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Investigating the types and mechanisms of *Mycobacterium tuberculosis* resistance: why Indonesia continues to experience high case rates compared to other nations

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ABSTRACT

Tuberculosis (TB) cases in Indonesia have been a major issue in public health. Although antimicrobial therapies such as Isoniazid and Rifampicin are available, Indonesia still struggle to control its spread and yet to eradicate the infection. This is due to the resistance developed by *Mycobacterium tuberculosis*, the main cause of TB, causing an increasing number of Extensively Drug-Resistant Tuberculosis (XDR-TB). This problem exacerbates by the inadequacy of healthcare infrastructure to effectively detect and treat TB. Hence, this study is established to address the challenges and strategies for controlling TB and XDR-TB in Indonesia. The analysis involves epidemiological studies, genetic research, and public health policy reviews to identify the factors contributing to TB drug resistance and to propose targeted interventions. The findings reveal that high drug resistance and inadequate healthcare infrastructure are major barriers. Evidence-based interventions and enhanced diagnostic capacity are crucial for controlling TB in Indonesia. Socioeconomic factors like poverty and limited access to healthcare services also influence the spread of TB in Indonesia. Improving the healthcare system and addressing socioeconomic issues can help reduce TB and XDR-TB rates.

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1. Introduction

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) which predominantly targets the lungs (Batista et al., 2020). The infection is chronic and often enters a latent phase following the initial infection. In addition, *M. tuberculosis* is a slow-growing bacterium with notable resistance to many disinfectants (Gordon and Parish, 2018). As such, it is highly possible for bacteria to reactivate, especially immunocompromised individuals (Alsayed and Gunosewoyo, 2023; Parr et al., 2019; Tiberi, 2019).

The impact of TB around the world has been significant over the years. In 2019, approximately 10 million people globally contracted TB, with new cases showing only a slight decline. This persistent prevalence underscores the challenges in combating the disease on a global scale (WHO, 2019).

Indonesia particularly is one of the countries with the highest burden of TB, accounting for a significant portion of the global total, representing 10% of all TB cases worldwide. The high incidence of TB in Indonesia is closely linked to the prevalence of drug-resistant TB and several factors, including inadequate healthcare infrastructure, inconsistent treatment regimens, and insufficient monitoring of patient adherence (WHO, 2019).

The emergence of drug-resistant strains of *M. tuberculosis* has exacerbated the global TB crisis. TB drug resistance can be categorized into several types based on the specific drugs to which the *M. tuberculosis* strain is resistant. Monoresistance refers to resistance against a single first-line anti-TB drug (Palchowdhury et al., 2021). Polydrug resistance involves resistance to multiple first-line anti-TB drugs, excluding the simultaneous resistance to both isoniazid and rifampicin (Zhang et al., 2021). Multidrug-resistant TB (MDR-TB), defined as being resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs, poses a significant threat to the success of TB control programs worldwide (Lagutkin et al., 2022; WHO, 2022). The development of MDR-TB generally results from the inappropriate use of anti-TB medications. Such improper use can occur if patients fail to complete their full course of treatment, take incorrect dosages, or are administered substandard drugs (Mancuso et al., 2023). Meanwhile, extensive drug resistance (XDR) is defined as resistance to any fluoroquinolone and at least one of the three second-line injectable drugs (capreomycin, kanamycin, and amikacin) along with the resistant criteria for MDR (Brode et al., 2022; Udwadia et al., 2022). This study aims to investigate the types and mechanisms of *M. tuberculosis* resistance in Indonesia and to understand why the country continues to experience high TB case rates compared to other nations.

