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Effective Bacterial Factors Involved in the Dissemination of Tuberculosis

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Abstract: Tuberculosis is one of the leading health-threatening globally, especially in developing countries. Several factors such as bacterial, environmental, and host factors contribute to the spreading of this disease. With the emphasis on bacterial factors, different lineages of *Mycobacterium tuberculosis* have different dissemination rates due to genetic variation, proteome content diversity, and different drug-resistance rates, as well as differences in their virulence rate, which has made diversity in the prevalence of these lineages and their dissemination in certain geographical areas. Among different *M. tuberculosis* lineages, Beijing strains in lineage 2 are more transmissible than other strains due to their specific characteristics, making them more adapted to intracellular life and increasing pathogenicity in the host. Measures such as rapid diagnosis and timely treatments are needed to control tuberculosis effectively. The disease will be widespread in the community if preventive measures are delayed. This study aimed a comprehensive, complete, and objective investigation of the bacterial factors that are effective in the transmission of tuberculosis and their mechanisms in disease progression to be aware of them in the effective control of the disease.

Keywords: tuberculosis; *Mycobacterium tuberculosis*; bacterial factors; transmission.
Abbreviations: VNTR, Variable number tandem repeat; TNF, Tumor necrosis factor; PGL, Phenylglycolipid; pks1511, intact polyketide synthase; TLR2, toll-like receptor2; Hsp65, heat shock protein 65; IL10, interleukin 10; PPE, Personal Protective Equipment; PhoR, Phosphate Regulon sensor protein; DIM, Dimycocerosates of phthiocerol; NTF, noise transfer function; BCG, Bacillus Calmette–Guérin; DR, Drug-resistance; MDR, Multidrug-resistance; XDR, extremely drug resistance; RR, rifampin-resistance; SLID, second-line injectable drug; DST, diagnostic sensitivity test; DosR, dormancy survival regulon.

1. Introduction

Tuberculosis is one of the principal reasons for mortality globally, affecting millions of people every year, and about one-tenth of these people die from the disease [1, 2]. This disease can interfere with all body organs, but it is more likely to involve the lungs [3]. Human is the

only reservoir for *Mycobacterium tuberculosis*, and the infected person can transmit the disease to other people, which increases the number of cases in the world [4].

Safe immunity is necessary to prevent *M. tuberculosis* infection, and infection with immunosuppressive diseases such as type 2 diabetes, human immunodeficiency virus (HIV), malnutrition, and immune system suppression increases the risk of tuberculosis [5, 6]. More than 90% of tuberculosis cases occur in developing countries, and Africa, Eastern Europe, and Southeast Asia have the highest incidence of tuberculosis in the world [7, 8].

Several factors, such as the social and health status, the risk of acquired immunodeficiency syndrome (AIDS), the reduced efficacy of the Bacillus Calmette–Guérin (BCG) vaccine, the migration of individuals, and the emergence of drug-resistant strains, are effective in the sustainability and relapse of tuberculosis [9]. Effective tuberculosis transmission is associated with a lung lesion that results in bacterial coughing that the patient can transmit bacteria to other people by coughing, sneezing, and even speaking by spreading the pathogen in the air [10].

M. tuberculosis is an intracellular microorganism that can save its life in the macrophages by preventing the formation of phagolysosomes and resistance against macrophage's bactericidal mechanisms, ultimately causing asymptomatic infection in the patient's body [11]. About 90% of patients infected by tuberculosis respond to the bacteria by the production of granuloma without any clinical signs and symptoms; in 10% of these patients that have a specific immunological status, the asymptomatic infection begins to grow and become an active infection and show the symptoms related to the disease, which in both asymptomatic and symptomatic conditions, the disease can be transmitted [12] (Figure 1).

