking and frequent occupational exposure to sources of infection **(Lee et al. 2024)**.

Additionally, a recent study conducted in Southeast Asia by Kumar et al., supports these findings, revealing that women are more susceptible to environmental and nutritional factors such as iron deficiency and chronic malnutrition that weaken immunity and facilitate the development of extra-pulmonary TB **(Kumar et al., 2023)**.

These findings underscore the importance of integrating gender-based differences into TB screening, diagnostic, and awareness strategies, especially since extra-pulmonary TB may not present with clear symptoms and requires careful medical attention particularly among women, where it appears to be more prevalent according to our study data.

VI.2.2. The effect of biological factors

VI.2.2.1. Gender Impact on Biochemical Markers among Tuberculosis Patients

Our results showed that the levels of creatinine, C-reactive protein (CRP), and uric acid were significantly higher in men compared to women, with statistical significance recorded respectively p = 0.0378, p = 0.0005 and p = 0.0290 **(Table 11)**. The increase of creatinine may reflect mild renal impairment or differences in muscle mass, as creatinine is known to be influenced by muscle mass, which is generally greater in men **(Zhou et al., 2024)**. In this context, a recent study by Zhou and colleagues showed that elevated creatinine levels are associated with an increased risk of developing drug-resistant tuberculosis (DR-TB) and are considered an indicator of renal stress resulting from prolonged use of certain anti-tuberculosis drugs, such as aminoglycosides, particularly in male patients with comorbidities such as diabetes or hypertension **(Zhou et al., 2024)**. Regarding CRP, the increase indicates a greater or more severe inflammatory response in men, which may be associated with advanced disease or immunodeficiency. A study by Lee and colleagues showed that elevated CRP levels were closely associated with disease activity and inflammation severity, and were more pronounced

in men with active pulmonary TB. It was also noted that declining CRP levels as treatment progressed were an indicator of the effectiveness of the treatment plan, and patients whose levels did not decline rapidly were more likely to experience serious complications or treatment failure **(Lee et al., 2024)**. Concerning uric acid, the increase is likely related to an unbalanced diet or the use of anti-TB drugs that affect purine metabolism, such as pyrazinamide, which can lead to hyperuricemia. In this context, a recent study published in 2023 in the International Journal of Public Health revealed that hyperuricemia is associated with an increased risk of mortality in older adults, especially men, due to its association with oxidative stress and microvascular inflammation, which may worsen the condition of TB patients with comorbidities **(Li et al., 2023)**.

VI.2.2.2. Gender-Based differences in immune cells response in tuberculosis patients

When comparing white blood cell indicators particularly neutrophils, monocytes, eosinophils and basophil, the present study revealed that the average of neutrophil rates was significantly higher in males compared to females ($p = 0.0091$) **(Table 11)**. Similarly, men showed significantly elevated levels of monocytes ($p = 0.0236$), eosinophils ($p = 0.0216$) and basophils ($p = 0.0716$), although this difference did not reach full statistical significance. These findings are consistent with a recent study by Liu et al., which examined gender differences in white blood cell profiles among TB patients in four Asian countries. The study reported significantly higher neutrophil-to-lymphocyte ratios, along with elevated monocyte and eosinophil levels in males indicative of a stronger systemic inflammatory state. The researchers attributed these immune responses to both biological and behavioral factors, including greater exposure to environmental pollutants and higher smoking rates among men **(Liu et al., 2024)**.

Another study published in Frontiers in Immunology in 2025 by Hernandez et al. confirmed that sex hormones play a critical role in modulating immune cell function. Testosterone tends to suppress certain immune responses, while estrogen enhances them, which may explain the observed variations in immune cell activity between males and females. The study further emphasized that these differences contribute to the disparity in disease severity and recovery duration between the sexes **(Hernandez et al., 2025)**. Accordingly, the findings of the current study align with a growing body of evidence highlighting sex-based immunological differences in TB patients. These results emphasize the need to adopt diagnostic and therapeutic strategies that consider gender-specific variations in order to improve clinical outcomes for both men and women **(Hernandez et al., 2025; Liu et al., 2024)**.

Table 11: Comparison of biological parameters in women vs men.