2. Literature review

2.1. *Mycobacterium tuberculosis*

2.1.1. Structure of *Mycobacterium tuberculosis* and its infection

Taxonomically, *M. tuberculosis* is a member of the acid-fast bacterial species Genus *Mycobacterium tuberculosis*, Phylum Actinobacteria, Order Actinomycetales, Suborder Corynebacterineae, Family Mycobacterineae, Kingdom Bacteria. Its classification is based on its capacity to hold onto the Ziehl-Neelsen stain, which is a distinctive technique for identification (Yang et al., 2020). Due to the high lipid content in its cell wall, which makes it resistant to standard staining techniques, *M. tuberculosis* exhibits unique staining properties in contrast to other bacteria that are commonly classified as either Gram-positive or Gram-negative based on the makeup of their cell walls (Tiberi, 2019). The accurate diagnosis and treatment monitoring of TB infections depend heavily on this taxonomic and staining differentiation. It is characterized by its slow rate of replication and is an aerobic bacillus. It is a chemoorganotrophic bacterium, meaning it derives its energy by oxidizing organic compounds, such as sugars and fats, and relies on these organic molecules for both energy and carbon. *M. tuberculosis* is non-motile, lacking structures such as flagella or cilia for movement, and it is non-spore-forming, depending instead on its robust cell wall and ability to enter a dormant state within granulomas to persist in harsh environments (Gordon and Parish, 2018).

TB is an infectious disease caused by the bacterium *M. tuberculosis* (Miggiano et al., 2020). It predominantly targets the lungs but can disseminate to other body parts such as the lymph nodes, spine, and brain. Transmission occurs via airborne droplets expelled when an infected individual coughs, sneezes, or talks, releasing bacteria-laden particles into the air. Upon inhalation, these bacteria can lodge in the lungs and are subsequently ingested by alveolar macrophages, a type of immune cell. Despite this initial immune response, *M. tuberculosis* has evolved advanced mechanism to circumvent the host's immune defences, allowing it to persist within the host (Ankley et al., 2020). This persistence leads to the formation of granulomas, which are clusters of immune cells that attempt to isolate the infection.

However, granulomas can deteriorate over time, releasing bacteria and causing extensive tissue damage. This progression can manifest in symptoms such as a persistent cough, chest pain, fever, weight loss, and fatigue. The breakdown of granulomas not only facilitates the spread of the bacteria within the host but also increases the risk of transmission to others. If not adequately treated, TB can become a severe, life-threatening condition (Prasad et al., 2021). Treatment typically involves a lengthy course of antibiotics, which is essential for eradicating the bacteria and preventing the disease from drug-resistant. Due to its potential severity and ease of transmission, TB remains a significant public health concern worldwide.

2.1.2. Pathogenesis of *Mycobacterium tuberculosis*

Tuberculosis (TB) is transmitted through airborne aerosols (1–5 μm) generated by respiratory activities like coughing, sneezing, singing, and talking, but coughing is not required for transmission. All respiratory activities can release *M. tuberculosis* aerosols from the lungs via the bronchiole fluid film burst mechanism, significantly contributing to transmission (Patterson and Wood, 2019). These microscopic droplets can be inhaled by individuals in close proximity to the infected person, allowing the bacteria to enter the respiratory system. Once inhaled, the bacteria travel through the respiratory tract and reach the alveoli, the small air sacs in the lungs where gas exchange occurs (Abdelmoktader et al., 2020).

Upon reaching the alveoli, *M. tuberculosis* encounters the host's immune defense. The alveoli consist of type I and II epithelial cells with other primary line of defense involving alveolar macrophages, dendritic cells and neutrophils. The alveolar macrophages, which are specialized cells designed to engulf and digest foreign particles, including bacteria, through a process called phagocytosis (Bussi and Gutierrez, 2019). However, *M. tuberculosis* has evolved sophisticated mechanisms to avoid destruction within these macrophages. One such mechanism is the inhibition of phagosome-lysosome fusion, which is a critical step in the digestion of engulfed bacteria. By preventing this fusion, *M. tuberculosis* ensures its survival and replication within the macrophages (Carranza and Chavez-Galan, 2019).

M. tuberculosis manipulates host immune responses to favor its survival and growth. It uses lipoarabinomannans and lipomannans to alter immune signalling, suppressing protective responses and promoting conditions favorable for its persistence. The immune response to *M. tuberculosis* leads to the formation of granulomas, which are clusters of immune cells that try to contain the infection. Within these granulomas, the bacteria can enter a dormant state, evading the immune system and antimicrobial treatments. This leads to a state known as latent tuberculosis infection (LTBI) (Tiberi, 2019). During LTBI, the bacteria are dormant, which implies that bacteria are not actively multiplying but still alive. Individuals with LTBI do not exhibit symptoms and are not contagious. However, the bacteria can reactivate later when the environment is viable for growth, which usually happen when the host's immune system is compromised (Sia and Rengarajan, 2019).