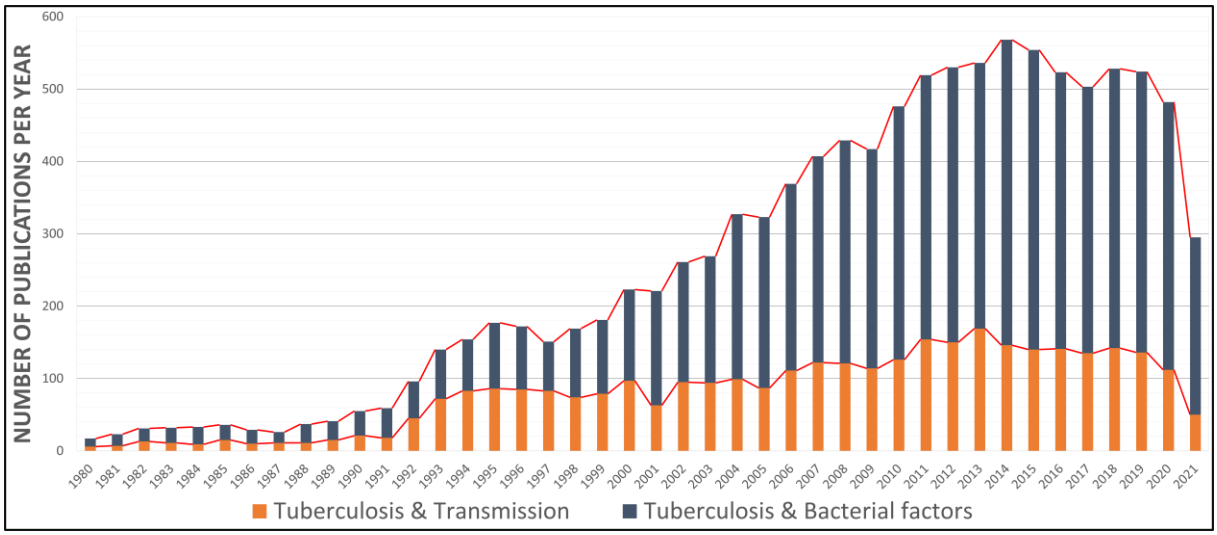

Figure 1. Illustrates the increase in papers reporting the relationship between bacterial factors, transmission, and *Mycobacterium Tuberculosis*. Comparison between the number of publications focused on the relationship between bacterial factors, transmission, and *Mycobacterium Tuberculosis* in PubMed 2021.

It is necessary to disrupt transmission in society to minimize the possibility of tuberculosis infection dissemination [13, 14]. Three environmental factors, such as crowds and nutrition, host factors, such as immunity status, and bacterial factors, are involved in spreading tuberculosis globally in various ways [15, 16]. Therefore, this study aimed a comprehensive, complete, and objective investigation of the bacterial factors that are effective in the transmission of tuberculosis and their mechanisms in disease progression to be aware of them in the effective control of the disease.

2. Genetic Diversity and Virulence Rate of the Strains

Different strains of *M. tuberculosis* are created due to their genetic diversity [17]. These strains can be identified by molecular techniques such as the restriction fragment length polymorphism (RFLP) based on IS6110, spoligotyping, and variable number tandem repeat (VNTRs) [18, 19]. Based on molecular methods and genetic analysis, *M. tuberculosis* is divided into seven main lineages. Each of these lineages has specific geographical distribution and transmission power, which has caused a difference in their dispersion rate [20].

The genotype of different strains of *M. tuberculosis* is identified by repetitive sequences such as IS6110 high-transmitted isolates often have the same IS6110 patterns [21]. Due to removing the TbD1 region in the genome of lineages 2, 3, and 4, these lineages are modern lineages with more genomic replication and higher transmission rates than lineages 1, 5, and 6 are known as ancestral lineages [22].