Patient	Women	Men	ID	x2	p-value
Comorbidities					
Diabete	17 (14.65%)	10 (9.25%)		1.536	0.2152
Hypertension	11 (9.48%)	7 (6.48%)		0.682	0.4090
Anemia	6 (5.17%)	4 (3.70%)		0.283	0.5948
Hepatique	2 (1.72%)	0 (0%)		1.879	0.1705
Cardiophate	4 (3.44%)	4 (3.70%)		0.011	0.9180
Biochemical parameters					
Creatinine	7.81 ± 3.18	8.75 ± 0.20	-1.8271 to 0.0529		**0.0378**
Glycaemia	1.01 ± 0.65	1.02 ± 0.51	-0.1235 to 0.1035		0.8626
Urea	0.46 ± 5.12	0.3 ± 4.65	-0.3214 to 0.6414		0.5140
Uric Acid	53.64 ± 34.01	62.90 ± 30.89	-17.5655 to -0.9545		**0.0290**
ALT	20.66 ± 19.03	22.65 ± 23.03	-7.3083 to 3.3283		0.4618
AST	26.08 ± 18.63	29.59 ± 23.34	-8.8080 to 1.7880		0.1931
CRP	21.09 ± 4.33	41.75 ± 41.93	-32.1472 to -9.2928		**0.0005**
Total bilirubin	6.48 ± 4.33	7.79 ± 13.06	-2.8710 to 0.2510		0.0998
Direct bilirubin	2.81 ± 8.27	3.07 ± 7.11	-1.8172 to 1.2972		0.7429
Indirect bilirubin	3.79 ± 3,25	3.37 ± 3.30	-0.4382 to 1.2782		0.3361
BK test	19 (48.71%)	18 (43.90)		0.106	0.7452
Red Blood Cells	4.41 ± 1.75	4.61 ± 1.93	-1.1498 to 0.3098		0.2121
Neutrophils	52.84±194.39	263.15±1038.54	-367.9893 to 52.6307		**0.0091**
Lymphocytes	15.92±103.92	44.95 ± 270.69	-77.2905 to 13.2305		0.1647
Monocytes	6.51 ± 30.18	21.34 ± 76.00	-27.6558 to -2.0042		**0.0236**
Eosinophils	2.39 ± 11.60	8.22 ± 29.89	-10.7972 to -0.8628		**0.0216**
Basophils	0.50 ± 2.32	1.36 ± 5.49	-1.7962 to 0.0762		0.0716

AST (TGO): Aspartate Aminotransferase, also known as **TGO** in French (Transaminase Glutamique Oxaloacétique).**ALT (TGP)**: Alanine Aminotransferase, also known as **TGP** in French (Transaminase Glutamique Pyruvique).**CRP**: C - reactive protein

VI.3. Comparative analysis of clinical and biological characteristics depending on successful and unsuccessful treatment outcomes

The study demonstrated encouraging results regarding the overall success of tuberculosis treatment among patients **(Fig. 34)**. The successful treatment group included 650 patients, while only 55 cases were recorded in the unsuccessful treatment group. These findings reflect a high treatment success rate, indicating the effectiveness of the standard therapeutic regimen when properly implemented and adhered to. However, the occurrence of 55 treatment failure cases, although representing a relatively small proportion, highlights the need for further investigation to understand the underlying causes. These may include poor adherence to treatment, the presence of comorbidities, delayed diagnosis, or a high inflammatory burden.

As demonstrated in the study conducted by Ninfa et al., the results indicated that tuberculosis treatment, particularly for drug-sensitive TB, is largely effective when treatment protocols are properly followed, achieving high success rates of approximately 80% in adults and 85% in children. However, treatment effectiveness remains limited in cases of multidrug-resistant and extensively drug-resistant TB, where success rates decline significantly. The study also highlights that factors such as treatment adherence, early response (negative sputum smear at two months), younger age, and absence of HIV infection are associated with increased likelihood of treatment success. Based on these findings, it can be concluded that the standard tuberculosis treatment is generally effective **(Ninfa et al., 2019)**.