Immunocompromise causes the granulomas to deteriorate, releasing dormant *M. tuberculosis* bacilli, transitioning LTBI to active TB (Chokkalingam et al., 2023). Once reactivated, the bacteria may disseminate from the initial site of infection to other parts of the lungs. In severe cases, the bacteria can disseminate through the bloodstream to other organs, a condition known as miliary TB (Pinzon et al., 2021). This systemic spread can affect multiple organs, including the liver, spleen, and brain, leading to widespread disease.

2.1.3. Immune evasion of *Mycobacterium tuberculosis*

M. tuberculosis employs three primary mechanisms to evade the host immune system, allowing it to persist and remain difficult to eradicate: survival within immune cells, interference with immune activation, and suppression of immune response.

To evade the host, *M. tuberculosis* hides within the macrophage, the immune cells responsible for engulfing and digesting pathogens. In general, macrophage undergoes phagosome-lysosome fusion in digesting pathogens. However, *M. tuberculosis* prevent the fusion, enables the bacteria to survive and replicate within macrophages, shielded from immune detection. By evading these degradation processes, it remains undetected and, therefore, unchecked (Carranza and Chavez-Galan, 2019). This strategy allows *M. tuberculosis* to hide within the immune system, enhancing its persistence.

Beyond macrophage evasion, *M. tuberculosis* actively disrupt the immune system by targeting dendritic cell to prevent bacterial antigen presentation that will activate the adaptive immune system. Some examples are Hip1, which cleaves immunogenic proteins needed for immune signalling, decoy antigens such as Ag85B and TB10.4 to stimulate immune response to these antigens, taking away the focus of the immune system from the actual infected cells, undermining the immune system (Chandra et al., 2022).

M. tuberculosis uses lipid and protein-based tactics in dampening the immune system. The bacterial cell wall blocks the expression of immune-stimulating molecules on infected cells, preventing T cell activation. Additionally, specific proteins also capable to inhibit apoptosis of the infected immune cells, which result in delaying the immune response. This suppression provides

the bacterium time to evade immune detection, resulting in prolonged infection and increasing the risk of spread (Chandra et al., 2022).

Collectively, these mechanisms underscore M. tuberculosis's complex immune evasion strategy, effectively compromising antigen presentation, inhibiting T cell activation, and undermining the host's adaptive immune response. This multifaceted approach allows the pathogen to persist within the host by systematically weakening key immune defences.

2.2. Drug resistance in tuberculosis

2.2.1. Mechanism of drug resistant in tuberculosis

Treatment of tuberculosis (TB) typically begins with a combination of first-line drugs, consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide. This drug combination is taken for the first 2 months of the treatment for rapid kill of the bacteria. It is then continued with combination of INH and TIF for 6 months, prolonged up to 9 months depending on the severity of the infection. In the case where patients do not show improvement in symptoms, it is highly likely that the TB infection is drug resistant. In such cases, second-line drugs such as fluoroquinolones or injectable are prescribed to replace the first-line drugs. This also implies that the treatment duration is also prolonged up to 24 months, depending on the severity of TB resistance.

Drug resistance in *M. tuberculosis* presents a significant challenge to the treatment and control of TB. The primary mechanisms of drug resistance include genetic mutations that alter drug targets or interfere with drug activation. In addition, *M. tuberculosis* employs various adaptive strategies to survive under antibiotic pressure, resulting to both primary resistance and drug tolerance. While mutations are a common bacterial response to antibiotics, specific mutations in *M. tuberculosis* are linked to resistance against particular drugs. Among these mutations, those leading to resistance against ethambutol are particularly well-studied. The most common mechanism of ethambutol resistance involves mutations in the embB gene, which encodes the arabinosyl transferase enzyme. These mutations reduce the binding affinity of ethambutol to its target enzyme, thereby decreasing the drug's efficacy in inhibiting cell wall synthesis. Another mutation associated with ethambutol resistance is through increased activity of efflux pumps. The pumps expel antibiotics from the bacterial cell, reducing intracellular drug concentrations and thereby lowering the drug's efficacy. Genes encoding efflux pumps, such as the Rv1258c gene, have been implicated in ethambutol resistance. As a result, ethambutol becomes less effective or fails to work (Boni et al., 2022).