M. tuberculosis can resist host immune responses, survive in the macrophages of the patient's lung, transmit to new hosts through the respiratory system, and cause infection. The more strain pathogenicity is, the more pollutants are released [23]. Modern lineages 2, 3, and 4 have more pathogenicity than other lineages, which can be associated with delayed inflammatory responses of the body to them, and inducing less cytokine production by them within the host macrophages, causing them to make disease in the host rapidly, severely, and with high transmissibility [24, 25].

Among the various strains of *M. tuberculosis*, Beijing strains in lineage 2 (East Asian) have higher pathogenicity than other strains associated with a variety of factors, especially the low presentation of its antigens because of high levels of tumor necrosis factor (TNF) and interleukin 10 (IL10) production, and low-level expression of toll-like receptor 2 (TLR2), TLR4, and major histocompatibility complex (MHCII) in the host, which hides the bacteria from the host immune cells, that makes this lineage more scattered and intense [26-28].

Beijing strains produce phenylglycolipid (PGL) by intact polyketide synthase (pks1511) gene, which causes severe virulence called hypervirulence, that suppresses host immune responses, and reduces the production of inflammatory cytokines by macrophages, which can cause bacteria to escape from the host immune system [29]. The strains of this lineage have a mutT2 gene, which reduces the metabolism of bacteria in food shortages, enabling them to have more adaptation to living inside their host[30]. Unlike other strains, there is no mutation in the replication and transcriptional genes of Beijing strains that led to the increased compatibility [27].

Beijing strains have a high expression of alpha-crystalline proteins and low expression of heat shock protein 65 (Hsp65), PstS1 phosphate transfer protein, and 47 kDa protein compared to other strains [31]. They also have phospholipase C, which creates triacylglycerol as a source of energy storage in the bacteria during the latent infection stage by hydrolyzing phospholipids and producing diacylglycerol as a precursor leading to increased survival in the host body and increased bacterial pathogenicity [32]. These strains can adapt to the anaerobic and microaerophilic conditions and grow with the dormancy survival regulon (DosR regulon) system, which increases the ability of the bacteria to cause latent infection [33].

Personal Protective Equipment (PPE) proteins have been expressed on surfaces of various strains of *M. tuberculosis*, which are antigenic polymorphic, cause antigenic diversity in the different strains of *M. tuberculosis*, which ultimately helps the bacteria to evade the host immune system, and thus increase the pathogenicity of them [34, 35]. Beijing strains have a

member of the PPE protein family called PPE44, which is more expressed in them than other strains, increasing their antigenic variation and leading to their increased pathogenicity and dissemination [36].

Lineage 1 (Indo-Oceanic) has less pathogenicity than other lineages. The strains of this lineage can highly induce TNF-α and IL-1b cytokines production by host macrophages and slow growth within them [37, 38]. These strains do not have the ability to produce phenylglycolipid (PGL), which causes less pathogenesis and transmissibility, which has reduced their prevalence in society [39].

Lineage 3 (EAI, including Delhi/CAS family) is highly capable of inducing pro-inflammatory cytokines production but cannot stimulate IL-10 anti-inflammatory cytokine production due to the lack of deletion mutations in their RD750 region, which has caused a problem in their living inside the macrophage, and less transmissibility and pathogenicity of them compared with other modern strains [40, 41].

The strains of lineage 4 (Euro-American / Haarlem), although they have a high ability to live in alveolar macrophages, having mutations in polyketide synthase locus, causes decreased PGL production by these strains, which reduces their pathogenicity compared to Beijing strains [22, 42]. In strains of lineage 5 and 6, due to the mutation in the position 71 of the Phosphate Regulon sensor protein (PhoR) gene, there is a problem with the phoR regulation system, which reduces the synthesis of surface lipids and the secretion of 6-kD target ESAT-6 that reduces the pathogenicity of these strains by increasing their permeability [22].