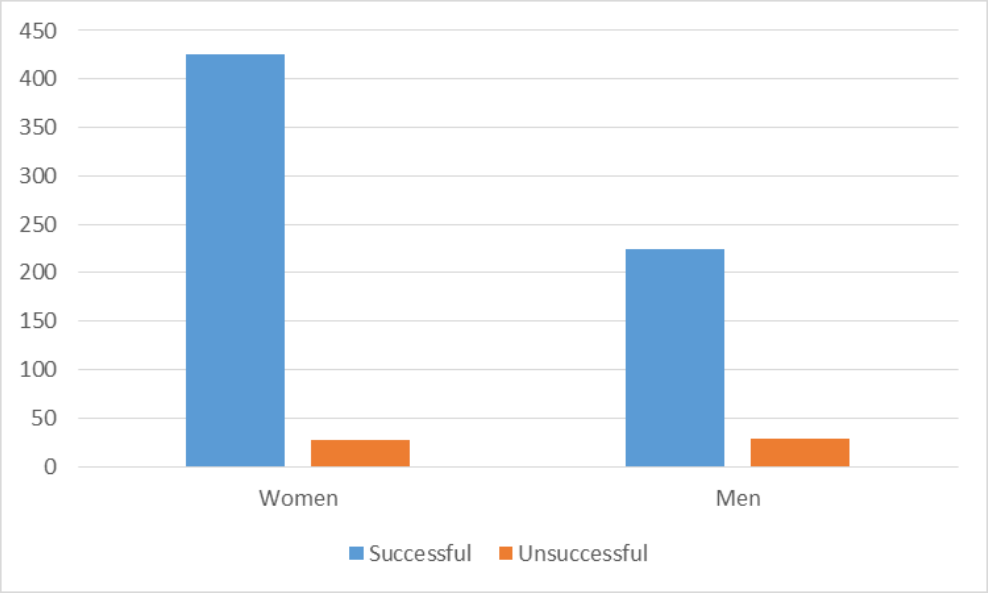


Figure 34: Treatment outcomes, successful treatment Vs the unsuccessful treatment.

VI.3.1. Clinical differences

After categorizing the treatment outcomes into two group's successful (649 patients) and unsuccessful (55 patients) a comparison of statistically significant results was conducted. Overall, patients who responded positively to treatment tended to have a significantly high body weight and were more frequently diagnosed with extra pulmonary tuberculosis **(Table 12)**. The majority of these patients underwent treatment for a period ranging from three to six months and had fewer comorbidities.

In contrast, patients for whom treatment outcome was unsuccessful were generally older and predominantly diagnosed with pulmonary tuberculosis. Their treatment duration was shorter, often limited to two months. This group also exhibited a higher prevalence of comorbidities, particularly diabetes, anaemia, and liver diseases **(Table 12)**.

Table12: Comparison of clinical and biological characteristics between successful and unsuccessful TB treatment outcome.

Patient	Treatment Outcomes		X^2	ID	P-value
	Successful	Unsuccessful			
Gender					
Women	426 (65.53%)	27 (49.09%)	5.973		**0.0145**
Men	224 (34.46%)	28 (50.90%)	5.973		**0.0145**
Age	42.56 ±19.09	55.14 ± 23.08		17.6645 to 7.4955	**0.0001**
18-29	215 (33.12%)	15 (27.27%)	0.79		0.374
30-39	144 (22.18%)	3 (5.45%)	8.594		**0.0034**
40-49	76 (11.71%)	2 (3.63%)	3.355		0.067
50-59	64 (9.86%)	5 (9.09%)	0.034		0.8536
60-69	54 (8.32%)	13 (23.63%)	13.812		**0.0002**
>70	96 (14.79%)	17 (30.90%)	9.774		**0.0018**
Weight	62.96 ± 14.65	56.27 ± 13.68		2.2214 to 11.1586	**0.0034**
TB types					
PTB	172 (24.46%)	34 (4.83%)	30.451		**0.0001**
EPTB	476 (67.70%)	21 (2.28%)	833.09		**0.0001**
Treatment duration	6.98 ± 2.31	6.68 ± 4.47		-0.6874 to 1.2874	0.5507