Pyrazinamide resistance is caused by mutations in the pncA gene which lead to the loss or reduction of PZase activity, thereby preventing the conversion of PZA to POA and rendering pyrazinamide ineffective. These mutations are highly diverse, spanning point mutations, insertions, and deletions, and can occur throughout the gene and its promoter region, affecting enzyme production or function. In addition to pncA mutations, mutations in the rpsA gene, which encodes the ribosomal protein S1, and the panD gene, encoding aspartate decarboxylase, have also been implicated in Pyrazinamide resistance. The rpsA mutations interfere with the interaction of POA with the ribosomal protein, which is thought to disrupt trans-translation, a process vital for bacterial survival under stress conditions. Meanwhile, mutations in panD, though less common, suggest a potential secondary pathway affecting Pyrazinamide susceptibility. The Pyrazinamide resistance rate was notably higher in strains resistant to all four first-line drugs, which include isoniazid, rifampicin, pyrazinamide, ethambutol, as well as in pre-extensively drug-resistant (pre-XDR) and extensively drug-resistant (XDR) strains (Shi et al., 2020).

As drug resistance evolves, strains of *M. tuberculosis* may become resistant to multiple drugs, progressing from rifampicin-resistant TB (RR-TB) to multidrug-resistant TB (MDR-TB) and even extensively drug-resistant TB (XDR-TB), which poses a serious global health threat due to the limited treatment options available.

2.2.2. Rifampicin-Drug Resistant Tuberculosis (RR-TB)

Rifampicin-resistant tuberculosis (RR-TB) is a subset of multi-drug resistant TB (MDR-TB), characterized specifically by resistance to rifampicin, one of the most critical first-line anti-TB drugs (Singh and Chibale, 2021). Rifampicin plays a pivotal role in the standard TB treatment regimen due to its potent bactericidal activity and ability to penetrate well into infected tissues. When a TB strain develops resistance to rifampicin, it significantly complicates the treatment process, as the effectiveness of the conventional treatment regimen is severely compromised (Dookie et al., 2022). Consequently, any case of TB that is resistant to rifampicin is classified as MDR-TB, even if it is still susceptible to other first-line drug, such as isoniazid.

The emergence of RR-TB is particularly alarming because it diminishes the available therapeutic options, making the disease harder to manage and cure. Rifampicin resistance often arises due to mutations in the rpoB gene of *M. tuberculosis*, which encodes the beta subunit of RNA polymerase, the enzyme targeted by rifampicin (Singh and Chibale, 2021). These genetic changes hinder the binding of rifampicin to the bacterial RNA polymerase, rendering the drug ineffective. In addition to genetic mutations, *M. tuberculosis* also employs several phenotypic adaptations to survive rifampicin exposure, including alterations in sigma factors that regulate bacterial transcription (Goossens et al., 2020). Treatment of RR-TB typically requires the use of second-line drugs, which are often less effective, more toxic, and necessitate longer treatment durations compared to first-line therapies (Dookie et al., 2022). Managing RR-TB thus demands comprehensive healthcare strategies, including accurate and timely diagnosis, the use of appropriate second-line treatment regimens, and robust patient support systems to ensure adherence to the lengthy and challenging treatment protocols.