In lineage 7, the strains are slowly growing due to many mutations in the genes responsible for the transport of carbohydrates, metabolism, energy production, and transcription [43]. The cell wall of these strains is weak against environmental factors because of the reduction of proteins and lipids responsible for cell wall synthesis, including RV2952, responsible for PGL production, and Dimycocerosates phthiocerol (DIM), which reduces bacterial growth and survival within macrophages [42]. Because of minor colon diameter and weight and lower virulence rate of linages 7 strains compared to other lineages, they are less transmissible than others, which decreases their dissemination in the society [44].

3. Diversity of Intrinsic Aptitude of Respiratory Transmitting of the Strains

Lineage 1 was mostly found in East Africa and Southeast Asia, with the limited transmission, pathogenicity, and geographic distribution. It has the most extraordinary genetic diversity among all strains of *M. tuberculosis* with high heterogeneity in its genome [45]. Better tuberculosis transmission depends on lung contamination, in which lineage 1 has a low transmission because of its more extrapulmonary contamination, which makes it impossible to transfer with air particles [46].

Beijing strains in lineage 2 are among the most successful strains in global distribution, with about 50 % of the strains found in East Asia and 13 % of the world's strains [27]. These strains are divided into two subclasses of modern (typical) and ancient (atypical) because of the presence or absence of the IS6110 in the area of the noise transfer function (NTF) region [47]. Unlike the ancient type, the modern type has a mutation in its putative mutator (mut) region, which plays a crucial role in coding the enzymes involved in DNA repair, has IS6110 in the NTF region, and has a higher pathogenicity and distribution rate than the ancient one [28, 48]. BCG vaccine, prepared from *Mycobacterium bovis*, is one of the influential factors in the emergence of Beijing strains because of its low protective effect against the Beijing strains compared to other strains, especially against typical Beijing strains than atypical [49].

Nowadays, recombinant BCG vaccines containing listeriolysin prepared from *Listeria monocytogenes* have induced high resistance in mice against the infections caused by Beijing strains, but this vaccine has not yet been successfully used for general immunization [27, 50].

Lineage 3 has the oldest strains of *M. tuberculosis* and is found mainly in sub-India and some other Eastern African countries. These strains have a lower transmission rate than other modern lineages because of cause more extrapulmonary tuberculosis [40]. Unlike the other lineages, lineage 4 is the most geographically widespread cause of human tuberculosis due to the immigrants who have traveled from Europe to Africa and America in the past [51]. The strains of lineage 4 differ in genotypes and phenotypes, which causes the diversity of these strains in various parts of the world [51, 52]. Lineage 4 strains are more heterogeneous than lineage 2 strains, which decreases the transmission rate compared with lineage 2 [27]. Lineages 5 and 6 include *Mycobacterium africanum*, confined to Western Africa, transmitted by aerosol particles like *M. tuberculosis*, making them possible to be transferred with air particles and spread in the community [53, 54]. Due to the higher levels of lineage 5 and 6 extrapulmonary contamination, these lineages have less respiratory transmission and have the lowest levels of dissemination rate among all lineages of *M. tuberculosis* [22]. The presence of tuberculosis from lineages 5 and 6 strains in outside areas of Africa is due to the birth of those people in West Africa and then their migration to those areas [50, 55].

The lineage 7 has recently been reported in Ethiopia and among Ethiopian immigrants in Djibouti. This lineage has the intermediate state of the modern and ancient lineages [56], which has the least genetic diversity among all lineages. The strains are the most geographically limited ones, along with the lineage 5 and 6 [22]. The strains of this slow-grown lineage cause mild symptoms in the patient, which makes identifying the agent and treatment of these patients difficult and increases the probability of spreading these strains [44].

4. Intrinsic Transmissibility Power of Strains

Diversity in the transmissibility of *M. tuberculosis* strains is due to the production of various types of infectious aerosols during coughing by patients, and the transmission of *M. tuberculosis* from someone who has acid-fast bacilli in their sputum to someone else happens much faster if there is a pulmonary cavity in that person [57-59].