0-2	8 (1.19%)	5 (0.74%)	46.858		**0.0001**
3_6	444 (66.07%)	7 (1.04%)	16.237		**0.0001**
7_9	141 (20.98%)	8 (1.19%)	1.797		0.1801
>10	55 (8.18%)	4 (0.59%)	1.933		0.1644
Comorbidities					
Diabetes	40 (6.20%)	12 (21.81%)	18.573		**0.0001**
Hypertension	36 (5.48%)	8 (14.54%)	0.037		0.847
Anemia	10 (1.55%)	4 (7.27%)	8.467		**0.0036**
Insuffisance hépatique	1 (0.15%)	1 (1.81%)	4.92		**0.0265**
Cardiac disease	13 (2.01%)	1 (1.81%)	0.01		0.9201
Biochemical characteristics					
Creatinine	8.03 ± 4.66	9.7 ± 8.4		-154.3999to151.0599	0.9829
Glycemia	1.01 ± 0.6	1.13 ± 0.67		-0.3227 to 0.0827	0.2454
Urea	0.41 ± 2.68	0.34 ± 0.31		-0.8088 to 0.9488	0.8757
Uric Acid	56.9 ± 33.81	59.75 ± 29.65		-16.8761 to 11.1761	0.6895
ALT	21.09 ± 19.67	20.35 ± 19.78		-6.5180 to 5.9980	0.935
AST	26.22 ± 18.9	28.9 ± 24.62		-8.8945 to 3.5345	0.3972
CRP	25.35 ± 28.5	58.96 ± 49.77		-53.5175 to -13.7025	**0.0011**
Total bilirubin	6.98 ± 8.86	6.8 ± 4.69		-2.7953 to 3.1553	0.9054
Direct bilirubin	2.94 ± 5.2	2.74 ± 2.5		-2.8589 to 3.2589	0.8978
Indirect bilirubin	3.74 ± 3.45	2.62 ± 1.52		-0.8543 to 3.0943	0.2649

BK test	42 (56.75%)	5 (71.72%)	0.565		0.4522
WBC	7.77 ± 4.15	9.51 ± 4.68		-3.1236 to -0.3564	**0.0138**
Neutrophils	6.2 ± 6.02	5.95 ± 1.93		-2.7264 to 3.2264	0.8688
Lymphocytes	2.36 ± 1.77	1.95 ± 1.26		-0.1803 to 1.0003	0.173
Monocytes	0.66 ± 0.68	0.94 ± 2		-4.7715 to 4.2115	0.9025
Eosinophils	0.32 ± 0.49	0.29 ± 0.21		-0.2208 to 0.2808	0.814
Basophils	0.3 ± 0.27	0.32 ± 0.2		-0.1553 to 0.1153	0.7713
RBC	4.49 ± 1.87	4.36 ± 1.2		-4.4753 to -3.2647	0.6732

AST (TGO): Aspartate Aminotransferase, also known as **TGO** in French (Transaminase Glutamique Oxaloacétique).**ALT (TGP):** Alanine Aminotransferase, also known as **TGP** in French (Transaminase Glutamique Pyruvique).**CRP:** C - reactive protein. **WBC:** White blood cells. **RBC:** Red blood cells.

VI.3.1.1. Impact of gender

The results obtain indicate a statistically significant association between treatment success and failure rates according to gender. Among females, the number of successful treatment cases was 426 out of 650, while treatment failure was recorded in 27 out of a total of 55 failure cases, with a confidence interval of 0.0145, reflecting a higher success rate among females compared to failure rates. For males, the number of successful cases was 224 out of 650, whereas 28 out of 55 cases experienced treatment failure, with the same confidence interval of 0.0145. Although treatment success rates were high in both genders, the slight difference-favouring females suggests that gender may be a contributing factor influencing treatment outcomes **(Fig. 34)**. In the study conducted by Sona et al. on the impact of sex on tuberculosis treatment outcomes, women demonstrated more favorable therapeutic results compared to men. They were less likely to exhibit a high bacterial load, with an adjusted odds ratio of 0.70 (95% CI: 0.56–0.87), and had a lower incidence of unfavorable treatment outcomes, with an adjusted incidence rate of 0.60 (95% CI: 0.43–0.85). This was primarily attributed to a reduced relapse rate among women (0.45; 95% CI: 0.23–0.86). Furthermore, women exhibited significantly higher concentrations of isoniazid ($P < 0.01$). Adverse outcomes in women were mainly associated with the presence of pulmonary cavities, whereas in men, they were linked to factors such as alcohol consumption, elevated body mass index, and lower

levels of glycated hemoglobin. These findings support the results obtained in our study, reinforcing the hypothesis regarding the influence of sex on treatment efficacy **(Sona et al., 2022)**.