2.2.3. Multi-Drug Resistant Tuberculosis (MDR-TB)

Multi-Drug Resistant Tuberculosis (MDR-TB) represents a significant challenge in the fight against TB, as it resists at least two of the most potent first-line anti-TB medications, isoniazid and rifampicin (Singh and Chibale, 2021). Isoniazid is a prodrug that, upon activation by the catalase-peroxidase enzyme KatG in *M. tuberculosis*, forms isonicotinoyl-NAD, which inhibits the key enzyme InhA involved in mycolic acid synthesis. This inhibition disrupts cell wall integrity and generates reactive oxygen species (ROS), contributing to INH's high bactericidal activity, particularly in the first two days of treatment. However, *M. tuberculosis* can develop INH tolerance, reducing its effectiveness over time. The primary mechanisms of INH resistance include genetic mutations and metabolic adaptations. Mutations in the katG gene reduce the enzyme's ability to convert INH to its active form, while mutations in the inhA promoter lead to overexpression of the target enzyme, requiring higher drug concentrations for inhibition (Goossens et al., 2020).

The emergence of MDR-TB is largely driven by inappropriate or incomplete treatment of standard TB, which selects for resistant strains (Sharma et al., 2021). This includes scenarios where patients do not adhere to their prescribed treatment regimens, healthcare providers prescribe incorrect treatments, or there is a lack of access to quality-assured drugs. As a result, the treatment of MDR-TB requires combination of second-line drugs and prolonged treatment. This TB infection not only poses a threat to individual patients but also to public health, as these resistant strains can spread to others. Effectively addressing MDR-TB requires a comprehensive approach,

incorporating second-line therapies, which are associated with more severe side effects and extended treatment timelines. Moreover, preventing the spread of MDR-TB demands robust public health measures, including rapid and accurate diagnostic capabilities, effective patient management, and ensuring the availability and correct administration of anti-TB medications.

2.2.4. Extensively-Drug Resistant Tuberculosis (XDR-TB)

Extensively drug-resistant tuberculosis (XDR-TB) represents an even more formidable challenge than MDR-TB (Stephanie et al., 2021). XDR-TB is characterized by resistance not only to the two most powerful first-line drugs, isoniazid and rifampicin, but also to any fluoroquinolone and at least one of the three key injectable second-line drugs: amikacin, kanamycin, or capreomycin. This extensive resistance severely limits the options available for effective treatment, making it one of the most difficult forms of TB to manage. The mechanisms behind XDR-TB involve complex genetic mutations that confer resistance to multiple classes of antibiotics, often due to improper or incomplete treatment of TB, which allows resistant strains to survive and proliferate (Desai et al., 2023).

Table 1. Differences of MDR-TB, RR-TB, and XDR-TB

Type of TB	Definition	Resistance
MDR-TB	Resistant to at least isoniazid and rifampicin	Resistant to multiple drugs
RR-TB	Resistant to rifampicin	Resistant to a key first-line drug
XDR-TB	Resistant to isoniazid and rifampicin, plus any fluoroquinolone and at least one injectable second-line drug	Resistant to most available drug

The clinical management of XDR-TB is extremely challenging and often associated with a higher mortality rate compared to other forms of TB. Patients with XDR-TB have significantly fewer therapeutic options, and the available treatments are often less effective, more toxic, and require prolonged administration, which can lead to severe side effects and poor adherence (Desai et al., 2023). The Table 1 summarizes the key differences which can be identified and listed between MDR-TB, RR-TB, and XDR-TB.

2.3. Current trend of tuberculosis

2.3.1. Epidemiology and global tuberculosis trend

Despite extensive studies conducted, TB remains to be one of the leading causes of death from infectious diseases globally, with approximately 10 million new cases and 1.5 million annual deaths (Bharadwaj, 2021; Varshney et al., 2021). A comprehensive analysis of the global spread of TB reveals significant challenges in the management. Factors such as non-compliance, inconsistent adherence to treatment protocols, and improper therapeutic management contribute to the emergence of drug-resistant strains due to failure to completely eradicate the bacteria. When patients fail to comply the treatment course, the drug dose is insufficient to completely eliminate the bacteria. Remaining bacteria can enter the dormant state and adapt to the suboptimal drug concentrations, developing mutations to become resistant to the given antibiotics. This selective pressure creates a breeding ground for resistant strains, which can then multiply and spread, making future treatments less effective and significantly complicating disease control (Bharadwaj, 2021; Fuady et al., 2022; Varshney et al., 2021).