The strains of *M. tuberculosis* are divided into two groups with high and low transmission power; patients with low transmissible strains have more bacterial burdens than high transmissible strains and produce more lipid aerosols within macrophages, which lead to the formation of foamy macrophages [60, 61].

Although most studies of tuberculosis have been conducted on the H37Rv strain of *M. tuberculosis*, new strains have appeared that have various pathogenicity, immune stimulation, and transmissibility, which can be problematic for the health of the community [62]. One of the critical factors in tuberculosis transmission is the intrinsic ability of some *M. tuberculosis* strains in transmission, which, regardless of the type of lineages, has a significant ability to distribute among communities [62]. For example, the strains of lineages 2, 3, and 4 have high transmissibility, which, in addition to the ability of the strains to develop drug resistance and high virulence, also depends on their high intrinsic and genetic ability to transmit [63].

5. Multidrug-Resistant (MDR) strains

The drugs utilized in treating tuberculosis and inhibiting the growth of pathogenic bacteria lead to the selection of resistant bacteria to these drugs, which is due to the inappropriate use of drugs when treating the disease [64-66]. Among the drug-resistant cases, resistance to a drug such as isoniazid (DR), multidrug-resistance to isoniazid and rifampin (MDR), and extensively drug resistance (XDR) can be highlighted, which makes tuberculosis widespread by creating many problems in controlling the disease [67]. The diagnosis of drug-resistant strains is performed by the diagnostic sensitivity test (DST), which lasts 4-6 weeks after the isolation of the bacterium [68-70].

The emergence of *M. tuberculosis* drug-resistant strains, in addition to chemotherapy and the incorrect use of drugs in the treatment of tuberculosis, can result from spontaneous genetic mutation or transmission from a patient with drug-resistant tuberculosis [71]. The study of WHO in recent years shows that 3.3% of new cases and 18% of previously treated cases have rifampin-resistant tuberculosis (RR-TB) or multidrug-resistant tuberculosis (MDR-TB), and from the 10 million people affected by tuberculosis, about 465 000 were reported to be resistant to rifampin, which 78 % of them were multidrug-resistant tuberculosis (MDR-TB) [1]. Russian, India and the China Federation have half of the cases of MDR / RR-TB [72].

The pathogenicity of drug-resistant strains is minor compared to the susceptible strains due to their reduced transmissibility, which causes limited dissemination [73]. Although resistant strains are spreading globally, they are less transmissible due to the loss of some of their essential characteristics. Still, the mortality rate of these strains is more than susceptible ones [74].

Among the different strains of *M. tuberculosis*, the Beijing strains have successful spread, and one of the causes of that is their drug resistance of them, which leads to escape from the immune system and long-term living of them in the host cells in the absence of the effects of drugs [75-78]. The study of the genotype of Beijing strains shows that mutations in their katG315 gene are the leading cause of their resistance to isoniazid. Resistance to rifampin is also the result of the mutation in the rpoB gene [27]. One of the reasons that have led to the expansion of drug insistence in Beijing strains is the high rate of mutation in the putative mutator (mut) genomic region, which plays a crucial role in coding the enzymes involved in DNA repair, which makes the regeneration of the bacterial genome difficult [27, 79].

The strains of lineage 1 have a lower drug-resistance rate than lineage 2, and resistance to isoniazid in these strains occurs due to a mutation in the promoter region of the inhA-15 C to T gene, which causes poor drug resistance in these strains [80]. Haarlem and Beijing strains have the highest drug resistance rate, and their genetic variations have a significant role in their prevalence [81].

Drug-resistant strains that have a successful global distribution have a deletion mutation in their embR locus, which is a transcription regulator that plays a role in resistance to ethambutol and also acts as a regulator of the ratio of lipomanan to lipoarabinomannan conversion, which is a factor in the pathogenicity of tuberculosis and increases the bacterial distribution rate in the community [22, 82].