VI.3.1.2. Impact of Age

The study results showed a clear association between patient age and the success of tuberculosis treatment. The mean age in the group of patients with treatment unsuccessful was significantly high, averaging 55.14 ± 23.08 years, compared to 42.56 ± 19.09 years in the treatment success group, with a strong statistical significance ($p = 0.0001$). When analysing age ranging groups, the 30 to 39 years age group was notably more represented among those with successful treatment outcomes (144 out of 649) compared to only 3 out of 55 in the treatment unsuccessful group ($p = 0.0034$). In contrast, the rate of treatment unsuccessful increased among older age groups. For instance, in the 60 to 69 age group, 13 out of 55 patients experienced treatment unsuccessful, compared to 54 out of 649 in the success group ($p = 0.0002$). Among patients aged 70 years and older, 17 out of 55 experienced treatment unsuccessful, while 96 out of 649 belonged to the success group ($p = 0.0018$). These findings suggest that advanced age may be a negative prognostic factor affecting TB treatment success, highlighting the need for special attention to elderly patients during treatment planning and monitoring. A study conducted by Ninfa et al. also indicates a clear association between age and the success of tuberculosis treatment. The study showed that patients under the age of 65 were twice as likely to achieve successful treatment outcomes compared to those aged 65 and above, with an odds ratio (OR) of 2.0 and a 95% confidence interval (CI) of 1.7–2.4 **(Ninfa et al., 2019)**. Furthermore, findings from a study conducted in Brazil revealed that patients over the age of 50 had a 2.8 times higher likelihood of treatment failure. These results can be attributed to several factors that commonly affect older adults, including age-related weakening of the immune system and the presence of comorbid chronic diseases **(Ninfa et al., 2019)**. Another study conducted by Do Kyung et al. indicated that older adults were more likely to die during treatment **(Do Kyung et al., 2024)**. However, they demonstrated greater adherence to the treatment regimen compared to younger patients, who were less likely to die but more likely to discontinue treatment. The study highlighted that early mortality during treatment primarily due to poor general health status or the presence of comorbidities was the main cause of treatment failure among older adults. Additionally, potential difficulties in accessing appropriate healthcare services further contributed to this outcome, underscoring the need for enhanced

support systems to ensure treatment continuity and success in this vulnerable population **(Do Kyung et al., 2024)**.

IV.3.1.3. Impact of tuberculosis form on treatment effectiveness

Regarding the distribution of tuberculosis forms, EPTB was more prevalent in patient who had successful treatment outcomes, while it was lower among patient who had unsuccessful treatment outcomes **(Fig. 35)**. These findings suggest that TB treatment regimen is more likely to be effective on extra pulmonary TB rather than on pulmonary TB. Patients suffering from pulmonary TB appearing to respond less favourably to treatment compared to those with extra pulmonary TB. Indeed, the treatment regimen is one of the most controversial aspects of the management of EPTB. On the one hand, certain international bodies, such as the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease, recommend the same regimen for both EPTB and pulmonary TB (**World Health Organization; 2003**). While most extrapulmonary TB can be treated with the same duration as pulmonary TB (6 months), some forms, like TB meningitis and bone/joint TB, may require longer treatment (**World Health Organization; 2010**). In fact, our patients who had successful treatment outcomes almost exhibited an EPTB form. For these patients, treatment duration was, in mean, was longer that those who had unsuccessful treatment outcomes (Table 7); In light of the above, it can be concluded that there is evidence to support the hypothesis that a more than 6-month treatment regimen for EPTB is ideal.

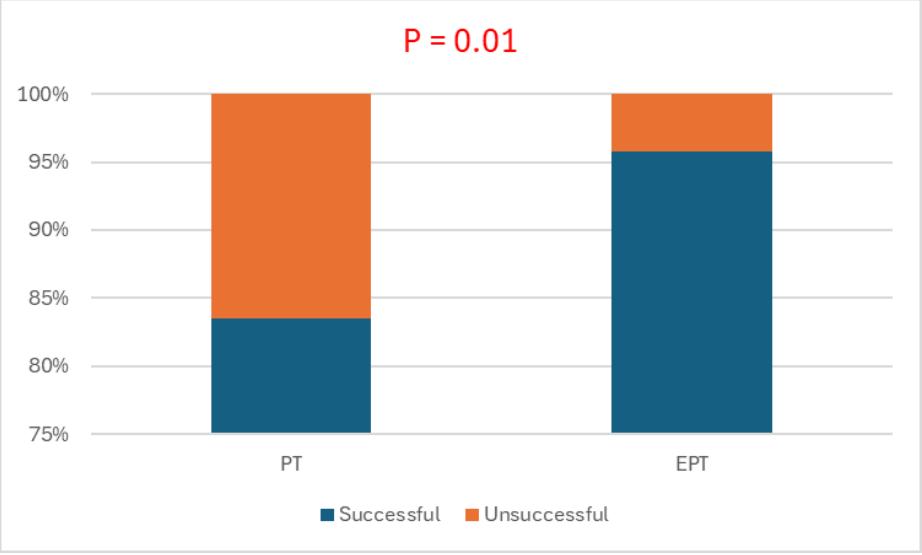


Figure 35: Distribution of tuberculosis forms ; successful Vs unsuccessful treatment outcomes.