The emergence of extensively drug-resistant TB (XDR-TB) further intensifies these challenges by drastically reducing the available treatment options, increasing the cost of care, extending treatment durations, and significantly elevating the risk of treatment failure and mortality. This case is prevalent in regions with high rates of TB, limited resources and healthcare infrastructure (Dadu et al., 2020). Socioeconomic factors, like poverty and lack of access to healthcare, as well as lifestyle factors, exacerbate the risk of TB infection and drug resistance in these areas (Fuady et al., 2022). Advancements like the GeneXpert MTB/RIF test have improved diagnostic accuracy, yet accessibility challenges remain in high-burden regions, particularly those with limited resources (Merker et al., 2020).

Aside from treatment compliance, TB control also emphasize preventive measures to reduce transmission. TB vaccination, particularly Bacillus Calmette-Guerin (BCG) vaccine has been widely utilized and became the gold standard for primary prevention of TB infection, especially in young children. Community-level education is also essential to manage the socioeconomic factors by raising awareness about TB infection and transmission, highlighting the importance to comply to treatment regime to completely clear the infection and reduce risk in resistant development and transmission rate (WHO, 2020).

Epidemiologically, increasing drug-resistant TB is not preferred as it is more difficult to control and treat. It leads to increased transmission rates and elevated mortality (Fuady et al., 2022). Indonesia is a large and geographically diverse country. With its size, our country faces significant disparities in socio-economic development, with many regions remaining underdeveloped, especially in rural and remote areas. In the context of healthcare, this uneven development often translates into lack of adequate healthcare infrastructure and facilities in rural and remote areas. Therefore, the spread of XDR-TB is exacerbated by insufficient diagnostic capabilities, substandard infection control measures, and limited access to effective treatment options. The absence of advanced diagnostic tools hinders the timely detection of drug-resistant TB cases, while overcrowded healthcare settings and inadequate isolation protocols further facilitate transmission (Chowdhury et al., 2023). These challenges place a significant strain on healthcare systems, as complex and costly treatment regimens required for XDR-TB exceed the capacity of resource-limited areas. Furthermore, the stigma surrounding TB can impede timely healthcare-seeking behaviour, thereby perpetuating the transmission of the disease (Fuady et al., 2022)

Therefore, in order to address TB in Indonesia effectively, enhanced diagnostics, equitable healthcare access, and community-driven education initiatives are essential. A multifaceted approach, involving integration of improved diagnostic capabilities, comprehensive treatment protocols, and public health policies tailored to the socioeconomic context of Indonesia—remains a crucial piece to eradicate TB in Indonesia (Soedarsono et al., 2021; Siswanto et al., 2021).

2.3.2. Comparison of tuberculosis cases in Indonesia with advanced countries

Tuberculosis (TB) remains a significant public health issue in Indonesia due to a combination of socio-economic and healthcare challenges (Soedarsono et al., 2021). High levels of poverty contribute to poor living conditions, including overcrowded housing and inadequate nutrition, which increase the risk of TB transmission and progression from latent to active disease. Limited access to healthcare exacerbates the problem, as many individuals cannot afford or reach medical facilities for timely diagnosis and treatment (Fuady et al., 2022). Additionally, Indonesia faces substantial hurdles in implementing effective infection control measures in healthcare settings and the community, allowing the disease to spread more readily. Ensuring patient adherence to lengthy TB treatment regimens is another critical challenge, as incomplete or inconsistent treatment can lead to the development of drug-resistant TB strains, further complicating control efforts (Soedarsono et al., 2021; Siswanto et al., 2021).

Indonesia faces a significant burden of TB, including multidrug-resistant (MDR) and extensively drug-resistant TB (XDR-TB). The prevalence of TB varies significantly across Indonesia, influenced by diagnostic methods and regional healthcare capabilities. Areas like Sumatra and other islands show higher TB prevalence, partly due to diagnostic disparities (Noviyani et al., 2021). National surveys reveal a substantial gap in TB detection, with many cases remaining undiagnosed, presenting a significant barrier to effective TB control in Indonesia (Kak et al., 2020).