6. Extensively Drug Resistance (XDR) of Strains

A rare form of tuberculosis, extensively drug-resistant tuberculosis (XDR-TB), is the most intense and complex form of resistant tuberculosis, first reported in South Africa in 2005

[83]. This form of the *M. tuberculosis*, in addition to the resistance to first-line drugs, rifampin, and isoniazid, is also resistant to fluoroquinolone and at least a second-line injectable drug (SLID) such as kanamycin, capreomycin, and amikacin [84-86]. These strains are developed due to the genetic mutations, including mutations in codons 88 to 94 in the gyrA gene and mutations, which convert organic base A to G in codon 1400, C to A in codon 1401, and G to T in codon 1483 in the rrs gene that encodes 16srRNA of the bacteria [87].

Despite long-term and severe therapeutic regimens, the mortality rate in patients with XDR-TB is very high [88-92]. For this reason, its rapid diagnosis is vital for initiating treatment and preventing its distribution, especially in countries with high epidemics of this form of disease [93]. Despite the importance of the rapid diagnosis of XDR, many countries have a problem with quick diagnosis and control [71]. There are no effective drug therapies for XDR-TB due to their severe disease, which increases the release of these strains, which has increased the incidence of the people [87].

Successful interventions in XDR-TB treatment in some countries show that recovery rates for these patients are between 30% to 50%. However, the rate of treatment for these patients depends on various factors, including the degree of drug resistance, the severity of the disease, and the status of the host immune system [94]. Drug-resistant strains require long-term treatments with expensive drugs that do not have much effect and have severe side effects, leading to reduced control [81] (Figure 2).