VI.3.1.4. Impact of treatment duration

Regarding treatment duration, it was observed that shorter durations (two months or less) were more common among the unsuccessful treatment group, with 5 cases out of 24, compared to only 8 out of 648 in the successful treatment group (p = 0.0001). Conversely, treatment durations ranging from 3 to 6 months were significantly more prevalent among patients who responded successfully to treatment, with 444 out of 648 cases, compared to only 7 out of 24 in the failure group (p = 0.0001). These findings are consistent with those of a study conducted by William and colleagues, in which the researchers emphasized that adherence to treatment throughout the entire prescribed duration plays a critical role in determining treatment outcomes. The study further demonstrated that shortening the treatment duration whether due to early discontinuation or missed doses is clearly associated with an increased risk of adverse outcomes, treatment failure, relapse, and even the development of drug resistance. In this context, the importance of close monitoring of patients becomes evident, particularly during the early stages of treatment. Evidence has shown that early discontinuation often leads to incomplete treatment, thereby increasing the likelihood of failure. Moreover, tuberculosis patients who experience side effects or face challenging social and economic conditions are more likely to abandon treatment prematurely. This underscores the need for early and proactive intervention by healthcare providers to ensure treatment continuity and improve overall outcomes **(William et al., 2022)**.

VI.3.1.5. Impact of comorbidities

Comorbidities were also found to play a significant role in treatment outcomes, particularly diabetes mellitus. Among the treatment failure group, 12 out of 55 patients were diagnosed with diabetes, compared to only 36 out of 645 patients in the successful treatment group (p = 0.0001). Based on the findings of our study, the association between diabetes mellitus and tuberculosis treatment failure aligns with the results reported by Wang et al. in their study conducted in China, which demonstrated that diabetes nearly doubles the risk of pulmonary tuberculosis relapse (HR: 2.40, 95% CI: 1.68–3.45). These findings suggest that the impact of diabetes is not limited to an increased risk of relapse following treatment completion, but also identifies it as a major contributing factor to treatment failure from the early stages. This can be explained by the detrimental effect of diabetes on the immune system, which compromises the body's ability to combat infections, including *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Additionally, diabetes may affect the efficacy of anti-

tuberculosis medications by altering their absorption or metabolism, thereby reducing their therapeutic effectiveness **(Wang et al., 2024)**.

On the other hand, our study findings are in agreement with those reported by Mariana et al. regarding the association between anemia and poor treatment outcomes in pulmonary tuberculosis. Both studies demonstrated a statistically significant association between the presence of anemia and increased rates of treatment failure or mortality. In our study, anemia was more prevalent among patients who did not respond to treatment, with 10 cases recorded among 645 patients in the treatment success group, compared to 4 cases among 55 patients in the treatment failure group, with a statistically significant difference ($p = 0.0036$). This finding suggests that anemia may be a contributing factor to poor treatment response, which is consistent with the results of the other study, showing that the severity of anemia particularly moderate and severe grades was associated with a higher risk of death during the treatment period, even after adjusting for confounding factors such as HIV infection, diabetes mellitus, and body mass index **(Mariana et al., 2023)**. Another study conducted by Yukiko and colleagues investigated the relationship between erythrocytes and pathogenic *Mycobacteria.* The study demonstrated that *Mycobacterium tuberculosis*, *Mycobacterium avium*, and *Mycobacterium* intracellular adhere to erythrocytes through specific receptors, including complement receptor one (CR1) and cell-surface sialo-glycoproteins. Notably, this adhesion does not result in the destruction of erythrocytes but rather promotes the extracellular growth and proliferation of the bacteria **(Yukiko et al., 2022)**.