Developed nations with extensive TB control programs, such as the United States, the United Kingdom, and several European countries, include timely diagnosis, adherence to established treatment procedures, and efficient surveillance systems (Rojano et al., 2019). These initiatives have helped to effectively control drug-resistant TB strains and lower TB incidence rates. On the other hand, high rates of HIV co-infection, a lack of adequate healthcare infrastructure, and socioeconomic variables make treating TB in Indonesia extremely difficult (Pradipta et al., 2021). Research contrasting the frequency of XDR-TB and the diversity of strains in Indonesia shows how regional differences in TB control strategies and healthcare access have driven the evolution of distinct genetic profiles linked to treatment resistance (Sinulingga et al., 2023).

A thorough analysis reveals numerous issues with TB control and management in Indonesia, including socioeconomic factors, public health policies, healthcare infrastructure, and treatment practices that contribute to the high prevalence and spread of XDR-TB. Poverty, cramped living quarters, and restricted access to medical care worsen TB transmission and impede prompt diagnosis and treatment (Sulistyawati and Ramadhan, 2021). Effective disease management and surveillance are frequently hampered by implementation gaps and resource restrictions, despite the fact public health policies play a critical role in influencing TB control efforts (Kustanto, 2020). Inadequate drug susceptibility testing laboratory facilities and unequal provider distribution, particularly in rural and remote areas with high TB rates, are other issues plaguing Indonesia's healthcare system (Soeroto et al., 2019). Drug-resistant TB strains arise and spread due to treatment methods such as overuse of antibiotics and uneven adherence to standard treatment protocols.

2.3.3. Strategic approach to control TB and prevent transmission in Indonesia

To effectively tackle these intricate problems, concerted efforts are needed to fortify healthcare delivery networks, augment diagnostic proficiencies, elevate patient-centered treatment, and foster evidence-based policy initiatives customized to Indonesia's socioeconomic context. Improving TB and XDR-TB control in Indonesia requires discussing successful treatment strategies, national policies, and preventive initiatives from developed countries. Effective treatment plans in industrialized nations emphasize early diagnosis made possible by state-of-the-art laboratory facilities and quick molecular diagnostics such as GeneXpert MTB/RIF, which allow for the early identification of drug-resistant TB strains (Soeroto et al., 2019). Standardized treatment strategies that incorporate novel medications like bedaquiline and delamanid have demonstrated promise in improving treatment outcomes (Van de Berg et al., 2021).

National policies play a crucial role in TB control. Countries like the Netherlands and South Korea have developed comprehensive TB control programs that incorporate patient-centered treatment, active case discovery, and stringent infection control measures (Pradipta et al., 2021). By emphasizing TB prevention through immunization, contact tracing, and community-based health education initiatives, these strategies dramatically lower TB incidence and mortality rates (Hadisoemarto et al., 2022).

Local engagement is essential for successful eradication of TB in Indonesia. The approach shall be conducted in sync with other stakeholder including community health worker and local NGOs in delivering education on TB prevention, the importance of treatment adherence, and understanding the dynamic of TB transmission. Through this approach stakeholders are able to gain insight and identify barriers that the population faces, especially in rural and underdeveloped areas (Wulandari et al, 2016; WHO, 2020). By equipping healthcare professionals, the right skills to recognize TB and educating the population on treatment adherence, Indonesia could enhance TB management efforts and reduce transmission (Ministry of Health RI, 2021).

While specific programs and systemic approach are being adopted, it is also important to address the stigma surrounding TB. This is important as the stigma prevent individuals to seek for proper diagnosis and treatment, exacerbating the transmission risk. The stigma exists due to the misconception of associating TB with poverty and poor hygiene. Furthermore, fear of its infection also leads to discrimination in workplace, schools, and communities. Hence programs need to frame TB as preventable and treatable disease and tailored to Indonesian cultural context to reduce the social stigma. Community empowerment could encourage proactive healthcare-seeking behaviours, reduce discrimination, and improve public understanding of TB control (Hadisoemarto et al., 2022). Collaborative relationships between stakeholders: government agencies, healthcare providers, and non-governmental organizations; are crucial to implement these interventions and maintaining gains in TB control.