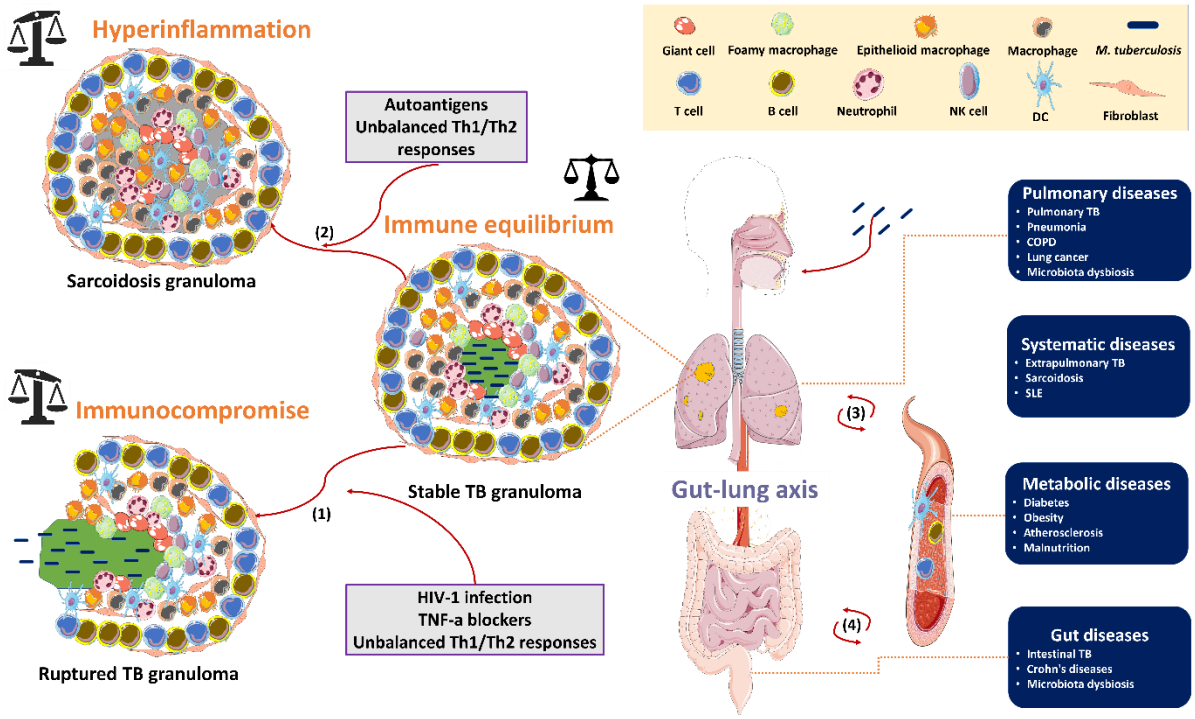

Figure 2. Immune system dysfunction in patients with tuberculosis predisposes them to the development of various disorders. As microscopic particles of *M. tuberculosis* enter the lung tissue, the immune cells come together in the form of granulomas to separate and remove the uncleaned bacteria that subsequently step into dormancy. In the continuation of this process, simultaneously with the violation and weakening of the immune status of the host, *M. tuberculosis* becomes active and propagates in large quantities, and spreads through the granuloma caseating, liquefying, and cavitating (1). After removal of the bacteria, non-caseating granulomas may form continuously, which manifest as sarcoidosis if severe inflammatory conditions are present in the host (2). *M. tuberculosis* constituents, infected cells, secretions, and immune-related elements such as chemokines and cytokines are able to enter the general circulatory system, which in turn increases the likelihood of other infections in the host (3). Intestinal microbial populations also interact directly with *M. tuberculosis* and its pathogenicity through the gut-lung axis and can play a stimulatory or inhibitory role (4).

7. Proteome Contents Diversity of Strains

Bacteria have multiple structural and functional protein content called proteome, which has various roles in their viability and pathogenesis and are studied by proteomic methods [95-97]. Novel development of proteomic analysis tools provides new insights for the study of tuberculosis, especially interactions between the microorganism and the host cells [98, 99]. Each lineage of *M. tuberculosis* has the protein profile that distinguishes it from other lineages that can be identified using different proteomic methods [100-102]. A study of proteome analysis of Beijing strains identified 1,868 proteins, most of which were enzymes responsible for long-chain fatty acid biosynthesis, and proteins responsible for their degradation had low amounts, which provides a reason for the increased transmissibility power of Beijing strains [103]. Also, higher levels of Rv0129c, Rv0831c, Rv1096, Rv3117, and Rv3804c virulence proteins and decreased levels of Hsp65 (Rv0440), Pst1 (Rv0934), and Rv1886c antigenic proteins in Beijing strains indicates their high ability to escape from host immunity systems [104-106]. Beijing strains also have a high ability to cope with stressful situations, including the ability to produce proteins associated with their adaptation to harsh conditions, such as the production of respiratory nitrate reductase delta chain protein, which is effective in nitrate metabolism during the adaptation of the bacteria to difficult intracellular situations and the latent tuberculosis creation [107].

Prevention of tuberculosis, in addition to controlling the bacterial factors, requires controlling environmental factors such as exposure to closed spaces and exposure to sunlight, as well as host factors such as HIV, diabetes, alcohol consumption, and smoking, which by controlling these factors and disrupting the disease transmission chain, the infection can be controlled and ended [108, 109].

8. Conclusions

Investigating the influential bacterial factors in the transmission of tuberculosis showed that strains with high drug resistance and high ability to live in host macrophages have higher virulence, which increases their transmission probability. By identifying effective bacterial factors in the transmission of tuberculosis, it is possible to prevent the spreading of tuberculosis in the community by cutting off the transmission of this microorganism effectively and trying to eradicate it. All drug resistance lines are increasing due to the absence of large potential drug knowledge. The possible molecular mechanism for this drug resistance pattern has needed the latest prompt therapies with anti-tuberculosis drugs. It provides us progressive paths to investigate how specific bacteria can withstand all drugs via changing their genetics and allows us to find ever more effective drugs.

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Conflicts of Interest

The authors declare no conflicts of interest.

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