VI.3.2. The effect of biological factors

The results of the statistical analysis revealed the presence of several biological markers that maybe associated with treatment outcomes in tuberculosis patients. Statistically significant differences were observed between patients who responded to treatment and those for whom treatment unsuccessful. Regarding C-reactive protein, the mean level in the group of patients with treatment failure was 58.96 (standard deviation = 49.77, n = 10), compared to 25.35 in the successful treatment group (standard deviation = 28.5, n = 117), with a strong statistical significance ($p = 0.0011$). This elevated CRP level indicates a severe inflammatory state, which may partially explain the poor treatment response due to chronic inflammation or uncontrolled infection. As for white blood cells, the mean count was higher in the treatment failure group (9.51, standard deviation = 4.68, n = 38) compared to the successful treatment group (7.77, standard deviation = 4.15, n = 510), with statistical significance ($p = 0.0138$). The elevated white blood cell count may reflect an active inflammatory response, suggesting persistent

resistance or ongoing infection in patients who did not respond to treatment. The findings of Simona and colleagues indicate that CRP, one of the major acute-phase proteins of inflammation, is widely used as a marker of active inflammatory response. The literature has shown that elevated CRP levels at the initiation of treatment, or their persistence during therapy, are associated with an increased risk of treatment failure or delayed clinical response. Accordingly, periodic measurement of this biomarker may serve as an effective tool for monitoring disease progression and predicting treatment outcomes. In addition, the white blood cell count particularly neutrophils constitutes a traditional marker for assessing the severity of inflammation. Studies have shown that patients with active or drug-resistant infections often exhibit persistently elevated white blood cell counts, reflecting a chronic inflammatory state that may negatively impact the effectiveness of treatment response **(Simona et al., 2021)**.

Conclusion:

Tuberculosis is one of the oldest infectious diseases known to humanity. Despite continuous medical progress, it remains a global health threat, particularly in low-resource countries, where it is still a major cause of illness and death. In this context, our study aimed to monitor and evaluate 717 tuberculosis patients who were followed up at three public health institutions in Mila Province. The results showed significant differences between genders, with women presenting higher infection rates than men. A general overview of the study's findings indicates that several demographic, medical, and biological factors significantly influence the success or failure of tuberculosis treatment. Regarding gender, treatment success rates were higher among females compared to males. In terms of age, older individuals were clearly associated with increased rates of treatment failure. Moreover, full adherence to the prescribed treatment regimen was identified as a crucial determinant of favorable outcomes, while treatment interruption or non-compliance increased the risk of failure and relapse. The presence of comorbidities also demonstrated a negative impact on treatment outcomes, with diabetes and anemia being among the most prominent conditions associated with poor prognosis, Pulmonary or extra pulmonary tuberculosis type also had an impact on treatment outcomes. From a biological perspective, elevated inflammatory markers such as C-reactive protein and white blood cell count were correlated with treatment failure, suggesting the persistence of an inflammatory state that may hinder therapeutic response. Accordingly, the findings highlight that treatment success or failure is influenced by a complex interplay of medical and biological factors. These variables may offer predictive insight into treatment outcomes and allow for closer monitoring of patient progress. Therefore, the development of improved treatment strategies that take these factors into consideration is essential to enhance therapeutic efficacy and improve patient outcomes. Finally, we recommend conducting broader future studies that include nutritional, immunological, and socio-economic factors in order to deepen our understanding of TB and contribute to more effective prevention and control strategies.

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الملخص

تُعد الأمراض التنفسية من أبرز المشكلات الصحية شيوعًا، من بينها السل. ويُعتبر داء السل من أكثر الأمراض التنفسية انتشارًا منذ القدم، وهو ناجم عن الإصابة ببكتيريا المتفطرة السلية، التي تُصيب الجهاز التنفسي بالدرجة الأولى. ويعتمد علاج هذا المرض أساسًا على مجموعة من المضادات الحيوية تُعطى بانتظام ولفترة زمنية محددة. وفي هذا السياق، تم إجراء دراسة تحليلية شملت البيانات السريرية والبيولوجية لـ 717 مريضًا بالسل، موزعين على ثلاث مؤسسات للصحة العمومية: فرجيوة، ميلة، ودراجي بوصلاح، بالإضافة إلى المؤسسة العمومية الاستشفائية لفرجيوة.