While strategic approach outlined offers promising framework to enhance TB control in Indonesia, the success implementation faces significant challenges. The healthcare infrastructure, especially in rural and remote areas, is a constant key barrier to provide consistent and widespread access to proper TB treatment and diagnostic (Ministry of Health RI, 2021). Funding to scale up and update for advanced diagnostic and treatment is also another limitation for early diagnostic and management (Wulandari et al, 2016). In addition, as Indonesia has vast diversity of geography and socioeconomic condition, the disparities of healthcare delivery is significant and creates a challenge to design a standard approach that applicable across regions (WHO, 2020). Hence, stakeholders shall work together to address these limitations to develop strategies that is suitable for Indonesia.

2.4. Future research challenges and opportunities

Identifying the primary challenges in TB and extensively drug-resistant TB (XDR-TB) control in Indonesia, along with research opportunities to develop more effective and sustainable interventions, reveals critical areas for improvement in public health strategies. Important obstacles include low treatment adherence among tuberculosis patients, inadequate diagnostic skills, and socio-economic inequities impacting access to healthcare services (Pradipta et al., 2021; Soeroto et al., 2019). Treatment outcomes are further complicated by the high prevalence of drug-resistant TB strains, such as XDR-TB, which calls for expensive and perhaps harmful second-line therapy (Chaidir et al., 2019; Sinulingga et al., 2023).

In order to address these issues, public health interventions must focus on research projects that will improve tuberculosis (TB) surveillance, increase diagnostic accuracy by using cutting-edge molecular techniques, and create innovative treatment plans that are specific to regional epidemiological profiles. Ensuring sustainable progress in tuberculosis (TB) control efforts throughout Indonesia’s different regions requires putting evidence-based policies into place and improving the country’s healthcare infrastructure. Investigating novel strategies including community-based interventions to improve treatment adherence, digital health technology for real-time disease monitoring, and vaccine development against drug-resistant TB strains present research prospects. To effectively reduce the burden of tuberculosis (TB) and

XDR-TB researchers, legislators, and healthcare professionals (Wahyuningsih et al., 2023).

3. Conclusion

Tuberculosis (TB) remains a critical global health challenge due to its persistent prevalence, high mortality rates, and the emergence of drug-resistant strains. *M. tuberculosis*, the causative agent, exhibits complex pathogenic mechanisms, including slow growth, immune evasion, and the ability to enter a dormant state, complicating both diagnosis and treatment. The burden of TB is especially pronounced in countries like Indonesia, where inadequate healthcare infrastructure, inconsistent treatment regimens, and socio-economic factors contribute to high incidence rates. The rise of drug-resistant TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), exacerbates the crisis. These strains pose significant challenges to TB control programs, requiring more complex, expensive, and prolonged treatment regimens with second-line drugs that are often less effective and more toxic. Resistance mechanisms involve genetic mutations that alter drug targets or interfere with drug activation, as well as adaptive strategies such as efflux pumps and inhibition of phagosome-lysosome fusion, which further complicate treatment efforts.

Addressing these challenges requires robust public health strategies, including early and accurate diagnosis, effective treatment protocols, and comprehensive patient management. Enhanced infection control measures, improved healthcare infrastructure, and socio-economic interventions are crucial, particularly in high-burden regions like Indonesia. Strengthening healthcare systems to ensure consistent and accessible TB care involves investing in the training of healthcare professionals, providing adequate medical supplies, and implementing widespread awareness campaigns to educate the public about TB prevention and treatment. Additionally, fostering community engagement and addressing social determinants of health, such as poverty, malnutrition, and overcrowded living conditions, can play a significant role in TB prevention and control. Continued research into new treatments and diagnostic tools is essential, focusing on developing shorter, more effective, and less toxic treatment regimens. Coordinated international efforts, including funding and technical support, are necessary to support high-burden countries in their fight against TB. Reducing the global TB burden and preventing the spread of drug-resistant strains will require a sustained and multifaceted approach, emphasizing collaboration, innovation, and commitment at both local and global levels. International agencies, governments, and non-governmental organizations must work together to implement evidence-based interventions, monitor progress, and adapt strategies as needed to effectively combat TB.

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Conflict of interest

The authors declare no conflict of interest in this research.

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