أظهرت نتائج الدراسة أن النساء سجلن أعلى نسبة إصابة بالسل مقارنة بالرجال، وكان السل العقدي اللمفاوي هو الشكل الأكثر شيوعًا كما ان نوع السل الرؤوي اوالخارج رؤوي كان له ايضا تاثير على نتائج العلاج. كما تم رصد فروقات في نسب الإصابة حسب الفئات العمرية. من جهة أخرى، كانت نتائج العلاج أفضل لدى النساء، حيث سُجلت أعلى نسبة نجاح ضمن مجموعة المرضى الذين نجح علاجهم، والتي كانت تضم في الغالب أشخاصًا من الفئة العمرية الأكبر سنًا. أما فشل العلاج، فقد ارتبط بعوامل متعددة مثل ارتفاع مستوى البروتين المتفاعل C (CRP)-، ووجود أمراض مصاحبة كداء السكري، مما يبرز ضرورة إيلاء اهتمام خاص لهذه الفئة من المرضى في التشخيص والمتابعة والعلاج

وفي الختام، تُبرز هذه الدراسة أهمية مواصلة الجهود لتحسين استراتيجيات تشخيص وعلاج مرض السل في الجزائر، مع التركيز على المتابعة المنتظمة والدعم الشامل للمرضى لضمان فعالية العلاج والحد من انتشار المرض.

Resumé

Les maladies respiratoires vrai problème de santé publique dont la tuberculose constitue un exemple marquant. La tuberculose est l'une des maladies respiratoires les plus répandues depuis l'antiquité, et est causée par bactérie *Mycobacterium tuberculosis*, qui affecte principalement le système respiratoire. Le traitement repose essentiellement sur l'administration régulière d'une combinaison d'antibiotiques sur une période déterminée. Dans ce cadre, nous avons mené une étude rétrospective incluant 717 patients atteints de tuberculose et répartis entre trois établissements de santé publique de la wilaya de Mila. Pour ces patients nous avons les caractéristiques démographiques et épidémiologiques, évaluer l'efficacité des méthodes de diagnostic et de traitement sur différentes formes de tuberculose, ainsi qu'identifier les facteurs influençant la propagation de la maladie ou compliquant ses cas. Les résultats ont montré que les femmes présentaient un taux d'infection à la tuberculose plus élevé que les hommes, et que la tuberculose ganglionnaire était la forme la plus fréquente Le type de tuberculose, qu'elle soit pulmonaire ou extra pulmonaire, avait également un impact sur les résultats du traitement. Des différences selon les tranches d'âge ont également été observées. Par ailleurs, les résultats du traitement étaient meilleurs chez les femmes, avec le taux de réussite le plus élevé observé chez les patients âgés dont le traitement a réussi. En revanche, l'échec thérapeutique était associé à plusieurs facteurs, notamment un taux élevé de protéine C-

réactive (CRP) et la présence de comorbidités telles que le diabète, ce qui souligne la nécessité d'une attention particulière pour cette catégorie de patients lors du diagnostic, du suivi et du traitement. Enfin, cette étude met en évidence l'importance de poursuivre les efforts pour améliorer les stratégies de diagnostic et de traitement de la tuberculose en Algérie, en mettant l'accent sur le suivi régulier et le soutien aux patients afin de garantir l'efficacité du traitement et de limiter la propagation de la maladie.

Abstract

Respiratory diseases are among the most prevalent health problems, with tuberculosis being a prominent example. Tuberculosis is one of the most widespread respiratory illnesses throughout history and is caused by infection with *Mycobacterium tuberculosis*, which primarily affects the respiratory system. Treatment of the disease relies mainly on a combination of antibiotics administered regularly over a defined period. In this context, an analytical study was conducted involving the clinical and biological data of 717 former tuberculosis patients. These patients were distributed across three public health institutions—Ferdjioua, Mila, and Deraâhi Bousselah—as well as the Public Hospital of Ferdjioua**.** The study results showed that women had a higher tuberculosis infection rate compared to men, and lymph node tuberculosis was the most common form Pulmonary or extra pulmonary tuberculosis type also had an impact on treatment outcomes. Differences in infection rates were also observed across age groups. Moreover, treatment outcomes were better among women, with the hightest success rate recorded among older patients in the treatment success group. In contrast, treatment failure was associated with several factors such as elevated levels of C-reactive protein (CRP) and the presence of comorbidities like diabetes, highlighting the need for greater attention to be given to this category of patients during diagnosis, follow-up, and treatment.

In conclusion, this study highlights the importance of continuing efforts to improve tuberculosis diagnosis and treatment strategies in Algeria, with a focus on regular follow-up and comprehensive patient support to ensure treatment effectiveness and limit the spread of the disease.